

## Response Letter

February 7<sup>th</sup>, 2023

Assoc. Prof. Massimiliano Leigheb, MD, PhD  
Editor-in-Chief  
World Journal of Orthopedics

Dear Prof. Leigheb,

We are submitting a revision for manuscript with reference No. 83228 entitled “Subclinical ankle joint tuberculous arthritis: the role of scintigraphy – A cases series”. We would like to thank the editors and referees for their valuable time and precious contribution. We greatly appreciate the inputs that will definitely improve this manuscript.

We are addressing the comments from reviewers as follows:

Reviewer #1

1. **The author introduced a new modality for the diagnosis of osteoarticular tuberculosis in 3 cases. The method was well interpreted in the discussion. And I will suggest authors say something about the application of the method currently.**

The application of this method in our institution were added in line 219-220

2. **The laboratory tests in tuberculosis need not to be focused, thus it may be better to shorten the discussion about blood test**

Thank you for your suggestion. We opt to keep all the discussion to emphasize that normal laboratory findings do not always mean that tuberculosis can be excluded, therefore this discussion is one of key points of this report.

3. **Please interpret the figures, including the x-ray appearance. As for case 3, is the lung uptake shown in Figure 2c significant or just physiological uptake?**

The x-ray interpretations were included in each case presentations. For case 3, the lung uptake was significant as the patient still had active pulmonary tuberculosis.

Reviewer #2

4. **Specificity of the technetium-99m-ethambutol assay is in question. The cited studies did not include normal controls or individual with infections other than tuberculosis. Since individuals with tuberculosis are not immune from suppurative infections, additional workup would have been appropriate – aspiration or biopsy.**

The reference no. 7 that was cited in this studies was actually comparing the findings with

relevant histopathological or microbiological test. It would be difficult to include a series of normal control for the examination due to ethical reasons. Aspiration or biopsy would be beneficial, but as this report's purpose was to avoid unnecessary invasive procedures, we decided to present this report without those methods. However, future larger scale study with appropriate controls is still needed.

We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Thank you very much for your consideration.

Yours Sincerely,

Corresponding author

A handwritten signature in blue ink, appearing to read 'Randri', is positioned above the printed name.

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Mr. Jin-Lei Wang  
Vice General Manager  
World Journal of Orthopedics / Baishideng Publishing Group

Dear Mr. Wang,

We are submitting a 2<sup>nd</sup> round revision for manuscript with reference No. 83228 entitled “Subclinical ankle joint tuberculous arthritis: the role of scintigraphy – A cases series”. We would like to thank the editors and referees for their valuable time and precious contribution. We greatly appreciate the inputs that will definitely improve this manuscript.

We are addressing the comments from reviewer as follows:

1. **Title does reflect**
2. **Abstract reflects**
3. **Should add infectious arthritis to key words**

Keyword has been added

4. **Background discussed, but specificity of the technetium-99m-ethambutol assay is in question. The cited studies did not include normal controls or individuals with infections other than tuberculosis.**

The cited study (reference no. 7) had shown that 78% subjects were positive on 99mTc-ethambutol scintigraphy and microbiological/histopathological finding, and 14.9% subjects presented negative results on both examinations, so that the specificity was more than 90%. However, there are still 12 discordant results (7.1%) between both examinations. (Added in page 10)

Examining scintigraphy in normal controls or other infection source would be difficult ethically, so we do not think it would be feasible in human subjects.

5. **Methods adequate discussed**
6. **Results presumptive, not confirmed by culture or histology. Actually, x-rays are not normal. Suggest review by a skeletal radiologist**

This article was not intended mainly for diagnostic studies. Instead, this report was aimed to report that there were many subclinical tuberculosis cases without clear sign and symptoms in which a scintigraphy examination would help to avoid underdiagnosis.

Yes indeed, the x-rays in Figure 1 was not fully normal. But as tuberculosis arthritis is thought to present a Phemister triad, those features was not found on the x-rays.

7. **Adequately discussed, but**

- a. **Line 129 – those findings are not pathognomonic, but also found with suppurative infections.**

We had changed the word “pathognomonic” to “suggestive”

- b. **Line 173 – “at the suspected site” is erroneous if trying to identify localized bone involvement. Any uptake would have significance, independent of location.**

Scintigraphy is not intended to be a bone survey, therefore, a differential diagnosis should be made first at suspected site. Not any uptake would have significance, considering the pharmacokinetics and pharmacodynamics of the scintigraphy agents.

- c. **Lines ending on 191 and 192 – need citations.**

Citations added

- d. **Specificity of the technetium-99m-ethambutol assay is in question. The cited studies did not include normal controls or individuals with infections other than tuberculosis.**

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Examining scintigraphy in normal controls or other infection source would be difficult ethically, so we do not think it would be feasible in human subjects.

8. **Adequate illustrations**

9. **Biostats – n/d**

10. **Units – CRP needs clarification**

CRP units (measured in mg/L) is clarified

11. **References – reasonable**

12. **Organization – reasonable**

13. **Presumptive, not definitive as seemingly suggested**

This article was not intended mainly for diagnostic studies. Instead, this report was aimed to report that there were many subclinical tuberculosis cases without clear sign and symptoms in which a scintigraphy examination would help to avoid underdiagnosis.

We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Attached is the revised version of the manuscript. Thank you very much for your consideration.

Yours Sincerely,  
Corresponding author

Andri Primadhi