

## **A review of the presentation and outcome of sarcoidosis in COVID-19**

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Handling editor:

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*Department of Pharmaceutics, Utrecht University, the Netherlands*

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1<sup>st</sup> Editorial decision  
23-Jul-2021

Ref.: Ms. No. JCTRes-D-21-00109

A review of the presentation and outcome of sarcoidosis in COVID-19  
Journal of Clinical and Translational Research

Dear Dr Lal,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Aug 22, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author.

You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The paper is clear and well-written. Our comments are as follows:

16 : Add 'i' to questionnaire

120 : Remove 's' from responses

163 : use ', and based' instead of .And based

254 : We believe you meant to say : the best-5 year survival rates and not mortality rates

Reviewer #3: The authors intend to review the presentation and outcome of sarcoidosis patients who develop infection with the SARS-CoV-2 virus. To accomplish this task, they review pooled data from 10 articles involving patients with sarcoidosis and COVID-19. The studies they review are retrospective case reports and case series. The authors report "that there were no significant differences found in the clinical manifestations of patients with sarcoidosis presenting with COVID-19". The also conclude that the "rate of hospitalization in [their] study was 34.7%" and the "overall mortality in [their] study is 8.6%, higher than the global average." In turn, they conclude that "neither the diagnosis of sarcoidosis nor ongoing treatment with steroids, methotrexate or other immunosuppressants is associated with a poorer prognosis in these patients."

While I believe that studies evaluating patients with sarcoidosis and COVID-19 are important, there are several major limitations to the manuscript that make it unpublishable at the current time.

1. Do the authors intend to say that there were no clinical differences in the study patients compared to sarcoidosis patients without COVID-19 or to COVID patients without sarcoidosis?
2. What does the rate of hospitalization and mortality have to do with clinical manifestations? The rate of hospitalization and mortality are outcomes data.
3. On what basis do they conclude that "neither the diagnosis of sarcoidosis nor ongoing treatment with steroids, methotrexate or other immunosuppressants is associated with a poorer prognosis in these patients"? They offer no data to support their conclusion. The conclusion has nothing to do with the stated aim of the study.
4. Based on the title, it appears that the authors intend to conduct a review of the existing literature. They perform this review but provide little data to support their conclusions. At the same time, they provide management recommendations, more akin to a practice guideline. However, there are no data to support their recommendations.
5. There are two tables provided. Table 1 is very difficult to read. There are no statistical analyses.
6. The biomarkers section of the manuscript is out of place and unrelatable to the overall

study concept.

7. There are numerous grammatical errors and multiple citations, which are missing.

Reviewer #4: In the introduction, it will be helpful to emphasize the frequency of lung involvement in sarcoidosis, thus providing context of why COVID-19 may be particularly dangerous in the sarcoidosis population

In the Results, please clarify how you chose the 10 articles from the initial 33 that were identified.

In the biomarkers section, besides ACE and KL6, should also consider discussing a role for other biomarkers of inflammation including CRP and ferritin that are also commonly trended in COVID-19.

In the section discussing management of sarcoidosis during the COVID-19 pandemic, can you clarify if the risk for infection refers to risk for any infection or risk for COVID-19 specifically? Also, during this section, it is important to emphasize that current evidence for treatment of sarcoidosis during the COVID-19 pandemic is limited and recommendations are largely based on expert opinion.

In the section discussing management of COVID-19 in sarcoidosis, in reference to the following statement: "Stepping up the dose of steroids may be done in appropriate situations"; is this statement in reference to all COVID-19 patients or specifically to sarcoidosis patients? would consider removing/reassessing this statement as the reference provided predates the RECOVERY trial findings

In the section discussing limitations, it is important to emphasize that current evidence in sarcoidosis and COVID-19 is limited and further research is necessary

I would recommend revising/removing figure 1 as it detracts from the clarity of the overall manuscript.

Reviewer #5: Hi and good day  
Dear colleague,

I hope you are healthy and well. The article title is interesting and new. Clearly, you had many difficulties preparing this article. However, the result is satisfactory. I hope my comments don't make you disappointed or upset.

1-Abstract, lines 4-29: According to the journal policy and article type, the number of words in the abstract section is about 150 to 250 words. The reader will be tired and confused in understanding the article.

2-Abstract, Results, line 18: It seems that the review of only 10 articles for conclusion in a review article is very weak. This needs more search and assessment.

3-Abstract, Results, line 20: "The rate of hospitalization in our study was found to be 34.7%". Between how many patients? They had what severity of Covid-19 and Sarcoidosis?

4-INTRODUCTION, line 31: Please remove the name of "China" in the study to prevent any political impression and use the continent of "Asia" instead.

5-INTRODUCTION, line 36: Please add this phrase to the first sentence: In different observed virus variants the most common symptoms ... .

6-Two heads of the age range (youth and elderly) may be asymptomatic patients or virus carriers.

7-INTRODUCTION, line 38: Two heads of the age range (youth and elderly) may be asymptomatic patients or virus carriers.

8-Investigations, line 77: SARS-CoV-2 RT-PCR test is not practicable in some forms of Indian virus variants.

9-DISCUSSION: Please express all the predisposing factors of COVID-19 disease.

10-DISCUSSION, line 114 and Radiology, line 161: Please inform some of the readers of the CO-RADS classification.

Good Luck

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Authors' response

Dr Michal Heger,  
Editor-in-Chief,  
Journal of Clinical and Translational Research

Date: August 18, 2021

Re: JCTRes-D-21-00109 Revision

Dear Editor,

Thank you for the time and consideration given to our manuscript. We are grateful for the careful thoughts from the reviewers that have made a significant impact to improve the quality of the manuscript.

In the following pages we have attempted to respond to all the comments raised by the reviewers and the appropriate changes have been made in the manuscript as well.

**Amos Lal, M.B.B.S, M.D, FACP**

Assistant Professor, Mayo Clinic College of Medicine

Division of Pulmonary, Critical Care and Sleep Medicine

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Reviewer #1: The paper is clear and well-written. Our comments are as follows:

16 : Add 'i' to questionnaire

120 : Remove 's' from responses

163 : use ', and based' instead of .And based

254 : We believe you meant to say : the best-5 year survival rates and not mortality rates

Response: Thank you very much for your comments. These comments have been accepted and the errors rectified in the revised manuscript.

Reviewer #3: The authors intend to review the presentation and outcome of sarcoidosis patients who develop infection with the SARS-CoV-2 virus. To accomplish this task, they review pooled data from 10 articles involving patients with sarcoidosis and COVID-19. The studies they review are retrospective case reports and case series. The authors report "that there were no significant differences found in the clinical manifestations of patients with sarcoidosis presenting with COVID-19". The also conclude that the "rate of hospitalization in [their] study was 34.7%" and the "overall mortality in [their] study is 8.6%, higher than the global average." In turn, they conclude that "neither the diagnosis of sarcoidosis nor ongoing treatment with steroids, methotrexate or other immunosuppressants is associated with a poorer prognosis in these patients."

While I believe that studies evaluating patients with sarcoidosis and COVID-19 are important, there are several major limitations to the manuscript that make it unpublishable at the current time.

1. Do the authors intend to say that there were no clinical differences in the study patients compared to sarcoidosis patients without COVID-19 or to COVID patients without sarcoidosis?

Response:

The data has been modified and updated to August 14<sup>th</sup> 2021. Among the patients diagnosed with COVID-19, a pre-existing diagnosis of sarcoidosis alone did not contribute to significant mortality or ICU admissions. This is because it was observed in the review that all patients who were admitted to the ICU, or who died, had additional medical comorbidities. Though the global case fatality rate of COVID-19 (as reported by the WHO) as of 13<sup>th</sup> august 2021 is 2.11% and is much lesser than that seen in our review, prospective studies by R.P Baughman et al on sarcoidosis patients with COVID-19 also show the case fatality rates of 1.2%. A larger number reported in our study may be due to smaller sample size and reporting bias.

2. What does the rate of hospitalization and mortality have to do with clinical manifestations?

Response:

The rate of hospitalization and mortality are patient centric outcomes that are important for resource allocation and planning. This information in the review should provide information to the readers about the expected course and inpatient requirements for this subset of patients.

3. On what basis do they conclude that "neither the diagnosis of sarcoidosis nor ongoing treatment with steroids, methotrexate or other immunosuppressants is associated with a poorer prognosis in these patients"? They offer no data to support their conclusion. The conclusion has nothing to do with the stated aim of the study.

Response

The aims of the study have been modified to include outcome measures. The odds ratio for oxygen requirement, ICU admission and death among patients on steroids and immunosuppressants was 0.13. Other prospective studies by Baughman R P et al also show similar results.

4. Based on the title, it appears that the authors intend to conduct a review of the existing literature. They perform this review but provide little data to support their conclusions. At the same time, they provide management recommendations, more akin to a practice guideline. However, there are no data to support their recommendations.

Response

Most of the recommendations made in the management are based on published expert opinions. Corrections have been made to clarify this in the manuscript

5. There are two tables provided. Table 1 is very difficult to read. There are no statistical analyses.

Response

Thank for your comments. Necessary corrections have been made. The table serves to briefly elucidate the clinical summary of the patients, described in case reports, analysed in our review. In the current narrative review we have not performed any additional analysis and should not be confused with a meta-analysis.

6. The biomarkers section of the manuscript is out of place and unrelatable to the overall study concept.

Response

Thank you for your comments, corrections have been made.

7. There are numerous grammatical errors and multiple citations, which are missing.

Response

Thank You for your comments, corrections have been made.

Reviewer #4: In the introduction, it will be helpful to emphasize the frequency of lung involvement in sarcoidosis, thus providing context of why COVID-19 may be particularly dangerous in the sarcoidosis population

Response

Thank you for your comments, corrections have been made.

In the Results, please clarify how you chose the 10 articles from the initial 33 that were identified.

Response

Thank You for your comments, corrections have been made. The data has been modified and updated to August 14<sup>th</sup> 2021. We have also added a consort diagram to elucidate the same.

In the biomarkers section , besides ACE and KL6, should also consider discussing a role for other biomarkers of inflammation including CRP and ferritin that are also commonly trended in COVID-19.

Response

Thank You for your comments, corrections have been made and the role of other biomarkers has been added to the manuscript.

In the section discussing management of sarcoidosis during the COVID-19 pandemic, can you clarify if the risk for infection refers to risk for any infection or risk for COVID-19 specifically? Also, during this section, it is important to emphasize that current evidence for treatment of sarcoidosis during the COVID-19 pandemic is limited and recommendations are largely based on expert opinion.

Response

Thank You for your comments, corrections have been made.

In the section discussing management of COVID-19 in sarcoidosis, in reference to the following statement: "Stepping up the dose of steroids may be done in appropriate situations"; is this statement in reference to all COVID-19 patients or specifically to sarcoidosis patients? would consider removing/reassessing this statement as the reference provided predates the RECOVERY trial findings.

Response

Thank You for your comments. We have modified the line in accordance to it.

In the section discussing limitations, it is important to emphasize that current evidence in sarcoidosis and COVID-19 is limited and further research is necessary

Response

Thank you for your comments. The limitations of the present study have been added to the manuscript.

I would recommend revising/removing figure 1 as it detracts from the clarity of the overall manuscript.

Response

Thank you for your comments, table 1 has been revised.

Reviewer #5: Hi and good day  
Dear colleague,

I hope you are healthy and well. The article title is interesting and new. Clearly, you had many difficulties preparing this article. However, the result is satisfactory. I hope my comments don't make you disappointed or upset.

1-Abstract, lines 4-29: According to the journal policy and article type, the number of words in the abstract section is about 150 to 250 words. The reader will be tired and confused in understanding the article.

Response

Thank you for your comments. The abstract has been modified.

2-Abstract, Results, line 18: It seems that the review of only 10 articles for conclusion in a review article is very weak. This needs more search and assessment.

Response

The articles have been updated till 14<sup>th</sup> august 2021

The number of articles assessed was 177. Of which only 14 articles met the inclusion criteria being case series/ case reports with sufficient data that could be pooled together to analyse as a data set.

3-Abstract, Results, line 20: "The rate of hospitalization in our study was found to be 34.7%". Between how many patients? They had what severity of Covid-19 and Sarcoidosis?

Response

The hospitalisation rates have been modified to 48.1% by including case reports published till 14<sup>th</sup> august 2021. A total of 27 patients were included. Staging of sarcoidosis has been provided only for 3 patients.

4-INTRODUCTION, line 31: Please remove the name of "China" in the study to prevent any political impression and use the continent of "Asia" instead.

5-INTRODUCTION, line 36: Please add this phrase to the first sentence: In different



observed virus variants the most common symptoms ... .

6-Two heads of the age range (youth and elderly) may be asymptomatic patients or virus carriers.

7-INTRODUCTION, line 38: Two heads of the age range (youth and elderly) may be asymptomatic patients or virus carriers.

Response

Thank You for your comments, corrections have been made.

8-Investigations, line 77: SARS-CoV-2 RT-PCR test is not practicable in some forms of Indian virus variants.

Response- SARS-CoV-2 RT-PCR has been used as the modality of diagnosis in 48.1% of the patients identified in the reported case series/ case reports.

9-DISCUSSION: Please express all the predisposing factors of COVID-19 disease.

10-DISCUSSION, line 114 and Radiology, line 161: Please inform some of the readers of the CO-RADS classification.

Response: Thank you for your comments. The relevant sections have been modified.

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2<sup>nd</sup> Editorial decision  
25-Aug-2021

Ref.: Ms. No. JCTRes-D-21-00109R1

A review of the presentation and outcome of sarcoidosis in COVID-19  
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Sep 24, 2021.

To submit a revision, go to <https://www.editorialmanager.com/jctres/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger  
Editor-in-Chief

Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The comments have been addressed as suggested.

Could you please make the following modifications :

Line 65 : Remove non-English articles

Line 69 : (Figure 1 : Consort Diagram) should be moved below the figure 1.

Line 184 : Add 'and' before (Lymphocyte:neutrophil ratios).

Line 285 : Use one in every (three) patients instead of one in every (third) patient.

Line 290 : Add (it) in the sentence : those who did receive (it)

Reviewer #4: In the results section under clinical features, it needs to be made clear that the clinical features are referring to sarcoidosis; it is currently not very clear

What data are you using to make the conclusion that presentation of COVID-19 does not differ significantly in sarcoid vs nonsarcoid patients?

I would consider removing section on biomarkers as the studies you selected for review did not comment on use of biomarkers for prognostication

Reviewer #5: Hi and good day  
Dear Colleague,

I hope you are healthy and well. Thanks for your efforts. Your revised article is now acceptable for publication.

Good luck

Editor:

Please ensure that the manuscript conforms to academic level English and that all grammar/spelling/syntax mistakes are eliminated before resubmission. We uphold a strict policy in this respect. Thank you, Michal Heger, editor.

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Dr Michal Heger,  
Editor-in-Chief,  
Journal of Clinical and Translational Research

Date: August 26, 2021

Re: JCTRes-D-21-00109 Revision

Dear Editor,

Thank you for the time and consideration given to our manuscript. We are grateful for the careful thoughts from the reviewers that have made a significant impact to improve the quality of the manuscript. In the following pages we have attempted to respond to all the comments raised by the reviewers and the appropriate changes have been made in the manuscript as well.

**Amos Lal, M.B.B.S, M.D, FACP**

Assistant Professor, Mayo Clinic College of Medicine  
Division of Pulmonary, Critical Care and Sleep Medicine  
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RESPONSE

[Thank you for your comments. The necessary changes have been made.](#)

Reviewer #4: In the results section under clinical features, it needs to be made clear that the clinical features are referring to sarcoidosis; it is currently not very clear

What data are you using to make the conclusion that presentation of COVID-19 does not differ significantly in sarcoid vs non sarcoid patients?

RESPONSE

[Thank you for your comments. The necessary changes have been made. The most common symptoms noted in patients in our review were fever \(40.7%\), myalgia \(40.7%\) cough \(37%\), dyspnoea \(37%\), and decreased appetite \(18.5%\), which is similar to those noted in the general population. The article aims at an overall review of presentation and outcome of COVID 19 in patients with sarcoidosis.](#)

I would consider removing section on biomarkers as the studies you selected for review did not comment on use of biomarkers for prognostication

RESPONSE

[The section on biomarkers has been included to stress upon the similarities and differences in the levels of KL-6 and ACE respectively in Sarcoidosis and COVID-19. Based on your suggestion this section has been removed from the manuscript.](#)

Ref.: Ms. No. JCTRes-D-21-00109R2

A review of the presentation and outcome of sarcoidosis in COVID-19  
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger  
Editor-in-Chief  
Journal of Clinical and Translational Research

Comments from the editors and reviewers: