Reviewer's report

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

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Reviewer: Jay K Varma

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

Abstract / Background
1. “This study is sought to identify individuals who are at higher risk of death.” In fact, the study compared individuals that died to those that did not die. The sentence should be re-written to say: “This study sought to identify characteristics associated with increased risk of death.”

Abstract/Results
2. Use the term “rate” not “ratio” for deaths, because you are comparing “number of persons that died” to the “number of persons that were enrolled.”

Abstract/Conclusions
3. The conclusions are quite weak. These could have been written without any study being conducted. The authors should write conclusions that extend directly from the results. How can the study’s findings about advanced age or smear positivity or co-morbidities directly translate into interventions right now?

Methods
4. A brief justification should be added about why the authors chose to restrict their analysis to culture-positive cases and not study bacteriologically positive (smear or culture positive) cases.

5. Is the sputum smear positive definition two of three smears positive or any smears positive? If using definitions identical to the WHO definitions, the authors can just say so and don’t need to explain the definition.

6. I have some concerns about the definitions used for cause of death and the exact follow-up that occurred. The authors write: “The cause of death was determined based on the treatment outcome monitoring. TB death was defined as a TB case whose treatment outcome was recorded the cause of death as caused or contributed by TB. All remaining deaths were defined as non-TB deaths...In the present study, follow-up was censored at one year after treatment.” My concerns are:

   (a) The WHO definition of a TB death is standardized and widely accepted: Any death that occurs during TB treatment is a TB death. Deviating from this
definition is acceptable if there is highly reliable cause of death data (e.g., autopsies) or the cause of death was indisputably not TB related (e.g., traffic accident). For this study, what assurances exist that TB program staff at the local level can accurately adjudicate when a cause of death is TB related or not TB related? Death certificate data, if it was used, is highly unreliable in every setting in which it has been evaluated. Do the results remain the same when the WHO definition is used (all deaths during TB treatment are TB deaths)?

(b) I am not clear what the exact follow up was. Does this mean that all patients were followed during TB treatment and then for one year after TB treatment? The results section makes it sound as if all patients were followed up for one year after they initiated treatment “rather than “one year after treatment.” Is it standard practice for the Chinese national TB program to follow TB patients for 6 months (6 months of treatment + 6 months after treatment = 12 months treatment) after treatment? If so, the nature and duration of follow-up after TB treatment should be described, since this is not normally done in other high-burden TB countries.

7. What is “serious H. pylori infection”? Are the authors referring to peptic ulcer disease and characterizing “severe” as upper gastrointestinal bleeding? I am not aware that there is a standardized, clinically relevant definition of “severe” H. pylori infection – the severity of infection is measured by the clinical presentation (symptoms, hemorrhage, gastric cancer, etc) and H. pylori is a causative agent in some, but not all, ulcers.

8. The statistical methods are appropriate if follow-up was identical for all patients, e.g., using the WHO definition of death during treatment as a TB death and follow-up extends only as long as treatment does. If follow-up occurred after TB treatment and/or the duration of TB treatment varied, then a proportional hazards analysis should be done.

9. How were missing values handled? Was data highly complete (>90%) for most variables? (Data on MDR is presented later so it’s clear later on that a complete case analysis was done to handle missing MDR data).

10. What methods are used for culture? How many sputum specimens are routinely tested?

Results

11. How were patients with treatment failure were analyzed? Figure 1 makes it seem as if no patients failed initial TB treatment. This seems impossible given the rate of MDR in the study population. Were failure patients grouped in with the comparison group (those that lived)?

12. Were other patterns of resistance analyzed? For example, INH monoresistance or RIF monoresistance? Would be worth mentioning that these were analyzed and found not to be risk factors for death?

13. What percentage of patients were HIV-infected? HIV is the most powerful risk factor for death among TB patients. If there is no data about HIV status, this should be stated in the results and the highlighted as an important limitation in
the Discussion.

14. The authors presented the age cutoff using the median yet present data in Table 1 using categorical age categories. Why not use the categorical age categories for the analysis? These are likely to be epidemiologically more meaningful than simply using the median age of the study population.

15. Table 3 is unnecessary since only 4 factors are presented and this can easily be summarized in the text.

Discussion

16. The authors devote the entire second paragraph of the Discussion to the issue of what proportion of deaths during treatment / follow-up were TB related. This is not appropriate, given that there is no reliable methods or data discussed to let the reader know how accurately these assessments were made. I would suggest that this section, rather than being a topic to highlight, should actually be considered a major limitation.

17. Other major limitations include the very small number of patient characteristics evaluated (What about compliance with DOT? What about treatment regimen? What about social or economic factors? Adverse drug events?) and the lack of data about specific co-morbid factors, especially HIV infection.

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

[NONE]

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

Discussion

18. I did a quick Medline search to evaluate the authors’ claim to primacy re: first study of risk factors for death in TB patients. I found at least one other article that looks at factors associated with treatment success, which are, not surprisingly, the inverse of those that are risk factors for death. See: Qing-Song Bao, Yu-Hua Du, Ci-Yong Lu. Treatment outcome of new pulmonary tuberculosis in Guangzhou, China 1993–2002: a register-based cohort study BMC Public Health. 2007; 7: 344. There’s also the well known study from Hong Kong, which admittedly is old and not from mainland China (Allan WG, Snell NJ, Hill LE, Fayers PM, Scadding JG, Fox W. A survey of deaths in Hong Kong attributed to tuberculosis. Tubercle. 1981 Mar;62(1):1-11.)

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.