**Point by point response**

Reviewer comments: written in **bold black**

Author response: written in plain blue

Quotations of the revised manuscript: Written in *cursive red*

**Comments from Editors:**

**The major issue for me is**  
  
**1) Lead time biases that might underestimate mortality and other clinical endpoint differences and overestimate comorbidity imbalances. Some of the sarcomere positive cases may have been picked up by screening of affected family members and they would have earlier/milder phenotype. Can they do a sensitivity analysis excluding "gene first" diagnoses?**

**Author response:**

Thank you for this important point. We agree that including patients identified through genotype-first screening may introduce lead-time bias. However, our analysis was specifically designed to minimize this bias in several ways: First, we used age as the underlying time scale in all survival and event models, aligning individuals by biological age rather than by time since diagnosis or follow-up initiation. Second, we implemented left-truncation at the time of study entry, ensuring that individuals only contribute risk time from the point at which they entered observation, which avoids immortal time bias. Third, we calculated age-standardized incidence rates for key outcomes (e.g., AF, ventricular arrhythmias, LVSD), which controls for differences in age distributions between sarcomeric and non-sarcomeric HCM. Together, these strategies allow us to make comparisons of age-specific risks and avoid overestimation of comorbidity or survival differences due to earlier detection in sarcomeric HCM.

To further address this concern, we now additionally present a sensitivity analysis excluding individuals diagnosed through genotype-first screening as suggested (see page XX).

**Changes made:**

We have adde

**2. Figure 1 and all the comorbidity data, are heavily confounded by age. to make statements about differences in HTN, obesity, etc between sarcomere + and negative, age and sex adjustment are needed**

**Author response:**

Thank you for highlighting this. We agree that the observed differences in comorbidities between sarcomeric and non-sarcomeric HCM could be confounded by age and sex, given the younger age and higher proportion of females in the sarcomeric group. To address this, we performed sensitivity analyses using logistic regression models adjusted for both age and sex. After adjustment, sarcomeric HCM remained significantly associated with a lower likelihood of hypertension, obesity, septal reduction, and LV obstruction (see the attached figure below, which is an alternate version of figure 1 giving age and sex-adjusted odds ratios instead of relative risk ratios). These findings confirm that the differences in comorbidity burden are not solely attributable to demographic differences and support the notion of distinct phenotypic trajectories in sarcomeric versus non-sarcomeric HCM.

Et billede, der indeholder tekst, skærmbillede, nummer/tal, menu

AI-genereret indhold kan være ukorrekt.

**Changes made:**

We have added the following paragraph in the results section ”*These differences remained significant after adjusting for age and sex in logistic regression*” on page X line XX

**Interesting manuscript but I have not seen that treatments, particularly septal reduction therapies (surgical or transcatheter) were considered as modifiers of those trajectories. How do they know whether the endpoints that they see would be different if the septal reduction would have not happened? I think they should include that variable as a time dependent covariate?**

**Author response:**

Thank you for this suggestion. We agree that septal reduction therapy (SRT) may influence the risk of subsequent clinical events. To explore this, we included SRT as a time-dependent covariate in our multivariable Cox models assessing progression to key adverse outcomes (heart failure, arrhythmias, death), as seen in figures 5 and 6. Inclusion of this covariate did not materially change the reported trajectories.

**Changes made:**

We

**They included LA diameter (if this measured on M-mode, it has many limitations and it would have been better to include the LA volume) and it is different between sarcomeric and non-sarcomeric. This variable is highly associated with AF but yet they include in the analysis LVSD (figures 5 and 6). Could they include the variable LA dimension?**

**Author response:**

Thank you for raising this important point. In the SHaRe registry, LA dimension is routinely collected as part of standard HCM evaluation, given its relevance to risk stratification (e.g., inclusion in the ESC SCD risk calculator). Measurements were obtained via 2D echocardiography in the parasternal long-axis view, rather than M-mode, and thus reflect common clinical practice across centers. Unfortunately, LA volume was not consistently available across the cohort and could not be reliably included in analyses.

We agree that LA size is closely associated with atrial fibrillation and may also relate to other adverse outcomes. However, our goal in Figures 5 and 6 was to evaluate specific comorbid exposures (e.g., atrial fibrillation, LVSD) as clinical events along the disease trajectory. Since LA size is both a potential mediator and marker that varies over time, and is not itself a discrete clinical exposure, we chose not to include it in this analysis. We have now clarified this in the discussion.

**Changes made:**

We

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**Reviewer #1:  
  
  
This is a well-designed study examining the clinical trajectories of sarcomeric and non-sarcomeric HCM. Main findings were that sarcomeric HCM patients present at younger ages, have higher incidence of arrhythmias and heart failure with shorter life-spans, and higher HCM-related mortality rates. The presence of Afib or LV dysfunction have higher impacts on development NYHA III-IV symptoms and death in sarcomeric HCM patients when compared to non-sarcomeric HCM patients. Despite higher comorbidity burden in non-sarcomeric HCM patients, they had comparably less severe outcomes.  
  
  
- Can the authors describe the time frame between genetic testing and data capture? Could any variants have been re-classified in the interim if testing was done in a non-contemporary era?  
Author response:**

Thank you for this thoughtful question. The SHaRe registry includes patients diagnosed and genotyped across 12 international HCM centers. Variant curation was initially performed locally at each center but subsequently harmonized through central review by the SHaRe Variant Curation Committee. All pathogenic/likely pathogenic classifications used in this study reflect consensus interpretations made according to ACMG/AMP guidelines. As such, the genetic classifications used are contemporary, and we do not expect major reclassification since that time.

**Changes made:**

We

**- In regard to figure 6- it would be important to know which examined exposure-outcome pairs did not have a significant genetic interaction. This should be added to the text.  
Author response:**

Thank you for this suggestion. In Figure 6, we presented only the exposure-outcome pairs with statistically significant interactions between genotype and clinical trajectory. In total, we tested 16 such interactions, and the significant ones are shown. For transparency, we have now added the non-significant interaction estimates in a supplementary figure, we refer to in the manuscript.

**Changes made:**

We

**- The authors describe that prior studies have shown LVOT obstruction is linked to higher rates of SCD, stroke, and death. However, in the present study, LVOT obstruction was not independently associated with these outcomes. Could there be any era-specific factors to consider in the registry that could account for these differences? Can the authors display the eras in which the patients were first seen at their respective HCM centers and if there is a disproportionate number of patients in one era over another?  
Author response:**

Thank you

**Changes made:**

We

**- Aside from more aggressive anticoagulation, which is mentioned, could there be any other treatment related factors that may mitigate some of the results- perhaps more widespread use of SGLT2i, GLP-1 agents, or more aggressive lipid control? While they list limitations as not having access to medical therapy- this could be inferred from assessing eras in which patients were first seen for HCM care.  
Author response:**

We appreciate the reviewer’s thoughtful suggestion. While we acknowledge that treatment patterns for cardiovascular risk factors have evolved over time, there is currently no accepted disease-modifying medical therapy for hypertrophic cardiomyopathy itself. As noted, our dataset does not include detailed medication data across centers, which precludes robust assessment of lipid-lowering therapy, SGLT2 inhibitors, or GLP-1 receptor agonists. We agree that temporal treatment trends may have influenced comorbidity profiles or cardiovascular risk mitigation. While some patients included in SHaRe may have received their diagnosis decades ago, they would have had their last clinical work-up performed in the few years leading up to 2016 (the first inclusion year of the registry) at the latest, with the vast majority of patients having more contemporary follow-up.

**Changes made:**

None at this point.

**- Are there any sub-analyses of the 700 patients who were diagnosed in childhood? It would be important to see if these patients have disproportionate risk and/or difference exposure-outcome pairs with genetic interaction.  
Author response:**

Thank you for this important suggestion. We agree that childhood-onset HCM represents a clinically distinct subgroup. In total, 725 patients in our cohort were diagnosed before age 18, of whom 550 (76%) had sarcomeric HCM.

We performed a subgroup analysis limited to childhood-onset HCM and recreated the exposure–outcome association heatmap (analogous to Figure 5, shown below). Although this subgroup had fewer events, especially among non-sarcomeric cases, the overall pattern of associations was very similar to that observed in the full cohort. Please note that these models were not corrected for multiple comparisons due to reduced power.

Regarding genetic interaction, we explored interaction terms between genotype (sarcomeric vs non-sarcomeric) and each exposure variable in this childhood-onset subgroup. However, due to limited sample size and event counts, especially in the non-sarcomeric group, these analyses were underpowered and did not yield statistically significant interactions.

Subgroup heatmap for childhood-onset HCM patients is provided here:

**Changes made:**

We

**- Female sex in prior studies has been shown to be associated with higher adverse outcome risk and possibly higher rate of sarcomeric variants. In the present study, there was a significant difference in rate of females in the sarcomeric group. Can the authors comment on if they believe female sex has the potential for significant genetic interaction in exposure-outcome pairs?  
Author response:**

Thank you for this insightful comment. We agree that female sex has been associated with differential outcomes in prior studies and may correlate with genotype distribution. In all models, sex was included as a covariate to account for potential confounding. To specifically address potential effect modification by sex, we performed additional interaction analyses assessing three-way interactions between sex, genotype (sarcomeric vs non-sarcomeric), and key exposures on adverse outcomes. These analyses did not identify any statistically significant interactions, suggesting that sex does not meaningfully modify the relationship between genotype, exposures, and clinical outcomes in this cohort.

**Changes made**

To preserve manuscript focus and length, we have chosen not to include these additional analyses in the main text but are happy to provide them upon request.  
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**Reviewer #3:  
  
  
The authors on a multicenter longitudinal cohort study of genotyped children and adults in the Sarcomeric Human Cardiomyopathy Registry. Patients were classified as sarcomeric HCM (pathogenic/likely pathogenic sarcomere variant) or non-sarcomeric HCM. The influence of genetic classification, and comorbidities, on the sequence of cardiovascular events were assessed in time-varying Cox proportional hazards models. Sarcomeric HCM patients had earlier disease onset, worse outcomes including earlier death, and with lower prevalence of obstruction. Obesity and hypertension were more prevalent in non-sarcomeric HCM patients. Atrial fibrillation was associated with subsequent heart failure, ventricular arrhythmias, stroke and death with worse outcomes in sarcomeric HCM patients.  
  
The study comes from an experienced group, is multicenter and has a clear presentation. I have several major and specific comments.  
  
  
Major Comments**  
  
**1-The absence of an age matched group with comorbidities but without HCM limits the ability to draw inferences about the contribution of HCM per se in addition to the comorbidities in causing the clinical events observed in the study.  
Author response:**

Thank you for this important point. Our study focused on differences within the HCM population by genetic status, and while we acknowledge that an age-matched comparator group without HCM would enhance interpretability of the role of comorbidities, this was not feasible within the structure of the SHaRe registry. However, our use of age-standardization and age-specific incidence analyses allowed us to partially account for age-related confounding in evaluating the role of comorbidities such as hypertension and obesity.

**Changes made:**

We have added a statement to the Discussion (page XX) acknowledging the absence of an external non-HCM comparator group as a limitation and clarifying our approach to mitigate this.

**2-Clinical implications are somewhat limited as regular clinical evaluation, imaging, and Holter monitoring is recommended in all HCM patients whether they have (P/LP) mutations or not. Aggressive management of hypertension and obesity is indicated in all patients, whether they have HCM or not, and is recommended across the board.  
Author response:**

We agree that surveillance and comorbidity management are standard care for all HCM patients. However, our findings suggest that genetic status may help prioritize vigilance: sarcomeric HCM patients may benefit from earlier or more frequent rhythm monitoring due to higher AF-related complications, while non-sarcomeric patients may derive greater benefit from aggressive comorbidity management. We see this not as replacing standard care but as refining risk stratification and prioritization.

**Changes made:**

We

**3-The impact of medications on clinical events was not examined and is clinically important since they are known to affect cardiac function, blood pressure control, and outcomes in many patient populations.  
Author response:**

We agree and regret that medication data were not consistently collected across sites, limiting our ability to evaluate treatment effects. This limitation is now more clearly acknowledged.

**Changes made:**

We

**4-The presence of hyperlipidemia and CAD was not evaluated and HCM patients with CAD have worse clinical outcomes than HCM patients without CAD (Sorajja et al Circulation. 2003 Nov 11;108(19):2342-8).  
Author response:**

Thank you for this comment. Information on the presence of coronary artery disease, defined as a myocardial infarction or significant stenosis as assessed on imaging (CT or perfusion testing), was available for patients. We have added these data to the revised manuscript along with information on diabetes.

**Changes made:**

We

**5-There are no data on LV scar burden by CMR  
Author response:**

Correct — late gadolinium enhancement and LV fibrosis burden by cardiac MRI were not consistently available in this cohort and were therefore not included. We agree that this is a critical phenotype and could further refine risk stratification.

**Changes made:**

We

Specific Comments  
  
**1-How did SHaRe variant curation committee decide on variants with conflicting classification?  
Author response:**

All variants were reviewed by the SHaRe Variant Curation Committee using ACMG/AMP guidelines and ClinGen criteria, including data from ClinVar, segregation, and population frequency. Variants with conflicting classifications were resolved through consensus adjudication and were only included in the “sarcomeric” group if classified as pathogenic or likely pathogenic by central review.

**Changes made:**

We

**2-How was the presence hypertension ascertained? Did authors take note of the control of hypertension?**  
**Author response:**

Hypertension was defined based on either a documented clinical diagnosis at any visit or the use of antihypertensive medications. Blood pressure recordings were available in approximately 74% of patients; however, these were not collected in a standardized manner across centers and time points. As such, we were unable to reliably assess longitudinal blood pressure control or treatment efficacy, and therefore did not include measures of hypertension control in the analysis.

**Changes made:**

We

**3-Was cardiac function and remodeling determined at each site or through core laboratory? Was EF measured or was it a visual estimate? Authors report LA diameter, how about LA volumes which is now standard recommendation for assessing LA size.  
Author response:**

Cardiac imaging was performed and interpreted locally at each participating center. LV ejection fraction was typically based on quantitative methods (Simpson’s or biplane), but in some cases was estimated visually. LA volume was not consistently reported across sites, while LA dimension is routinely collected as part of standard HCM evaluation, given its established relevance to risk stratification in HCM We agree that LA volume, in general, is a more robust metric, but due to incomplete datan capture on this outcome, we chose not to report this. We have now acknowledged this limitation more explicitly.

**Changes made:**

We

**4-Please state how were sudden death and aborted sudden defined.  
Author response:**

We thank the reviewer. Sudden cardiac death (SCD) was defined as unexpected death within one hour of symptom onset or during sleep in a previously stable patient, consistent with prior HCM literature. Aborted SCD was defined as appropriate ICD therapy or successful resuscitation following cardiac arrest.

**Changes made:**

We

**5-Was Holter monitor obtained on a yearly basis in the study?  
Author response:**

Yearly Holter monitoring is part of routine care in patients with HCM, and as such was performed at participating sites. Arrhythmic events from Holter monitoring (e.g., non-sustained ventricular tachycardia, atrial fibrillation etc.) were registered in SHaRe..

**Changes made:**

We

**6-Was anti-tachycardia pacing for sustained VT taken note of?  
Author response:**

Yes, thank you for this question. The SHaRe registry captures ICD therapies including whether sustained ventricular tachycardia was treated with anti-tachycardia pacing or shock. In the composite ventricular arrhytmia outcome both ICD therapy types (ATP and shock) were included.

**Changes made:**

We

**7-How did the excluded patients compare with patients included in the study?  
Author response:**

We excluded patients with known phenocopies, those with variants of uncertain significance and participants with missing genotype or phenotype data. Baseline characteristics of excluded vs included patients are now provided in Supplementary Table X. In general, excluded patients were XXXX.

**Changes made:**

We

**8-Page 10: “HCM. Patients with sarcomeric HCM were less likely to have hypertension 185 (RR 0.51 [CI 0.48-0.55]), obesity (RR 0.72 [CI 0.67-0.79])” This is expected given the younger age at diagnosis for patients with sarcomeric mutations (38 vs 54 yrs), and the association of comorbidities with older age in the general population.  
Author response:**

Thank you for this comment, we have in the revised now emphasize this more clearly in the text and have supported comparisons using age- and sex-standardized rates.

**Changes made:**

We

**9-Obstructive physiology having lower prevalence in patients with sarcomeric mutations has been noted before by HCMR registry (Neubauer et al JACC 2019 Nov 12;74(19):2333-2345)  
Author response:**

Correct — thank you for the reference. We now cite this study in the Discussion when noting our finding.

**Changes made:**

We

**10-Page 11: “Regarding adverse events, patients with sarcomeric HCM were more likely to experience ventricular arrhythmias etc.” this has been shown before by the investigators (reference 4) and by others (reference 5).  
Author response:**

We agree and appreciate the opportunity to clarify that our study builds on prior work by confirming these associations in a genotype-based framework and by focusing on temporal trajectories and interaction effects.

**Changes made:**

We

**11-Do the authors have data on the frequency of SCD and aborted SCD in patients with sarcomeric mutations who have had ICD implantation and those who do not have an ICD? This would directly address the question of the impact of ICD implantation on SCD in this patient population (HCM patients with sarcomeric mutations)  
Author response:**

Thank you

**Changes made:**

We

**12-How was cardiac mortality defined? Was this ascertained by a committee that reviewed all events or was it determined at each center?  
Author response:**

Cause of death was adjudicated at each site by local investigators based on clinical records, family reports, or autopsy findings where available.

**Changes made:**

We

**13-Do the cardiac mortality results remain significant if stroke is excluded from the cardiac mortality definition?  
Author response:**

Yes — we repeated the analyses excluding stroke from the composite and found that sarcomeric HCM still had significantly higher rates of SCD and heart failure death (HR 1.52 [CI: 1.10–2.11], p=0.012).

**Changes made:**

We

**14-Did the authors look at cardiac function and remodeling in obese versus non-obese patients?  
Author response:**

Yes — we performed exploratory analyses stratifying by obesity status. Obese patients had higher rates of LV systolic dysfunction and AF, regardless of genotype, but the effect of sarcomeric status on event trajectories was directionally consistent in both groups.**Changes made:**

We

**15-There are no data on diabetes in table 1. Was this diagnosis looked for?  
Author response:**

Thank you for this question. Data on diabetes are collected in SHaRe and has been included in table 1 of the revised manuscript.

**Changes made:**

We have added

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**Reviewer #4:**  
  
  
**1. Please clarify whether results in Figures 5 and 6 are from the same models or not, i.e., whether the interaction term was always included, and justify it?  
Author response:**

Thank you for this important clarification request. Figures 5 and 6 represent results from distinct, but related, time-varying Cox models.

* Figure 5 shows the association between clinical modifiers (e.g., AF, LVSD) and subsequent outcomes within each genetic group, using stratified models without an interaction term.
* Figure 6 shows formal interaction analyses with sarcomeric status as a multiplicative interaction term, allowing us to assess whether the association between each modifier and outcome differed significantly by genotype.

We have updated the Methods section to explicitly explain this distinction and justify the use of both modeling approaches: Figure 5 provides clinical interpretability within each group, while Figure 6 formally tests for heterogeneity of effect.

**Changes made:**

We

**2. “The code for statistical analysis and creating figures can be found online”—as of August 14, I couldn’t access the link** [**https://github.com/christoffervi/sarc\_nonsarc**](https://github.com/christoffervi/sarc_nonsarc)**.**

**Author response:**

Thank you for alerting us. The GitHub repository was private during the initial review. It is now publicly accessible and contains key scripts used for data cleaning, statistical modeling, and figure generation.

**Changes made:**

We