Journal of Clinical and Translational Research
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# The genetics of cardiac failure: role of a G protein-coupled receptor polymorphism in therapeutic response in an Indian population

Sudha Ramalingam*, Shanmugasundaram R, Tamil Arasu K, Rajendiran G, Meenu S, Ramalingam Sankaran*

*Corresponding author
Sudha Ramalingam and Ramalingam Sankaran
*PSG Center for Molecular Medicine and Therapeutics, PSG Institute of Medical Sciences & Research, Coimbatore - 641 004, Tamil Nadu, India.*

Handling editor:
Michal Heger
*Department of Pharmaceutics, Utrecht University, the Netherlands*
*Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China*

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1st Editorial decision
27-Mar-2021

Ref.: Ms. No. JCTRes-D-21-00035
The Genetics of Cardiac Failure– Role of a G Protein Coupled Receptor Polymorphism in therapeutic response in an Indian population
Journal of Clinical and Translational Research

Dear Dr. Sankaran,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Apr 26, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I had the privilege of reviewing the manuscript draft entitled "The Genetics of Cardiac Failure- Role of a G Protein Coupled Receptor Polymorphism in Therapeutic Response in an Indian Population." The study is fairly well-conducted and the data are compelling, however, there are several limitations that should be addressed.

Major comments:
Introduction-
1. The introduction is well-done and clearly communicates the premise of the study.
2. The acronym SNP was not defined at first use.
3. The last paragraph prior to the methods section should list the objectives and hypotheses of the study. The results could be moved to the first paragraph of the discussion.

Methods-
1. More detail about the setting is needed. What type of hospital is it?
2. Were these admissions all-cause or HF specific?
3. It would be helpful to include a subsection that describes the variables (independent and covariates) in your study.
4. Did your Cox model adjust for covariates? If so, describe them.
5. Did you perform any subgroup analysis? Can you describe the outcomes by HF sub-type? Analyzing patients irrespective of EF likely dilutes the effect of the GRK5 polymorphism. What data do you have to support the rationale for including patients with diastolic dysfunction in this analysis?
6. What are the Framingham criteria? You should mention the pertinent information in the text of the paper so that the reader can understand the inclusion criteria.
7. What is the mean follow up duration?
8. What are the time frames for beta blocker use? The paper describes "initial" and "final" doses of beta blocker, but more detail is needed here.
9. Define the acronyms TDI, DNA, EDTA on first use.
10. The genotyping section is very thorough, but this level of detail might be more than is needed for the journal's readership.

Results-
1. Notably, the baseline EF was higher in the non beta blocker group. Beta blocker use is not indicated for diastolic dysfunction. Why include HFpEF in this analysis? If you keep both HFpEF and HFrEF in the main effects analysis, it is essential to perform subgroup analyses regarding different HF characteristics.
2. Do not assume causation from your results. For example the sentence on page 16, line 30 should be tempered. GRK5 variants did not reduce the dose, but rather were associated with a lower dose, on average.
3. Can you perform a time-to-event analysis? Were patients with the AT/TT variant more often admitted within 30 days?

Discussion-
4. It is customary to include a paragraph that summarizes the study's findings prior to getting into the details of the discussion. You can move the current final 2 sentences of the introduction here.
5. Again, any language that suggest causation should be tempered (e.g., page 20 lines 44-47).

Tables and figures
Table 1.
1. What is the follow up time mean and range?
2. How is coronary artery disease etiology different from ischemic heart disease. These descriptions should be defined in the methods section.
3. LV systolic, diastolic, biventricular, and PAH are not HF etiologies. These rows could be classified as HF characteristics.
4. Include the n's for the beta blockers used in addition the percentages.
Figure 3.
1. This figure is a bit confusing to interpret because each of the 3 panels are showing completely different data. Consider making this 2 or 3 separate figures. If you are limited in the number of figures to include, consider omitting the current Figure 1.

Minor issues:
In general, the paper would benefit from editing for grammar and clarity.

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Authors' response

**Reviewers' comments:**

**Reviewer #1**: I had the privilege of reviewing the manuscript draft entitled "The Genetics of Cardiac Failure- Role of a G Protein Coupled Receptor Polymorphism in Therapeutic Response in an Indian Population." The study is fairly well-conducted and the data are compelling, however, there are several limitations that should be addressed.

**Major comments:**

**Introduction**

**1. The introduction is well-done and clearly communicates the premise of the study.**

**2. The acronym SNP was not defined at first use.**

**Response:** As suggested by the reviewer, the full form of SNP (Single Nucleotide Polymorphism) has been mentioned in the abbreviation section as well as at the first use.

**3. The last paragraph prior to the methods section should list the objectives and hypotheses of the study. The results could be moved to the first paragraph of the discussion.**

**Response:** As suggested by the reviewer, this paragraph has been modified by focusing on objectives and hypotheses of the study. The results were moved to the first paragraph of the discussion in accordance to the suggestion by the reviewer.

The following lines were included in this paragraph: "The hypothesis behind this study was that as GRKs impose βAR blockade by desensitization, the presence of genetic GRK variants might alter the outcome in HF patients. Therefore, the main aim of this study was to identify the GRK5 variants and to study their reponse to β blocker treatment which might allow curtailing the β-adrenergic receptor blocker usage in these selected patients to avoid potential harmful effects."

**Methods-**

**1. More detail about the setting is needed. What type of hospital is it?**

**Response**: It is a multispeciality hospital giving tertiary care to the patients along with its academic affiliations to medical college, focussing on both academics and quality healthcare.

This line was included in the method section: "The study was conducted in a multispecialty, tertiary care hospital."

**2. Were these admissions all-cause or HF specific?**

**Response:** Out of the patients attending the Cardio OPD as well Cardiology in patient ward, the HF specific patients were recruited for this study.

**3. It would be helpful to include a subsection that describes the variables (independent and covariates) in your study.**

**Response:** As suggested by the reviewer, this line was included in the subsection variables "The independent variables were age, sex and sociodemographic data and covariates were EF%, comorbidities, use of β blockers, and use of medications".

**4. Did your Cox model adjust for covariates? If so, describe them.**

**Response:** As suggested by the reviewer, the covariates adjusted for the analysis was described in the methods section. "The covariates adjusted for hospitalization free survival were age, sex, EF% and comorbidities."

**5. Did you perform any subgroup analysis? Can you describe the outcomes by HF sub-type? Analyzing patients irrespective of EF likely dilutes the effect of the GRK5**

**polymorphism. What data do you have to support the rationale for including patients with diastolic dysfunction in this analysis?**

**Response:** As suggested by the reviewer, HF subgroup analysis was done. The HF subtypes were HF patients with systolic dysfunction, diastolic dysfunction, biventricular dysfunction and PAH. The hospitalization free survival was analysed for these subgroups with different *GRK5* genotypes. The patients with PAH showed increased survival and the ones with systolic dysfunction showed lower survival than other groups. All the subgroups with AT/TT genotype showed increased hospitalization free survival than subgroups with AA genotype (Fig. 7).

The rationale behind including patients with diastolic dysfunction in this analysis is that GRK5 has been established in systemic inflammation and progression to heart failure and diastolic dysfunction may involve a systemic proinflammatory state suggesting a role of GRK5 expression ( Faßbender *et al.,* 2018, Characterization of the GRK5 Gene Promoter and Association with Diastolic Dysfunction in CABG Surgery Patients). GRK5 also plays role in regulation of metabolic pathways like hypertension, diabetes mellitus, obesity which are known risk factors for diastolic dysfunction, thus indirectly involved in diastolic dysfunction.

**6. What are the Framingham criteria? You should mention the pertinent information in the text of the paper so that the reader can understand the inclusion criteria.**

**Response:** As suggested by the reviewer, the Framingham criteria were elaborated in the method section as follows: “The Framingham criteria for heart failure diagnosis should include either 2 major criteria or 1 major and 2 minor criteria. The major criteria include acute pulmonary edema, cardiomegaly, hepatojugular reflex, neck vein distention, paroxysmal nocturnal dyspnea or orthopnea, pulmonary rales and third heart sound (S3 Gallup Rhythm). The minor criteria include ankle edema, dyspnea on exertion, hepatomegaly, nocturnal cough, pleural effusion and tachycardia (Heart Rate >120 beats per minute).”

**7. What is the mean follow up duration?**

**Response:** “The mean follow up duration was 3.7 years for and 3.5 years for the β blocker group and non β blocker group”. This line was included in the method section of the manuscript as suggested by the reviewer.

**8. What are the time frames for beta blocker use? The paper describes "initial" and "final" doses of beta blocker, but more detail is needed here.**

**Response**: As suggested by the reviewer, the details of the doses of beta blocker were included in the method section as follows “The β blocker dosages were monitored during the follow up period. Initial dosage refers to the dosage administered at the start of the beta blocker therapy after the diagnosis of heart failure. The final dosage refers to the dosage followed at the last follow up time.”

**9. Define the acronyms TDI, DNA, EDTA on first use.**

**Response:** As suggested by the reviewer, the acronyms TDI, DNA and EDTA were defined on its first use.

**10. The genotyping section is very thorough, but this level of detail might be more than is needed for the journal's readership.**

**Response:** The genotype section was shortened as suggested by the reviewer. The changes made were highlighted in the manuscript.

**Results-**

**1. Notably, the baseline EF was higher in the non beta blocker group. Beta blocker use is not indicated for diastolic dysfunction. Why include HFpEF in this analysis? If you keep both HFpEF and HFrEF in the main effects analysis, it is essential to perform subgroup analyses regarding different HF characteristics.**

**Response:** As suggested by the reviewer, EF% analysis was compared only among the beta blocker group as the baseline EF was higher in the non beta blocker group and therefore, HFpEF were excluded from this analysis. The changes were made in the result section and in Fig. 3 and Fig. 4.

**2. Do not assume causation from your results. For example the sentence on page 16, line 30 should be tempered. GRK5 variants did not reduce the dose, but rather were associated with a lower dose, on average.**

**Response:** As suggested by the reviewer, the line was modified as follows:" Thus, the GRK5 Leu41 variants in the homozygous and heterozygous forms were associated with a lower dose of β blockers.

**3. Can you perform a time-to-event analysis? Were patients with the AT/TT variant more often admitted within 30 days?**

**Response:** The time –to-event analysis for AA and AT/TT groups was done in Fig. 6b to compare hospitalization free survival after beta blocker therapy between the two groups.

To compare the frequency of admission between AA and AT/TT groups within a month, the rate of hospital admission/month between the two groups were compared. AA group patients were significantly frequent in their admission to hospital than AT/TT group ($p<0.0001$).The results were shown in Fig. 8a. When subgroups were compared, HF patients on beta blockers and non beta blocker group with AA genotype were frequent in their admission to hospital than AT/TT group (Fig. 8b).

**Discussion-**

**4. It is customary to include a paragraph that summarizes the study's findings prior to getting into the details of the discussion. You can move the current final 2 sentences of the introduction here.**

**Response:** As suggested by the reviewer, the two sentences of the introduction were moved to the discussion.

**5. Again, any language that suggests causation should be tempered (e.g., page 20 lines 44-47).**

**Response**: As suggested by the reviewer, Page 20 (lines 44 -47) were modified as follows: "Coinciding with these data, our study reconfirms that GRK5 Leu41 allele improved the quality of life (QoL), promoted hospitalization free survival of South Indian HF patients. Independently, both the administration of β blocker therapy and the presence of Leu41 allele had positive outcome on hospitalization free survival".

**Tables and figures**

Table 1.

**1. What is the follow up time mean and range?**

**Response:** The mean follow up time was 3.7 years and 3.5 years for the β blocker group and non β blocker group. The range was 3 – 7 years for both the groups. This has been included in Table 1.

**2. How is coronary artery disease etiology different from ischemic heart disease. These descriptions should be defined in the methods section.**

**Response:** The coronary artery disease and the ischemic heart disease were considered the same. Therefore, the Table 1 has been modified as suggested by the reviewer.

**3. LV systolic, diastolic, biventricular, and PAH are not HF etiologies. These rows could be classified as HF characteristics.**

**Response:** As suggested by the reviewer, LV systolic, diastolic, biventricular, and PAH were classified as HF characteristics in Table 1.

**4. Include the n's for the beta blockers used in addition the percentages.**

**Response:** As suggested by the reviewer, the n's for the beta blockers used in addition the percentages were included in Table 1.

**Figure 3.**

**1. This figure is a bit confusing to interpret because each of the 3 panels are showing completely different data. Consider making these 2 or 3 separate figures. If you are limited in the number of figures to include, consider omitting the current Figure 1.**

**Response:**

As suggested by the reviewer, Fig.3 was subdivided into 2 figures (Fig. 3 and Fig. 4). Fig.3 indicates the percentage of HF patient cohort improved in their cardiac output and Fig. 4 shows the Improvement in ejection fraction (%) in HF patient cohort.

**Minor issues:**

**In general, the paper would benefit from editing for grammar and clarity.**

**Response:** The manuscript was grammar checked as suggested by the reviewer.

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2nd Editorial decision
12-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00035R1
The Genetics of Cardiac Failure– Role of a G Protein Coupled Receptor Polymorphism in therapeutic response in an Indian population
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by May 12, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for submitting a revised version of your manuscript to JCTR.

The editor has carefully studied the requested changes by the reviewer and the implemented changes by you, and deemed the manuscript suitable for publication pending minor changes. Your manuscript will not be re-reviewed as long as you comply with the requests.

The manuscript is replete with spelling/grammar errors that we kindly ask you to eliminate.

To cite a few examples in a non-exhaustive manner (manuscript page #/line #):

- 11/23: (Fig.1) should read (Fig. 1) -> insert space between value and unit/sign/symbol. Same applies to line 25, (p =0.595), which should be (p = 0.595). Please do this throughout manuscript.
- 11/11: why is there a period behind "blocker"?
- 10/53: ACE definition should read angiotensin-converting enzyme
- 10/38: why is the M capitalized in mellitus?
- 10/36: why are the first letters in Pulmonary Artery Hypertension capitalized (it is inconsistent with most of the other listed conditions). There is no need to capitalize the second, third, etc. word.
- 10/15: correct spelling is non-B blocker (with hyphen)
- 10/24: please use hyphen symbol consistently, and not a long hyphen and short hyphen interchangeably. Stick to the short variant throughout the text.
- 10/23: heart rate is reported as beats per minute.
- 9/21: the HF patient cohort is singular (-> was instead of were)

I think you get the gist of it. Please peruse critically and thoroughly over the manuscript and correct all other errors to comply with our author guidelines regarding academic level English (https://www.jctres.com/en/author-guidelines/).

Thank you and kindest regards,

Michal Heger
Editor

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Authors' response

**Reviewers' comments:**

- 11/23: (Fig.1) should read (Fig. 1) -> insert space between value and unit/sign/symbol. Same applies to line 25, (p =0.595), which should be (p = 0.595). Please do this throughout manuscript.

**Response:** As suggested by the reviewer, the Fig. 1 was modified and was checked throughout the manuscript.

- 11/11: why is there a period behind "blocker"?

**Response:** As suggested by the reviewer, the period was removed.

- 10/53: ACE definition should read angiotensin-converting enzyme

**Response:** As suggested by the reviewer, the ACE definition was changed to angiotensin-converting enzyme in Table 1.

- 10/38: why is the M capitalized in mellitus?

**Response:** As suggested by the reviewer, the M in mellitus was changed to lower case in page 10/38 and page 9/36.

- 10/36: why are the first letters in Pulmonary Artery Hypertension capitalized (it is inconsistent with most of the other listed conditions). There is no need to capitalize the second, third, etc. word.

**Response:** As suggested by the reviewer, the Pulmonary Artery Hypertension was changed to Pulmonary artery hypertension in Table 1.

- 10/15: correct spelling is non-B blocker (with hyphen)

**Response:** As suggested by the reviewer, the spelling was corrected as non-β blocker throughout the manuscript.

- 10/24: please use hyphen symbol consistently, and not a long hyphen and short hyphen interchangeably. Stick to the short variant throughout the text.

**Response:** As suggested by the reviewer, the short hyphen was maintained throughout the manuscript.

- 10/23: heart rate is reported as beats per minute.

**Response:** As suggested by the reviewer, the heart rate (beats/minute) was included in Table 1.

- 9/21: the HF patient cohort is singular (-> was instead of were)

**Response:** As suggested by the reviewer, the line was changed as “the HF patient cohort was (n = 584) was considered for the study”.

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3rd Editorial decision
15-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00035R2
The Genetics of Cardiac Failure– Role of a G Protein Coupled Receptor Polymorphism in therapeutic response in an Indian population
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by May 15, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Although the modifications as I pointed out have been largely implemented, which is appreciated, the request to peruse over the entire manuscript and apply the principles that underlie my corrections in a broader sense is still insufficiently met. This is a real shame as I would like to move to accepting your work asap.

Please look at the following:

- Figure legends still contain non-hyphenated version of non-B blocker;
- Why are BVD and PAH abbreviated in the abstract if these are used only once?
- In the list of abbreviations the phrases are still unnecessarily capitalized
- 4/22: evidence is used only in singular form
- 4/30: mortality and morbidity should not be preceded by an article (the) unless you are referring to rate -> ...reduced the mortality and morbidity rate. The phrase "over years" is also lacking proper syntax. Please specify the approximate time frame, such as "over the past decade".
- 4/34: central is improper syntax
etc.

Please, engage a native speaker to help out with the language. I do not want to repeat these cycles with you as it is time-consuming for both of us and leads to nowhere.

Thank you,

Michal Heger
Editor

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Authors' response

**Reviewer's comments and responses:**

**- Figure legends still contain non-hyphenated version of non-B blocker;**

**Response:** The hyphenated version, "non-B blocker" has been included in the figure captions and figure legends as suggested by the reviewer.

**- Why are BVD and PAH abbreviated in the abstract if these are used only once?**

**Response**: The abbreviations in the abstract were removed.

**- In the list of abbreviations the phrases are still unnecessarily capitalized**

**Response**: The list of abbreviations was modified and the capitalized words were uncapitalized.

**- 4/22: evidence is used only in singular form**

**Response:** The lines were modified as follows: Growing evidence showed that mortality rates as a result of HF were higher in Indian patients

**- 4/30: mortality and morbidity should not be preceded by an article (the) unless you are referring to rate -> ...reduced the mortality and morbidity rate. The phrase "over years" is also lacking proper syntax. Please specify the approximate time frame, such as "over the past decade".**

**Response:** The line has been modified as follows:"The use of β-adrenergic receptor (βAR) antagonists continues to be the standard treatment for HF [5] and has effectively reduced the mortality and morbidity rates over the past decade."

**- 4/34: central is improper syntax**

**Response:** The line was modified as follows: β-adrenergic receptor, one of the G protein coupled receptors expressed by cardiomyocytes has been documented as important for effective cardiac function

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4th Editorial decision
27-Apr-2021

Ref.: Ms. No. JCTRes-D-21-00035R3
The Genetics of Cardiac Failure - Role of a G Protein Coupled Receptor Polymorphism in therapeutic response in an Indian population
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at

http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by May 27, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Please engage a native speaker to correct your manuscript. Your work is important and clinically relevant, but the writing is still subpar.

There are services you may engage to correct the English grammar, spelling and syntax.

JCTR has in-house staff that could also help for a fee.

Thank you,

Michal Heger
Editor

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Authors' response

**Reviewer's comments and responses:**

Please engage a native speaker to correct your manuscript. Your work is important and clinically relevant, but the writing is still subpar.
**Response:**
The journal English grammar correction service was availed to proofread the manuscript and the corrections were highlighted as suggested by the reviewer.

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5th Editorial decision
10-May-2021

Ref.: Ms. No. JCTRes-D-21-00035R4
The Genetics of Cardiac Failure - Role of a G Protein Coupled Receptor Polymorphism in therapeutic response in an Indian population
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jun 09, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Still English errors (in just the abstract):

- increased hospitalization free survival than (increased than does NOT exist in the English language)
- showed an increased hospitalization free survival than (increased than does NOT exist in the English language)
- the cardiac function in HF patients -> remove article and look up rules to properly use articles (https://www.grammarly.com/blog/articles/?&utm_source=google&utm_medium=cpc&utm_campaign=11862361106&utm_targetid=dsa-929611691643&gclid=Cj0KCQjws-OEBhCkARIsAPhOkIZSwNG5P6CEp82npyxjqUwJEqfMjIR1P58-u91ijhkgPuMEYWB-EqEaAhKbEALw_wcB&gclsrc=aw.ds). Here, you should have used what's called a "zero article".

Many more errors in the body of the manuscript.

Good research, poorly written. This is unfortunate.

Please keep correcting until the paper can be accepted on the basis of abiding by academic-level English.

Thank you,

Michal Heger
Editor

6th Editorial decision
16-Jun-2021

Ref.: Ms. No. JCTRes-D-21-00035R5
The genetics of cardiac Failure - role of a G Protein coupled receptor polymorphism in therapeutic response in an Indian population
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: