Author’s response to reviews

Title: Treatment outcomes and factors affecting treatment outcomes of new patients with tuberculosis in Busan, South Korea: A retrospective study of a citywide registry, 2014-2015

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# Because our `Responses to the Editor and Reviewers` includes some tables, and it is impossible to add tables to this comments section,

we have also attached .DOC file as supplementary document. Please refer to attached file.

Responses to the Editor and Reviewers

Dear editor and reviewers,

We appreciate your thorough review and constructive comments, which helped us to revise and improve the manuscript. Our point-by-point responses to your comments are listed below. We hope that you are satisfied with our responses and with the revised manuscript.

Reviewer reports:

Majid Marjani (Reviewer 1): An interesting study about treatment outcome of TB patients in the Busan, south Korea.
1. In the abstract, the part of "results" is needed to rewrite. It is somewhat vague. For example: "notified as having TB twice or more", "being in quantile Q4 and Q5".....

[Response] We have changed “notified as having TB twice or more” to “registered as TB-positive at least twice.” Q4 and Q5 refer to the fourth and fifth quintiles, respectively, of the regional deprivation index values. We have revised the results section of abstract as follows (page 2):

Results: A total of 4,732 patients were included in this study (mean age, 52.5 ± 19.9 years; 58.4% male). The overall treatment success rate was 83.9% (cured, 20.2%; completed, 63.7%); 8.0% of patients died, and 3.6% were lost to follow-up. In multivariate analyses, a higher rate of loss to follow-up was associated with foreign nationality, registered as TB-positive at least twice, and being in Q4 (fourth quintile) or Q5 (fifth quintile) of the regional deprivation index. Conversely, a lower rate of loss to follow-up was associated with female gender, smear-positive for pulmonary TB (PTB), and the treatment outcome being reported by a public health centre. Higher mortality was associated with old age (≥ 75 years), smear-positive PTB, treatment outcome being reported by the hospital, and being registered as TB-positive twice. Lower mortality was associated with female gender, treatment outcome being reported by a public health centre or clinic, and Q5 of the regional deprivation index.

2. What's the meaning of: .... We used the raw data to determine the final treatment outcome. (P6L22)

[Response] If patients are transferred to other hospitals during TB treatment, they are again notified by that hospital; thus, they have at least two treatment outcomes. If their latest treatment outcomes were "not evaluated," we searched for other treatment outcomes in the raw notified data. For example, if a patient’s treatment outcomes were “lost to follow-up” and “not evaluated,” we selected “lost to follow-up” as the final treatment outcome. We have revised the manuscript as follows (page 6, lines 135-138):

For patients who were registered as TB-positive more than once, we selected the latest treatment outcomes. However, if the latest treatment outcomes were “not evaluated,” we examined the notified raw data of each patient and, if possible, selected treatment outcomes other than “not evaluated.”

3. Definition of "cure" is problematic: "who was smear or culture- negative in the last ......" (P6L44). As you said smear negative, culture positive case in the last month is grouped as cured case (I group him as failure).
For the 2014 cohort, the treatment outcomes were defined according to those of the WHO (see the table below). In the WHO definition, “cured” is defined as “…who was smear- or culture-negative…”

[Table - WHO. Definitions and reporting framework for tuberculosis - 2013 revision]

However, in 2015 (for the 2015 cohort), the Korean CDC revised the definitions of treatment outcomes, such that only culture results (not smear results) were included in the definition of “cured.” We have added the following explanation to the revised manuscript (page 7, lines 154-156):

In 2015, the KCDC revised the definition of “cured” by eliminating the smear criterion. Thus, in the 2015 cohort, the treatment outcome “cured” was evaluated based only on culture results.

4. Just 38.8% of pulmonary TB cases had positive smear results (P7-L56). It is lower than standard. Sensitivity of sputum smears for diagnosis of TB is about 60-70%. How do you interpret this finding. Does it mean high proportion of empirical therapy (not confirmed cases)?

[Response] We agree. The smear- and culture-positive rates of TB patients are about 40% and 70%, respectively, in Busan as well as in the rest of South Korea. This positive smear rate is lower than that in the rest of the world, likely due to the mandatory medical check-up programs in S. Korea. S. Korea is an intermediate TB-burden country (formerly a high TB-burden country); thus, medical check-ups, including for TB, are frequently required when starting a new job, entering the military, and so forth. As a result, asymptomatic TB patients whose bacillary burden is low are often diagnosed with TB in the early phase of disease. Based on the high positive culture rate (about 70%), we believe that a low proportion of TB patients in S. Korea undergo empirical therapy.

5. As you said: 1021 cases were registered twice or more (p6L17) (P8L1; ...more than twice!). Did you exclude repeated cases? I didn't find that in the flowchart of study (Fig 1).

[Response] A patient who was registered more than once (due to transfer from one hospital to another during treatment) was regarded as one patient from the beginning of data extraction. Such patients are included in the 6,256 patients in Figure 1. We have added the following to the inclusion/exclusion criteria (page 5, lines 103-106):

A patient could be registered more than once if they had been transferred from one institution to another during treatment. In total, 1,021 (21.6%) of the patients in our cohort were registered at
two or more different institutions. We regarded this patient as one case from the beginning of data extraction.

6- Definition of Failure is problematic. Please check again in WHO guidelines.

[Response] We have changed the definition of “treatment failure” to match that in the WHO guidelines (see the table below) (page 6, lines 149-150)

[Table - WHO. Definitions and reporting framework for tuberculosis - 2013 revision]

treatment failed (TB patient whose sputum smear or culture was positive at month 5 or later during treatment)

7- I prefer "sputum smear" in comparison to "sputum stain". It is just an advise.

[Response] We have changed “stain” to “smear.”

8- Did you evaluate the relation between degree of sputum smear positivity (1+, 2+, 3+) and outcome?

[Response] Unfortunately, the Korean National TB Surveillance System (NTSS) does not include information regarding the grade of sputum smear positivity; thus, we could not evaluate its association with outcomes. Addition of such information would improve the Korean NTSS.

Ramnath Subbaraman (Reviewer 2):

This study is a helpful, clearly written, and straightforward retrospective analysis identifying risk factors for poor TB treatment outcomes in this population. The dataset used is substantial in size and quality and the research methodology is straightforward and well-executed. I have no major critical comments or concerns regarding this manuscript. I have only the following minor comments, which will may provide better clarify to the reader regarding the study findings:
1. The authors make it clear the RR-TB or MDR TB were excluded from this study. How were other forms of drug resistance - in particular INH-monoresistant TB - handled? It would be interesting to see if INH-monoresistant individuals had a different outcome in the regression analysis, as they may have been included based on the case definitions here.

[Response] We agree. In our cohort, 99 patients (2.1%) had INH-monoresistant TB. However, we believe this to be an underestimate because phenotypic DST was performed in only culture-confirmed TB patients and genotypic DST is not universally recommended for new TB patients in S. Korea. Also, some patients with positive culture results might not undergo phenotypic DST for various reasons. In our cohort, the treatment success rate of patients with INH-monoresistant TB was 83.9%, similar to patients with non-INH-monoresistant TB. Also, INH-monoresistance was not associated with treatment outcomes in multivariate analyses, most likely due to the small number of patients with INH mono-resistant TB. Because of the small number of patients and nonsignificant results, we did not describe the patients with INH-monoresistant TB in detail. However, we believe this to be an interesting topic for a future study.

2. Please explain the regional deprivation index more in a few sentences in the methods section. In general, what does it represent? Does it use geographic location (e.g., zip code or pin code) as a proxy for socioeconomic status? How well does it serve as a proxy for income differences or socioeconomic status?

[Response] The regional deprivation index is used to estimate the socioeconomic status of an area (town-level in our study). The regional deprivation index is an indirect indicator of the socioeconomic status of patients in a given area (town). It is defined as the sum of the following nine socioeconomic variables: house environment, educational level, social class of head-of-household and proportion of elderly people, single household, household without a car, non-apartment housing, female-headed household, and divorced or separated household. Higher deprivation index values indicate greater deprivation. We have added the following brief description of the regional deprivation index to the manuscript (page 7, lines 157-166):

The Korean NTSS does not record socioeconomic data of patients. Therefore, we used a regional deprivation index. The regional deprivation index is used to estimate the socioeconomic status of an area (town-level by address in our study), and is regarded as an indirect indicator of the socioeconomic status of patients in a given area. The index is the sum of the following nine socioeconomic variables: house environment, educational level, social class of head-of-household and proportion of elderly people, single household, household without a car, non-apartment housing, female-headed household, and divorced or separated household. Higher index values indicate more deprivation, with Q5 (fifth quintile) corresponding to the most severe deprivation, and Q1 (first quintile) to the lowest level of deprivation [12].
3. Please provide a bit more clarity on what it means to be notified twice or more. If I am reading this right, does this serve as a proxy for transfer of care to a different site?

[Response] If patients are transferred to other hospitals during TB treatment, they are again notified (registered) by that hospital. We have altered “notified as having TB twice or more” to “registered as TB-positive at least twice.” Also, we have added the following to the inclusion/exclusion criteria (page 5, lines 103-106):

A patient could be registered more than once if they had been transferred from one institution to another during treatment. In total, 1,021 (21.6%) of the patients in our cohort were registered at two or more different institutions. We regarded this patient as one case from the beginning of data extraction.

4. Why do you think those in Q5 (the poorest wealth quintile I believe) had lower mortality? This is a surprising finding; however, it might be explained by the higher loss to follow-up in Q5. Could it be that mortality might be low in Q5 because some of the loss to follow-up might represent deaths? The authors thoughts on this in the discussion would be helpful.

[Response] We agree. We also believe that the lower mortality rate in the Q5 group is attributable to its higher rate of loss to follow-up. We estimate that a significant proportion of the patients lost to follow-up in the Q5 group were indeed dead. Further, as we described in the Discussion, the area-level regional deprivation index might not reflect the socioeconomic status of an individual patient. We have revised the manuscript as follows (pages 10-11, lines 249-252; page 12, lines 297-299):

- Unexpectedly, Q5 of the regional deprivation index was associated with lower mortality. However, this was attributable to the higher rate of loss to follow-up in the Q5 group; we estimate that a significant proportion of the patients lost to follow-up in the Q5 group were indeed dead.

- Because the regional deprivation index is based on the data of a given area (town level), not a patient, it might not reflect the socioeconomic status of the individual patient.

5. In the Discussion the authors cite studies supporting the benefits of DOT. However, given recent systematic reviews - see Tian et al., Pasipanodya et al. and Karumbi's Cochrane review - the authors might be more cautious and acknowledge at minimum that the data on the benefits of DOT (versus self-administered therapy) are debated.

[Response] We agree. In several recent studies, including a meta-analysis, the efficacy of DOT was uncertain. We have revised the manuscript as follows (page 12, lines 291-292):
Although studies of the efficacy of directly observed therapy (DOT) have reported inconclusive results, DOT may be considered for non-compliant patients [3, 35, 40, 41].

6. Can the authors comment on why proportion cured may have been so much lower in 2015 as compared to 2014?

[Response] The definition of “cured” was in accordance with the WHO guidelines (see the table below). However, in 2015 (for the 2015 cohort), the Korean CDC revised the definitions of treatment outcomes, such that only culture results (not smear results) are included in the definition of “cured.” The lower proportion of “cured” in the 2015 cohort was likely caused by this revision of the definitions.

[Table - WHO. Definitions and reporting framework for tuberculosis - 2013 revision]

We have added the following explanation (page 7, lines 154-156):

In 2015, the KCDC revised the definition of “cured” by eliminating the smear criterion. Thus, in the 2015 cohort, the treatment outcome “cured” was evaluated based only on culture results.

7. Finally, foreign individuals seem to have poorer treatment outcomes. Could the authors provide more insights into what kinds of countries these individuals come from in general and what their socioeconomic status is like in general? This will help the readers to better picture and understand the implications of these findings.

[Response] Unfortunately, information on the nationality of non-South Korean TB patients was not provided because Busan City was concerned about diplomatic issues. We guess that the majority of such patients in our cohort were from other countries in southeastern Asia or from China.