Author’s response to reviews

Title: Global Longitudinal Strain as an Indicator of Cardiac Iron Overload in Thalassemia Patients

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Response to Reviewers’ comments

Dear Editor:

Thank you so much for your kind attention and we appreciate the valuable reviewers’ comments. Sorry for the delay in submitting the revision. Following the request of your reviewers, we sent our manuscript for an English editor, which caused the delay. Some explanations as well as the correction considering their comments are below:

Reviewer #1:

Review

This interesting paper aimed to investigate the role of speckle tracking and Doppler echocardiography in early detection of iron overload in thalassemia major patients. The authors conclude that global longitudinal strain (GLS) may be used to detect the early and subclinical stages of iron deposition. For deserve the publication the manuscript needs a major revision, following the suggestions reported.
Response: Many thanks for your valuable comment. In fact, applying your comment on our manuscript, had made a great progress in its structure.

MAJOR ISSUES

1) Page 7 Line 4 Methods (MRI studies): It is not cited any paper on T2* technique for the iron overload quantification. For the methodology I suggest citing robust papers as Ramazzotti et al, J Magn Res Imaging, 2009, about the validation and reproducibility of the technique.

Response: The mentioned referenced is added in the revision.

2) Page 7 Line 7 Statistical analysis: Pearson's r is a measure of the linear correlation between two variables. I suggest to use the Spearman rank correlation test, which does not carry any assumptions about the distribution of the data. Moreover, in our experience T2* and ferritin variables are not normally distributed.

Response: We have corrected this issue considering your comment.

3) Page 7 Lines 17-19 Results: The results explained are different from those reported in Table 1. Table 1 shows echocardiographic findings and their correlation with MRI T2* findings and serum ferritin level. Please, adjust the abstract, the results and the discussion based on the table.

Response: The explanation in the text refers to the whole studied population, but in Table 2 the data are separated based on MRI T2 level and that’s why they are different.

4) Page 8 Discussion: Please, comment in details the data from table 2.

Response: We have added some comment on the details.

5) Page 8 Discussion: I strongly suggest citing more briefly the results of the other studies that support authors' hypothesis. The discussion section is more a description of the literature, than a real discussion about the results in comparison to literature data. For the discussion I suggest to consider recent studies, as Pizzino F. et al. Int J Card Imag 2018 that evaluates correlation between GLS and MRI T2* and the risk of a pathological MRI T2* in patients with a impaired GLS.

Response: We have changed the discussion according to your comment.
6) Page 8 line 9 Discussion: The authors state that ferritin levels were not significantly associated with MRI T2* findings. The sentence is not supported in the result section or in the Table. Please, add it.

   Response: We have added the data.

7) Page 10 line 18 Discussion: Please, restate the sentence about the correlation between GLS and T2* values. GLS is correlated with the T2* value with a low r coefficient.

   Response: The sentence is changed according to you comment.

8) Page 10 line 19 Discussion: Please reformulate the sentence "…when taking a threshold of 20 as the cut off value it could differentiate early stages of Iron deposition with by 82.14% sensitivity and 86.36% specificity". The threshold is 19.5, not 20. Remove "early stages" because this is a cross-sectional study.

   Response: The sentence is changed according to you comment.

9) Page 10 line 23 Discussion: I strongly suggest restating the sentence about the role of GLS as gatekeeper for cardiac MRI. It could be proposed as useful tool in countries with a limited MRI availability for logistic and economic reasons. Today in the other countries it is not acceptable to lose about 20% of iron loaded patients, because it has been clearly demonstrated that a tailored MRI chelation therapy has significantly reduced the mortality of this population. Please, align also the conclusion in the abstract.

   Response: The sentences are changed according to you comment.

10) Page 11 Conclusion: Remove "early and subclinical stages", because this is a cross-sectional study, as stated in the Limitations section.

    Response: The sentence is changed according to you comment.

MINOR ISSUES

11) I strongly suggest correcting the method used to cite text abbreviations. For example, in Introduction section (page 5 line 1), substitute "EF (Ejection fraction)" with "Ejection fraction (EF)". Please, check the accuracy of all the abbreviations used.

    Response: Some corrections are made according to your comments.
12) Page 2 line 10 Abstract: I suggest to reformulate the sentence "Cardiac MRI was done and T2* images were considered as the golden standard of evaluating cardiac iron deposition." as follows "Cardiac MRI was done and T2* images were considered as the non invasive gold standard for evaluating cardiac iron deposition." Biopsy continuous to be considered the gold standard, although it is invasive.

Response: This sentence was revised.

13) Page 5 Study design and patients: When the patients underwent echocardiographic and MRI examinations? In the same day?

Response: The explanation was added.

14) Page 6 line 18 Methods: For "2D STE method", please, add a reference. Moreover, the method abbreviation "2D STE" is not explained.

Response: Corrections are made according to your comment.

15) Page 7 line 16 Results: The units of measurement for ferritin and T2* are not specified.

Response: Units are added.

16) Page 8 lines 1-3 Results: Please, do not repeat results that are shown also in table 1.

Response: Repeated parts are omitted except very important findings.

17) Page 9 lines 11-13 Discussion: Please, reformulate the sentence "These findings are in agreement with ours which indicates that septal systolic myocardial velocity is reduced in early stages of myocardial iron deposition" as follows "These findings are in agreement with ours which indicates that septal systolic myocardial velocity is correlated with the T2* value".

Response: The sentence is corrected according to your comment.

18) Page 9 Lines 19-20 Discussion: This sentence is a result. Move it also to the result section or to Table2.

Response: The requested correction was applied.
19) Table 1 and Table 2: The units of measurement for echocardiographic findings are not indicated. It is not explained what are the data concerning echo findings shown in the first column. If they are mean ± standard deviation, please, indicate.

Response: Corrections are made according to your comment.

20) Figure 1 legend: Please, reformulate the legend as follows "Receiver-operating characteristic (ROC) curves for global longitudinal strain (GLS) and magnetic resonance imaging (MRI) T2*. Moreover, add in the figure AUC, p value, and the cut off for GLS.

Response: Corrections are made according to your comment.

21) It is suggested to review the paper by an English native speaker.

Response: A native speaker has revised the revision.

Reviewer #2:

This study is undeniably applicative, especially for low-income countries, in which T2* MRI is not always available. However, the English must be improved to help the readers get a better understanding. The line numbers on the left side are not in line with the sentences; hence, I give my comments as points for each section. Here are my comments:

Response: Many thanks for your valuable comment. In fact, applying your comment on our manuscript, had made a great progress in its structure.

Introduction

1) The reference no. 1 is too old. Please use the updated one.

Response: This reference was replaced with a new one.

2) Please revise the sentence "In thalassemia patients…… relieve thalassemia major manifestations"

Response: This sentence is revised in the revision.
3) Within the last three years, there were many studies evaluating the sensitivity and specificity of GLS to detect cardiac iron overload in Iran, with greater number of subjects and enrollment of control normal group. Please add the aims of this study.

Response: The aim of the study is added in the introduction in the revision.

Material and methods

4) Since a diagnostic study must be reproducible, please state the brand for each examination tools, along with the company's name.

Response: This correction is made in the revision.

5) Please state the no. of ethical approval

Response: It has been added.

6) In the statistical analysis, only Pearson's correlation was used. Had the authors addressed data distribution for each variable? Please clarify and add it in the text.

Response: Some corrections in the statistical method are done in the revision according to your comments.

Results

7) Demographic distribution data must be typed in the first paragraph, along with the percentage of iron chelation treatment

Response: This correction is done in the revision.

8) It is not acceptable to use mean±SD along with interquartile range. Please choose one of them that in accordance with the result of data distribution.

Response: This issue is considered in the revision.

9) Table 1 results are quite confusing. How can one T2* MRI value has multiple correlations with the ferritin value. Please explain clearly.

Response: Explanations are added in the revision. This table shows the correlation between various echocardiographic findings with T2* MRI value and ferritin level. It did not mean to show a correlation between MRI and ferritin level.
Discussions

10) Please explain further why systolic velocity correlated significantly with the T2* MRI value, while diastolic velocity was not.

    Response: An explanation according to the issue is added in the revision

Limitations

11) All "iron overload" phrases must be added by "cardiac" before the word "iron".

    Response: We have made this change.