Author’s response to reviews

Title: Incidence rates of tuberculosis in chronic hepatitis C infected patients with or without interferon based therapy: a population-based cohort study in Taiwan

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Author’s response to reviews:

Dear Editor,

A point-by-point response to the peer reviews of our original manuscript, # MS: 4705416191378548, is presented in this reply letter according to the reviewers’ comments and suggestion. All authors have read and agreed to the re-submitted version of the manuscript. The reviewers’ queries and suggestions are addressed item by item as follows, highlighted in Bold format:

We do appreciate the reviewer’s comments and suggestion to improve the manuscript. Many thanks.

Major Compulsory Revisions
(which the author must respond to before a decision on publication can be reached)

1. I still think that the paragraph staring with line 184 should be clarified (even though you have attempted to explain in response 4b). You have defined the non-treated cohort as 7587 patients who did not receive IPT. Then, you say you randomly selected 2460 control subjects. First, you need to say that you selected the control subjects FROM the non-treated cohort. Second, the selection was NOT random even though you say it was – in fact, you have selected control subjects by matching (by age, sex, and year/month of visit) to the IBT treated cohort. This is not random. You say that the control subjects were matched with the non-treated cohort, even though the control subjects were matched (non-randomly) to the TREATED cohort. You should say that 95.98% of the IBT
treated subjects were matched at a ratio of 1:4 with the non-treated cohort – not
that 95.98% of the control subjects were matched at a ratio of 1:4 with the
non-treated cohort.

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This selection was not random and we revised this sentence as reviewer’s
comments. Thanks for reviewer’s kind comments!
P11 line 199-202

2. You have added AHRs in the abstract but you still refer to incidence. Why?
Why not say hazard? Also, it might be advisable to stay away from ascribing
“significance” to your results merely based on the confidence interval (what I
assume you are doing). There is no notion that the AHR of 2.81 has any
meaning… you just say that it is not significant. One could argue that this is an
effect that communicates both magnitude and directionality, but one that suffers
from less than optimal precision (due to low numbers of events, e.g.). Instead it is
just dismissed as not significant, and it is concluded that IBT is not a risk factor.
What might you expect if you had a greater sample size? Are you really sure that
IBT is not a risk factor, or might your data be limited in their ability to isolate its
effects? I would at least qualify your main conclusion.

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a. We revised the conclusion as reviewer’s recommendation.
P4 line 67-69, P19,20 line 360-362

b. We added the discussion the meaning of AHR of 2.81 (95% CI: 0.61–12.98) in
this article.
P18 line 332-336

3. In response 14 (and in the paper), you say that you excluded patients who
were less than 20 years old. Why not clarify that you took those who were 20 or
older from the sample of one million (sampled from the 24 million), so the reader
doesn’t think (as I did) that the sample of one million was drawn from the subset
of the 24 million that was over 20 years old?

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We revised this sentence according to reviewer’s comments.
P 9 line 153,154

4. You have given the information requested in response 15, but why not add this
to the paper? It would help to clarify what you did – the reader might very well
have the same questions that I did.

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Thanks for reviewer’s recommendation. We added these sentences to make readers easily to understand the definition of diseases from this database. P9 155-167

5. Looking at your response 16, I don’t think you understand my comment. My point is that you define HCV infection (line 153) as “individuals who had at least two service claims of ambulatory or inpatient care for the treatment of HCV between 2000 and 2008.” Then below you say “A total of 12,547 subjects with an HCV infection were identified.” So, the reader logically would think that you have found 12,547 individuals who had at least two service claims of ambulatory or inpatient care for the treatment of HCV between 2000 and 2008. But no – you have actually found 12,547 individuals WITH HEPATITIS C VIRUS and only subset of those had two service claims. So, do not define INFECTION as having two service claims. Can you clarify this?

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Thanks for reviewer’s comment! To clarify this, we revised this sentence as “A total of 12,547 subjects with ICD-9-CM codes of HCV were identified.” P9 line 170

6. Re: comment 17: You didn’t really address my questions in the response or in the paper. I still think it would be good to clarify what happened when TB was diagnosed AT THE SAME TIME as HCV was treated – were these cases removed? I still don’t know. Also I asked whether you were talking about HCV treatment rather than diagnosis, and you didn’t change anything in the paper (it still says diagnosis). But you are not talking about diagnosis with HCV; you are talking about treatment for HCV – right? I have the same comment on response 18.

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a. Yes, these cases were excluded and we revised this sentence in P 10 line 173,174.
b. Yes, we are talking about HCV treatment, not HCV diagnosis.

To clarify it, we revised “…HCV diagnosis…” to “…HCV diagnosis coding…” P 10 line 175 and line 189

7. Re: response 18b: Thanks for the explanation, but I think it would be good to
explain in the paper (if possible) why these 77 were excluded; other readers may have the same question that I did.

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We add these statements in P 10,11 line 189-195

8. Re: responses 20 and 21: It is still not clear to me how you are calling it random sampling of controls if you are matching by age, sex, and visit timing. You say “We randomly selected 2460 control subjects.” If you randomly selected from the 7587, how did they match on those characteristics? I really think this needs to be clarified; readers will have the same question. In the paper, you should also justify the decision to match based on the groups not being comparable, as you have in the response.

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Thanks for reviewer’s kind comments, we deleted “…randomly…” and revised this sentence as “We selected 2,460 control subjects from…”

P 11 line 199

9. Re: response 22: I still think it is confusing to say that you allowed for at least a 1-year follow-up period even though individuals did not necessarily have one year of follow-up (due to death, TB diagnosis, drop out, etc.)

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Sorry for this confusing sentence and we modified this sentence. Many thanks

P11 line 208,209

We do competing risk analysis (including death), as following. There was no obvious difference in both models.

10. Re: response 23: OK, but can you at least acknowledge in the discussion that you’re not really looking at TB incidence? You’re looking at TB treatment which may be a proxy (or best possible approximation based on available data) of TB incidence.

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Thanks for reviewer’s kind comments. We added the limitation about the definition of TB in this study in the section of discussion.

P18,19 line 346-351

11. Re: response 23: Thanks for giving the references in the response, but I think you should give the references in the paper to substantiate your statement that
these factors need to be accounted for.

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We assumed reviewer’s comments were about “Re: response 24” Then we cited references to substantiate these statements.

a. For covariate factors reference:

  - P13 line 236

b. Because IBT is used with caution in patients with cirrhosis and is contraindicated in patients with decompensated liver disease, we clarified the etiology and severity of liver disease by ICD-9 codes to adjusted these situations by multivariate-adjusted Cox proportional hazards mode. For this we cited reference:

  - P13 line 240

12. Re: response 26: OK, so if you’re not talking about DETECTION, don’t say detection. Say “The end point of follow-up in the subjects developing was the date of 1) having taken two anti-TB medications for more than 90 days, and 2) having a TB-specific ICD-9 code. Do you see why I am confused about you calling it DETECTION? That implies identification of the organism. Re: “coded by the date of their last visit” – this must be a language issue. I think maybe you should just say “those lost to follow-up were censored on the date of last visit” if this is the case.

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We revised these sentences according to reviewer’s comments, P 14 line 253-256

Many thanks!

13. Re: response 27: I still think it would be nice to say how covariates were CODED (e.g., were all binary?)

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Covariates included all variables shown in Table 1, in which diseases were coded as yes/no and defined by ICD-9-CM codes.

P13 line 245,246

14. Re: response 35c: Why not add this explanation to the paper? Also, my main point is that you (arguably) used a stringent definition of TB (i.e., treatment with
two drugs). I was hoping you could speculate in the discussion on how your results may have been impacted if you would have used a different definition if the data were available (i.e. identification of the organism, a clearer reflection of incidence). This is also my point in comment 42.

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Thanks for reviewer’s comments
We added the explanation in the section of “The definition of active TB” in P12 219-227
Then, we discuss the possible impact with this definition of active TB in P 19 line 346- 351.

Minor Essential Revisions
(such as missing labels on figures or the wrong use of a term which the author can be trusted to correct)

1. Thank you for adding the sentence to the abstract. But it does not make sense to say “to estimate the hazard ratio OF RATE OF active TB.” Just say “Cox proportional hazards models were used to estimate hazard ratios (HR) for active TB, and associated confidence intervals (CIs), comparing IBT to no IBT.” Or write something similar to that.

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Thanks for reviewer’s kind comments, we modified this sentence as recommendation.
P3 line 53-55

2. Line 234: Say hazard not risk.

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We revised “risk” to “hazard ratio”.
P14 line 258