Author's response to reviews

Title: Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study.

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Author's response to reviews: see over
REPORTS:

Referee 1:

In discussion section:

1. There are contradictory statements: Using univariate analysis, early ICU admissions and VAP as most important factors associated with patient mortality.? In next paragraph authors have written that: surprisingly, we found in univariate and multivariate analysis that VAP was a further protective factor for mortality, in contrast with prior results.? We have changed the statement in the first paragraph: “Using multivariate analysis, we identified early ICU admission as the most important factor independently associated with patient mortality. In addition, VAP was as a protective factor for mortality.”

2. In results it is mentioned that cultures were positive in 35 (52.2%) patients. However with description it is not clear whether authors are talking about mycobacterium tuberculosis or some other organisms.

We have changed to: “Mycobacterial cultures were positive in 35 (52.2%) patients…”.

3. Authors have mentioned that: other reasons were cardiopulmonary arrest (10.4%), septic shock (7.5%), sepsis (6%) and altered sensorium (6%)?. However, in next paragraph it is written that: most patients had sepsis (95.5%) and septic shock (83.3%). These statements are giving different meanings and should be clarified.

The first statement refers to the reasons for ICU admission. The second statement mentions how many patients developed sepsis and septic shock during ICU stay. We have changed the second statement: “Although only 6.0% and 7.5% of patients had sepsis and septic shock, respectively, most of the patients developed sepsis (95.5%) and septic shock (83.6%) during ICU stay.”

In Method and Materials section:

4. Why there was failure to treat within 24 hrs of admission.
We think that failure to treat within 24 hrs of admission is related to delayed diagnosis possibly due to atypical presentations, but we did not evaluate it in our study.

5. Various drug regimens (ATT) used should be included in the manuscript. Why some patients did not receive Rifampicin based regimen?

We have included all drug regimens used in the manuscript. Sixty three (94%) patients used rifampicin, isoniazid and pirazynamid; 3 (4.5%) used streptomycin, isoniazid and ethambutol; 1(1.5%) used rifampicin, isoniazid and ethambutol. Only 3 patients did not receive rifampicin-based regimen because of hepatotoxicity. We have included in the text: “Sixty three (94%) patients used rifampicin, isoniazid and pirazynamid; 3 (4.5%) used streptomycin, isoniazid and ethambutol; 1(1.5%) used rifampicin, isoniazid and ethambutol. Only 3 patients did not receive rifampicin-based regimen because of hepatotoxicity.”

6. Variables in univariate analysis with p-value of <0.20 were considered significant. Why that cut off was taken is not clear.

We have chosen this widespread adopted cutoff because using a more traditional level ($P < 0.05$) might fail to identify variables known to be important. In addition, confusion variables can affect estimates even when their level of significance does not reach 0.05. We have changed the statement to: “Variables with $p < 0.20$ in the univariate analysis were analyzed in the multivariate analyses. We have chosen this widespread adopted cutoff because using a more traditional level ($P < 0.05$) might fail to identify variables known to be important. In addition, confusion variables can affect estimates even when their level of significance does not reach 0.05.”

In results sections:

7. In results there is no mention of effect of Hypoalbuminemia, dyselectrolytemia and Liver functions including Serum alkaline phosphatase on mortality. These all have been found to be associated with mortality in these patients. e.g. Sharma SK, Mohan A, Pande JN, Prasad KL, Gupta AK, Khilnani GC. Clinical profile, laboratory characteristics and outcome in miliary tuberculosis. QJM. 1995 Jan;88(1):29-37.
We report a retrospective series of 100 non-HIV adult patients with miliary tuberculosis (MTB) treated in a tertiary care centre. There were 51 males. Their mean age was 35 years. Predisposing conditions existed in 34. Twelve patients had larger-than-miliary (> 2 mm) shadows in their chest roentgenograms. Five presented with acute respiratory failure, and early treatment cured four of them. Hyponatraemia occurred in 42/60 patients (70%) for whom values were available. Twelve patients (12%) died of MTB. Temperature > or = 39.3 degrees C (p < 0.01), hypoalbuminaemia (p < 0.01), hyponatraemia (p < 0.001), history of vomiting (p < 0.001) and presence of crepitations on auscultation (p < 0.001) were independent predictors of mortality. Diagnosis of MTB is difficult even in an endemic area, as the clinical symptoms are non-specific and the chest roentgenograms do not always reveal classical miliary changes. A high index of clinical suspicion and diligent efforts in confirming the diagnosis are needed, as early therapy yields good results. Neither hypoalbuminemia nor hepatic dysfunction had effect on mortality. We did not evaluate the effect of hyponatremia. We have included in the text: “Neither hypoalbuminemia (p=0.111) nor hepatic dysfunction (p=0.999) had effect on mortality.”

Minor essential revisions

In introduction section:

1. Typographical error ? incidence of TB. Was of 50 cases/100.000???.100 cases/ 100.000?.. the annual death rate from TB in brazil was estimated at 4.0/100.000 population per year in 2006. It is probably cases/100,000?

There was a typographical error. It is cases/100,000.

2. Please mention counts as CD4 /mm3.

This has been corrected.
Discretionary Revisions

3. Authors have not found an association between diagnosis of HIV and mortality in ICU patients. However it is not only infection with HIV, the mortality depends on the stage of disease, level of immunosuppression and whether the patient is on effective HAART or not. Data may be analysed keeping this in foresight.

We have found no association between diagnosis of HIV and mortality, regardless of level of immunosuppression and use of HAART. We have included in the text: “We have found no association between diagnosis of HIV and mortality (p=0.999), regardless of level of immunosuppression and use of HAART.”

4. Along with MDR TB and absorption problems, drug interactions among Antitubecular drugs and HAART are also important factors.

We have included this observation in the text: “Drug interactions among antituberculosis drugs and HAART are also important factors.”

Referee 2

1. Are the methods appropriate and well described?

The retrospective cohort is not the ideal method but may be all the data that is available. The authors need to elaborate on how many outpatients the hospital sees per year and how many inpatients. How many in each have TB-that would give the reader a sense of the denominator that they are dealing with.

In our hospital, in 2008 for example, we had approximately 29,000 hospitalizations per year, with 185 cases of pulmonary TB. In addition, the number of outpatient visits was 551,968, but we do not have data on TB treatment, because our hospital does not provide TB treatment for outpatients; in Brazil, patients are treated in public outpatient health care services. We have included in the text (Methods section): “In our hospital, in 2008 for example, we had approximately 29,000
hospitalizations per year, with 185 cases of pulmonary TB. In addition, the number of outpatient visits was 551,968, but we do not have data on TB treatment, because our hospital does not provide TB treatment for outpatients; in Brazil, patients are treated in public outpatient health care services.

2. Are the data sound?

The study had 44 non survivors and they have included ~12 variables in the multivariate analysis and also adjusted for age and sex. This is NOT methodologically sound.

Because of the small sample size, we have used the forward method (Methods section), with variables added on at a time until the addition of another variable accounts only for a small amount of variance, then only the most significant were included in the final model.

Also the major part of the discussion relates to the univariate analysis and some of this data is clearly due to small sample size- increased mortality in patients with rifampicin. This has lead to long explanations trying to explain these findings which I think need to be deleted or considerably shortened.

We have shortened this paragraph to: “We found that patients who used rifampicin-based regimens had a higher mortality rate, even though not confirmed in multivariate analysis. One hypothesis to explain such observation is the possibility of multidrug-resistant tuberculosis (MDR-TB). However, culture and sensitivity test to antituberculosis drugs were not routinely performed, so we could not estimate the prevalence of MDR-TB in our sample. On the other hand, uncertain enteric absorption in critically ill patients [24] and subtherapeutic serum levels of rifampicin, especially in HIV-positive population [25-26], have been related to death [27-29]. Drug interactions among antituberculosis drugs and HAART are also important factors to be considered. In addition, low serum albumin levels could impair drug absorption and was associated with low rifampicin and ethambutol concentrations [30]. Whereas the great majority of our study sample is composed by
HIV-positive patients and hypoalbuminemia was a prevalent finding, it is possible that some patients had low serum rifampicin levels that went undetected.”

While the authors need to be commended on being the first in Brazil to do this study, I feel that the contribution of the study is more in the description of the types of cases and the outcomes rather than the analysis of risk factors for mortality.

We have changed the text to: “To our knowledge this is the first study in Brazil that described TB cases and their outcomes in patients requiring intensive care”