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OPEN PEER REVIEW

Radiomic Analysis of Native T1 Mapping Images for Differential Diagnosis of Left Ventricular Hypertrophy Etiologies

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

7 comments · 1 Feb 2021 – 27 Feb 2021

Referee 1 Reviewer

REJECT 1 Feb 2021

The text requires editing by a native English speaker. There are several grammatical mistakes.
In the introduction, three causes are mentioned as common causes of LVH. Is amyloidosis a common cause of LVH?
In the introduction, is a myocardial biopsy necessary for the diagnosis of hypertensive heart disease or HCM?
In the introduction, "The sensitivity and specificity of SAX T1 value. ... .. significantly improved (77%, 71%, respectively)." How do the authors demonstrate this improvement?
In the methods, in the inclusion criteria for AC, the definition applies only to AL type amyloidosis, and there is no relevant definition for ATTR or other causes of amyloidosis.
Furthermore, was frost glass-like change the only echocardiographic finding for amyloidosis?
Were the only positive findings in CMR LV hypertrophy and myocardial late enhancement?
The native T1 values for hypertensive heart disease and HCM are in the same range; therefore, extracting the radiomics data based on these results is compromised.
The results of post hoc analysis should be mentioned.
The discussion section is brief and the text reviews are incomplete.
The inclusion criteria for case selection are vague and miscellaneous.

Afsaneh Alikhassi Reviewer

MINOR REVISION 8 Feb 2021

- The topic is interesting and has enough novelty.

- In the introduction, we are not supposed to review the literature in detail as in the discussion. Please provide background information and present the goals of the study in the introduction.

- In the background, first paragraph: you can give more reasons to show why we may use radiomics T1 instead of late gadolinium enhancement.

- Discussion, paragraph 1: it seems this study is not the first article in this field: Neisius U, El-Rewaidy H, Nakamori S, Rodriguez J, Manning WJ, Nezafat R. Radiomic Analysis of Myocardial Native T1 Imaging Discriminates between Hypertensive Heart Disease and Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging. 2019 Oct; 12(10):1946-1954. Doi: 10.1016/j.jcmg.2018.11.024. Epub 2019 Jan 16. PMID: 30660549; PMCID: PMC7032053.

- There are some language errors, such as "however" in line 50 and "better diagnostic" in line 215, ...

Referee 2 Reviewer

MINOR REVISION 9 Feb 2021

This manuscript is well written in terms of the structure of scientific writing, but its methodology needs revision as follows:
1. The case-control study design should be stated in the abstract and the methods section of the full text.
2. The study period, study location, and sampling method should be stated in the abstract and the methods section of the full text.
3. At the beginning of the abstract, the demographic characteristics of the patients should be stated.

4. The concept and calculation method for all statistical indicators (such as AUC, precision, recall, and F1-score) presented in the results section should be explained in the statistical analysis section of the methods.
5. Statistical analysis: One-way analysis of variance and Mann-Whitney tests are not equivalent to each other. The statistical analysis section states that the Mann-Whitney test was used if the parametric assumptions were not met. Moreover, the chi-square test must be used to compare qualitative variables such as sex.
6. The titles of the tables and figures should be complete and self-explanatory. The acronyms used in the tables should be explained below the tables.
7. What is the meaning of the precision, recall, and F1-score indicators in Table 3? They must be presented with a 95% confidence interval.

Referee 3 Reviewer

ACCEPT 10 Feb 2021

Dear Associated Editor
Many thanks to the authors for their valuable article submitted to the Iranian Journal of Radiology.
The study design and writing are appropriate.
The references and citations are good.
The results and discussion are interesting and valuable.

Referee 4 Reviewer

MINOR REVISION 19 Feb 2021

The authors submitted a manuscript titled “Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy.”
The authors found that T1 mapping radiomics analysis accurately distinguished LVH phenotypes. The manuscript is well written.
Here are my concerns:

1- Having no healthy control group makes the comparison between radiomic native T1 and native T1 less robust.

2- The inclusion criteria for the amyloidosis group are not clear. Did you select patients if any of the three mentioned criteria were positive? Please define the pattern of late gadolinium enhancement that you use as a selection criterion in the AC group.

3- There are minor typos.

Referee 5 Reviewer

MAJOR REVISION 25 Feb 2021

The article is a descriptive work delineating the value of Radiomics Analysis of Native T1-mapping for differentiating different types of cardiac hypertrophy.
The work, which includes amyloidosis cases, seems to have novelty and can add to existing knowledge.
The English needs some polishing and editing. For example, the word “thus” at the beginning of the objective section seems to be redundant, and some grammar issues, especially in the discussion section, need to be rectified. There are some punctuation issues as well.
Please make sure to spell out abbreviations at their first appearance (for example, AUC in the abstract and SAX, FISP or SPSS later in the text).
Please include the year of manufacture of the MRI machine.
According to the figure 1 flowchart, the total number of patients in the three groups, before exclusions, is less

than the study sample size of 207. This needs clarification. The title of this chart is incomplete (ending with cardiac). For the amyloidosis group, it is better to include the number of patients in whom amyloidosis was confirmed by biopsy (biopsy samples from other organs vs imaging-based diagnosis) to add to the reliability of the study.
Please provide more comprehensive legends for figures 2, 3 and 4.

Best regards.

Editor-in-Chief MAJOR REVISION 27 Feb 2021

Dear authors,
Your article needs Major Revision.
Regards

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response letter

Dear Prof. Kavous Firouznia (Editor-in-Chief),

We appreciate the timely and thoughtful comments from you and the reviewers on our manuscript (113335) entitled " Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy". We thoroughly reviewed all comments and have carefully revised our manuscript accordingly.

Attached is our revised manuscript and detailed responses to the comments point by point. We hope that you will find our changes satisfactory.

Again, thank you very much and we look forward to hearing from you soon!

Sincerely,

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Comments to the Author:

Reviewer #1

The text requires native English Edith. There are several grammatical mistakes.

Response: Thanks for your comment. The relevant content has been updated.

In the introduction part, three reasons for LVH had mentioned as common causes of LVH. Is amyloidosis being a common cause of LVH???

Response: Thanks for your comment. Our expression is not rigorous. In non-ischemic cardiomyopathy, the main causes of left ventricular hypertrophy are HCM and HHD, we found that the incidence of AC is not high after consulting the literature. However, the onset of AC is obscure with diverse clinical manifestations, the clinical manifestations of AC lack specificity, which lead to that AC is often misdiagnosed as HCM and HHD. Therefore, it is often necessary to perform differential diagnosis of these three diseases. We have updated the relevant content.

In the introduction, does a myocardial biopsy necessary for the diagnosis of Hypertensive heart disease or HCM???

Response: Thanks for your comment. The risk of endocardial biopsy is high, and the etiological diagnosis of hypertensive heart disease and hypertrophic cardiomyopathy is not an indication for endocardial biopsy [1]. Therefore, endocardial biopsy is not necessary for the diagnosis of HCM and HHD. The diagnosis of HHD and HCM mainly depends on the patient's clinical symptoms, ultrasound and CMR, as well as family history [2, 3].

[1] Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol. 2007;50(19):1914-1931

[2] Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733-2779.

[3] Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension [published correction appears in J Hypertens. 2019 Jan;37(1):226]. J Hypertens. 2018;36(10):1953-2041.

In the introduction, "The sensitivity and specificity of SAX T1 value……. significantly improved (77%, 71%, respectively)." How do the authors reveal this improvement??

Response: Thanks for your comment. We feel sorry that there is problematic expression. We have updated the relevant content.

In the method, inclusion criteria of AC, the definition is only for AL type amyloidosis, and there is no relevant definition for ATTR or other causes of amyloidosis.

Furthermore, the echocardiography findings for amyloidosis were only frost glass-like change?

Response: Thanks for your comment. All patients with AC enrolled in the study were AL type. The underlying reason may be that the positive rate of extracardiac tissue biopsy with ATTR is relatively low, and the diagnosis is often confirmed by endocardial myocardial biopsy [1], but the endocardial biopsy in the study failed to proceed smoothly. The limitation of the study has added in the revised manuscript. In the later period, we will pay attention to the patient with ATTR to make our model more convincing.

The echocardiography finding for AC are left ventricular myocardium hypertrophy, decreased diastolic function of the left ventricle. Some patients may combine with left ventricular myocardium hypertrophy, enlargement of the right ventricular cavity, and decreased diastolic function of the right ventricle. The amyloid

deposited in the myocardial tissue in the middle and late stages of AC leads to frost glass-like change, which is representative but not unique for AC.

[1] Fine NM, Arruda-Olson AM, Dispenzieri A, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol. 2014;113(10):1723-1727.

Were the only positive findings in CMR LV hypertrophy and myocardium late enhancement?

Response: Thanks for your comment. The patients enrolled were positive findings in CMR LV hypertrophy. About myocardium late enhancement, all patients with AC were positive findings in late enhancement, patients with HCM or HHD were not positive findings for everyone.

The native T1 values for hypertensive heart disease and HCM are in the same range; therefore, extracting the radiomics data based on these results is compromised.

The results of post hoc analysis should be mentioned.

Response: Thanks for your comment. The relevant content has updated.

The discussion section is brief and the text reviews are incomplete.

Response: Thanks for your comment. The relevant content has updated.

The inclusion criteria for case selection is vague and miscellaneous.

Response: Thanks for your comment. The inclusion criteria of HCM refer to the 2014 ESC guidelines on diagnosis of HCM [1]. The inclusion criteria of HHD refer to the thesis of Chobanian [2]. The inclusion criteria of AC refer to the study of Falk [3].

[1] Elliott PM, Uk C, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014; 35: 2733-79.
[2] Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206-52
[3] Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112(13):2047-2060

Reviewer #2

Overall, the article and the idea behind it are vague, and I suppose that it is not competent enough to be considered for publication. Some points to be mentioned:

• This manuscript bears several grammatical mistakes.

Response: Thanks for your comment. The relevant content was updated.

• The authors presented left ventricular hypertrophy as a condition that results from just 3 pathophysiologic processes. They also introduced amyloidosis as a common underlying cause. These sentences need reconsideration.

Response: Thanks for your comment. We have updated the relevant content.

• In the definition of the diagnostic criteria of amyloidosis cardiomyopathy, just the AL subtype is defined. However, everywhere in the text, it is not mentioned that only AL amyloidosis is evaluated.

Response: Thanks for your comment. The limitation of the study has added in the revised manuscript.

• I have lots of questions about the way of patient selection, study design, and data analysis; As an example, the authors did an ANOVA test and concluded that the mean native T1 values are different among the groups, but they did not compare the groups two-by-two. The mean T1 values are very close to each other in HHD and HCM groups.

Response: Thanks for your comment. The purpose of this study is to identify HCM, HHD and AC by using radiomics simultaneously. Therefore, we emphasized the comparison between the three groups in the study.

The results that compared the group two-by-two have been added to the article.

Reviewer #4

-The topic is interesting and has enough novelty.

- In the introduction, we are not supposed to review the literature in detail such as discussion. Please give a background and present the goals of study in the introduction.

Response: Thanks for your comment. The relevant content was updated in revised manuscript.

-In background, first paragraph: you can give more reasons to show why we may use radiomics T1 instead of late gadolinium enhancement.

Response: Thanks for your comment. The relevant content was updated in revised manuscript.

-Discussion, paragraph 1: it seems this study is not the first article in this field: Neisius U, El-Rewaidy H, Nakamori S, Rodriguez J, Manning WJ, Nezafat R. Radiomic Analysis of Myocardial Native T1 Imaging Discriminates between Hypertensive Heart Disease and Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging. 2019 Oct;

12(10):1946-1954. Doi: 10.1016/j.jcmg.2018.11.024. Epub 2019 Jan 16. PMID: 30660549; PMCID: PMC7032053.

Response: Thanks for your comment. We have updated the relevant content.

- Some language errors such as: line 50 however, line 215 better diagnostic,...

Response: Thanks for your comment. The relevant content was updated.

Reviewer #5

This manuscript is well written in terms of the structure of scientific writing, but according to the methodology, it needs to be edited, which include:

1. The study design that is case-control that should be written in the abstract and full text method.

Response: Thanks for your comment. We added the required information in the revised manuscript.

2. The time calendar, place of study, and sampling method should be stated in the abstract and full-text method.

Response: Thanks for your comment. The time calendar and place of study have stated in the abstract and full-text method. About the sampling method, there is no sampling method in this study, we just included all patients who meet the inclusion criteria.

3. At the beginning of the abstract, the demographic characteristics of the patients should be written.

Response: Thanks for your comment. We added the required information in the revised manuscript.

4. All statistical indicators (such as AUC, precision, recall, and F1-score) which were presented in the results section; their concept and calculation method should be explained in the statistical analysis section of the method.

Response: Thanks for your comment. We added the required information in the revised manuscript.

5. Statistical analysis: One-way analysis of variance and Mann-Whitney tests are not equivalent to each other. In the statistical analysis section mentioned that if the parametric assumptions are not met, Mann-Whitney test was used. Moreover, for comparison of qualitative variable such as sex, it must be used of chi-square test.

Response: Thanks for your comment. I feel sorry about the clerical error. In statistics, we used the Kruskal-Wallis test for the variables which did not conform normal distribution. We have corrected the related content. Meanwhile, we used the chi-square test for categorical variables in statistics, and we have added the missing content.

6. The titles of the tables and figures should be complete and self-explanatory. The acronyms words of tables should be explained below the tables.

Response: Thanks for your comment. We added the required information in the revised manuscript.

7. What is the meaning of precision, recall, and F1-score indicators in Table 3? They must be presented with a 95% confidence interval.

Response: Thanks for your comment. The relevant content has added in “Method-Classification and evaluation of models” Section. With respect to 95% confidence interval, we added the AUC 95% confidence interval since AUC is based on prediction likelihood, when bootstrapping samples, threshold distribution is still equivalent for each point. On the other hand, recall, precision and

F1-score are fixed number. Bootstrapping to evaluate the confidence interval just like blindly sampling from a bag with a fixed number of black (incorrect prediction) and white (correct prediction) balls with replacement. With greatest luck, you may get as good as current result. Thus, we suppose the AUC confidence interval is reasonable to show the performance of current model.

Reviewer #7

The authors submitted a manuscript with the title of "Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy."

The authors found T1 mapping radiomics Radiomics analysis accurately distinguished LVH phenotypes. The manuscript is well written.

Here are my concern,

1- Having no healthy control group makes the comparison between radiomic native T1 and native T1 less robust.

Response: Thanks for your comment. In this study, our main purpose was to classify the three causes of left ventricular hypertrophy by using T1 mapping radiomics, healthy control group was not included because of normal left ventricular thickness. In the later period, we will also include the normal control group to make our model more convincing.

2- The inclusion criteria in amyloidosis group is not clear. Did you select if any of the three mentioned criteria were positive? Please define the pattern of late gadolinium enhancement that you use for selection criteria in the AC group.

Response: Thanks for your comment. The inclusion criteria of AC were: (1) be diagnosed as multiple myeloma by pathology or other organ showed amyloidosis by biopsy; (2) and CMR showed LV hypertrophy and myocardium late enhancement; (3) and

echocardiogram suggested cardiac involvement. The above three conditions are all met. The patterns of LGE were subendocardial enhancement or diffuse dusty enhancement. The relevant content was updated.

3- There are minor typos.

Response: Thanks for your comment. The relevant content was updated.

Reviewer #8

Public Comment:

The article is a descriptive work for delineation of value of Radiomics Analysis of Native T1-mapping for differentiation of different type of cardiac hypertrophy.

The work with including amyloidosis cases seem to have novelty and can add to existing knowledge.

English writing needs some polishing and editing. For example, the word “thus” in the beginning of objective section seems to be redundant and some grammar issues especially in discussion section need to be rectified. There are some punctuation issues as well.

Response: Thanks for your comment. The relevant content was updated.

Please make sure to spell out words in their first appearance (for example AUC in the abstract and SAX, FISP or SPSS later in the text).

Response: Thanks for your comment. We added the required information in the revised manuscript.

Please include the year of manufacture of MRI machine.

Response: Thanks for your comment. We added the required information in the revised manuscript.

According to figure 1 flowchart, the summation of patients in three groups, before excluding some, is less than 207 as the sample size of the study. This need clarification. The title of this chart is incomplete (finishing with cardiac). For amyloidosis group, it is better to include the number of patients who biopsy have proved to be amyloidosis (sample biopsy from other organs vs imaging based diagnosis) to add to the reliability of the study.

Response: Thanks for your comment. 207 patients with left ventricular (LV) hypertrophy were collected from April 2018 to April 2019, of which 130 were non-ischemic cardiomyopathy, 72 were ischemic cardiomyopathy, and 5 were unclear diagnosis. In order to avoid ambiguity, the relevant content has been updated. For amyloidosis group, the inclusion criteria of AC were extracardiac tissue showed amyloidosis by biopsy and other cardiac examinations suggest heart involvement.

Please provide more comprehensive legends for figures 2, 3, and 4.

Response: Thanks for your comment. We added the required information in the revised manuscript.

2 Revision 1

6 comments · 2 Apr 2021 – 18 Apr 2021

Referee 2 Reviewer — ACCEPT 2 Apr 2021

At present, it can be said that the authors have appropriately addressed all comments in the manuscript. Therefore, this paper is acceptable from a methodological point of view.

Referee 1 Reviewer — MINOR REVISION 6 Apr 2021

The paper has undergone major revision according to the reviewer's comment, but there are still some points that need revision:
LVH is not always a compensatory change like in HCM. But in the article, LVH is stated as a compensatory change.
The various methods for differentiating the three types of LVH mentioned should be described first, and then the role of LGE should be explained.
The statistical analysis section is incomplete regarding the work done in this article.
The technical problem is the reason why the result of the mapping technique is not strong at the LV apical level, not the presence of normal myocardium in the LV apex.
The comparison between the hypertensive and HCM groups should be explained in detail (p-value, confidence interval, and mean difference).

Referee 3 Reviewer — ACCEPT 12 Apr 2021

Dear associate Editor
Thank you for your kind invitation.
I've just reviewed revision 1 of the article entitled Radiomics Analysis of Native T1 –mapping for the differential Diagnosis of Left ventricular Hypertrorhy.
The authors have revised the article and addressed the points mentioned by the previous reviewer.
So I think the article is acceptable now.
Yours sincerely

Afsaneh Alikhassi Reviewer — ACCEPT 13 Apr 2021

All my previous comments were considered and addressed by the authors; thank you.

Associate Editor — REJECT 16 Apr 2021

Dear authors

I appreciate your nice effort in revising the manuscript, but there are still several points to correct in the manuscript titled:

Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy

Please change the first sentence of the article.
Amyloidosis cardiomyopathy is not as common as HCM and HHD, and several causes of LVH are more common than amyloidosis.
The remarkable overlap in T1 values between HCM and HHD (HCM: 1304±42, HHD: 1309±62, AC: 1449±68) is the most important issue.
The number of cases is low.
Please have the English writing and grammar checked by a professional editor.

Decision

Rejected

REVIEWER 1

The effort of the authors is admirable. I think that this article still needs revisions to be considered for publication.
The manuscript suffers from several English language problems. I think that the authors should request a professional native English editing service.
The statistical analysis section should be described clearly and in detail.
No control group is described in the method section. It should be explained in detail.
No comparison between groups (two-by-two) is included. It would be better to add a table to show the differences.
I suppose that the authors should clarify their results in the discussion section. That might better describe the power of their models in differentiating the entities (two-by-two).
Best Wishes!
Decision:
Major revision

REVIEWER 2

The paper has undergone major revision according to the reviewer's comment, but there are still some points that need revision:
LVH is not always a compensatory change, as in HCM. But in the article, LVH is stated to be a compensatory change.
The various methods for differentiating the three types of LVH mentioned should be described first, and then the role of LGE should be explained.
The statistical analysis section is incomplete regarding the work done in this article.
The technical problem is the reason why the result of the mapping technique is not strong at the LV apical level, not the presence of normal myocardium in the LV apex.
The comparison between the hypertensive and HCM groups should be explained in detail (p-value, confidence interval, and mean difference).

Decision:
Minor revision

REVIEWER 3
-The English writing still needs some editing and correction. For example, in the first line of the abstract, the word “presented” has to be changed to “presenting with”.
- The inclusion criteria for amyloidosis cases are not satisfactory enough in terms of reliability, and this may

lead to bias in the conclusion.
-My other concerns were addressed acceptably.

Decision:
Major revision

REVIEWER 4
I've just reviewed revision 1 of the article titled Radiomics Analysis of Native T1 –mapping for the differential Diagnosis of Left ventricular Hypertrorhy.
The authors revised the article and corrected the points mentioned by the previous reviewer.
So I think the article is acceptable now.

REVIEWER 5

At present, it can be said that the dear authors appropriately addressed all comments in the manuscript. Therefore, this paper is acceptable from a methodological point of view.

REVIWER 6
The revised version of the manuscript has improved significantly in terms of content, and the authors address the reviewers' comments sufficiently. However, there are still some parts that are hard to read, and English polishing is needed. Here are some examples:
- (And the clinical manifestations of amyloid cardiomyopathy (AC) lack specificity with diverse clinical manifestations, which lead to that AC is often misdiagnosed as HCM and HHD)
- (However, the research of identifying the three diseases using T1 mapping of radiomics is insufficient)

Decision:
Minor revision

REVIEWER 7

All the points I commented on before were considered by the authors and addressed; thank you.

Decision:
Accept

Editor-in-Chief

MAJOR REVISION 18 Apr 2021

Dear authors,
According to the reviewers, your revised article is not acceptable now, and any decision depends on your reply to the reviewers and a major revision.
Regards

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response letter

Dear Prof. Kavous Firouznia (Editor-in-Chief),

We appreciate the timely and thoughtful comments from you and the reviewers on our manuscript (113335) entitled " Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy". We thoroughly reviewed all comments and have carefully revised our manuscript accordingly.

Attached is our revised manuscript and detailed responses to the comments point by point. We hope that you will find our changes satisfactory.

Again, thank you very much and we look forward to hearing from you soon!

Sincerely,

Liming Xia

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Comments to the Author:

Associate Editor #1

Dear authors

I appreciate your nice effort for revision, but there are still several points for correction titled.

Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy.

Please change the first sentence of the article.

The amyloidosis cardiomyopathy is not as common as HCM and HHD and several causes of LVH are more common than amyloidosis.

Response: Thanks for your comment. The relevant content has been updated.

Remarkable overlap in T1 values of HCM, HHD (HCM: 1304±42, HHD: 1309±62, AC: 1449±68) is the most important issue

Response: Thanks for your comment. The native T1 value is determined by the myocardial tissue and the pathophysiological changes that occur in it. The T1 value of patients with HHD usually lower than that of patients with HCM, but this is not absolute. The reason for the issue may be due to the small sample size in the study. On the other hands, the patients with HHD and HCM included in the study were diagnosed in strict accordance with the guidelines [1, 2]. Although the overlap in T1 values of HCM and HHD exist, we think the issue will not affect our conclusion.

[1] Elliott PM, Uk C, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014; 35: 2733-79.

[2] Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206-52

The low number of cases.

Response: Thanks for your comment. Due to the high price of CMR and the low incidence of myocardial amyloidosis, we were unable to obtain a larger sample size. We have clarified the point in the limitation section. In the later period, we will continue to expand the sample size to verify the universality of our model.

English writing and grammar check by a professional editor.

Response: Thanks for your comment. The relevant content has been updated.

Reviewer #1

The effort of the authors is admirable. I think that this article still needs revisions to be considered for publication.

The manuscript suffers several English language problems. I think that the authors should request a professional native editing service.

Response: Thanks for your comment. The relevant content has been updated.

The statistical analysis section should be described in detail and clearly.

Response: Thanks for your comment. The relevant content has been updated.

No control group is described in the method section. It should be explained in detail.

Response: Thanks for your comment. In this study, our main purpose was to classify the three causes of left ventricular hypertrophy by using T1 mapping radiomics, healthy control group was not included because of normal left ventricular thickness. In the later period, we will also include the normal control group to make our model more convincing.

No comparison between groups (two-by-two) is added. It would be better to add a table for revealing the differences.

Response: Thanks for your comment. The comparison between groups (two-by-two) has been added in Table 1. # means significant differences compared with AC and * means significant differences compared with HHD. The table you needed was added in Supplementary Table 2.

I suppose that the authors should clarify their results in the discussion section. That might be better describe the power of their models in differentiating the entities (two-by-two).
Best Wishes!

Response: Thanks for your comment. The idea of our work is to make three-category models to differential diagnosis of HCM, HHD and AC. The three-category models are more valuable in clinical work. On the other hand, if reviewer means to evaluate the two-category model performance between groups under the three-category model, we can directly calculate the corresponding sensitivity, specificity and AUC indicators according to the confusion by removing the sample size of the third category. We can provide later if necessary.

Reviewer #2

There is a major revision of the paper according to the reviewer's comment, but there is still some points needs revision:
LVH is not always a compensatory change like in HCM. But in the article, LVH is stated as a compensatory change.

Response: Thanks for your comment. The relevant content was updated.

The various methods for differentiating the three types of mentioned LVH should be described first and then explain the role of LGE.

Response: Thanks for your comment. The relevant content was updated.

The statistical analysis section is incomplete regarding the work done in this article.

Response: Thanks for your comment. The relevant content was updated. The routine statistical analysis was described in *statistical analysis* section. And the statistical analysis related to the radiomics model parameter was described in *classification and evaluation of models* section.

The technical problem is the reason why the result of the mapping technique is not strong in the LV apical level not the presence of normal myocardium in the LV apex.

Response: Thanks for your comment. The relevant content was updated.

Comparison between hypertensive versus HCM groups should be explained in detail. (p-value, confidence interval, and mean difference).

Response: Thanks for your comment. The relevant content was added in supplementary Table 2.

Reviewer #3

-The English writing still needs some editing and rectifying. For example, in the first line of the abstract, the word “presented" has to be changed to “presenting with”.

Response: Thanks for your comment. The relevant content was updated in revised manuscript.

- The inclusion criteria for amyloidosis cases is not satisfactory enough, in term of reliability and this may lead to bias in conclusion.

-My other concerns were addressed acceptably.

Response: Thanks for your comment. Due to the limitation of endocardial biopsy application, the confirmatory diagnosis of amyloidosis is mainly dependent on extracardiac tissue biopsy combined with other non-invasive examinations instead of

endocardial biopsy [1], which was known as clinically confirmed cases. This may indeed lead to bias in conclusion, and we have clarified the point in limitation section.

[1] Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112(13):2047-2060

Reviewer #6

The revised version of the manuscript has improved significantly in terms of contents and the authors address the reviewers' comments sufficiently. However, there are still some parts that are hard to read, and English polishing is needed. Here are some examples

- (And the clinical manifestations of amyloid cardiomyopathy (AC) lack specificity with diverse clinical manifestations, which lead to that AC is often misdiagnosed as HCM and HHD)

- (However, the research of identifying the three diseases using T1 mapping of radiomics is insufficient)

Response: Thanks for your comment. The relevant content was updated in revised manuscript.

3 Revision 2

1 comment · 24 May 2021

Associate Editor

REJECT 24 May 2021

The article still had major issues.

• They did not include a control group to compare their cases with standard myocardial T1 values.

• The inclusion criteria for HCM diagnosis were insufficient, which makes the study fundamentally flawed.

76 .Inclusion criteria of HCM were: LV maximal wall thickness ≥15mm in adults without
77 .HCM family history or ≥13mm in the adult with HCM family history without other disease
78 .caused LV hypertrophy; normal LV cavity size [19].

• The diagnosis of cardiac amyloidosis should be confirmed by endomyocardial biopsy; neither a biopsy of other organs nor the presence of multiple myeloma is sufficient to confirm cardiac amyloidosis.

Inclusion criteria of AC were:
82 (1) be diagnosed as multiple myeloma by pathology or other organ showed
83 amyloidosis by biopsy; (2) and CMR showed LV hypertrophy and myocardium late
84 enhancement (subendocardial enhancement or diffuse dusty enhancement)

• Table 2: The radiomic analysis is completely vague.

• The discussion section provided weak support for their findings.

Reject

Best regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response letter

Dear Prof. Kavous Firouznia (Editor-in-Chief),

We appreciate the timely and thoughtful comments from you and the reviewers on our manuscript (113335) entitled " Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy". We thoroughly reviewed all comments and have carefully revised our manuscript accordingly.

Attached is our revised manuscript and detailed responses to the comments point by point. We hope that you will find our changes satisfactory.

Again, thank you very much and we look forward to hearing from you soon!

Sincerely,

Liming Xia

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Comments to the Author:

Associate Editor #1

Associate Editor 1:

The article still had major issues.

• They did not consider the control group to compare their cases with standard myocardial T1 values.

Response: Thanks for your comment. The relevant content was added in article.

• The inclusion criteria for HCM diagnosis was not enough and it makes the study wrong fundamentally.
76 .Inclusion criteria of HCM were: LV maximal wall thickness ≥15mm in adults without
77 .HCM family history or ≥13mm in the adult with HCM family history without other disease
78 .caused LV hypertrophy; normal LV cavity size [19].

Response: Thanks for your comment. The inclusion criteria of HCM refer to the 2014 ESC guidelines on diagnosis of HCM [1]. And the study published on JACC: cardiovascular imaging by Neisius et al. has the same inclusion criteria [2].

[1] Elliott PM, Uk C, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014; 35: 2733-79.
[2] Ulf Neisius, Hossam El-Rewaidy, Shiro Nakamori, et al. Radiomic Analysis of Myocardial Native T1 Imaging Discriminates Between Hypertensive Heart Disease and Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging. 2019 Oct; 12(10): 1946-1954

• The diagnosis of cardiac amyloidosis should be confirmed by endomyocardial biopsy, neither the biopsy of the other organs nor the presence of multiple myeloma are eligible for cardiac amyloidosis.
Inclusion criteria of AC were:
82 (1) be diagnosed as multiple myeloma by pathology or other organ showed
83 amyloidosis by biopsy; (2) and CMR showed LV hypertrophy and myocardium late
84 enhancement (subendocardial enhancement or diffuse dusty enhancement)

Response: Thanks for your comment. The inclusion criteria of AC refer to the study of Falk [1]. Due to the limitation of endocardial

biopsy application, the confirmatory diagnosis of amyloidosis is mainly dependent on extracardiac tissue biopsy combined with other non-invasive examinations instead of endocardial biopsy [2], which was known as clinically confirmed cases. The study published on Clinical Radiology by Schofield et al. has the same inclusion criteria [3]. And this may lead to bias, we have clarified the point in limitation section.

[1] Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112(13):2047-2060
[2] Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol. 2007;50(19):1914-1931
[3] Schofield R, Ganeshan B, Fontana M, et al. Texture analysis of cardiovascular magnetic resonance cine images differentiates aetiologies of left ventricular hypertrophy. Clin Radiol. 2019;74(2):140-149.

• Table 2, Radiomic analysis is completely vague.

Response: Thanks for your comment. The relevant content has been updated. Table 2 showed the name of selected radiomics features of each radiomics models.

• The discussion part was weakly supported their findings.

Response: Thanks for your comment. The relevant content has been updated.

4 Revision 3

1 comment · 11 Sep 2021

Editor-in-Chief

MINOR REVISION 11 Sep 2021

Dear authors,
Your article needs Minor Revision.
Regards

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response letter

Dear Prof. Kavous Firouznia (Editor-in-Chief),

We appreciate the timely and thoughtful comments from you and the reviewers on our manuscript (113335) entitled " Radiomics Analysis of Native T1-mapping for the Differential Diagnosis etiologies of Left Ventricular Hypertrophy". We thoroughly reviewed all comments and have carefully revised our manuscript accordingly.

Attached is our revised manuscript and detailed responses to the comments point by point. We hope that you will find our changes satisfactory.

Again, thank you very much and we look forward to hearing from you soon!

Sincerely,

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Comments to the Author:

Reviewers' Comments:

Reviewer 1:

Reference numbers 20-24 are not cited in the manuscript. pls cite them.

Response: Thanks for your comment. The relevant content was added in article. Reference numbers 20-24 appears in Method section "**Patients** " and "**Classification and evaluation of models**", respectively.

Associate Editor's Comments:

Associate Editor 1:

Please refer to EIC.

Associate Editor 2:

1-it seems following title is better: “Radiomics Analysis of Native T1-mapping for the Differential Diagnosis of Left Ventricular Hypertrophy etiologies”

Response: Thanks for your comment. The relevant content was corrected in article.

2-please add full term of abbreviations when they are used for the first time in abstract and paper separately [for example, CMR, ……]. In addition, abbreviations should be introduced in abstract and paper separately. [for example, AC should be defined in line 38]

Response: Thanks for your comment. The relevant content was added in article.

3-authors mentioned: “Area under the curve (AUC), precision, recall and F1-score were 0.96, 0.84, 0.82, 0.83 and 0.96, 0.90, 0.89, 0.88 in independent test dataset, respectively” this sentence seems wrong as we have 8 numbers but the authors mentioned 4 indices for only one dataset [that is independent test dataset]

Response: Thanks for your comment. The relevant content was corrected in article.

4-authors mentioned: “an alternative to late gadolinium enhancement” it seems better version is “an alternative to late gadolinium enhancement imaging”

Response: Thanks for your comment. The relevant content was corrected in article.

5-line 42 and 84 please correct to electrocardiography.

Response: Thanks for your comment. The relevant content was corrected in article.

6-the word respectively seems should be deleted in this sentence: "Previous studies showed that native T1 value can distinguish HCM, HHD and AC from control, respectively"

Response: Thanks for your comment. The relevant content was corrected in article.

7-in line 56, "can improve" should be "can be improved"

Response: Thanks for your comment. The relevant content was corrected in article.

8-please add sequential numbers for titles and sub-titles [patients is 3.1, ….]

Response: Thanks for your comment. The relevant content was added in article.

9-in line 184, please correct as follow: "P < 0.05 indicates statistical significance."

Response: Thanks for your comment. The relevant content was corrected in article.

10-please correct: "Comparison of sex distribution and mean age of train dataset and test dataset did not show statistical difference (mean age: 49.4±15.1 and 52.4±15.1, respectively, p= 0.305, male percentage: 44 [73%] and 14 [82%] respectively; p= 0.105,)."

Response: Thanks for your comment. The relevant content was corrected in article.

11-please change p=0.000 to p<0.001.

Response: Thanks for your comment. The relevant content was corrected in article.

12-please correct: “Performance of native T1 value model of three diseases differential diagnosis simultaneously were as follows: AUC 0.72 (95% confidence interval [CI]=0.618 – 0.825), precision 0.61, recall 0.63 and F1-score 0.62 (table 3).”

Response: Thanks for your comment. The relevant content was corrected in article.

13-please correct: 1 (95% CI=0.991 – 1.000) and 0.96 (95% CI=0.894 – 1.000)

Response: Thanks for your comment. The relevant content was corrected in article.

14-please correct: 0.99 (95% CI=0.986 – 1.000) and 0.86 (95% CI=0.660 – 0.997)

Response: Thanks for your comment. The relevant content was corrected in article.

15-it is better in line 213 the authors replace identify with differentiate.

Response: Thanks for your comment. The relevant content was corrected in article.

16-please correct figure 1 legend as: “Flowchart of Patients’ Enrollment”

Response: Thanks for your comment. The relevant content was corrected in article.

17-in figure 4, please correct: "receiver operating characteristic curve" or they can delete these parts as the legends denote it.

Response: Thanks for your comment. The relevant content was corrected in article.

18-I have a suggestion, it is better the authors change “True positive rate” to “Sensitivity” and “False positive rate” to “1-Specificity” in ROC curves.

Response: Thanks for your comment. The relevant content was corrected in article.

19-reference 21 could not be seen in paper. please cite it in the paper.

Response: Thanks for your comment. The relevant content was added in article.

5 Revision 4

1 comment · 19 Sep 2021

Editor-in-Chief

ACCEPT 19 Sep 2021

Dear authors,
Your article is acceptable for publication in IJR.
Regards