OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

International Journal of Cancer Management
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Peer Review Report for "A Review of Literature on Updates of Bisphosphonates Administration, Cancer Biomarkers for Bisphosphonate Therapy, and Bisphosphonate-related Osteonecrosis of the Jaw in Breast Cancer"

Author(s): Mina Khayamzadeh, Farnoosh Razmara, Amirali Asadi, Ghazal Shabankare

Review Timeline:

Submit Date:	17 Mar 2020
Revised Date:	15 Nov 2020
Accepted Date:	1 Dec 2020

Revision (0)

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

REFEREE: Reviewer | **Revision** (0) 8 Apr 2020

Dear AE,
Thanks for the submission of this invaluable manuscript. There are some hints for the authors that can improve the quality of this submitted paper, as follows:
** Title
- Correct the “Bisphophonate therapy” to “Bisphosphonate therapy”
** General
* Follow the IJCM guideline for headings and subheadings;
You can find it in
“http://intjcancermanag.com/knowledgebase/category/tree.html#article_body.html”
* Try to correct typographical and grammatical errors. It is advised that the manuscript be reviewed by a native English speaker (preferred) or an academic English learner. You can use the special services provided by IJCM. Some of them are as follow:
- Page 1, Line 9: Omit colon sign after "on"
- In case of multiple items that are presented in a sequence follow this rule:
A, B, and C.

- Page 1, Line 23: The correct is CAPG and GIPC1. The acronyms of macrophage-capping protein (CAPG) and PDZ domain-containing protein GIPC1 (GIPC1). Also, put the reference regard these molecules in the text. One of the references is:
“CAPG and GIPC1: Breast Cancer Biomarkers for Bone Metastasis Development and Treatment”. DOI: 10.1093/jnci/djv360
- Keywords: Omit the quotation signs.
- Page 3, Line 20: put “full stop mark” after question.
- Page 4, Line 14: Put the full-term of SRE in this section instead of the next paragraph.
- Page 4, Line 35: omit colon sing after "after"
- Page 5, Line 8: preimenopausal => correct it!
- Page 5, Line 12: hgher => correct it!
- Page 5, Line 21: What is n-BPs? Put the full-term.
- Page 5, Line 23: Change semicolon to the comma.
- Page 5, Line 26; Remove extra-space between “(TNBC)” and “has”
- Page 5, Line28: Put space after “cells.”
- Page 6, Line 7: CIPG1 => Correct it! … also correct other same errors
- Page 6, Line 34: Change “and compared with” to “in compare with”.
- Page 6, Line 37: Put space after “terminal”.
- Page 7, Line 21: rsk => Correct it!
- Table 1: residronate: The dictation is incorrect.
Risedronate is the more accepted dictation.
- Table 1: regarding Gralow et al. Put the space between “toxicity” and “and”.
- Table 2: regarding coleman et al. postmenpausal => Correct it! … is => are
* Page 5 Line 34: What does this sentence mean? ". Surprisingly, TLR9 and CD73 have illustrated inverse relationship in TNBC cells. "
** Discussion
- You should include a paragraph (just before the conclusion paragraph) speculating what is not known in the area of Bisphosphonate, future research directions and why are they important. A good review should provide some insight into the future and not just a catalog of past observations.
** Table 1
- Pls, add an extra column containing the short conclusion of the studies to provide the reader with an informative rapid glance.
Also, try to shorten the contents of the “Result” column. And use your own words, instead.
** References
- Reference (1): Use this reference, instead:
Cancer statistics, 2020
You can find it in:
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590
- Correct the citation of the 11 to including the title.
For example
“Kroep JR, Charehbili A, Coleman RE, et al. Effects of neoadjuvant chemotherapy with or without zoledronic acid on pathological response: A meta-analysis of randomised trials. Eur J Cancer. 2016;54:57–63. doi:10.1016/j.ejca.2015.10.011”
Thanks.

REFEREE: Associate Editor | **Revision** (0) 10 Apr 2020

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

REFEREE: EIC | **Revision** (0) 11 Apr 2020

Dear Author,
Please consider the comments of the associate editor and reviewer in your manuscript and resubmit.
Thanks.

OPEN PEER REVIEW

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.

Reply to Reviewers

1. Q: Title
   - Correct the “Bisphophonate therapy” to “Bisphosphonate therapy”
   A: “Bisphophonate therapy” is corrected “Bisphosphonate therapy”.

2. Q: ** General
   * Follow the IJCM guideline for headings and subheadings;
   You can find it in
   “http://intjcancermanag.com/knowledgebase/category/tree.html#article_body.html”
   A: According to the IJCM guideline for headings and subheadings, **Times New Roman** font (size 12) for the body, size 12 bold for subheadings, size 14 for headings and size 14 bold for the title is used. The font size of the contents of table 1 is changed to size 12 from size 10.

3. Q: * Try to correct typographical and grammatical errors. It is advised that the manuscript be reviewed by a native English speaker (preferred) or an academic English learner. You can use the special services provided by IJCM. Some of them are as follow:

   3.1 Q - Page 1, Line 9: Omit colon sign after "on"
   A: the colon sign is omitted.

   3.2 Q: - In case of multiple items that are presented in a sequence follow this rule:
   A, B, and C.
   A: All of the similar errors have been detected and corrected: page 1 (lines 18 & 23), page 2 (line 36), page 3 (lines 1, 3, 9, 10, and 11), page 4 (lines 2, 20, and 31), page 5 (line 9), page 8 (lines 3, 7, 14, and 19).

   3.3 Q: - Page 1, Line 23: The correct is CAPG and GIPC1. The acronyms of macrophage-capping protein (CAPG) and PDZ domain-containing protein GIPC1 (GIPC1). Also, put the reference regard these molecules in the text. One of the references is: “CAPG and GIPC1: Breast Cancer Biomarkers for Bone Metastasis Development and Treatment”. DOI: 10.1093/jnci/djv360

   A: GIPC1 is corrected in page1 (line 23), page 6 (lines 4, 8, and 14), and page 8 (line 8). Also, the suggested reference is already cited in the reference list (reference number 15, Westbrook JA, Cairns DA, Peng J, Speirs V, Hanby AM, Holen I, et al. CAPG and gipc1: Breast cancer biomarkers for bone metastasis development and treatment. J Natl Cancer Inst. 2016;108(4):1–10.)

   3.4 Q: - Keywords: Omit the quotation signs.

A: quotation signs are omitted.

3.5 Q: - Page 3, Line 20: put “full stop mark” after question
A: a full stop mark has been put after question.

3.6 Q: - Page 4, Line 14: Put the full-term of SRE in this section instead of the next paragraph.
A: the full-term of SRE has been mentioned in the desired paragraph.

3.7 Q: - Page 4, Line 35: omit colon sing after "after"
A: the colon sign has been omitted.

3.8 Q: - Page 5, Line 8: preimenopausal => correct it!
A: the term has been cprrected.

3.9 Q: - Page 5, Line 12: hgher => correct it!
A: it has been corrected to “higher”

3.10 Q: - Page 5, Line 21: What is n-BPs? Put the full-term.
A: the full-term (nitrogen-containing bisphosphonates) has been replaced.

3.11 Q: - Page 5, Line 23: Change semicolon to the comma.
A: semicolon has been changed to comma.

3.12 Q: - Page 5, Line 26; Remove extra-space between “(TNBC)” and “has”
A: the extra-space has been removed.

3.13 Q: - Page 5, Line28: Put space after “cells.”
A: space has been put after “cells”.

3.14 Q: - Page 6, Line 7: CIPG1 => Correct it! ... also correct other same errors
A: according to A 3.3, all the similar errors have been corrected.

3.15 Q: - Page 6, Line 34: Change “and compared with” to “in compare with”.
A: the phrase has been changed to the desired one.

3.16 Q: - Page 6, Line 37: Put space after “terminal”.
A: space has been put after “terminal”.

3.17 Q: - Page 7, Line 21: rsk => Correct it!
A: it has been corrected to “risk”.

3.18 Q: - Table 1: residronate: The dictation is incorrect. Risedronate is the more accepted dictation.
A: residronate has been replaced by the suggested drug name. The same change has been made to page 2 (line 21) as well.

3.19 Q: - Table 1: regarding Gralow et al. Put the space between “toxicity” and “and”.
A: the space has been put between the two words.

3.20 Q: - Table 2: regarding coleman et al. postmenpausal => Correct it! ... is => are
A: the error has been corrected.

4. Q: * Page 5 Line 34: What does this sentence mean? ". Surprisingly, TLR9 and CD73 have illustrated inverse relationship in TNBC cells. "
A: as no further information had been provided by the authors of the related study demystifying this statement, we decided to omit it for avoiding ambiguity.

5. Q: ** Discussion
- You should include a paragraph (just before the conclusion paragraph) speculating what is not known in the area of Bisphosphonate, future research directions and why are they important. A good review should provide some insight into the future and not just a catalog of past observations.
A: the discussion paragraph has been included in the revised manuscript.

6. Q: ** Table 1
- Pls, add an extra column containing the short conclusion of the studies to provide the reader with an informative rapid glance.
Also, try to shorten the contents of the “Result” column. And use your own words, instead.
A: an extra column has been added to Table 1.
Also, we rephrased and tried to summarize the results of each study as much as possible.

7. Q: ** References
- Reference (1): Use this reference, instead:
Cancer statistics, 2020
You can find it in:
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590
A: the desired reference has been used instead.

8. - Correct the citation of the 11 to including the title.
For example
“Kroep JR, Charehbili A, Coleman RE, et al. Effects of neoadjuvant chemotherapy with or without zoledronic acid on pathological response: A meta-analysis of randomised trials. Eur J Cancer. 2016;54:57–63. doi:10.1016/j.ejca.2015.10.011”
A: the format of citation has been corrected.

OPEN PEER REVIEW

Revision (1)

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

REFEREE: Reviewer | **Revision** (1) 30 Apr 2020

Dear AE,
I appreciate the authors' kind attention and meticulous answers to the comments.
All of the comments has been corrected, except for one item, as follows:
- Follow the IJCM guideline for headings
Change “context” to “ Background & Objectives”
Change “ Evidence acquisition“ to “ Materials & methods”
* Also apply these changes to the abstract.
Thanks.

REFEREE: Associate Editor | **Revision** (1) 30 Apr 2020

Dear EIC,
All of the comments has been corrected, except for one item that should be addressed by the authors, as follows:
- Follow the IJCM guideline for headings
- Change “context” to “ Background & Objectives”
- Change “ Evidence acquisition“ to “ Materials & methods”
* Also apply these changes to the abstract.
Thanks.

REFEREE: EIC | **Revision** (1) 30 Apr 2020

Dear Author
Please consider the comments of the associate editor in your manuscript and resubmit.
Thanks.

OPEN PEER REVIEW

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.

Reply to Reviewers

1. Q: Follow the IJCM guideline for headings
   Change “Context” to “Backgrounds & Objectives”
   Change “Evidence acquisition” to “Materials & methods”
   Also apply these changes to abstract
   A: the desired change has been made both to the abstract and body of the manuscript.

OPEN PEER REVIEW

Revision (2)

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

REFEREE: Reviewer | **Revision** (2) 22 May 2020

Dear AE,
I appreciate the authors' meticulous attention to correct all the issues.
Thanks.

REFEREE: Associate Editor | **Revision** (2) 24 May 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: Reviewer | **Revision** (2) 14 Jun 2020

Dear AE,
The topic could be an interesting one however there are some problems in the manuscript that should be considered by the authors for revising.
- The title of this article has been selected properly and reflects content appropriately.
- Abstract describes the content accurately but all of the keywords must be selected from MeSH.
- Introduction: this part doesn't include what we know and what we don't know clearly. Please refer to more and up to date studies about your aims.
Methods:
- Please explain your review protocol, and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
- Please present a full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Discussion:
- This part, has written so brief. Please provide a more detailed explanation and refer to the new guidelines.
Kind Regards

REFEREE: Associate Editor | **Revision** (2) 21 Jun 2020

Dear EIC,
The authors should consider the comments of the reviewer in the manuscript.
Thanks.

REFEREE: EIC | **Revision** (2) 21 Jun 2020

Dear author,
Please revise your article according to the comments of the reviewer then resubmit.
thank you.

OPEN PEER REVIEW

Revision (3)

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.

Hello
Dear Editors we have answered the questions separately

Reviewer 1:

Thank you for your attention

Reviewer 2:

Thank you for your attention.

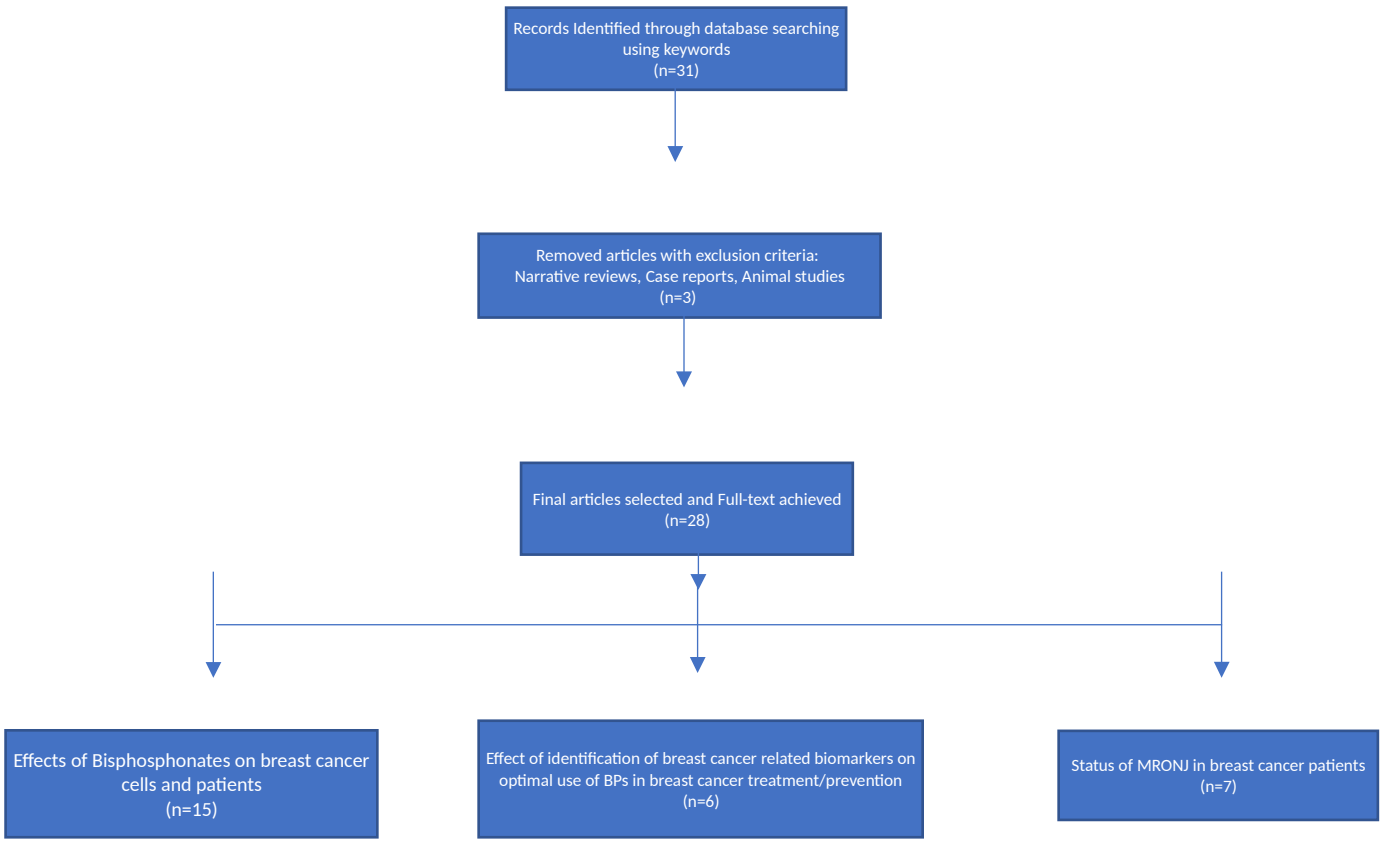
1. All the keywords must be selected from MeSH => We have changed all the keywords from MeSH. “biomarkers, diphosphonates, breast neoplasm, osteonecrosis”
2. Introduction: Please refer to more and up to date studies about your aims => We have added some new up to date studies in the introduction. Such as the paragraphs below:

“Recent studies indicate that bisphosphonates is bone-modifying agent used in patients with breast cancer and bone metastases to decrease the incidence of skeletal-related events (5, 6). Bisphosphonates are structurally similar to pyrophosphates and have high affinity for hydroxyapatite, primarily decreasing osteoclast activity. Previous reports have shown that bisphosphonates given as adjuvant treatment for postmenopausal women with early stage of breast cancer may prevent recurrences, delay onset of bone metastases, and improve breast cancer-specific and overall survival (7, 8). Although, not all studies indicate an association between adjuvant bone-modifying agent and improved results, however, a meta-analysis reported that the advantages of adjuvant bisphosphonate therapy in breast cancer were limited to a reduction in bone metastases, with no effect on cancer mortality. On the other hand, postmenopausal women who received bisphosphonates had lower recurrence rates and improved breast cancer-specific survival (9).”
“Van Hellemond et al. (12) reported that no association was observed between a reduced bone mineral density and distant recurrence-free survival . Neither did they observe an impact of bisphosphonates on distant recurrence-free survival.
Overall, bisphosphonates doses used for adjuvant therapy are lower than those used for the treatment of bone metastases, but they are greater than the doses used for treatment osteoporosis (5). In this regard because of serious adverse events, such as osteonecrosis of the jaw, the route of administration is important (13). Thus far, a little study have investigated the effects of Bisphosphonates administration on breast cancer patients.”

3. Methods: We have extended our search program in the online libraries. Number of the articles included were increased. According to the chart below we have searched the databases PUBMED, MEDLINE, and EMBASE with MeSH key words ‘Diphosphonates’, ‘osteonecrosis’, ‘breast cancer’, and ‘biomarker’. Inclusion criteria of article was "clinical trials, meta-analysis, and randomized controlled trial” published in English from October-2015 to October-2020. Exclusion criteria were case report, animal study, were not written in English, lacked documentation, narrative reviews, studies

without clinical outcomes data, systematic reviews that did not pool data or perform a meta-analysis, and technique articles without outcomes.

For example we searched “Diphosphonates osteonecrosis breast cancer biomarker” at pubmed and resulted 12 articles…



4. Discussion: we have added new 2020 articles to describe more about Updates of Bisphosphonates Administration, Cancer Biomarkers for Bisphosphonate Therapy, BRONJ of the Jaw in Breast Cancer.

“The method of use and also the duration of use of bisphosphonates play an important role in causing jaw necrotic lesions, so that in the injectable type and consumption of more than two years, the risk increases. Previous literature indicate that bisphosphonates are used in breast cancer patients with bone metastasis and generally administrated every 4 weeks to lessen the risk of subsequent skeletal-related events. Also, bisphosphonates administration every 12 weeks is recommended in some guidelines. But recent clinical trials suggested that bisphosphonate treat with reduced frequency (every 12 weeks) to be non-inferior to standard therapy. Yang and Yu (30) conducted an extensive study to contrast the efficacy and safety of these two treatment strategies. They reported that bisphosphonate administration every 12 weeks was non-inferior to administration every 4 weeks. There were no significant difference in on-study skeletalrelated events, renal dysfunction, and osteonecrosis of jaw. In the

exploratory experiment, patients who received intravenous bisphosphonates before enrollment experienced less on-study skeletal-related events and significant difference was observed between groups. Finally, they concluded that de-escalation treatment with bisphosphonates may be superior to standard treatment in terms of efficacy, safety, and economic costs. But it would be better that all the patients receive bisphosphonates every 4 weeks for several months before de-escalation. According to Eguia et al. (31) not only bisphosphonates are capable of inducing ONJ. A growing list of medications maybe have this same side effect, with a higher or/ lower risk. Although a high level of evidence does not exist for these drugs, it would be important, to apply clinical protocols that are the similar to the ones used for patients administered bisphosphonates or denosumab. Over the next 2 to three years, it would be advisable to treatment with particular care those patients under treat with new biologic antiresorptives and anti-inflammatory drugs, and any other new antiangiogenic or immunosuppressant factors. Adjuvant bisphosphonates, can decrease breast cancer recurrence and death, when given in a low-estrogen environment. Guidelines of treatment include recommendations for adjuvant bisphosphonates in postmenopausal patients. Gralow et al. (19) using 3 years of intravenous zoledronic acid, oral clodronate, or oral ibandronate in patients with stage I–III breast cancer, have reported that osteonecrosis of the jaw was highest for zoledronic acid compared with clodronate and ibandronate. They concluded that found no evidence of differences in efficacy by type of bisphosphonate, either in overall analysis or subgroups. Despite an increased rate of osteonecrosis of the jaw with zoledronic acid, overall grade of toxicity differed little across arms. Concidering that patients expressed preference for oral formulation, efforts to make oral agents available in the United States should be considered."

-We have changed "context" to "background & objectives" and "Evidence acquisition" to "Materials & Methods".

-We have also changed all the key words according to MeSH.

Thank you very much

OPEN PEER REVIEW

Revision (3)

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** (3) 1 Dec 2020

Dear EIC,
Thanks for revising this manuscript.
Thanks.

REFEREE: EIC | **Revision** (3) 1 Dec 2020

Dear authors,
Thank you for revising your manuscript.
Thanks.