

## Peer Review File

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### Reviewer A

This is an interesting manuscript on the prognostic value of fractal analysis of ventricular trabecular complexity in hypertrophic cardiomyopathy. The study applies a novel approach to cardiovascular magnetic resonance images interpretation based on commonly used sequences. The topic contributes to current controversy on ICD implementation guidelines in HCM. The paper is written clearly and pleasant to read. The conclusions are reasonable and supported by the data. The results are of potential clinical use.

My concerns are listed below:

TRIPOD checklist: the line numbers given in the table do not correlate correctly with the line numbers in the manuscript. Item 3b in the Introduction section is not clearly specified ( whether the study describes the development or validation of the model or both). Item 4b: when was the end of follow-up? Item 5a needs addendum: the location of centers.

Reply: We revised the checklist item 3b location as introduction paragraph 3 (page 4, line 87-90). We added the end of follow up (item 4b) which is December 2021 (see page 5, line 96). We added the location of centers (item 5a) (see page 5, line 98).

Lines 106-107. Please explain why either the AHC/ACC guidelines or the ESC guidelines were used for diagnosis? The criteria differ substantially, the study is retrospective so uniform criteria seem adequate. Was the diagnosis center-dependent? How many patients were included according to American criteria? My main concern is this could influence the number of participants with LV dysfunction and possible phenocopies.

Reply: We are sorry that our former expression leads to mis-understandings. The diagnosis criteria is the same in both centers. We used a widely accepted criteria which is in accordance with both guidelines. "HCM group individuals in this study met one of the following criteria: 1) The left ventricle wall thickness (LVWT) was above or equal to 15mm at the end-diastolic stage and cannot be explained by a loading condition; 2) The LVWT was 13 to 14mm with a relevant HCM family history and cannot be explained by a loading condition" (see page 6, line100-103).

Lines 188-194. The numbers of primary events are much higher than expected in general HCM patient population. It seems that your population is higher-risk biased. Please include this topic in the discussion section, explain the potential reasons and try to estimate if this could influence the results.

Reply: According to the 2014 ESC guidelines, the annual incidence for cardiovascular death is 1–2%. We have 6% subjects had sudden cardiac death with a median follow-up of 2 years, which is slightly higher than the guidelines. The potential reason may be some patients with mild symptoms didn't visit our centers for medical help. We have added this

topic in the discussion section (see page 15, line 316).

#### **Reviewer B**

It was a pleasure to review the manuscript on prognostic value of fractal analysis in patients with hypertrophic cardiomyopathy. The authors have retrospectively analysed the trabecular complexity and LGE in 284 patients with HCM and used Cox regression analysis to predict outcome. LV maximal apical FD was independent predictor of outcome in the multivariate model with inclusion of ESC criteria as well as LGE percentage although the HR was marginally above 1.

It is a well written article and meticulous work, specifically including the LGE, ESC predictors and fractal analysis in the same model is informative and would be of interest to readers. The authors have also provided reproducibility data for fractal analysis which is useful. Limitations were mentioned appropriately in discussion.

#### **Reviewer C**

This is a very interesting study on the effect of trabeculations of the LV and the RV on the risks of cardiac events. The limitations of the study have been properly described. I am really wondering what the effects of manual interactions on the FD calculations are on the results. For example, the user has to manually delineate mid-wall myocardium on the ED phase cine-images. Also, on the actual calculations of the FD results, how dependent are these on certain settings? Have these been optimized? That is not clear from the paper and may have a significant effect on the results. More clearness on the algorithmic part and additional validations are necessary in my opinion.

Reply: The manual drawing step in the mid-wall myocardium is only a raw cropping of the image to get rid of useless background. Then the software automatically identifies the endocardium contour. It is more like placing a geometry ROI to the original cine images rather than delineation (we changed the expression see page 7, line 135), so that the manual step has very little effect on the calculations of endocardium (FD). We have also done reproducibility test (see page 13, line 260 and in supplemental material) of FDs, in which we repeated the manual drawings. The intra- and inter reproducibility were excellent. The examples of manual drawing circle or moon-like borders in the mid-myocardium are shown in the figure below.

