

Decision Letter (JCQ-2025-0005)

From: [REDACTED]

To: yumoto@yokohama-cu.ac.jp

CC: f.kashizaki@gmail.com

BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0005

Body: 10-Feb-2025

Dear Dr Yumoto:

Manuscript ID JCQ-2025-0005 entitled "Clinical Features of Simultaneous Diagnoses of Lung Cancer and Non-Tuberculous Mycobacterium Lung Disease: A Systematic Review and Pooled Analysis" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.

1. Access to <https://mc.manuscriptcentral.com/jcq> and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
3. Click "Manuscripts with Decisions" on Author Dashboard page.
4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Professor EIC JCQ
Editor in Chief, Journal of Clinical Question
jqceic@gleampub.com

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author

The submission provides nice images and is a good teaching case to show how it actually appears.

Reviewer: 2

Comments to the Author

General Assessment

This manuscript explores the clinical characteristics of simultaneous diagnoses of lung cancer and non-tuberculous mycobacterial lung disease (NTMLD) through a systematic review and pooled analysis of 92 cases. The study aims to determine whether there is a mutual influence between these two diseases, particularly when lesions coexist in the same lung lobe.

The topic is clinically relevant, given the increasing recognition of NTMLD in respiratory medicine and its potential interaction with malignancies. However, several key issues need to be addressed before this manuscript is suitable for publication.

Major Concerns

1. Causal Relationship Between NTMLD and Lung Cancer

The manuscript suggests that NTMLD and lung cancer may have a mutual influence, particularly when located in the same lung lobe. However:

While tumor microenvironmental factors are known to contribute to carcinogenesis, there is no established consensus that chronic NTMLD or prior inflammation directly increases lung cancer incidence. The authors must clearly differentiate correlation from causation and provide stronger mechanistic evidence if they claim a direct interaction.

If the argument is merely observational, it should be explicitly stated that the study cannot confirm causality.

2. Incidental Diagnosis vs. True Association

The study suggests that the simultaneous diagnosis of NTMLD and lung cancer in some cases is due to mutual interaction.

However, a more plausible explanation is that lung cancer is incidentally detected during imaging or investigation for NTMLD. This alternative hypothesis should be emphasized.

The manuscript would benefit from discussing whether NTMLD patients are more likely to undergo imaging and thus have incidental lung cancer detection rather than assuming a direct relationship.

3. Lack of Strong Supporting Data

The claim that NTMLD promotes lung cancer progression lacks direct biological or epidemiological evidence.

If this hypothesis is to be maintained, the authors should consider citing additional references or conducting a mechanistic discussion.

If such evidence is unavailable, the claim should be softened to avoid misleading conclusions.

4. Effect of Lung Cancer Treatment on NTMLD Progression

Did patients with lung cancer experience NTMLD exacerbation due to chemotherapy-induced immunosuppression?

Immune checkpoint inhibitors (ICIs) have been associated with worsening tuberculosis and NTMLD. Were any of the 92 patients treated with ICIs, and if so, did their NTMLD worsen?

Given previous reports on ICIs and mycobacterial infections, this should be addressed.

5. Limited Generalizability of Findings

The study is based on 92 cases from literature reviews, primarily from case reports and small case series. Given the selection bias inherent in published case reports, these findings cannot be generalized to broader clinical populations.

This limitation should be stated more explicitly in the Discussion and Conclusion sections.

Minor Concerns

Terminology Consistency

Ensure consistent terminology when referring to NTMLD and lung cancer interaction. Phrases like "mutual influence" should be clarified.

Statistical Limitations

The methods section states statistical significance, but given the heterogeneity of included cases, statistical power is limited. This should be acknowledged.

English Clarity and Grammar

Some sentences could be made more concise and clear. A professional English language review is recommended.

Conclusion

This manuscript addresses an interesting clinical question but requires revisions to ensure a more cautious and evidence-based discussion of NTMLD and lung cancer interaction. The key revisions should focus on:

Clarifying incidental diagnosis vs. true interaction

Providing stronger evidence for causality, or softening the claims

Discussing the impact of cancer treatments on NTMLD progression

Clearly acknowledging the limitations of case-based data

If these concerns are addressed, the manuscript could provide valuable insights into the coexistence of these two conditions in clinical practice.

Date Sent: 10-Feb-2025

Response Letter

Dear Reviewers,

We express our gratitude to you for reviewing our manuscript [JCQ-2025-0005] entitled, 'Clinical Features of Simultaneous Diagnoses of Lung Cancer and Non-Tuberculous Mycobacterium Lung Disease: A Systematic Review and Pooled Analysis'. We appreciate your valuable comments and insights, which have significantly improved our manuscript. In response, we have addressed all concerns raised, as detailed in our point-by-point responses below. Changes to the manuscript are highlighted in red font.

Responses to Reviewer 1

Major Comments

- 1) While tumor microenvironmental factors are known to contribute to carcinogenesis, there is no established consensus that chronic NTMLD or prior inflammation directly increases lung cancer incidence.
The authors must clearly differentiate correlation from causation and provide stronger mechanistic evidence if they claim a direct interaction.
If the argument is merely observational, it should be explicitly stated that the study cannot confirm causality.*

Response: We appreciate the reviewer's insightful comment on this point. As the reviewer points out, no established reports confirm that NTMLD infection increases the risk of lung cancer. We have revised the wording to indicate that this remains controversial. (Page 3 line 3-5, Page 5, Page 12 line 11-14)

- 2) The study suggests that the simultaneous diagnosis of NTMLD and lung cancer in some cases is due to mutual interaction.
However, a more plausible explanation is that lung cancer is incidentally detected during imaging or investigation for NTMLD. This alternative hypothesis should be emphasized.
The manuscript would benefit from discussing whether NTMLD patients are more*

likely to undergo imaging and thus have incidental lung cancer detection rather than assuming a direct relationship.

Response: As the reviewer pointed out, this was a case where lung cancer or NTMLD was diagnosed either due to respiratory symptoms or incidentally during a health check or an evaluation for another condition. Therefore, we stated in the paper that these cases were detected incidentally. (Pages 3 conclusions, Page 12 line 4-6, Page 15 line 2-4).

- 3) *The claim that NTMLD promotes lung cancer progression lacks direct biological or epidemiological evidence.*

If this hypothesis is to be maintained, the authors should consider citing additional references or conducting a mechanistic discussion.

If such evidence is unavailable, the claim should be softened to avoid misleading conclusions.

Response: As the reviewer pointed out, there is no evidence that NTMLD accelerates lung cancer progression. Therefore, we have adjusted the wording to be more neutral. Additionally, we revised some wording to reflect the possibility that NTMLD may be exacerbated by airway obstruction caused by lung cancer. (Page 12 line 11-14, Page 13 line 3-4 and 14-16)

- 4) *Did patients with lung cancer experience NTMLD exacerbation due to chemotherapy-induced immunosuppression?*

Immune checkpoint inhibitors (ICIs) have been associated with worsening tuberculosis and NTMLD. Were any of the 92 patients treated with ICIs, and if so, did their NTMLD worsen?

Given previous reports on ICIs and mycobacterial infections, this should be addressed.

Response: Thank you for the valuable reviewer input. We believe that our study and the exacerbations caused by ICI use provide important insights into the pathophysiology. Therefore, we have incorporated this information into the discussion section. (Page 11 line 14-20)

- 5) *The study is based on 92 cases from literature reviews, primarily from case reports and small case series.*

Given the selection bias inherent in published case reports, these findings cannot be generalized to broader clinical populations.

This limitation should be stated more explicitly in the Discussion and Conclusion sections.

Response: Thank you for highlighting this important point. As this study is retrospective and involves a population prone to publication bias due to the rarity of

the cases, we have added a statistical consideration to the limitation.(Page 13 line 17-19, Page 15)

Minor Comments

- 1) *Ensure consistent terminology when referring to NTMLD and lung cancer interaction. Phrases like "mutual influence" should be clarified.*

Statistical Limitations

Response: The ambiguous expressions have been revised for clarity.

- 2) *The methods section states statistical significance, but given the heterogeneity of included cases, statistical power is limited. This should be acknowledged.*

Response: Thank you for highlighting this important point. We have added a statistical consideration to the limitation.(Page 13 line 18-20)

- 3) *Some sentences could be made more concise and clear. A professional English language review is recommended.*

Response: We have requested further English editing, as noted by the reviewer. The ambiguous expressions likely made the sentences difficult to understand.

Responses to Reviewer 2

We appreciate your dedicated peer review.

We sincerely appreciate the reviewers for their valuable comments and suggestions, which have significantly enhanced the quality of our manuscript. We have carefully addressed each comment and incorporated the necessary revisions. We hope our responses and the updated manuscript meet the reviewers' expectations.

Thank you for considering our work for publication. We look forward to your further feedback.

Sincerely,