Peer Review File

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Reviewer A

This is an interesting and elegant paper investigating the relationship between the mitral insufficiency grade and LVH subtypes, exploring the impact of unhealthy habits on LVH development in patients with MR. The structure is well-organized. The conclusions are reasonable and supported by the data. The paper is relevant and valuable to the study of mitral patients and LV hypertrophy. The introduction effectively conveys the authors' motivation. The results are presented clearly, and the tables and figures are accurate. The discussion is very detailed and specific. Limitations of the study are adequately understood and described.

We thank Reviewer A for the valuable comments.

Comment 1: 'I am particularly interested in the topic of mitral regurgitation grading by cardiac magnetic resonance and I feel it would be very useful to cover this area in greater detail'

Reply 1: This study was conducted with retrospectively collected data and the mitral insufficiency grading was done by an experienced radiologist using the current guidelines set by ACC/AHA. The CMR protocol and the MR grading are elaborated in sections 2.3-2.5 as advised. Please see pages 9-10, lines 154-168 (2.3 Cardiac Magnetic Resonance Protocol), pages 10-11, lines 171-191 (2.4 Post Processing), pages 11, lines 194-200 (2.5 Mitral Insufficiency Grading).

Comment 2: 2.3 Cardiac Magnetic Resonance Protocol:
Line 119: „In addition, for volumetric assessment, a three-dimensional (3D) magnetic resonance angiography (MRA) of the entire heart was performed with the administration of 0.2 mmol/kg gadolinium contrast (Gadovist, Bayer, Canada)". Please describe the sequence used in detail. I suppose you mean 4-D flow sequence, not standard angiography? The routine MR grading in CMR is usually done by 2D flow phase contrast series. If you used 4D flow for this routinely, your material is very interesting and innovative, and I would like to know the specifics.

Reply 2: This study utilized 2D phase-contrast cardiac MRI which is the standard-of-care cardiac MRI, to quantify standard flow parameters for grading MR. The 4D flow sequence was not used. We apologize for the miscommunication regarding this. We have extended the 2D PC sequence information in the section '2.3 Cardiac Magnetic Resonance Protocol' followed by section 2.4 post-processing.
Changes in the text: We have modified the CMR protocol that was followed for this study (Please see Pages 9-10, lines 158-168), and added the post-processing part (Please see Pages 10-11, lines 171-191).

Comment 3: 2.4 Mitral Insufficiency Grading
Line 124: The references given are a bit confusing, especially [9] Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imaging. 2020 Sep 1;21(9):94958.
I think that as far as EACVI guidelines are concerned, it would be more appropriate to use
Lancellotti P, Pibarot P, Chambers J, La Canna G, Pepi M, Dulgheru R, et al. Multi-modality imaging assessment of native valvular regurgitation: an EACVI and ESC council of valvular heart disease position paper. European Heart Journal - Cardiovascular Imaging. 2022 May 1;23(5):e171–232.
It seems you used also the classification suggested in

Gelfand EV, Hughes S, Hauser TH, Yeon SB, Goepfert L, Kissinger KV, et al. Severity of Mitral and Aortic Regurgitation as Assessed by Cardiovascular Magnetic Resonance: Optimizing Correlation with Doppler Echocardiography. Journal of Cardiovascular Magnetic Resonance. 2006 Jan 1;8(3):503–7.

Reply 3: This study followed the ACC/AHA guidelines for MR grading. We acknowledged the confusion regarding referencing EACVI guidelines and in the revised version, we have removed the reference as advised and added only the guideline by ACC/AHA which was solely followed. As for the grading criteria, we followed the severity grading A-to-D for chronic primary MR. Additionally, we have removed the range of EROA from Table 1 as it was not used for this study. Additionally, we upgraded the references with the cut-off ranges followed for this study.
Changes in the text: Please see page 11, lines 194-200 (2.5 Mitral Insufficiency Grading). We referred to the guidelines by ACC/AHA,2020, and the cut-off for MR grading.

Comment 4: Please specify exactly the cutoffs you used for MR grading, describe the methods used for CMR post-processing and the methodology for calculating the EROA. It would be appropriate to add RV, RF, EROA to the Table 2.

Reply 4:
Cut-off for MR grading: This study used only CMR parameters to classify both the LVH and MR. Particularly for MR classification, we used the regurgitant fraction, and the cut-off range is demonstrated in Table 1 and the reference can be found on page 11, line 199 (Ref #19).

CMR post-processing: The CMR post-processing is demonstrated in the methodology section after the CMR protocol.
Changes in the text: We extended a section to describe the post-processing. The details can be found on pages 10-11, lines 171-191.

Methodology of calculating EROA: Since we did not follow the echocardiographic assessment for this study, we removed the EROA range from Table 1. However, we have demonstrated the calculation of SV, RV, RF, and EF which were used for MR grading. The details are demonstrated in the sections "2.3 Post Processing" and "2.4 Mitral Insufficiency Grading".
Changes in the text: The EROA range is removed from Table 1. Additionally, we revised the RV and RF range that was followed in this study and updated the reference. Please see page 46, line 955. Reference can be found in the section "2.4 Mitral Insufficiency Grading" (Please see page 11, Line 194-200).

Update in Table 2: The mean difference of the RF is demonstrated in Table 2 among MR severities for the transparency of the analyses as advised.
Changes in the text: Please see page 46, line 956 (Table 2: RF).

Minor issues:

Comment 5: • line 65: "Conversely, left ventricular hypertrophy (LVH) is a compensatory response to increased workload" – it is important to note that in hypertrophic cardiomyopathy (HCM) this is not the case.
Reply 5: The intention was to introduce left ventricular hypertrophy (LVH) and the comment is acknowledged. The sentence is updated as "On the other hand, left ventricular hypertrophy (LVH) is a condition in which there is an increase in left ventricular mass, either due to an increase in wall thickness, left ventricular cavity enlargement, or both".
Changes in the text: Please see page 6, lines 85-87.

Comment 6: • Reference 8: s0140-6736_2803_2915268-3 (?)
Reply 6: Thank you for pointing out this error. The reference error is corrected and updated in the reference list.

Changes in the text: Currently the reference number is 10 on the reference list. Please see page 37, lines 759-76.

Comment 7: • Line 332: "Our main findings derived from MRI assessment demonstrated that: (1) Classification of LVH using CMR parameters was an easier approach" – easier than echo? No comparison was performed. Perhaps feasible would be better?

Reply 7: The study was only conducted using CMR parameters, and no comparison was made with echocardiographic parameters. Therefore, feasible would be the appropriate word, and the sentence is updated as "Our main findings derived from MRI assessment demonstrated that: (1) Classification of LVH using CMR parameters was a feasible approach". Thank you for the feedback.

Changes in the text: Please see page 22, lines 446-447.

Comment 8: • Line 371: "Age is one of the most powerful cardiovascular risk factors and progresses notably when present earlier in life" (5) – seems true, but consider rephrasing.

Reply 8: The sentence is updated as "The aging and elderly population has a higher risk of developing cardiovascular disease".

Changes in the text: Please see page 24, lines 490-491.

Reviewer B

Thank you for submitting your paper to be considered for publication in the Cardiovascular Diagnosis and Therapy Journal.

We thank Reviewer B for the valuable comments.

Comment 1: Mitral regurgitation is not a single pathological entity. Primary mitral regurgitation, ventricular-secondary mitral regurgitation and atrial-secondary mitral regurgitation are distinct pathological entities. Lack of characterization of mitral regurgitation into these 3 types invalidates the effort of the researchers, particularly in such a small study.

Reply 1: Thank you for pointing out this lack of information in this study. The study population was characterized as chronic primary mitral regurgitation based on ACC/AHA guidelines. We focused on the relationship between severity grading and each type of left ventricular hypertrophy. Therefore, we generalized the chronic primary mitral regurgitation as MR which leads to this confusion. We apologize for this. We acknowledge that the conclusion with 71 cases needs further validation with a larger dataset and we documented this as our limitation.

Changes in the text: We have updated the information regarding the types of MR throughout the manuscript. The type of MR considered in this study is mentioned in section 2.1 "Study Population" under the Methods. Please see page 8, line 127. For documented limitations, please see pages 33-34, lines 683-686.

Comment 2: It is well established that in primary mitral regurgitation left ventricular dilatation occurs as an adaptation mechanism, with scope to maintain forward stroke volume; this dilatation does not imply left ventricular myocardium hypertrophy, it is not "eccentric hypertrophy" like in left ventricular adaptation for aortic regurgitation where both cavity dilatation and left ventricular myocardium hypertrophy occur.

Reply 2: Thank you for the feedback. We acknowledge this information, and this is correct. Just for clarification, the LVH was classified without knowing the severity grading of MR. The analysis was done to investigate how the severity grading of patients with MR is associated with each type of LVH. After the LVH classification, it appeared that most patients with severe MR (based on ACC/AHA) were also classified with eccentric LVH based on the mass-to-volume-based classification method.

Comment 3: In secondary mitral regurgitation, it is the dilatation of the respective chamber that causes the mitral regurgitation, with many subtle mechanisms involved in the consequent mitral regurgitation severity. Left ventricular hypertrophy with small cavity size with associated left atrial dilatation and consequent atrial-secondary mitral regurgitation is present in HFpEF type of physiology / restrictive cardiomyopathy, with the hypertrophy of the myocardium here being caused by a cardiomyopathic mechanism and being unrelated with the mitral regurgitation severity.

Reply 3: As mentioned, this study is focused on chronic primary MR, and we did not consider the secondary MR which is a downfall of this study. As future direction, we documented that, the secondary MR shall be considered to conclude the impact of severity grading on developing LVH.

Comment 4: Please review imaging to define the mitral regurgitation correctly into the 3 types and reanalyze the data to draw correct conclusions.

Reply 4: This is a retrospectively collected dataset and we analyzed the patients with chronic primary MR. We acknowledge that drawing a precise conclusion requires the analysis of other types of MR. Therefore, we have documented this limitation as part of our future tasks.

Changes in the text: Please see page 33, lines 683-686 under "Limitations and Future Directions".

Reviewer C

It's a nice article, appreciate the effort.

We thank Reviewer C for the valuable comments.

Comment 1: However, if you could elaborate more on the criteria you used for MR classification: What was the cut limit of severe MR for example? and did you use regurgitation volume or fraction to grade severity?

Reply 1: We used regurgitation fraction as the key marker for MR classification. The cut-off ranges can be found in Table 1. We have also updated the references to support that. Additionally, we have updated Table 2 with the regurgitant fraction among mitral severity groups for the transparency of the analysis. The reference for the RF range can be found on page 11, line 199 (Ref #19).

Changes in the text: Please see page 11, lines 194-200 (section 2.5 Mitral Insufficiency Grading) for all the references of cut-off ranges used in Table 1 (Ref #4, 17, 18, 19).

Comment 2: Also did you exclude secondary MR? Grading secondary MR would be different than primary MR (in my institution we use regurgitation volume rather than fraction for secondary MR)

Reply 2: Thank you for pointing out this. Yes, the reported cases were chronic primary MR who had defective mitral valve apparatus such as torn anterior mitral valve leaflet, posterior flail leaflet, mitral valve prolapses etcetera. The regurgitant fraction was used to grade the cases into mild-severe and the cut-off is demonstrated in Table 1. For better clarification on the considered type of MR, we updated the type of MR as chronic primary MR throughout the manuscript additionally we clarified it in the section "2.1 Study Population" under Methods.

Changes in the text: We modified our text to address the question. Please see page 8, line 127.