Author’s response to reviews

Title: Acute Biliary Events During Anti-Tuberculosis Treatment: Hospital Case Series and Nationwide Cohort Study

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Responses to Reviewer #1

Major Comments:

1. Some statistical methods and some p values calculated are not correct. For numbers <5, Fisher exact test should be used rather than chi-square test. The t-test part, which I cannot recalculate, also need careful calculations.

Answer: We thank for reviewer’s instructive comment. I am sorry about we did not mark which item was compared by Fisher exact test, and which by chi-square test. We have added an annotation for the categorical variables and rechecked the p-value for continuous variables. Thank you.

2. Although statistically significant, the RR of age (1.02-1.04) was no higher than 1.0. Therefore, the conclusion that age is a major risk factor for ABEs is not clinically convincible.

Answer: Thank you for the reminder. We agree with the reviewer that the RR for per-year increment in age is too small to convince the reader that age does matter. In the revised
manuscript, we calculate the RR for per-10-year increment in age (RR: 1.32 [1.21-1.44]) (Page 6, Para 3, Line 34 and Page 17, Para 3, Line 58). Thank you for the comment.

Minor Comments:

1. The language needs corrections before being published.

Answer: Thank you for the suggestion. Prior to this submission, we have had our manuscript reviewed by a native English editor.

Responses to Reviewer #2

Major comments

1. Formation of gall stones (Cholelithiasis) is a gradual process which takes years to form. It is hard to believe that it happens within 4 weeks of anti-TB treatment. Possibility is that person is already having Cholelithiasis without symptoms and it might become evident due to assault caused by anti-TB drugs to TB patient.

Answer: Thank you for the comment. We totally agree with the reviewer that patients who developed acute biliary event are likely to have asymptomatic cholelithiasis before anti-TB treatment. When treatment begins, isoniazid and rifampin may inhibit the bile salt export pump and accelerate the formation of cholesterol stone using the previous asymptomatic stone as nucleus, resulting in a higher risk of ABE (Page 21, Para 1, Line 1-14). Because neither abdominal sonography nor computed tomography (CT) is routinely performed prior to starting anti-TB treatment, only a prospective study can confirm this finding and explore the natural course. However, in case 3 of the study, the result of CT with a slide thickness of 5 mm and an interval of 1.2 mm prior to anti-TB treatment showed no cholelithiasis. The gallstones were later demonstrated by abdominal echo 2 weeks after anti-TB treatment. Therefore, the risk of new onset of cholelithiasis under anti-TB drugs may still presents.

2: Authors have mentioned the incidence of hepatotoxicity in Taiwan, what is the incidence in world population according to WHO. Authors can consider mentioning it in the manuscript?

Answer: Thank you for your thoughtful comment. Although we tried to use the WHO standard population distribution to calculate the worldwide incidence of hepatotoxicity, we did not get the
data of hepatotoxicity incidence risk according to age distribution. So we use the data from the American Thoracic Society (ATS) documents published in 2006. The risk of drug induced liver injury in treat active TB is around 5% to 33%. We have revised our manuscript accordingly (Page 7, Para 2, Line 39~43).

3: Authors can mention 2016 TB report instead of 2014 in the first paragraph of introduction. There were 1.8 millions deaths due to TB in 2016.
Answer: Thanks for the suggestion. We have revised our manuscript accordingly (Page 7, Para 1, Line 4~14).

4: Authors can consider including ethics statement as separate heading in materials and methods section.
Answer: Thanks for the suggestion. We have revised the ethics statement accordingly (Page 9, Para 2, Line 29~43).

5: Between 2010 and 2015, Total of 3936 patients (2704 patients at National Taiwan University Hospital + 982 patients at Hsinchu Branch = 3686 patients). 3936-3686 = 250 patients. What about the missing 250 patients. Authors can check the numbers
Answer: Thanks for the careful review. Our laboratory is the contract laboratory of other hospitals, especially about TB examination. The missing 250 patients received anti-TB treatment at the other hospitals and their respiratory samples were sent to our hospital for examination. We apologize for this mistake and have corrected it in the revised manuscript (Page 10, Para 2, Line 14~43).

6: Definition of ABE should come before identification of ABE in hospital based cohort study in materials and methods section.
Answer: Thank you for the nice suggestion. We have revised our manuscript accordingly (Page 9, Para 3, Line 55~ Page 10, Para 1, Line 8).
Why only 4 cases were chosen for detailed report.

Answer: We are sorry about the mis-understanding. In the hospital-based cohort, a total of 4 cases with ABE during anti-TB treatment was identified among the 3686 patients with pulmonary TB in the study period. So in the first part of the study, the detailed clinical course of the 4 patients were reported.

Table 2: Authors can mention optimum levels of ALT and bilirubin in healthy people in brackets

Answer: Thank you for the suggestion. We have added the optimum levels of ALT and bilirubin in Table 2.

Authors can add AST data also to Table 2.

Answer: We have added the peak AST data and the normal range of AST in Table 2. Thanks for the suggestion.

Case 1: In text it was mentioned 1 week post TB treatment and in table 2 it is mentioned 2 weeks. Authors need to check and correct. Case 2: In text it was mentioned 4 week post TB treatment and in table 2 it is mentioned 5 weeks. Authors need to check and correct. Case 3: In text it was mentioned 2 week post TB treatment and in table 2 it is mentioned 3 weeks. Authors need to check and correct.

Answer: We are sorry for the ambiguous descriptions. What we want to say is that: the next week after “n” weeks is the “n+1”th week. We have unified the presentation style in Table 2.

Authors need to check ALT levels mentioned for case 2 in text and Table 2. Numbers are not matching. Authors need to check ALT, bilirubin levels mentioned for case 3 (after TB treatment) in text and Table 2. Numbers are not matching. Authors need to check bilirubin levels mentioned for case 4 (after TB treatment) in text and Table 2. Numbers are not matching.

Answer: We apologize for the confusion. The numbers in the text were the abnormal data during important clinical events (when the clinician found acute biliary event, ordered examinations, or started intervention), whereas the numbers in Table 2 were the peak levels of abnormal liver function. Thank you for the clarification.
12: Why 19 weeks for onset of ABE was mentioned in case 4 (table 2). I understand that these 4 cases of ABE occurred within 4 weeks of Anti-TB drug treatment.

Answer: We apologize for the mistake. We have corrected it in the revised manuscript (Page 6, Para 2, Line 12~17). Thank you for the reminder.