Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-23-202

Reviewer A

Comment 1: "The authors showed that during a median follow-up of 3.9 years (I would say long-term follow-up), apical HOCM was associated with preserved LV ejection fraction but abnormal mechanics and myocardial work indices."
Reply 1: We agree with the reviewer.
Changes in text: 'Mid-term follow-up' was changed to 'long-term follow-up' throughout the manuscript, where appropriate.

Comment 2: "Please explain better 'follow-up GLS' or 'follow-up LV mechanics' in the abstract."
Reply 2: We agree with the reviewer.
Changes in text: The abstract has been edited and clarified (page 2, lines 1-21; page 3, lines 1-3).

Comment 3: "Please specify 'mitral annular velocity' whether you refer to tissue Doppler velocities (systolic S' or diastolic e') or MAPSE?"
Reply: We agree with the reviewer.
Changes in text: A brief description of the diastolic assessment performed for the study is included in the 'Methods' section (page 7, lines 8-11), and all mentions of mitral annular velocity throughout the manuscript and tables were updated accordingly.

Comment 4: "Did the authors test the prognostic value of regional strain (basal, mid, apical)?"
Reply: In assessing the potential of regional strain as a prognosticator, no specific thresholds were identified.
Changes in text: None.

Comment 5: "Basal strain was preserved from baseline to follow-up. Can we say basal sparing in apical HOCM in contrast to apical sparing in amyloidosis patients. Please include a Bull eye's plot showing basal sparing pattern strain."
Reply: We agree with the reviewer.
Changes in text: The 'basal sparing' hypothesis has been added to the revision, and a bullseye plot has also been included as a figure (page 12, lines 5-8; page 25, lines 24-30).

Comment 6: "In how many patients a contrast echo was performed to look for apical aneurysm which can be challenging in some patients with poor acoustic window?"
Reply: Unfortunately, this information is not available. We can confirm that contrast was not universally performed for all patients, and thus, the prevalence of apical aneurysm may be underestimated. We acknowledge this as a study limitation.
Changes in text: This relevant limitation has been included in the revised 'Discussion' (page 14, lines 19-20).

Reviewer B

Comment 1: “GLS is particularly difficult to correctly perform in HCM, and especially in the apical forms, as detailed below. This is not acknowledged as significant limitation.”
Reply: We agree with the reviewer.
Changes in text: This has been added as a study limitation in the ‘Discussion’ section (page 14, lines 5-7).

Comment 2: “The outcome and endpoint include myocardial infarction, which is not a typical complication of apical HCM. This changes all prognostic data and analysis.”
Reply: Myocardial infarction is an important complication that has been noted in studies of patients of apical HCM. In a landmark long-term analysis by Rakowski and colleagues at the University of Toronto, myocardial infarction occurred in 10% of patients over a mean follow-up of 14 years, and was the second most common morbid event (J Am Coll Cardiol 2002;39:638). Furthermore, microvascular disease and obstruction, persistence of apical contraction into the early diastolic period, and myocardial bridging have been shown to induce repetitive myocardial ischemia, documented myocardial perfusion defects, and angina symptoms in patients with apical HCM. These latter instances, which may be interpreted as ‘demand’ ischemia or type II non-ST-segment elevation myocardial infarction, are important events (Int J Cardiol 2018;251:65; J Am Heart Assoc 2020;9:e015294). It is accepted that myocardial infarction from any cause carries increased risk of adverse outcomes in the general population. Thus, we believe the prognostic data and analysis are clinically relevant.

In the context of the reviewer’s comments, however, we do acknowledge that there is a limitation to our definition of ‘myocardial infarction’, which did not differentiate between type I (atherthrombotic coronary artery disease) and type II (oxygen supply and demand mismatch).
Changes in text: The study definition of ‘myocardial infarction’ has been added as a limitation in the ‘Discussion’ section (page 14, lines 8-11).

Comment 3: “The main author is an editorial board member of the JTD. This represents a potential conflict of interest that may be addressed of course through an equidistant and independent review process.”
Reply: We are in agreement and conform to the editorial standards of the journal.
Changes in text: This has been included under the ‘Conflict of Interest’ statement (page 15, lines 12-13).

Comment 4: (Abstract) “In fact, the apical HCM is not really increasingly recognized for morbidity. It is more complicated. It has long been considered a “milder and better” version of HCM, and lately several studies demonstrated that significant complications exist also in this form.”
Reply: We agree with the reviewer.
Changes in text: The background statement in the ‘Abstract’ has been edited accordingly (Page 2, lines 1-2).

Comment 5: (Abstract) “Here you describe the LV strain and myocardial work indices, not really the function and mechanics of the LV.”
Reply: We referred to the assessment of myocardial function using strain techniques as cardiac mechanics as outlined by The American Society of Echocardiography and their dedicated guideline documents (J Am Soc Echocardiogr 2011;24:277; J Am Soc Echocardiogr 2015;28:183). We do agree with both reviewers in the necessity to be consistent in the nomenclature.

Changes in text: The abstract has been edited and clarified (page 2, lines 1-21; page 3, lines 1-3).

Comment 6: (Abstract) “Why was myocardial infarction defined as complication of apical HCM?”
Reply: Please refer to the response for comment 2.
Changes in text: Please refer to the changes for comment 2.

Comment 7: (Abstract) “Myocardial work indices are not widely accepted as LV function assessment; therefore you should define them before presenting the results.”
Reply: We agree with the reviewer.
Changes in text: A description of how myocardial work is calculated using speckle-tracking echocardiography was added to the ‘Methods’ section of the abstract (Page 2, lines 7-9).

Comment 8: (Abstract) “(□=0.37, P186 mmHg%” is out of place after AF.”
Reply: We believe that this is an error in the submission system which asks for a separate upload of the abstract, which was corrected. Please note that this error is not present in the full manuscript.
Changes in text: None.

Comment 9: (Introduction) “Myocardial infarction is not a classical complication of apical HCM. Although remotely possible (apical aneurysm, thrombus, coronary embolism: this falls rather in the category stroke/embolic events than in myocardial infarction), it is still not related to HCM.”
Reply: Please refer to the response for comment 2.
Changes in text: Please refer to the changes for comment 2.

Comment 10: (Methods) “By the definition of the mid-cavity obstruction and aneurysm, you provide a very good and old reference from 1976. More recent work has looked in-depth at this aspect from a modern perspective see DOI: 10.1016/j.echo.2015.08.015 and DOI: 10.1016/j.echo.2022.04.010.”
Reply: We agree with the reviewer.
Changes in text: The reference *J Am Soc Echocardiogr 2022;35:846-56* is included in the revised manuscript (page 6, line 15; page 18, lines 5-7).

Comment 11: (Methods) “By diastolic function assessment you do not need to cite both the American and European guidelines, they are essentially the same document. Please use only one reference that is most appropriate.”
Reply: There is only one citation for diastology referenced in the methods (reference 22). The American and European guidelines are a single document.
Changes in text: None.

Comment 12: (Methods) “Please define the average systolic TDI motion (s’?/e’?/a’?).”
Reply: We agree with the reviewer.
Changes in text: A brief description of the diastolic assessment performed for the study is included in the ‘Methods’ section (page 7, lines 8-11), and all mentions of mitral annular velocity throughout the manuscript and tables were updated accordingly.

Comment 13: (Results) “In table 1 I see one patient with septal myectomy. In this case, was it really an apical form?”

Reply: Yes. Apical HCM can be classified into 3 distinct subtypes: 1) isolated apical hypertrophy ("pure"); (2) both apical and septal hypertrophy but with the apex thickest ("mixed"); and (3) early ApHCM phenotype which shares diagnostic criteria with the pure form ("relative") (J Am Heart Assoc 2020;9:e015294).
Changes in text: None.

Comment 14: (Results) "In table 2 you describe the LV geometry and use the wording: normal geometry/conc remodeling/conc or ecc hypertrophy. Do these really apply in apical HCM, where from the start the geometry is abnormal and the pattern of hypertrophy does not fit any of these descriptions? I would delete this section."
Reply: We agree with the reviewer.
Changes in text: The LV geometry parameters have been removed from table 2.

Comment 15: (Results) "In your description of the evolution of the echo parameters you use "marginal decrease" for LVEF and "significant progressive impairment" for GLS. But looking at the numbers the LVEF was highly significant and marginal (p=0.008) and GLS marginal (11.9 vs 10.7, in spite of p=0.006) although significant. In the results I would suggest using a neutral tone, keeping the characterization for the discussion."
Reply: We agree with the reviewer.
Changes in text: The 'Results' description has been revised as requested (page 10, lines 1-3).

Comment 16: (Results) "How do you explain the RV worsening? Was there RV involvement?"
Reply: The current study was not designed or approved by the institutional IRB to assess RV involvement or detailed mechanics, with inclusion in data abstraction and analysis of only TAPSE. However, we are in the process of conducting a separate study in apical HCM patients focusing on the right heart, and its associated mechanics and remodeling.
Changes in text: The finding and importance of RV dysfunction in HCM is mentioned in the revision, and the lack of detailed analysis has been included as a limitation (page 14, lines 14-18).

Comment 17: (Results) "Multivariate analysis: the average mitral velocity – how was it defined? Is it the systolic or one of the diastolic peaks? If it is the systolic peak, it is highly correlated to peak GLS, is there no collinearity in your analysis then?"
Reply: The mitral velocity measured was the average mitral annular e' velocity to reflect LV relaxation.
Changes in text: A brief description of the diastolic assessment performed for the study is included in the 'Methods' section (page 7, lines 8-11), and all mentions of mitral annular velocity throughout the manuscript and tables were updated accordingly.

Comment 18: (Results) "How many infarcts were embolic and how many due to coronary atherosclerosis? If they were due to coronary disease, do they pertain to the complications of HCM?"
Reply: Please refer to the response for comment 2.
Changes in text: Please refer to the changes for comment 2.

Comment 19: (Results) "CVA's were defined as ischemic or ischemic and hemorrhagic?"

Reply: Cerebrovascular accidents were defined as either ischemic or hemorrhagic, and the distinct prevalence of each subtype was not adjudicated. Although the overall event rate was low, the difference in prognosis is acknowledged as a potential confounder.
Changes in text: This limitation has been added to the revised 'Discussion' section (page 14, lines 11-14).

Comment 20: (Results) "The patient with combined hypertrophy had another phenotype of HCM, I would not include."
Reply: Apical HCM can be classified into 3 distinct subtypes: 1) isolated apical hypertrophy ("pure"); (2) both apical and septal hypertrophy but with the apex thickest ("mixed"); and (3) early ApHCM phenotype which shares diagnostic criteria with the pure form ("relative") (J Am Heart Assoc 2020;9:e015294).
Changes in text: None.

Comment 21: (Discussion) "LVEF is not primarily a reflection of radial contraction in the Simpson/3D assessment; it is so in Teicholz. The GLS is not a measure of ejection, but it takes into account indeed the full wall function."
Reply: We agree with the reviewer's comment.
Changes in text: The discussions of LVEF limitations and GLS assessment have been edited and tempered in the revision (page 11, lines 20-23; page 12, lines 1-2).

Comment 22: (Discussion) "While I agree that GLS applies in a lot of instances, and provides very interesting insights in the LV mechanics, it is precisely the "full wall" assessment which is difficult in the apical form of HCM. Current software does not adapt to the very peculiar geometry of the apical HCM; there is simply no possibility to adjust the ROI tracing only in the apical region where the muscle may reach diameters between 15 and even above 30mm. This applies to GE but also other vendors. This is a consequence of the standardization efforts for strain measurements which you cited in the introduction. Furthermore, the apical LV is in the near field (where also artifacts occur), where the wall motion is not in the direction of the ultrasound, which has been proven to alter strain assessment (it is not completely "direction independent"), and the particular geometry leads to further challenges in the view orientation. This is to say that strain in apical HCM is not very easy to do, and not so readily useful as a clinical tool."
Reply: In our imaging laboratory we use the GE EchoPAC system which does indeed allow for both auto-generated and user-defined ROI, the latter of which can be adjusted to the differing thickness and contour of the LV, when appropriate. We do not agree with the statement regarding the utility of GLS in HCM as a clinical tool, but do acknowledge that there is a lack of published data in the subgroup of apical HCM which was the motivation behind performing our study. We have clearly outlined the limitations of our study and carefully stated that larger studies and longer-term follow-up are important to confirm our data. Additionally, we included a new limitation as outlined in the response to comment 1 from the reviewer regarding the difficulty of GLS assessment in certain patients with HCM.
Changes in text: Please refer to the response for comment 1.

Comment 23: (Discussion) "Why do you state that the GLS worsening suggests a higher-risk population? Your data does not indicate that these patients had a worse outcome, i.e., higher risk than other HCM patients."

Reply: We agree with the reviewer.
Changes in text: The ‘Discussion’ has been edited to remove the “higher-risk” statement (page 12, lines 17-19).

Comment 24: (Discussion) “It is interesting to present the threshold of global wasted work which identified complications, but is it worth going through all those calculations in order to achieve a prognosis for these patients?”
Reply: Yes, we believe that myocardial work provides an important an unique insight into the myocardial dysfunction underlying apical HCM patients, given their associated morbidity. Nevertheless, our findings are hypothesis-generating and require validation in larger cohorts with longer follow-up.
Changes in text: None.