Author's response to reviews

**Title:** Semiquantitative Assessment of Subchondral Bone Marrow Edema-like Lesions and Subchondral Cysts of the Knee at 3T MRI: A Comparison between Intermediate-Weighted Fat-Suppressed Spin Echo and Double Echo Steady State Sequences

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**Author's response to reviews:** see over
Dear Editor,

Thank you for giving us this opportunity to revise our manuscript. Both reviewers have provided us very useful suggestions and constructive criticisms of our work. We worked on them to address all issues raised by the reviewers. This is an itemized letter to show how we responded to each comment made by reviewers.

Best regards,

Daichi Hayashi, MBBS PhD
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Reviewer's report (1):

1. Bone Marrow Oedema is an area which is still in its infancy in terms of both its imaging and establishing the pathological histological processes to which it relates. The paper has stated aim to compare two radiological image sequences. The authors have also differentiated between two types of lesions cystic and non cystic and refer to the paper relating cysts to OA.

Author response: Thank you for taking time to review our work and thank you for your comments and suggestions. We agree with the reviewer in regard to the above comment.

2a. The difficulty for the reader is that the lack of clear definition of what the authors are defining 1) In their use of sub-regions and 2) in their grading system is unclear.

Author response: We cited the original publication of WORMS [Peterfy et al. 2004] to direct readers if they wished to read the details of subregional approach. However, as the reviewer pointed out, we agree it would be more helpful if we included clearer explanation of what the subregional approach and the grading system entail.

Author action: We added figures to visually explain the methodology we used in regard to the subregional approach and the grading system. Please see new figures 1 and 2 and their captions. Original figures 1 and 2 are consequently numbered as figures 3 and 4 in the revised manuscript.

2b. The change is size of a cystic lesion between the methods needs to be explained and perhaps the use of the word "cystic" challenged.

Author response: In our original manuscript, we used the term 'BML' to represent any lesions that are located within bone marrow, and not just bone marrow edema-like lesions. This is why we used the terms 'cystic' and 'non-cystic'. However, we realize it is more common to refer to them as 'subchondral cysts (=cystic lesion with clearly defined margin)' and 'bone marrow edema-like lesions (=non-cystic lesion with ill-defined margin).
Author action: We changed the term 'cystic BML' to 'subchondral cysts' and 'non-cystic BML' to 'bone marrow edema-like lesions'. This was done to avoid causing confusion to readers. Consequently, the title of this manuscript was changed to "Semiquantitative Assessment of Subchondral Bone Marrow Edema-like Lesions and Subchondral Cysts of the Knee at 3T MRI: A Comparison between Intermediate-Weighted Fat-Suppressed Spin Echo and Double Echo Steady State Sequences."

We also added the following sentences to explain why the size of subchondral cysts appeared differently between two types of pulse sequences.

Discussion, Page 13, Line 16 now reads:
"Subchondral cysts are better delineated by the DESS sequence. In this situation, the insensitivity of GRE-type sequences to subchondral BMLs is actually advantageous [5], and the borders between subchondral BMLs and cysts are more clearly depicted than by FSE sequences. The IW fs sequence usually delineates less clearly the sclerotic rim of the cyst when compared to the DESS sequence, and thus a peripheral portion of the cyst might be attributed to be ill-defined on the IW fs sequence. This may be the reason why the cysts appear larger on the DESS sequence."

3. The Figures used are incorrectly labeled and need clearer annotation.

Author response: We are uncertain as to what exactly the reviewer meant by 'figures are incorrectly labeled' because there is no specific description. As far as we are aware, none of the figures are incorrectly labeled. However, perhaps the figure caption was not as clearly written as it should have been and we addressed this in the revised manuscript.

Author action: Because we changed the terms to describe subchondral BMLs and cysts in the main text, we also changed figure captions accordingly. We also revised the figure captions to make clearer what we are trying to show by the arrows and arrowheads in the images.

Caption for the figure 3 now reads: "61-year old woman with medial tibio-femoral knee osteoarthritis. a: Sagittal intermediate-weighted (IW) fat-suppressed image depicts a grade 2 subchondral bone marrow edema-like lesion at the central medial tibial plateau that extends to the anterior subregion (long white arrows show the approximate location of the ill-defined margin of the lesion). In addition, there is a grade 1 subchondral bone marrow edema-like lesion at the posterior medial femur (short white arrows show the approximate location of the ill-defined margin of the lesion). b: Sagittal Dual Echo Steady-State (DESS) image shows no bone marrow edema-like lesion in neither the femur nor the tibia."

Caption for the figure 4 now reads: "54-year old woman with knee osteoarthritis. a: Sagittal intermediate-weighted (IW) fat-suppressed (fs) image shows a large (grade 3) subchondral bone marrow edema-like lesion at the lateral femoral trochlea (white arrows). Within this lesion, there is a small subchondral cyst (grade 1) directly adjacent to the
subchondral plate (black arrowhead). b: Corresponding sagittal Dual Echo Steady-State (DESS) image only shows the small cyst (white arrow). The large bone marrow edema-like lesion is not depicted by the DESS. Consequently, the margin of the cyst is more clearly delineated when compared to IW fs sequence.”

4. One of the major findings of this study is that the Term Bone Marrow Oedema is in itself a catch all for a variety of changes which vary on different sequences and this is an area which should be highlighted in the discussion section.

Author response: We thank the reviewer for the suggestion.

Author action: We added the following paragraph to the Discussion and we also added a reference [23].

Discussion, Page 13, line 11 now reads:
"Although we focused on subchondral BMLs that are of degenerative origin only, they can represent a variety of pathologies [23]. Since this study demonstrated their appearance may vary depending on the MRI pulse sequence used, one should be cautious when evaluating BMLs even if they are non-degenerative in origin."

5. There is also no comment on the state of the hyaline cartilage which would be helpful.

Author response: It is true that we did not mention anything about cartilage in this study. However, visualization of subchondral bone marrow edema-like lesions and subchondral cysts should not be affected by the status of cartilage. Cartilage is certainly a very important structure of the knee and additional analysis involving such data could have provided more depth to this paper, but we believe it is outside the scope of this study. In fact, Roemer et al has already published a paper which compared how depiction of cartilage defects differs according to the MR pulse sequence chosen. Please refer to Roemer FW et al. Semiquantitative assessment of focal cartilage damage at 3T MRI: A comparative study of dual echo at steady state (DESS) and intermediate-weighted (IW) fat suppressed spin echo sequences. Eur J Radiol 2010 Sep 10. [Epub ahead of print. PMID: 20833493].

Author action: We added the following sentences to direct readers to the aforementioned article, should they be interested to read about depiction of cartilage defects using these two MR pulse sequences.

Discussion, Page 14, the last line now reads:
"Lastly, we did not evaluate the state of hyaline cartilage and their appearances in the two types of pulse sequences because it was deemed outside the scope of the present study. However, interested readers are directed to a recently published article which compared semiquantitative assessment of focal cartilage damage using the DESS and IW fs sequences [27]. They demonstrated that the IW fs sequence detected more and larger
focal cartilage defects than the DESS, but more intrachondral signal changes were observed with the DESS.

Reviewer's report (2):
The authors presented a study aimed in comparing two different MR techniques (fast spin echo (FSE) vs. gradient recalled echo (GRE)) regarding assessment of non-cystic and cystic BMLs in OA. This a well-written and well-discussed manuscript. Also, it is extremely relevant in OA research since several works published recently used GRE MR sequences to assess non-cystic BMLs. Most MSK radiologists and physicists agree that gradient-echo sequences are insensitive to bone marrow pathology, especially regarding the "edema" pattern.

Author response: Thank you very much for your positive feedback on our work. I have minor suggestions for your consideration:
1- In the second paragraph of background: the sentence "non-cystic BMLs may also exhibit cystic components" may be confusing for a general reader. Please rephrase.

Author response: Thank you very much for your suggestion. We agree this expression is confusing. This sentence was changed taking into account the changes of terminology we incorporated in the revised manuscript.

Author action: Page 5, line 12, now reads: "Subchondral cysts may be present within or adjacent to a BML [4]."

2- Background: the terms used for the MR sequences regarding the head-to-head comparison are not wrong, but may add confusion. The main purpose of this study is not really to compare a "fluid-sensitive" sequence with a "cartilage-dedicated" sequence, but rather to compare a "FSE" sequence with a "GRE" sequence, which is the real point in terms of BML assessment. Even if the terminology here is not wrong and widely accepted, it may lead to confusion since we may have a GRE fluid-sensitive sequence (if the fluid is bright and the fat is suppressed), as well as a FSE cartilage-dedicated sequence (like the new 3D FSE sequences such as in "Cube"). The terminology for comparison should be focused on FSE vs GRE everywhere in the text.

Author response: Thank you very much for your suggestion. We agree our original description can lead to confusion and misunderstandings.

Author action: We followed the reviewer's suggestion and changed the description to "FSE vs. GRE" throughout the manuscript.

3- In the last paragraph of background: the sentence "lesions were compared according to lesion conspicuity, lesion size and differentiation between cystic and
non-cystic part of BML” may be deleted since it is well explained in the methods section.

Author response: Thank you very much for your suggestion.

Author action: We deleted the aforementioned sentence from the background section (page6).

4- Please make it clear in the methods section that this is a cross-sectional study. A reader may realize it only when reading the limitations in the discussion section (where the authors stated they were unable to comment on longitudinal sensitivity).

Author response: Thank you very much for your suggestion. We agree our original description can lead to confusion and misunderstandings.

Author action: We added the following sentence in the Methods section of our manuscript. Page 7, line 11 now reads: "Although the JOG Study itself was a longitudinal study, the present study only involves a cross-sectional analysis based on the MRI examinations taken at the baseline."

5- Did the authors exclude knees presenting with BMLs of other origin (traumatic, vascular, other)? If yes please add such statement and how many knees were excluded. If no knees were excluded for that reason, just add a brief statement saying no BMLs of other origin (than degenerative) were found in this study.

Author response: Thank you very much for your suggestion.

Author action: We added the following sentence in the Methods section of our manuscript. Page 7, line 5 now reads: "No BMLs of non-degenerative origin (e.g. trauma) were found in this study."

- The End of Revision-

We would like to thank the reviewers once again for their suggestions and constructive criticisms of our manuscript.