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Peer Review Report for "Assessment of the Relationship Between Iron Overload Based on Cardiac T2* MRI and Fragmented QRS in Beta-Thalassemia Major Patients"

Author(s): Yazdan Ghandi, Danial Habibi, Aziz Eghbali

Review Timeline:

Submit Date: 24 Jul 2019
Revised Date: 12 Oct 2019
Accepted Date: 19 Oct 2019

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (0)

28 Sep 2019

Dear EIC,
The paper is well written but There are some comments which should be addressed by the author:
1- Throughout the paper, you have written that MRI was abnormal in 30 patients (75% with T2* values below 20 ms) while in table 1 the opposite is written (T2* value below 20 ms in 10 patients) !!
2- Please calculate and write the specificity and sensitivity of fQRS against MRI as the gold standard of your study
3- Who and how reviewed and calculated the fQRS? who reviewed the MRI? were they blinded or not?
4- As fQRS was abnormal in 10 patients only and MRI abnormal in 30 patients how the writers claims that fQRS is a good method against MRI?
5- As no follow-up is done the writers cannot claim in discussion that fQRS can detect early iron overload
6- The authors should clearly mention in discussion and conclusion sections that fQRS cannot substitute MRI and MRI should still be done in all patients and fQRS only can be

considered if MRI cannot be done in such patients. Especially when considering that the number of beta thalassemia major patients in our country is decreasing rapidly and cost is not a concern anymore

7- The authors should add and discuss the results of the following study in their paper

The Importance of Fragmented QRS in Evaluation of Cardiac Iron Burden, in Patients with β-Thalassemia Major

Nermin Bayar, Erdal Kurtoğlu, Şakir Arslan, Zehra Erkal, Burak Deveci, İsa Öner Yüksel, Erkan Köklü and Selçuk Küçükseymen

Thanks.

Kamran Bagheri Lankarani: EIC | **Revision (0)** 29 Sep 2019

Dear Author,

The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.

Thanks.

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Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Kamran B. Lankarani, M.D.

Thank you very much for the opportunity revision and also the valuable reviewer's comments.

Associate Editor 1:

1- Throughout the paper you have written that MRI was abnormal in 30 patients (75% with T2* values below 20 ms) while in table 1 the opposite is written (T2* value below 20 ms in 10 patients) !!

Answer: It is corrected in the results of abstract.

2- Please calculate and write the specificity and sensitivity of fQRS against MRI as the gold standard of your study

Answer: The sensitivity and specificity of the fQRS against MRI were equal to 50% and 83.3% respectively.

3- Who and how reviewed and calculated the fQRS? who reviewed the MRI? were they blinded or not?

Answer: The fQRS evaluated by one pediatric cardiology and the cardiac MRI reported by one radiologist who was expert in cardiac MRI. The pediatric cardiologist did not know about the Cardiac MRI report. (lines 6 and 7 in the method section)

4- As fQRS was abnormal in 10 patients only and MRI abnormal in 30 patients how the writers claims that fQRS is a good method against MRI?

Answer: The association of cardiac iron overload with fQRS on surface ECGs predicted based on our findings. On based our study, 50% of patients with T2 less than 20 had abnormal ECG, whereas in T2 more than 20 only 16% had an abnormality in ECG tracing. This finding suggested that effecting predictor fQRS is significant.(added in the discussion section)

5- As no follow-up is done the writers cannot claim in discussion that fQRS can detect early iron overload.

Answer: The presence of fQRS on ECGs could be a **major predictor** of the increase in cardiac iron overload in β-TM patients. The results showed that fQRS might indicate the need for close monitoring, in addition to aggressive chelation therapy. Our findings **suggested** that fQRS. . (added in the discussion section)

6- The authors should clearly mention in discussion and conclusion sections that fQRS cannot substitute MRI and MRI should still be done in all patients and fQRS only can be considered if MRI cannot be done in such patients. Especially when considering that the number of beta thalassemia major patients in our country is decreasing rapidly and cost is not a concern anymore.

Answer: We recommend performing cardiac imaging based on the proposed protocols, to further studies and long-term follow-up in patients with thalassemia major. Therefore, the fQRS cannot substitute cardiac MRI and T2* should still be done in all patients and fQRS only can be considered if MRI cannot be done in such patients.(added in the end of discussion section)

7- The authors should add and discuss the results of the following study in their paper

The Importance of Fragmented QRS in Evaluation of Cardiac Iron Burden, in Patients with β-Thalassemia Major

Nermin Bayar, Erdal Kurtoğlu, Şakir Arslan, Zehra Erkal, Burak Deveci, İsa Öner Yüksel, Erkan Köklü and Selçuk Küçükseymen

Answer: Nermin Bayar et al found of total of 103 patients (mean age 22.6 ± 6.6) with diagnosis of beta thalassemia major , 50 patients (48%), fQRS detected, 37 of them (74%), T2 * values were found to below. the presence of fQRS, low T2 * value to predict the sensitivity of 86.0% and specificity of 78.3%, respectively (16). In our study, presence of fQRS was 50% in T2 * value less than 20.

Best regards;

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Kamran Bagheri Lankarani: EIC | **Revision** (1) 6 Oct 2019

Dear Author,

There are improvement in the article.

As the sensitivity of the QRS changes are low near 50% , the discussion and conclusion should be revised.

The possibility of other causes of QRS changes should be discussed in more detail .

The text needs editing.

Thanks.

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Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Kamran B. Lankarani, M.D.

Thank you very much for the opportunity revision and also the valuable reviewer's comments.

1. As the sensitivity of the QRS changes are low near 50% , the discussion and conclusion should be revised.

Answer: It is corrected in the abstract and the conclusion section.

Conclusion: The absence of fQRS on ECGs could be a good predictor of the lack of cardiac iron overload in β-TM patients. The results showed that fQRS might indicate the no need for close monitoring for cardiac overload with cardiac MRI and aggressive chelation therapy.

2.The possibility of other causes of QRS changes should be discussed in more detail .
The text needs editing.

Answer: It is corrected in the conclusion section.

Finally, it should be kept in mind that fQRS can also occur for other causes, for example, cardiac ischemia related to myocardial scar/myocardial ischemia or myocardial fibrosis.

The fQRS is to be a good predictor of cardiac events due to CAD and patients with acute MI (17). Also in patients with non-ischemic cardiomyopathy, fQRS is related to a degree of fibrosis and dys-synchrony and influences the response for CRT (1).

At result , we should considers other causes of fQRS changes in patient thalassemia, such as fQRS is a marker of myocardial scar in coronary artery disease (CAD), arrhythmic events in non-ischemic cardiomyopathy, no ischemic cardiomyopathy (NICM) , arrhythmogenic right ventricular dysplasia /cardiomyopathy (ARVD/C), Brugada syndrome, acquired long QT syndrome and cardiac sarcoidosis (18).

The fQRS has reported in case of mitral stenosis, decreased mitral valve area and also in patients with mitral stenosis caused by rheumatic fever. Other causes of fQRS were hypertrophic cardiomyopathy (HCM), left ventricular non-compaction, heart failure associated with low EF, poor NYHA functional class and increased pulmonary pressure (19).

This finding shows that the presentation of fQRS is a nonspecific finding, and its interpretation should only be performed in the presence of clinical manifestations and type of myocardial involvement.

We revised the content for improving the quality of writing; hope it captures your criteria.

Best regards;

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Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision** (2) 19 Oct 2019

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.