

Comparison of clinical and laboratory profile of pulmonary and extrapulmonary tuberculosis in children: A single-center experience from India

Sachin Singh, Madhuradhar Chegondi*, Swathi Chacham, Prawin Kumar, Jagdish Prasad Goyal

*Corresponding author

Madhuradhar Chegondi

Division of Pediatric Critical Care Medicine, Stead Family Children's Hospital- Department of Pediatrics, Carver, College of Medicine, University of Iowa, 8600-H 200 Hawkins Dr, Iowa City, IA, United States

Handling editor:

Michal Heger

Department of Pharmaceutics, Utrecht University, the Netherlands

Department of Pharmaceutics, Jiaying University Medical College, Zhejiang, China

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Comparison of Clinical and Laboratory Profile of Pulmonary and Extrapulmonary Tuberculosis in Children

Journal of Clinical and Translational Research

Dear Dr. Chegondi,

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 Jun 09, 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 article reported a study on paediatric tuberculosis in India, a retrospective study on children attended pediatric TB clinic of All India Institute of Medical Sciences, Rishikesh from August 2015 to July 2017. The aim of the study was to evaluate and compare the clinical and laboratory profile of pulmonary TB (PTB) and extrapulmonary TB (EPTB) in children and adolescents to evaluate and compare the clinical and laboratory profile. The argument is of interest, even if do not add any adjunctive information on the theme.

Some questions need to be answer

1. Most of the patients enrolled are female, would the author comment this datum? What about the young male in the same family? Is the female gender more prone to develop TB who need to be hospitalized?
2. The authors find MTB positivity on sputum (direct microbiological analysis or PCRO, do they check also other biological samples (blood, urine, feces?). Have the authors never think to a lymph node biopsy? If no, would they argument that?
3. TNT was used as test for TB diagnosis, but it is known that in BCG vaccinated subjects it would be falsely positive, would the author comment why the test has been used in vaccinated children? Why the authors read positive a test >10mm being India a country with an high TB incidence?
4. Usually, high GB is not related with TB, otherwise high platelets values has been related whit TB, do the authors find any correlation?
5. In table 2 the authors reported 'abnormal chest Xray' could the authors specified and detailed cavity, tree in bud aspect, ground glass or high density pulmonary areas did they find?
6. I think that a microbiology confirmation of lymphonodal or extra pulmonary TB needs a biopsy, it is obvious that pulmonary TB is more significantly and easy related to a microbiological confirmation in absence of a tissue biopsy in EPTB.
7. The article lack of treatment data. It could be useful for readers to no therapy approach in paediatric TB, duration of treatment, adherence to therapy and the outcome. The authors are asked to provide these information.

Reviewer #2: Dear Author,

Thank you for your kind invitation.

It is a well written manuscript about childhood tuberculosis. Although there are many epidemiologic studies in literature with similar results investigating the clinical and epidemiological impact of tuberculosis, to report the different clinical experiences can further contribute to childhood tuberculosis. Because, tuberculosis is still an important public health problem.

The article can be approved after minor revision of English grammar.

Reviewer #3: comments:

1. The title is misleading. It should clearly state that this study pertains to India (which has a much higher TB rate than many countries worldwide).
2. Poorly written. Many grammatical errors, inconsistent words/phrases and misspellings - pediatrics vs. paediatrics for example.
3. The majority of children (69%) received BCG vaccination. TST is not the preferred confirmatory test in those who have received BCG vaccination. TB blood testing is the preferred method. This is a major weakness of this study.
4. There is no clear delineation as to how many children were diagnosed microbiologically vs. clinically. This is a major weakness of this study.
5. The manuscript does not compare how many children were tested with microbiologic tests in relation to how many children had positive microbiologic tests (positivity rate of those tested).
6. I don't believe that this study adds any additional information that is not already published.

Reviewer #4: I have gone through the manuscript entitled, "Comparison of Clinical and Laboratory Profile of Pulmonary and Extra-pulmonary Tuberculosis in Children" carefully. It is a fair attempt but not at all presented clearly. The manuscript needs some revisions. There are some concerns which need to be addressed. The comments are given below :

1. There are mistakes at some points. These have been highlighted in yellow pop-up notes in the manuscript. Manuscript has been attached herewith.
2. Key words - Please provide the region of study. It is important.
3. There is no need to explain in detail about PTB and EPTB.
4. There is no space between the sentences. After the full-stop, there should be a space for another sentence.
5. Table needs to be arranged properly. In the table, % is given before the numbers. This is not the format. Usually number is given first and then percentage in parentheses, i.e., n (%).
6. Gender - there are no males but in the Discussion section, it is written that there is no significant difference among the gender.
7. Similarly, BCG scar, it is not clear which positive or negative.
8. References - The authors need to carefully cite the references.
9. Although relevant references have been cited but they are not uniform.
 - a) In some, there are all authors and in some et al has been given. Generally, et al is given after the 6th author.
 - b) Some of the references are very old. 1994, 1997, 2000, 2004. Plz. Cite recent ones.

Reviewer #6: The authors mention this as a retrospective observational study fro review of records. It needs to be specified what outpatient records were reviewed? In day to day practice, it is challenging to obtain all requisite details from review of OPD records. Was a structured format used? This needs to be elaborated

The introduction needs to be made more crisp and text reduced.
Some grammatical and linguistic mistakes which need to be corrected.

What new information is being added by this study needs to be highlighted.
What were the clinical outcomes of these patients?

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

Reviewer Comments & Responses

Dear Michal Heger, editor-in-chief, JCTR
We are very grateful to the Editors and Reviewers for their relevant comments that substantially improved the manuscript.

All comments have also been addressed in this point-by-point response and the changes are highlighted in yellow in the manuscript.

Thank you for giving us the opportunity to revise our manuscript.

Yours sincerely,

Dr. Madhuradhar Chegondi and Dr. Jagdish Goyal, on behalf of the authors

Reviewer #1: The article reported a study on paediatric tuberculosis in India, a retrospective study on children attended pediatric TB clinic of All India Institute of Medical Sciences, Rishikesh from August 2015 to July 2017. The aim of the study was to evaluate and compare the clinical and laboratory profile of pulmonary TB (PTB) and extrapulmonary TB (EPTB) in children and adolescents to evaluate and compare the clinical and laboratory profile. The argument is of interest, even if do not add any adjunctive information on the theme. Some questions need to be answer.

Comment 1: Most of the patients enrolled are female, would the author comment this datum?

What about the young male in the same family? Is the female gender more prone to develop TB who need to be hospitalized?

Response: We thank the reviewer for his/her comment.

The following sentence has been added in the discussion.

“In our study, there was female preponderance. A similar finding was also observed in children and adolescents with drug-resistant TB from another study from India.²⁰ In India, especially in rural areas, gender inequality still exists in many social aspects including health care access. Our cohort’s predominant female gender might be explained by the lack of early medical attention seeking by the parents and tertiary care center referral when severely ill. However, our cohort doesn’t represent the community gender distribution for childhood TB. Moreover, our data are limited by a small sample size and retrospective/missing data.

Comment 2: The authors find MTB positivity on sputum (direct microbiological analysis or PCRO, do they check also other biological samples (blood, urine, feces?). Have the authors never think to a lymph node biopsy? If no, would they argument that?

Response: As per WHO and Revised National Tuberculosis Control Program (RNTCP) guidelines for children, we usually do not check biological samples like blood, urine, and feces. These samples are being used only for research purposes at selected Centres in our country. Moreover, the diagnostic yield with a biological sample is very low. We used body secretion such as pleural fluid, CSF and surgical specimen such as LN biopsy sample in EPTB patients. One patient in the EPTB group was microbiologically confirmed based on LN biopsy specimen CBNAAT/AFB positive.

We have made changes accordingly in the method section of our manuscript.

Comment 3: TST was used as test for TB diagnosis, but it is known that in BCG vaccinated subjects it would be falsely positive, would the author comment why the test has been used in vaccinated children? Why the authors read positive a test >10mm being India a country with a high TB incidence?

Response: We agree with the reviewer that TST may be falsely positive in BCG vaccinated. However, the Working Group on Tuberculosis, Indian Academy of Pediatrics (IAP) recommended TST positive if the induration is 10 mm or more irrespective of BCG status. In addition, existing literature suggests minimal effect on PPD reaction with the prior BCG vaccination.

We have included this in the discussion section.

Comment 4: Usually, high HGB is not related to TB, otherwise high platelets values has been related whit TB, do the authors find any correlation?

Response: Thank you for highlighting this interesting observation. We did not find any correlation between PTB or EBTB with HB or high platelet counts.

Comment 5: In table 2 the authors reported 'abnormal chest Xray' could the authors specified and detailed cavity, tree in bud aspect, ground glass or high density pulmonary areas did they find?

Response: We considered TB suggestive if X-ray showed hilar lymphadenopathy or cavity or miliary TB. Tree in the bud, ground glass, or HAM is findings are more specific to the CECT chest. We did not perform CECT chest in TB children as a routine as per RNTCP guidelines. The abnormal X-ray findings have been added in Table 2.

Comment 6: I think that a microbiology confirmation of lymphonodal or extra pulmonary TB needs a biopsy, it is obvious that pulmonary TB is more significantly and easy related to a microbiological confirmation in absence of a tissue biopsy in EPTB.

Response: We agree with the reviewer. The same has been clarified in comment 2, and changes have been made accordingly.

Comment 7: The article lack of treatment data. It could be useful for readers to no therapy approach in paediatric TB, duration of treatment, adherence to therapy and the outcome. The authors are asked to provide this information.

Response: We thank the reviewer for his kind suggestion to improve our manuscript. The suggestions have been incorporated into the manuscript, and we have updated treatment data in the results section as follows-

All patients received Isoniazid, rifampicin, pyrazinamide, and ethambutol for two months in the intensive phase, while Isoniazid, rifampicin, and ethambutol for four months in the

continuation phase. However, one patient with TB meningitis received the continuation phase for ten months as per the RNTCP guideline. More than 90% of patients were compliant with the treatment. The most common cause of non-compliance was gastrointestinal upset. There was no mortality among study participants. However, we found post-treatment sequelae in around 50% of patients in the form of fibrosis, loss of lung volume, and pleural thickening.

Reviewer #2: Dear Author,

Thank you for your kind invitation.

It is a well written manuscript about childhood tuberculosis. Although there are epidemiologic studies in literature with similar results investigating the clinical and epidemiological impact of tuberculosis, to report the different clinical experiences can further contribute to childhood tuberculosis. Because tuberculosis is still an important public health problem.

The article can be approved after minor revision of English grammar.

Response: We thank the reviewer for encouraging comments. We have edited the entire manuscript and addressed all the grammatical issues and highlighted in the manuscript.

Reviewer #3: Comments:

Comment 1: The title is misleading. It should clearly state that this study pertains to India (which has a much higher TB rate than many countries worldwide).

Response: We have changed the title as per the reviewer's suggestion to the following: "Comparison of Clinical and Laboratory Profile of Pulmonary and Extrapulmonary Tuberculosis in Children: A Single Center Experience from India".

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Comment 2: Poorly written. Many grammatical errors, inconsistent words/phrases and misspellings - pediatrics vs. paediatrics for example.

Response: We apologise for the grammatical errors. We have gone through the entire manuscript line by line made corrections accordingly.

Comment 3: The majority of children (69%) received BCG vaccination. TST is not the

preferred confirmatory test in those who have received BCG vaccination. TB blood testing is the preferred method. This is a major weakness of this study.

Response: We thank the reviewer for this comment. We neither used TST for confirmatory test nor any patient was diagnosed based on TST only. TST was used as supportive evidence for TB. Clinically diagnosed cases were defined based on symptoms, suggestive radiology, and positive tuberculin skin test (TST) results. Moreover, a comparison of TST and IGRA in the diagnosis of latent tuberculosis infection in a high TB-burden setting concluded TST remains the most preferred method for LTBI diagnosis in resource-limited, high TB-burden settings.

Ref: Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in Diagnosis of Latent Tuberculosis Infection in a High TB-Burden Setting. PLoS One. 2017;12(1):e0169539. Published 2017 Jan 6. doi:10.1371/journal.pone.0169539

Comment 4: There is no clear delineation as to how many children were diagnosed microbiologically vs. clinically. This is a major weakness of this study.

Response: Table 2 showed that out of 33 PTB cases, 18 cases were microbiologically confirmed and 15 were clinically diagnosed. In comparison, out of 25 EPTB cases, only one child was microbiologically confirmed. We have included the following in the results section.

“Microbiological confirmation of TB was possible in 54% of patients with PTB and only in 4% of EPTB patients.”

Comment 5: The manuscript does not compare how many children were tested with microbiologic tests in relation to how many children had positive microbiologic tests (positivity rate of those tested).

Response: We apologize for not being clear on this. We tested a total of 58 children and out of which 19 were tested positive. The same data has been shown in Table 2.

Comment 6: I don't believe that this study adds any additional information that is not already published.

Response: Although few previous studies published in the past, TB is still a major public health problem with significant geographic variability in disease burden. The report of different clinical experiences and outcomes can further contribute to understanding childhood

TB because of its paucibacillary nature and difficulty in diagnosis.

Reviewer #4: I have gone through the manuscript entitled, "Comparison of Clinical and Laboratory Profile of Pulmonary and Extra-pulmonary Tuberculosis in Children" carefully. It is a fair attempt but not at all presented clearly. The manuscript needs some revisions. There are some concerns which need to be addressed. The comments are given below:

Comment 1: There are mistakes at some points. These have been highlighted in yellow pop-up notes in the manuscript. Manuscript has been attached herewith.

Response: Thank you so much for highlighting the mistake. We appreciate your inputs. We have made changes accordingly.

Comment 2: Key words - Please provide the region of study. It is important.

Response: Thank you. We have added "India" to the title and to keywords.

Comment 3: There is no need to explain in detail about PTB and EPTB.

Response: The same has been deleted.

Comment 4: There is no space between the sentences. After the full-stop, there should be a space for another sentence.

Response: Thank you. We have corrected the same though out the manuscript.

Comment 5: Table needs to be arranged properly. In the table, % is given before the numbers. This is not the format. Usually number is given first and then percentage in parentheses, i.e., n (%).

Response: We have corrected the table as per your suggestion.

Comment 6: Gender - there are no males but in the Discussion section, it is written that there is no significant difference among the gender.

Response: In our study, there was female preponderance since 75% were female in both PTB and EPTB. We have added a sentence in the discussion regarding this contrasting finding.

Comment 7: Similarly, BCG scar, it is not clear which positive or negative.

Response: Thank you for highlighting this. We have corrected the same.

Comment 8: References - The authors need to carefully cite the references.

Response: We have rechecked the references and changes were made accordingly.

Comment 9: Although relevant references have been cited but they are not uniform.

a) In some, there are all authors and in some et al has been given. Generally, et al is given after the 6th author.

Response: We apologise for the inconsistent reference style. We have cited the references uniformly.

b) Some of the references are very old. 1994, 1997, 2000, 2004. Plz. Cite recent ones.

Response: We have removed old references and cited new references.

Reviewer #6:

Comment 1: The authors mention this as a retrospective observational study fro review of records. It needs to be specified what outpatient records were reviewed? In day to day practice, it is challenging to obtain all requisite details from review of OPD records. Was a structured format used? This needs to be elaborated

Response: In the pediatric TB clinic, we use a structured format to collect information. We included the following sentence in the methods-

“We have used our pediatric TB clinic structured format to collect the study variables.”

Comment 2: The introduction needs to be made more crisp and text reduced.

Response: Thanks. We have reduced the text in the introduction as per your suggestion and highlighted the deleted part.

Comment 3: Some grammatical and linguistic mistakes which need to be corrected.

Response: Thank you. The grammatical and linguistic mistakes have been corrected with the help of English language software and a language expert.

Comment 4: What new information is being added by this study needs to be highlighted.

Response: We have highlighted the same in the conclusion.

Comment 5: What were the clinical outcomes of these patients?

Response: Thank you. We have added the outcome at the end of the result as follows-

“There was no mortality among study participants. However, we found post-treatment sequelae in around 50% of patients in the form of fibrosis, loss of lung volume, and pleural thickening.”

2nd Editorial decision
07-Jun-2021

Ref.: Ms. No. JCTRes-D-21-00005R1
Comparison of Clinical and Laboratory Profile of Pulmonary and Extrapulmonary
Tuberculosis in Children
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:

Reviewer #2: Dear Editor,

Thank you for your kind invitation.

It is a well written manuscript about childhood tuberculosis. Tuberculosis is still an important public health problem. So, the manuscript can be approved.

Reviewer #4: The authors have incorporated the suggestions very well in the manuscript.