Author’s response to reviews

Title: Pulmonary tuberculosis: comparative detection with MR imaging and HRCT.

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Author’s response to reviews: see over
Dear Editor,

Please find enclosed the rebuttal letter for the manuscript “MS: 2112200388434367 Pulmonary tuberculosis: comparative detection with MR imaging and Helical CT” by Elisa BUSI RIZZI, et al, submitted to BMC ID.

Editorial Requests:

a) Abstract: Please include some context for your study in your abstract background.

**ANSWER. We modified accordingly.**

b) Ethics: Please name the ethical body that gave approval for your study.

**ANSWER. We modified accordingly.**

c) Please include statements of competing interests and authors contributions:

Competing interests - Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'. The questions that are asked of authors are:

Financial competing interests:
- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests: are there any non-financial competing interests (political, personal, religious, academic, ideological, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

**ANSWER. We modified accordingly.**

Authors' contributions - Please include an Authors' contributions section before the Acknowledgements and Reference list.

For the Authors' contributions we suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

An "author" is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) have been involved in drafting the manuscript or revising it
critically for important intellectual content; and 3) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

**ANSWER:** We modified accordingly.

Acknowledgements? Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements.

Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section. Authors must describe the role of the funding body, if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

**ANSWER:** We modified accordingly.

**Reviewer’s report**

**Title:** Pulmonary tuberculosis: comparative detection with MR imaging and Helical CT.

**Version:** 1 **Date:** 23 December 2010

**Reviewer:** Alberto Villanueva

**Reviewer’s report:**

General comments

The study is interesting. The hypothesis is original and very interesting: to compare the usefulness of STIR MRI sequences with CT in a group of patients with pulmonary tuberculosis (TB). It may help to avoid radiation in some patients. Since in the literature there is not much published about lung tuberculosis (TB) and MRI, and there is nothing about LDCT and MR in patients with lung TB. However, there are some important methodological errors, which make the report not suitable for publication as it is written. So it is unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions. The study defines as diagnostic criteria the presence of culture-proven pulmonary tuberculosis. On the abnormal images, there is no proof that the adenopathies on TC or MRI are secondary to TB since there is no histological or microbiological studies. This could be avoided if there were follow up CT and MRI studies performed one year after receiving treatment. However post-treatment follow up performed with imaging is lacking. There is only follow up studies of 10 patients. The follow up period is not documented and the images of these patients are not analysed in a separate group. Not having the complete follow up for all patients is a serious drawback which makes the study not suitable for publication. If the authors would have the information and if it is included in the study it may be considered for publication.
There are also concerns about the CT protocol that was employed and it should be described (see in the following).
Some corrections should be made to the manuscript.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1.- SUBJECTS AND METHODS. PATIENTS. The study defines as diagnostic criteria the presence of culture-proven pulmonary tuberculosis. On the abnormal images, there is no proof that the adenopathies on TC or MRI are secondary to TB since there is no histological or microbiological studies. This could be avoided if there were follow up CT and MRI studies performed one year after receiving treatment. However post-treatment follow up performed with imaging is lacking. There is only follow up studies of 10 patients. The follow up period is not documented and the images of these patients are not analysed in a separate group. Not having the complete follow up for all patients is a serious drawback which makes the study not suitable for publication. If the authors would have the information and if it is included in the study it may be considered for publication.

ANSWER: The referee is correct, “On the abnormal images, there is no proof that the adenopathies on TC or MR are secondary to TB since there is no histological or microbiological studies”. However all the patients enrolled had an active TB microbiologically confirmed without HIV infection or additional concomitant infectious diseases, as indicated in the text. Therefore the adenopathies found are very likely due to the damage caused by M. tuberculosis. Moreover the purpose of this study is not to demonstrate that MRI is able to correlate adenopathies with TB aetiology, but to demonstrate that MRI, compared with CT, is a complementary tool for assessing pulmonary abnormalities due to lung infectious diseases, in our series due to TB. CT itself is not a diagnostic tool for TB.

SUBJECTS AND METHODS. PATIENTS. Do you think that reporting more clinical data would make the study reproducible? For example, AIDS, TB type or stage. Patients with TB, specifically those which have AIDS usually have additional concomitant infectious diseases. Thoracic radiological findings may be different if the patient has or does not have some additional infectious diseases. The authors do not clarify if the patients have AIDS or they do not have AIDS. They do not refer if the patients have any co infection. The authors should reflect these clinical data about patients.

ANSWER: In our series the patients did not had AIDS or additional concomitant infectious diseases.

3.- SUBJECTS AND METHODS. CT. There are doubts the acquisition parameters and the protocol may not be reproducible. For example, it is not clear if two different MDCT acquisitions were obtained, a low dose one and a high resolution one, or if it was a low dose acquisition with reconstruction parameters for high resolution and 1mm slice.

ANSWER: We did not perform two different MDCT acquisitions, but only an acquisition, HRCT with low dose.

4.- SUBJECTS AND METHODS. CT. If a HRCT was obtained it should be manifested if it was a sequential protocol and the acquisition parameters should be described.

ANSWER: We performed a low dose HRCT, with 1-mm collimation and 10 mm spacing, 70 mAmp and 100 kV.
5.- SUBJECTS AND METHODS. CT. Please explain the use of 10 mm slice thickness.
ANSWER: We performed HRCT with 1-mm collimation and 10 mm spacing.

6.- SUBJECTS AND METHODS. CT. Please explain the use of high-resolution algorithm.
ANSWER: We used the high-resolution algorithm, that better depict the slightest interstitial changes, because with the reference standard, we want be sure of demonstrate all the pulmonary abnormalities.

7.- SUBJECTS AND METHODS. CT/MR. Please explain the comparison made with 5mm thickness slice on MR with 1mm thickness slice of each 10mm CT slice.
ANSWER: Nevertheless this discrepancy, there wasn’t any significative between the the images, that complicated our comparison.

8.- SUBJECTS AND METHODS. CT. It is not explained if a specific mediastinum reconstruction algorithm was employed. Did they use it? Did you evaluate the mediastinum using the high resolution reconstruction and mediastinum windowing?
ANSWER: Yes, a specific mediastinum reconstruction algorithm was employed, and the images were obtained on lung and mediastinal setting. We have add these data in the manuscript.

9.- SUBJECTS AND METHODS. IMAGING ANALISIS. How do you rule out bronchiectasis under the definition of cavitation?: “cavitation was defined as a gas-filled space, contained or not contained within a pulmonary consolidation, and with or without air fluid level. If not contained in a consolidation, the cavity must be surrounded by a wall whose thickness was greater than 1 mm.” The definition of the Fleischner Society for cavitation is “A cavity is a gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule” (Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008 Mar;246(3):697-722.) May be this definition exclude a bronchiectasy or a pneumatocele.
ANSWER: We modified accordingly to the Fleischner Society glossary.

10.- SUBJECTS AND METHODS. IMAGING ANALISIS. Criteria for pleural involvement should be described.
ANSWER: We modified accordingly.

11.- SUBJECTS AND METHODS. IMAGING ANALISIS. The authors compare CT IMAGES obtained in inspiration and MRI done in expiration. They should justify this aspect.
ANSWER: CT scans were acquired in inspiration because CT was the reference technique, and we choose to perform it according the standard criteria. However, even if MRI was performed in expiratory respiration and CT at the end of inspiration, there wasn’t any significative discrepancy between the breathing position of the images that complicated our comparison.

12.- DISCUSSION. In the discussion, reference is made to caseous necrosis not mentioning its diagnostic criteria nor the gold standard in material and methods section. Also in the results there is no mention of it. Even though it is explained that the lymph node signal is compared with muscle, the concept of caseous is not included. Caseous is an histological term. Since the study does not include histological material it would be better not to use the term in the tables that are included or indicate the signal intensity value as it is done in the text.
ANSWER: We modified accordingly.

13.- DISCUSSION. The use of a fast T2 axial imaging sequence on STIR
sequencing only (T2-weighted Fast Recovery Fast Spin-Echo (FR FSE T2) FAT SAT) should be justified. Authors should explain e.g. why they did not use diffusion imaging for adenopathies in these patients.

ANSWER: We did not perform FR FSE T2 sequence only, we performed diffusion imaging in adenopathies, but we will used these data for another study.

14. DISCUSSION. Some criteria is lacking, for example the definition of small sized adenopathies. It should be indicated that the lack of histopathological correlation or microbiological tests of the adenopathies is an important limitation of the study.

ANSWER: We modified accordingly.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1.-Title: We propose to change the title “Pulmonary tuberculosis: comparative detection with MR imaging and Helical CT.” For the following title: “Pulmonary tuberculosis: comparative detection with MR imaging and Low Dose MDCT.” Or “Pulmonary tuberculosis: comparative detection with MR imaging and HRCT” because these titles reflect more specifically the study.

ANSWER: We modified accordingly.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1.-SUBJECTS AND METHODS. It seems it is a prospective study, otherwise it should be specified.

ANSWER: We modified accordingly.

2.-SUBJECTS AND METHODS. CT.. Kernel should be changed for an algorithm.

ANSWER: We modified accordingly.

3.-SUBJECTS AND METHODS. CT First paragraph. Describe that the low dose CT parameters were obtained without contrast. This is mentioned in the discussion but not in the methods and material. The authors should also describe if the CT study was performed under inspiration or not.

ANSWER: We modified accordingly.

4.-SUBJECTS AND METHODS. MR. MRI in expiration may show non pathological processes such as small laminar atelectasis. Please describe this limitation in Discussion.

ANSWER: We modified accordingly.

5.-SUBJECTS AND METHODS. IMAGING ANALISIS. It should be mentioned if “The level of the inferior pulmonary veins “ refers to the level of origin of the inferior pulmonary veins.

ANSWER: We modified accordingly.

6.- DISCUSSION. The authors state that some lesions that give the appearance of tree in bud pattern are not well depicted in the MR imaged in this patient group. Could the authors describe a method for reducing this limiting factor?. For example one may consider performing MRI at end inspiration for those patients with tree in bud patterns and reducing the field of view to the pathological/doubtful areas.

ANSWER: We modified accordingly.

7.- DISCUSSION. Performing MRI in children with TB may be interesting since they may have lymph node involvement rather than lung involvement. The authors should explain that anaesthesia may be required. Also during pregnancy, MR imaging should be avoided during the first trimester. Authors should be explained that specific population studies are needed.

ANSWER: We modified accordingly.
ANSWER: We modified accordingly.

8.- DISCUSSION. Do the authors consider that combining the chest X ray findings with the MRI may add something to the comparison between MDCT and MRI?

ANSWER: We are convinced that chest X rays and MRI could be represent the new management in pulmonary TB and, as you suggest, we add a statement in discussion.

Reviewer’s report
Title: Pulmonary tuberculosis: comparative detection with MR imaging and Helical CT.
Version: 1 Date: 15 February 2011
Reviewer: Michael Puderbach
Reviewer’s report:
The manuscript “Pulmonary tuberculosis: comparative detection with MR imaging and Helical CT” focuses on the comparison of MRI with HRCT for assessing pulmonary tuberculosis.

Major Compulsory Revisions
The manuscript needs to be checked by a native speaker.
ANSWER: We modified accordingly.

Abstract:
- Ok

Introduction:
- There are several groups that work in the field of proton MR imaging of the lung in various diseases. The authors should give a more detailed introduction into this topic.
ANSWER: We modified accordingly.
- MR imaging of the lung is difficult due to several reasons. The authors should give some more background information here.
ANSWER: We modified accordingly.
- The authors state: “.... little information exists on MRI pneumonia patterns ....” and cite 4 papers. I don not think that this is little information and searching the literature the authors will find additional scientific articles on this topic.
ANSWER: We modified accordingly.

Subjects and Methods:
- Please provide details for how the pulmonary tuberculosis was proven.
ANSWER: We modified accordingly.
- When the images were take were the patients under treatment or not?
ANSWER: We modified accordingly.
- I am not sure if follow up examinations should be included in this evaluation as these are following treatment and do not show an acute situation.
ANSWER: We modified accordingly.
- MRI was performed in expiratory respiration. How was the CT performed, in expiration as well? If not this causes a discrepancy between the breathing position of the images and they might be complicated to compare.
ANSWER: CT scans were acquired in inspiration. Because CT was the reference technique, we choose to perform it according the standard criteria. However we did not encounter significative discrepancies.
- Only one MR sequence was used and evaluated? The sequence utilised shows a very low parenchyma signal (from my point of view one of the reasons why parenchyma findings were not that obvious like in the CT study, I
am not convinced that only the lower spatial resolution of the MRI is responsible for this discrepancy).

- The authors should have used a FR FSE T2 without fat sat for the visualization of the parenchyma. It is known that the fat sat destroys parenchyma signal.

**ANSWER:** Study protocol was selected on the basis of literature data, and optimised by GE specialists. In the sequences performed without FAT SAT there were more artifacts, which could interfere with the diagnostic value. However, as you suggest we will try new sequences without fat suppression.

- The sequence utilised took 120 s. The in-room time was 15 min. There is a discrepancy between study time and in room time. Were additional images acquired?

**ANSWER:** Including the positioning of the patient on the examination table, positioning of the coil, performance of the topogram, performances of the examination sequences, the resulting our room time was about 15 minutes.

- I guess the images were displayed in a pseudonymous fashion?

**ANSWER:** Yes, of course.

- Please describe the image evaluation in more detail. In detail it remains unclear to me how the images were evaluated. Was a scoring sheet used? How did the algorithm for independent reading and consensus reading exactly work?

**ANSWER:** Yes, we used a scoring sheet.

1) To avoid a bias from applying a highly individual interpretation, a previous consensus reading was reached about the MRI features which must be assessed, based on the CT criteria.

2) All MR images were independently analyzed, and the observers were unaware of CT results.

3) All CT images were considered reference scans, because CT is considered the gold standard technique, and were analyzed by the same radiologist in consensus, in a randomised order, two months after the analysis of the MR images.

4) MRI images were compared with CT examinations in consensus to verify the presence, distribution and characteristics of pathological features.

5) In the divergent cases, MRI and CT were re-examined to determine which imaging technique was correct. Disagreements in image scorings were resolved by consensus.

- It would have been nice to see the differences in-between both readers.

**ANSWER:** The differences between readers regarded bronchogenic spread.

- Why were the CT images not scored independently?

**ANSWER:** CT images were scored in consensus because CT is the gold standard and reference technique, moreover we did not insert too many variables.

- What influence did the direct comparison of the MRI and CT images have on the final results?

**ANSWER:** The direct comparison of the MRI and CT images hadn’t any relevant influence on the final results.

- I am a radiologist, not a statistician. Who performed the statistical evaluation? Was it performed by a statistician?

**ANSWER:** Yes, the statistical evaluations were performed by a statistician.

Results:

- The analysis of pleural effusion/pleural involvement remains unclear to me. Could it be that pleural effusion and signs of an inflammatory changes of the pleura are mixed up in this evaluation?

**ANSWER:** We modified accordingly.

- The analysis of the lymph node involvement and the “establishment” of MRI to
show “higher performance” remains unclear to me.

**ANSWER:** We modified accordingly.

**Discussion:**

- In the first paragraph of the discussion section the authors state: “..., MRI has currently no clinical application”. I think the authors should be a bit more differentiated in their statements reflecting the work of several groups that has been done in this field.

**ANSWER:** We modified accordingly.

- Further more the authors state: “... a significant advantage of using MRI over CT not appeared; ...” again I think the authors should be a bit more differentiated in their statements reflecting the work of several groups that has been done in this field.

**ANSWER:** We modified accordingly.

- The authors state that MRI failed to show tree in bud 4 times. As mentioned before this might be due to the sequence design with fat sat.

**ANSWER:** We modified accordingly.

**Literature:**

- The authors should include additional relevant literature in this manuscript and as mentioned before reflect some of their statements.

**ANSWER:** We modified accordingly.

**Minor Essential Revisions**

**Introduction:**

- Please introduce the abbreviation (TB) before using it.

**ANSWER:** We modified accordingly.

- The numbering of the figure legend and the figures is inconsistent.

**ANSWER:**

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.