

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The risk factors of drug resistant tuberculosis, the association between comorbidity status and drug resistant patterns: a retrospective study from previously treated pulmonary tuberculosis in Shandong, China, during 2004-2019
AUTHORS	Tao, Ning; Li, Yi-fan; Song, Wan-mei; Liu, Jin-yue; Zhang, Qian-yun; Xu, Ting-ting; Li, Shi-jin; An, Qi-qi; Liu, Si-qi; Li, Huai-chen

VERSION 1 – REVIEW

REVIEWER	Melkamu Merid Mengesha Arba Minch University, School of Public Health, Epidemiology and Biostatistics Unit
REVIEW RETURNED	06-Oct-2020

GENERAL COMMENTS	<p>The authors reported an interesting finding from a large study on drug resistance among retreated PTB cases in Shandong Province in China. I reviewed this paper with interest and wanted to raise the following issues for the authors' consideration.</p> <ol style="list-style-type: none">1. The authors in their title emphasized only the association of comorbidity with DR-TB while they have found different factors that even had a strong association with DR-TB. It would be good to justify this or correct the title.2. The abstract in general did not present a few details about how the outcome was measured, what exposure variables were considered, and the models used for analysis. I suggest including this as far as the journal style allows so that readers will understand the results better.3. The same results for the effect estimates (e.g OR for comorbidity) were repeated in the results section. It also not clear if the authors run different models for the DR types (this was not mentioned in the document).4. Under the subtitle "Laboratory diagnosis and drug susceptibility testing", the statement starting with 'the distinguish of MTB from other...' is not clear to understand.5. The results in the second paragraph under the subtitle "case estimates and risk factors of DR-TB" was repeated somewhere else in the same results section, see association between 'comorbidity and DR profiles of retreated PTB' subsection.6. Starting with the second paragraph, the discussion seems the introduction section. please check this and focus on discussing on the consistency of the results and also implications of the findings.
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REVIEWER	Dr Norbert NDJEKA National TB Programme-RSA National Department of Health Republic of South Africa
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REVIEW RETURNED	30-Nov-2020
GENERAL COMMENTS	Thank you for submitting a well-written paper. The abstract is complete. The study objective appears to have been achieved. The findings regarding the association between co-morbidity and DR-TB are clearly presented. However, the use of microscopy (ZN) for TB diagnosis is also a limitation just like the lack of DST. It is not clear in the paper as to what is the burden of HIV in Shandong and in China. The standard of written English is generally fine but there are a few errors that need your attention. Example on page 9 of 25, Line 12 you stated ...was supervise...It should be supervised. On page 16 of 25 Line 43, you stated ... higher to be death..It should higher to die...Line 51 ...and view all TB patients as a whole...should say "Viewed"....

VERSION 1 – AUTHOR RESPONSE

Replies to Reviewer #1:

The authors reported an interesting finding from a large study on drug resistance among retreated PTB cases in Shandong Province in China. I reviewed this paper with interest and wanted to raise the following issues for the authors' consideration.

1. The authors in their title emphasized only the association of comorbidity with DR-TB while they have found different factors that even had a strong association with DR-TB. It would be good to justify this or correct the title.

Answer: Thank you for the advice. We have revised the title as following **“The risk factors of drug resistant tuberculosis, the association between comorbidity status and drug resistant patterns: a retrospective study from previously treated pulmonary tuberculosis in Shandong, China, during 2004-2019”**.

2. The abstract in general did not present a few details about how the outcome was measured, what exposure variables were considered, and the models used for analysis. I suggest including this as far as the journal style allows so that readers will understand the results better.

Answer: we have rewritten the abstract in detail. (lines 28-59)

3. The same results for the effect estimates (e.g OR for comorbidity) were repeated in the results section. It also not clear if the authors run different models for the DR types (this was not mentioned in the document).

Answer: yes, part of the results for the effect of comorbidity on **DR-TB were repeated**. We deleted the repeated results.

The section of **“Statistical analysis”** elaborated the statistic methods. (lines 182-199)

Univariable analysis and multivariable logistic models were applied to identify the risk factors of drug-resistance among newly treated or retreated PTB cases. The associated results were shown in Figure 1 and elaborated under the section of **“Case estimates and risk factors of DR-TB”**

(paragraph two, lines 208-214). We found that comorbidity was a risk factor of DR-TB among retreated PTB cases.

To specific the effects of comorbidity on different DR types, such as mono-resistant tuberculosis, polydrug resistant tuberculosis, MDR-TB, .etc. Multivariable logistic models were used to estimate the influence of comorbidity on different DR types with the covariates adjusted by age, sex, BMI, drinking history, smoking history, and cavity according to published researches. The associated results were shown in Figure 5 and elaborated under the section "**Association between comorbidity status and DR profiles of retreated PTB**". (lines 253-260)

4. Under the subtitle "Laboratory diagnosis and drug susceptibility testing", the statement starting with 'the distinguish of MTB from other...' is not clear to understand.

Answer: this study only included patients with mycobacterium tuberculosis (MTB) infection, nontuberculosis mycobacteria (NTM) infection were excluded. After conventional biochemical testing (p-nitrobenzoic acid and 2-thiophene carboxylic acid hydrazide testing), the identified *Mycobacteria spp.* were further tested by 16S rRNA gene sequence analysis to the species level in China. Thus, *M. tuberculosis* was distinguish from NTM strains. We have rewritten this sentence as "The identification of *M. tuberculosis* were comprehensive considerations of results according to p-nitrobenzoic acid and 2-thiophene carboxylic acid hydrazide testing and 16S rRNA gene sequence analysis." (lines 150-153)

5. The results in the second paragraph under the subtitle "case estimates and risk factors of DR-TB" was repeated somewhere else in the same results section, see association between 'comorbidity and DR profiles of retreated PTB' subsection.

Answer: yes, part of the results for the effect of comorbidity on **DR-TB were repeated**. We deleted the repeated results.

6. Starting with the second paragraph, the discussion seems the introduction section. please check this and focus on discussing on the consistency of the results and also implications of the findings.

Answer: we rewrote the section of "**Dicussion**". (lines 262-345)

Replies to Reviewer #2:

Thanks for your positive comments for our study conception and we are greatly inspired by your affirmation to our work.

Thank you for submitting a well-written paper. The abstract is complete. The study objective appears to have been achieved. The findings regarding the association between co-morbidity and DR-TB are clearly presented. However, the use of microscopy (ZN) for TB diagnosis is also a limitation just like the lack of DST. It is not clear in the paper as to what is the burden of HIV in Shandong and in China.

Answer: yes, the use of microscopy (ZN) for TB diagnosis is also a limitation. We added “The diagnosis of TB based on microscopy inevitably underestimated the burden of TB.” in the section under “**Strengths and limitations of this study**”. (lines 67-68)

We also added some information of HIV in Shandong and in China. (lines 320-328)

The standard of written English is generally fine but there are a few errors that need your attention. Example on page 9 of 25, Line 12 you stated ...was supervise...It should be supervised. On page 16 of 25 Line 43, you stated ... higher to be death..It should higher to die...Line 51 ...and view all TB patients as a whole...should say "Viewed"....

Answer: thank for your suggestion, we have revised these sentences according to you suggestion. (line 163, 312, 315)

VERSION 2 – REVIEW

REVIEWER	Melkamu Merid Mengesha Arba Minch University, School of Public Health, Epidemiology and Biostatistics Unit
REVIEW RETURNED	06-Jan-2021
GENERAL COMMENTS	I have no further comments. The authors responded and corrected all my concerns raised in the previous submission.