Author’s response to reviews

Title: Risk factors for glial cell proliferation after idiopathic macular hole repair with internal limiting membrane flap

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Author’s response to reviews:

Dear Dr. Takeshi Iwase,

Thanks you very much for your comments and suggestions.

We have revised the manuscript, according to the comments and suggestions of reviewers and editor, and responded, point by point to, the comments as listed below. Since the paper has been revised significantly throughout the text, we feel it is better not to highlight the amendments in the revised manuscript. The Declarations section which includes the mandatory sub-sections has been added to the end of the manuscript. The revised manuscript has been edited and proofread by a medical editing company.

Reviewer reports:
Thank you very much for valuable comments of reviewers. We corrected and revised our manuscripts according to reviewers’ suggestions.

1. Atul Kumar, MD (Reviewer 1):
Comment 1 The authors elaborate on their study to evaluate the factors responsible for aberrant glial cell proliferation postoperatively after macular hole surgery. Whether the ethical committee approval was obtained or not? Contradictory statements have been produced in the "methods" section and in the "ethics approval" section.
Response 1 Thank you for your suggestion. Some of the text was ambiguous, and we have modified the text to be clearer (pg.3, line 88-90). And the ethical committee approval was obtained.
Comment 2: The demographic results might be included in the "results" section.
Response 2: We appreciate the reviewer's attention to detail, and we have corrected the text as suggested (pg.4, line 159-162).

Comment 3: A more proper definition of the two groups "normal healing" and "aberrant healing" must be provided. How was aberrant healing anatomically defined based on OCT? Based on what parameters? When was the reading done (post op day)? It is difficult to differentiate between ILM flap tissue and glial tissue on OCT. Without proper differentiation between two groups, the study looks like as if it is evaluating the factors responsible for poor closure.
Response 3: We thank the reviewer for this insightful comment. As the reviewer said, it is difficult to distinguish ILM flap tissue from glial tissue on OCT. The main criteria for distinguishing between normal and abnormal healing are the intensity of reflex signal and tissue continuity in OCT. And 1 month post operation was the reading time. We have altered the text to be clearer. (pg.3, line 104-111)

Comment 4: What was the macular hole closure rate? 100%?
Response 4: Thank you for your comment. During the observation period, 123 eyes were followed up, of which 3 were unclosed. The macular holes of the 52 eyes were closed after the first operation (pg.3, line 103-104).

Comment 5: The SSOCT specifications are given as: 840nm wavelength and 70000 scan rate. But these are spectral domain OCT specifications. As SS-OCT - works on 1050 nm and 1 lakh scan rate
Response 5: Thank you for your comment and the suggested test provided important information about our article. We revised it according to the reviewer's suggestions and the fact, and supplemented the detailed parameters of OCT (pg.3, line 114,118).

Comment 6: Was room air used as tamponade in all cases? Even in larger diameters MH?
Response 6: We appreciate the reviewer’s attention to detail, room air was used as tamponade in all cases, and we have corrected the text to be clearer (pg.4, line 133-134).

Because we haven't had expansion gas for more than three years, we were worried about room air filling at the beginning, but now for larger diameters MH and retinal detachment patients with high myopia macular holes, room air filling has been proven to be safe.

Comment 7: Microperimetry could have been performed to confirm the authors proposal of para foveal fixation.
Response 7: We thank the reviewer for this insightful comment. The reviewer's suggestion is very professional and important for us. Although I never met him, I just saw the reviewer's comments, but also had a feeling that I wanted to see him late. We have also realized the importance of microperimetry in IMH, and the results are being observed and summarized.

Comment 8: The ILM filling and abnormal glial proliferation - needs more statistical explanations.
Response 8: We thank the reviewer for this good comment. The relationship of ILM filling and abnormal glial proliferation was our speculation by observing many OCT results. Because there was no intraoperative OCT, we cannot quantify ILM filling. This year we have intraoperative OCT, so we can do this work in our future research.

Comment 9: More figures of sample cases can be provided.
Response 9: Thank you very much for valuable comment of reviewer. The figures are more convincing, and the magazine has a clear rule on the figures, we try to provide more figures of sample cases within the prescribed scope (Figure 5).

Comment 10: The entire article can be cut-short as there are ample repetitions.
Response 10: Thank you very much for your valuable comments, these comment are very important to improve the readability of the article. We have deleted the repetition contents in the methods, results and discussion sections.

Comment 11: Spell errors and grammatical errors need to be addressed.
Response 11: Thank you very much for your important suggestions. English is my second language. I had revised the spell errors and grammatical errors very carefully, and used the language editing
company and uploaded the editing certificate as an attachment to the editorial department.

2. GOVINDASAMY KUMARAMANICKAVEL (Reviewer 2):
Comment 1 Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.
Response 1 We appreciate the reviewer’s attention to the form of file upload, and we have corrected the upload format as suggested.
Comment 2 The data provided is based on one or two diagnostic assessments but the title says 'factors'.
Response 2 We thank the reviewer for this important comment. Title is the soul of the article and plays a very important role. Another reviewer also gave suggestions on the title of the article, which we carefully considered and revised accordingly (pg.1, line 1-2).
Comment 3 Since the surgery is done on the subjects, the authors are requested to assess the aqueous and vitreous humour for biochemical and cellular investigations and then see if there are any correlations associated in the study in terms of inflammatory molecules. They could also assess the tear samples pre and post operatively to identify any biomarkers.
Response 3 We thank the reviewer for this insightful comment. The suggested test is interesting and would provide important information for our further study. We are also aware of the important role of vitreous fluid testing in a variety of diseases and are exploring more rapid and effective detection methods. In addition to structural differences, there are differences in gender composition between group A and group B in this article (pg.4, line 159-160), suggesting that inflammation or other factors may play an important role between the two recovery modes. The reviewer's suggestion gives us good hints for future research and is a very valuable suggestion.

3. Michael A. Klufas (Reviewer 3):
Title
Comment 1 Title - would change to "Risk factors for glial cell proliferation after idiopathic macular hole repair with internal limiting membrane flap"
Response 1 We thank the reviewer for this important comment and good suggestion. We corrected and revised our title according to reviewer’s suggestion (pg.1, line 1-2).
Abstract
Comment 2 results would not use both 'more or deeper' - chose one adjective
Response 2 We appreciate the reviewer’s attention to detail, and we have corrected the text as suggested (pg.2, line 60).
Comment 3 Would also state in abstract if this was prospective or retrospective study or case control study
Response 3 Thank you very much for valuable comment of reviewer. We revised our manuscripts according to the reviewer’s suggestion (pg.2, line 49).
Background
Comment 4 I would elaborate a bit more on glial cell proliferation, though there have been studies on this, it is not a widespread feature commented on after routine macular hole repair
Response 4 Thank you for your suggestion. Some of the text was ambiguous, and we have modified the text to be clearer. We have also added relevant reference (pg.3, line 105-111).
Methods
Comment 5 Even if retrospective because this study involves use of patient data, would need IRB approval at most institutions
Response 5 Thank you for your comment. The IRB approval was obtained. (pg.3, line 88-90).
Comment 6 Demographics of the cohort should be in the results section
Response 6 We thank the reviewer for the attention to detail, and we have modified the text as suggested (pg.4, line 159-162).
Comment 7 Should specify if a single physician observe determined if this was group A or group B or
if concordance between two reviewers was needed
Response 7 We appreciate the reviewer’s attention to detail, and we have modified the text to be clearer (pg.3, line 121-123).

Comment 8 Line 116 - there should be period after inverted, before phacoemulsification
Response 8 We appreciate the reviewer’s attention to detail, and we have modified the text as suggested (pg.3, line 130).

Results
Comment 9 The MLD between the two groups is a confounding factor for the results Response 9 We thank the reviewer for this important comment. This information has been added to the results section (pg.6, line 234-235).

Comment 10 We need to know how the OCT structural measurements were done - single observer? Two observers with mean value? I do not think this is specified in the results section.
Response 10 We appreciate the reviewer’s attention to detail. This information is very important and has been added to the methods section (pg.4, line 148-150)

Comment 11 We also need to know if every single patient had an inverted ILM flap - as we know sometimes the flap can be lost or not ideal - I did not see mention in the results that ILM flap was attained surgically in 100% of patients, if so this should be stated.
Response 11 Thank you for your comment. Some of the text was ambiguous, and we have modified the text to be clearer. This information has been added to the results section (pg.3, line 103-104).

Discussion
Comment 12 Line 261 - it is confusing using both adjectives 'more and deeper' consider other phrases such as 'more extensive' or 'more robust'.
Response 12 We appreciate the reviewer's attention to detail, and we have corrected the text as suggested (pg.7, line 275).

Conclusion
Comment 13 The authors comment significantly about vision but do not mention the visual acuity disparities in the conclusion between the groups.
Response 13 Your suggestion is very important, and we have added this part of the content in the conclusion section (pg.2, line 64).

Figures
Comment 14 Figure 5 - I want to know if patient on the left is group A and patient on the right is group B? Not specified as in the supplemental figure.
Response 14 Thank you very much for your suggestions. We will pay more attention to details in our future work, and we have specified in the figures as suggested. Patient on the left is group A and patient on the right is group B (figures 5).

Comment 15 I think one of the supplemental files would be good to include or combine figures 5, S1, S2 into one figure.
Response 15 We thank the reviewer for this insightful comment, and we have corrected the text as suggested (figures 5).

Comment 16 It would be helpful for the authors to point out glial cell proliferation on a standard SD-OCT image as not all readers may be familiar with this pattern - alternatively it could be marked out with arrow on existing OCT images.
Response 16 We appreciate the reviewer’s attention to detail, and we have corrected the figures as suggested (figures 5).

Tables
Comment 17 Table 1 is good but could remove the text of this in the methods section, does not need to be repeated.
Response 17 We appreciate the reviewer’s suggestion, and we have corrected the text as suggested (pg.4, line 159-162).
I would like to re-submit this revised manuscript to BMC ophthalmology, and hope it is acceptable for publication in the journal.
Looking forward to hearing from you soon.
With kindest regards,
Yours sincerely
Dr. Chu