Author's response to reviews

Title: Deaths among tuberculosis cases in Shanghai, China: Who is at risk?

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Version: 4 Date: 31 March 2009

Author's response to reviews: see over
Dear Sabina Alam,

Thank you very much again for the comments from the reviewers and the Associate Editor on our manuscript. We revised our manuscript in accordance with the reviewers’ suggestions, and are submitting our revised manuscript. In the accompanying pages, we provide a point-to-point response to the concerns of the reviewers.

Yours sincerely,

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Title: Deaths among tuberculosis cases in Shanghai, China: Who is at risk?
Manuscript number: 1612824455238353
Version: 3 Date: 3 March 2009
Reviewer: Christie Jeon
Reviewer’s report:
- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
  Comment: The age categorization could be finer among the elderly, as there are many deaths in >60 years old category. For example, does TB-associated death or non-TB-associated death increase with age among the elderly?
  Response: We thank the reviewer for this suggestion. We redefined the age groups and changed the tables and text in the revised manuscript.

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
  Comment: The authors responded adequately to my question: “Were the retreatment cases followed up for a longer period of time? If so, I think it’s important to state average time of follow-up by previous treatment, as with longer follow-up you may find more non-TB associated deaths.” I would like this see the content of their answer in the text of the manuscript.
  Response: We agree with this suggestion, and added our response in the Results section.

  Comment: The separate analysis for TB-associated death and non-TB-associated death is quite interesting; I think the results of the separate outcomes would strengthen this manuscript.
  Response: We thank the reviewer for this suggestion. But as we replied before, we would like to analyze and compare the differences between TB associated deaths and non-TB associated deaths in a separate manuscript.

  Comment: I’m not sure if the authors were justified in using logistic regression, which doesn’t not take the censoring and person-time into account. The fact that the proportional hazards assumption was not well satisfied is an indication that time is an important covariate, at least as an effect modifier. It would be important to investigate why the proportional hazards assumption is not met (i.e. there is interaction with time and the covariate used to investigate the proportional hazards assumption.) For example, it would be of interest to the reader to know that a certain factor X increases one’s mortality towards the beginning of the treatment period, but not later, or vice versa. I think it is possible that the proportional hazards assumption is better met if you separate by TB-associated deaths and non-TB associated deaths. For more rigorous investigation, you could construct Kaplan-Meier curves by some covariates of interest to investigate where the hazards cross.
  Response: Yes, we performed stratified Kaplan-Meier curves for each covariate, and found that the survivor functions of different age groups, and of new cases versus treatment cases, intersected or crossed over each other. This finding was similar with our conclusion that the proportional hazards assumptions were not well satisfied (the proportional hazards
assumptions were met with other covariates in our analysis). As the reviewer suggested, we performed stratified Cox proportional hazard models by TB-associated deaths and non-TB associated deaths. Though proportional hazards assumption was much better satisfied in the separate analysis, we still opted not to present the results because this manuscript focuses on the risk factors for all deaths among TB cases.

Comments: The authors report only significant ORs. If a covariate had been included in the multivariate model, it would be kind to the reader to report the corresponding estimate regardless of the p-value.

Response: Yes, we only reported those adjusted ORs that were statistically significant in our multivariate logistic regression model. Our final multivariate model did not include non-significant covariates.
Title: Deaths among tuberculosis cases in Shanghai, China: Who is at risk?

Manuscript number: 161284455238353

Version: 3  Date: 3 March 2009

Reviewer: Associate Editor

Reviewer's report:
While I also wonder why the assumption of proportional hazards are not met, I agree with the authors’ use of a logistic regression and suggest that they use the term TB-related, on-treatment mortality somewhere (although the authors define TB death appropriately, the use of 'death' in the results is ambiguous).

Response: We apologize that we didn’t clarify how we assessed the proportional hazards assumption in the earlier version. We tested whether the effect of each predictor in our model changed over time (per: Sophia Rabe-Hesketh. Chapter 12: Survival analysis. A handbook of statistical analyses using Stata, Third edition. Chapman & Hall/CRC Press). That is, as the above reviewer suggested, we determined whether or not any of the covariates increased the risk of a TB-related death towards the beginning of the treatment period, but not later in the treatment period, or vice versa. The results showed that two covariates (age groups and TB treatment history) were time dependent, meaning that the assumptions of proportional hazards were violated for these specific predictors. We opted not to present the results of our Cox regression models, and instead analyzed the data using multivariate logistic regression.

We thank the Editor for the suggestion of using the term TB-related, on-treatment mortality. However, TB-related mortality could be considered as deaths directly caused by TB, and we analyzed risk factors for all deaths (deaths from any cause). As the term “death” is ambiguous in the Results section, we used the term “on-treatment mortality” in the revised manuscript.

Comment: It would also be useful to list the length of follow up (proportion of patients followed to 6 months, 9 month and 12 months).

Response: We thank the Editor for this suggestion, and added the sentence “Of the 7,999 cases initiated anti-TB treatment, 16.9% were followed up to 6 months, 49.2% were followed for up to 9 months, and 33.9% were followed for up to 12 months” in the Results section.

Comments: I also agree that the age could be analyzed further given that almost all deaths were aged over 52 years - perhaps divide into quartiles (or even deciles)?

Response: We thank the Editor for this suggestion. We redefined the age categories and changed the tables and text in the revised manuscript.