Reviewer's report

Title: Outcome correlation of Smear-positivity but Culture-negativity during Standard Anti-tuberculosis Treatment in Taiwan

Version: 1 Date: 3 November 2014

Reviewer: Deepak Behera

Reviewer's report:

This is a retrospective clinical study of significance of smear-positivity and culture-negativity (SPCN) in patients receiving antituberculosis treatment. The authors attempt to evaluate relations between SPCN and demographic information, risk factors, co-morbidity, severity of infection and disease symptoms/lab findings, as well as final disease and treatment outcomes. Their aim appears to be able to predict which patients are likely to develop SPCN as well as suggest possible changes in management in patients with SPCN.

Discretionary revisions:

1. The title of the manuscript is somewhat vague – including the main finding in the title will make it more attractive. (e.g., “SPCN during TB treatment is predicted by..... but does not affect outcome.”) (discretionary revision)

2. Abstract: Lines 35, 36 – Aim needs to be more specific. Line 40 – “chemotherapy data, demographics and sputum data is too vague.” Also, purpose of analysis could be included (e.g., “analyzed for association with incidence of SPCN” (Minor essential revision)

3. Aim of the study: The aim of the study can be somewhat better defined. The authors mention that the aim of the study is to “investigate risk factors and clinical impact of SPNC phenomenon”. It is unclear what risk factors and what outcomes are being investigated within the aim. (Minor essential revision)

4. Introduction: The purpose of the aim is also unclear - the statement of current problem in clinical practice or gap in current knowledge is undermined. There is no mention of the purpose in the abstract. The authors do mention “great clinical impact” in line 71 and “prolonged isolation and treatment failure” in line 73; however, these issues are undermined in the introduction by the brevity of mention. What are the clinical impacts of SPCN? Reflect a little on how different situations/conclusions can affect management differently. What are the implications of SPCN? What conclusions can you draw from the currently published literature? A short review of literature will be helpful to keep the study in perspective. (Minor essential revision)

a. Line 72: What does ‘final culture results’ mean? Does finality refer to a conclusive result or does it refer to the last test done at a certain time point (2 months? 6 months? 2 years?) (Minor essential revision)
b. Line 75: List the risk factors and why you chose them. List the outcomes that you decided to study. Were these risk factors determined a priori? (Minor essential revision)

5. The methods appear to be rigorous, appropriate and well described.
   a. Mention that the study was retrospective (or clarify otherwise). (discretionary revision)

6. The data appears to be sound.
   a. Lines 136-138: Was confounding due to relatedness of the factors studied taken into account? For example, males might be more likely to have SPCN simply because more males are smokers and alcoholics, which might be actual risk factors for SPCN. (discretionary revision)
   b. Lines 141-143: Was TB severity related to only SPCN positivity or was there some correlation with co-morbidity and/or co-existing risk factors such as smoking? (discretionary revision)
   c. Line 145: Please explain 'close'. It can be assumed that it was close in the time course of treatment, but this is not very clear. (discretionary revision)
   d. Line 147: Explain 'gap'. Unless someone looks at the Figure, it is difficult to understand 'gap', which might be misunderstood to mean 'something missing'. (discretionary revision)
   e. Lines 136-139 and Lines 151-153: Multivariate regression demonstrates that maleness, or alcoholism, or DM are unrelated to SPCN. Please reflect this in stating the results in Lines 136-139. The fact that these factors tend to be more closely associated with SPCN can be explained to be likely due to concurrent association with smoking. It could be misleading to present significant p values with maleness, alcoholism and DM, in such a case. (Minor essential revision)
   f. Line 171: Typographical error - Instead of "that significant for..." the authors probably mean "as significant as..." (Minor essential revision)
   g. Line 172: What is "final positive culture"? (discretionary revision)
   h. Line 185: Explain "on the basis of". Do you mean "possibly due to..."? (discretionary revision)

7. The figures appear to be genuine.

8. The discussion of the findings is primarily descriptive. There appears to be adequate literature search performed and correlations sought with prior literature. The authors recognize the limitations of their study and address the reasons while suggesting further studies wherever applicable. However, the discussion can benefit from the following:
   a. Discuss the importance of association of treatment duration with SPCN incidence. (discretionary revision)
b. Line 193: Within 3 years of what? (e.g., 3 years of 'completion of treatment' or 'initiation of treatment'?) (Minor essential revision)

c. Lines 229 and 231: please change “46.6%” and “28.6%” to “46.6% of those” and “28.6% of those”, otherwise the sentence structure refers that these values refer to the entire pool of 800 patients. Better still, simply mentioning the culture positivity is sufficient in conveying the message in these two sentences – similar to the two sentences that follow (Lines 232 and 235). (Minor essential revision)

d. Line 238-241: How did this study add to this conclusion from the previous study (reference 5)? A brief description of the incremental value provided by this study will be useful. (discretionary revision)

e. Line 257: Please expand NTM the first time it is used. (Minor essential revision)

f. The discussion could benefit from reflecting upon how the results affect the clinical management, pointing to specific changes in management practices, with a note that the efficacy of these suggestions should be evaluated by further prospective trials. (discretionary revision)

g. The authors' conclusions indicate that culture negativity carries less significance than smear negativity in indicating successful treatment outcome. Do the authors envision stratifying TB patients such that in a group of patients a smear only test can replace the currently practiced smear and culture test, thus saving time and cost? It may be worthwhile to discuss the pros and cons of such an approach. (discretionary revision)

9. Table 1:

a. The column of p-value may not be necessary. Since some of the factors are causally or incidentally related, it can be misleading as this column shows significance where multivariate analysis does not. Suggested removing this column from this table. (Minor essential revision)

b. Is the HbA1c averaged over the period of treatment? Is it standardized as to timing of measurement, type and length of treatment of Diabetes mellitus etc? Please indicate somewhere in the manuscript (perhaps in within methods).(Minor essential revision)

c. P values cannot be negative, so p <0.000 do not exist, and are mathematically incorrect. It is okay to say <0.001 to maintain the number of decimal points. (Minor essential revision)

d. Refer to Symptoms -> Cough -> under column “All”. The authors say “557 (18)”, which is perhaps a typographical error as 557 of 800 is not 18%. If otherwise, please explain. (Minor essential revision)

e. Refer to Laboratory findings -> Hemoglobin. All columns show hemoglobin measurements of 13+/−2 g/dL, however the p value of 0.095 (although not
significant) appears to be very low for such equal measurements. Is this a calculation or typographical error? (Minor essential revision)

10. The manuscript language has several minor typographical and grammatical errors, which can be easily corrected by close proofreading. (Minor essential revision)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests