Reviewer’s report

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

Version: 0 Date: 21 Jan 2019

Reviewer: Alessia Pepe

Reviewer's report:

Manuscript Number: CARU-D-19-00001

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.

MAJOR ISSUES

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.

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.

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.

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

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.
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.

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.

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.

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.

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

MINOR ISSUES

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.

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.

Page 5 Study design and patients: When the patients underwent echocardiographic and MRI examinations? In the same day?
Page 6 line 18 Methods: For "2D STE method", please, add a reference. Moreover, the method abbreviation "2D STE" is not explained.

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

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

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".

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

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.

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.

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

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal