Predictors of In-Hospital Mortality among Patients with Pulmonary Tuberculosis: A Systematic Review and Meta-analysis

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Background: There is uncertainty regarding which factors are associated with in-hospital mortality among patients with pulmonary TB (PTB). The aim of this systematic review and meta-analysis is to identify predictors of in-hospital mortality among patients with PTB. Methods: We searched MEDLINE, EMBASE, and Global Health, for cohort and case-control studies that reported risk factors for in-hospital mortality in PTB. We pooled all factors that were assessed for an association, and presented relative associations as pooled odds ratios (ORs). Results: We identified 2,969 records, of which we retrieved 51 in full text; 11 cohort studies that evaluated 5,468 patients proved eligible. Moderate quality evidence suggested an association with co-morbid malignancy and in-hospital mortality (OR 1.85; 95% CI 1.01–3.40). Low quality evidence showed no association with positive sputum smear (OR 0.99; 95% CI 0.40–2.48), or male sex (OR 1.09, 95% CI 0.84–1.41), and very low quality evidence showed no association with diabetes mellitus (OR 1.31, 95% IC 0.38–4.46), and previous TB infection (OR 2.66, 95%CI 0.48–14.87). Conclusion: Co-morbid malignancy was associated with increased risk of in-hospital death among pulmonary TB patients. There is insufficient evidence to confirm positive sputum smear, male sex, diabetes mellitus, and previous TB infection as predictors of in-hospital mortality in TB patients.

Tuberculosis (TB) continues to be a major public health issue worldwide, particularly in low and middle-income countries despite rigorous efforts to contain its spread and implementation of effective treatment strategies. In 2014 an estimated 12 million people worldwide were living with active pulmonary TB, with 9.6 million new cases and 1.5 million deaths due to TB occurring annually¹⁻⁷.

TB does not usually require hospital admission for treatment, but if symptoms such as shortness of breath, and deterioration in a systemic condition are present, hospitalization may be necessary. A large proportion of patients with TB are hospitalized⁸,⁹, and estimates of in-hospital mortality range from 2% to 12%¹⁰⁻¹⁴; most of the current costs of TB treatment result from hospitalization¹⁵.

A variety of predictors have been associated with a higher risk of death among TB patients, including poverty, homelessness, alcohol or drug addiction, irregular or inadequate treatment, late diagnosis of the disease, multidrug-resistant TB (MDR-TB), and advanced age¹⁶. Human immunodeficiency virus (HIV) infection is an important factor related to the increased morbidity and mortality of TB in different world regions¹⁷⁻¹⁸. In addition, diabetes has been reported to be associated with increased risk of mortality¹⁶⁻¹⁸. Also, men have higher rates of

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mortality and worse outcomes compared with women. Previous TB with multiple treatments has also been associated with in-hospital mortality. Furthermore, patients with malignant tumors are immunocompromised and can have unusual clinical presentations, both related to delayed diagnosis and high mortality.

In TB program monitoring, TB deaths are crucial indicators of the impact of TB control measures, especially in areas with high HIV and TB prevalence. Data on TB deaths should provide us with a better understanding of the factors associated with these deaths and help guide interventions to reduce mortality; however, there is uncertainty regarding which factors are associated with in-hospital mortality among patients with pulmonary TB.

We therefore conducted a systematic review and meta-analysis to establish predictors of in-hospital mortality among patients with pulmonary TB.

**Methods**

**Search strategy.** We used a multimodal search strategy focused on 3 bibliographical databases (MEDLINE, EMBASE and Global Health). An experienced librarian (RC) used medical subject headings, adding terms and keywords from a preliminary search to develop the database search strategies. In each database, the librarian used an iterative process to refine the search strategy through testing several search terms and incorporating new search terms as new relevant citations were identified. There were no language restrictions. The search included the following databases from inception to November 2015: MEDLINE, EMBASE and Global Health. The search consisted of three concepts combined using the AND operator: tuberculosis, hospitalization and mortality (Appendix 1). The protocol of this study was published elsewhere.

**Study selection.** Eligible criteria: cohort or case-control design; explored risk factors for in-hospital mortality among patients with pulmonary TB in an adjusted analysis.

**Assessment of study eligibility.** Two reviewers (CPBA and DRS) trained in health research methodology screened, independently and in duplicate, the titles and abstracts of all citations identified in our search. The same reviewers screened all full text articles for eligibility; disagreements were resolved by consensus, with consultation of a third investigator (JWB) when resolution could not be achieved. We measured agreement between reviewers with the kappa statistic to assess the reliability of full-text review using the guidelines proposed by Landis and Koch:

- <0.20 as slight agreement,
- 0.21–0.40 as fair agreement,
- 0.41–0.60 as moderate agreement,
- 0.61–0.80 as substantial agreement and
- >0.80 as almost perfect agreement.

**Assessment of study quality.** Two reviewers (CPBA and DRS) assessed risk of bias for each eligible study, independently and in duplicate, using the Newcastle-Ottawa quality assessment scale (NOS) for Cohort Studies. The scale consists of nine items that cover three dimensions: patient selection (4 items); comparability of cohorts on the basis of the design or analysis (2 items); and assessment of outcome (3 items). A point is awarded for each item that is satisfied by the study. The total score therefore ranges from zero to nine, with higher scores indicating higher quality. A total score ≥7 represents high quality.

**Data Extraction and Analysis.** Two reviewers (CPBA and DRS) extracted data from each eligible study, including demographic information (e.g. sex, age, race), methodology, and all reported predictors.

We performed meta-analysis for all predictors that were reported by more than one study. We used odds ratios (ORs) with associated 95% CI to measure the association of binary predictors and in-hospital mortality. We used random effects models for all meta-analyses. If a study reported more than 1 regression model, we used data from the most fully adjusted model presented. We also presented the results from the predictors explored by the studies that were not eligible for meta-analysis.

We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots, because statistical tests of heterogeneity can be misleading when sample sizes are large and CIs are therefore narrow. We used the software R.

**Publication bias.** For meta-analyses with at least 10 studies, we assessed publication bias by visual assessment of asymmetry of the funnel plot and performed the Begg rank correlation test.

**Quality of evidence.** We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the quality of evidence for all meta-analyses. We categorized the confidence in estimates (quality of evidence) as high, moderate, low or very low, on the basis of risk of bias, imprecision, indirectness, inconsistency and publication bias. We used GRADE evidence profiles to provide a succinct, easily digestible presentation of the quality of evidence and magnitude of associations. In case of doubt or missing details about the studies, authors were contacted for clarification.

**Ethics and Dissemination.** This study is based on published data, and therefore ethical approval was not a requirement. This systematic review and meta-analysis is expected to serve as a basis for evidence to reduce in-hospital mortality in TB patients, and as a guide for future research based on identified knowledge gaps. It is anticipated that findings from this review will be useful for informing policy, practice and research priorities, improving the management of in-hospital TB patients. We also plan to update the review in the future to monitor changes and guide health services and policy solutions.
Results

Search Results and Study Characteristics. We identified 2,969 unique records, of which we retrieved 51 English and 3 non-English language articles in full text; 11 cohort studies, published between 2003 and 2013, that evaluated 5,468 patients proved eligible. Figure 1 shows the study selection flow diagram. There was substantial agreement ($\kappa = 0.64$) at the titles and abstract screening stage and perfect agreement ($\kappa = 1.00$) between reviewers at the full-text review stage.

All 11 eligible studies 1,4,15,37–44 were single-center and there was one non-English (Chinese) study included in our analysis. Two studies38,42 were conducted in Japan, two40,41 in Taiwan, three15,39,43 in Korea, one37 in Germany, one4 in Israel, one1 in Iran and one44 in China. One study39 used TB-related mortality as defined by the World Health Organization (the number of TB patients who died during treatment, irrespective of cause)45, two38,42 used all-cause mortality, and eight1,4,15,37,40,41,43,44 used TB-related mortality as judged by the investigators. The majority (9 of 11) 1,4,15,37,39–41,43,44 acquired data from medical records, with eight retrospective cohorts1,4,37–42 and one prospective cohort study15 (Table 1).

Risk of bias. Overall, the quality, evaluated by the NOS checklist for the outcome “mortality”, was high (Table 2). We did not have a sufficient number of studies in our meta-analyses to assess publication bias.

Predictors of in-hospital mortality. A total of 11 studies, involving a total of 2,343 patients, reported the association of 60 factors with in-hospital mortality1,4,15,37–42. On the basis of our criteria, we conducted meta-analyses for 5 predictors of in-hospital mortality: acid-fast bacilli (AFB) smear positive1, diabetes mellitus4, malignancy4, history of previous TB, and male sex.

Moderate quality evidence showed a significant association between malignancy and in-hospital mortality among TB patients (OR 1.85; 95% CI 1.01–3.40). Low quality evidence showed no association between in-hospital mortality and AFB smear positive (OR 0.99; 95% CI 0.40–2.48), or male sex (OR 1.09; 95% CI 0.84–1.41). Very low quality evidence showed no association between mortality and diabetes mellitus (OR 1.31; 95% CI 0.38–4.46), or previous TB (OR 2.66; 95% CI: 0.48–14.87) (Fig. 2; Table 3).

Table 4 presents the associations with in-hospital mortality for the factors that were not amenable to meta-analysis.

Discussion

We found moderate quality evidence that co-morbid malignancy was associated with increased in-hospital mortality among TB patients. Low quality evidence showed that sex and AFB smear positive were not associated
with in-hospital mortality, and very low quality evidence showed no association with previous TB infection and diabetes mellitus.

Our review has a number of strengths. Our search, which had no language restrictions, was designed and implemented by a research librarian, and literature screening and data extraction were performed independently and in duplicate by two reviewers using pretested, standardized extraction forms. The main limitation of our review was the small numbers of events that contributed to our meta-analyses, resulting in wide estimates of precision for our pooled measures of association.

Other studies also found that malignancy increases the risk of death in TB patients. Patients with malignant tumors are immunocompromised due to the local or systemic effects of the disease itself, as well as to the treatment regimens, which can impair the immune system and make these patients particularly susceptible to developing TB. In addition, TB can have an unusual clinical presentation, making diagnosis more difficult in these patients, contributing to delay in diagnosis and high mortality rates.

While not significantly associated with mortality in our review, previous TB has been reported to be associated with in-hospital mortality in many studies. Patients who undergo multiple treatment regimens for TB can develop resistance to drugs with the subsequent emergence of MDR-TB and XDR-TB, conditions highly associated with greater risk of death. Further, in settings other than hospitals, studies have demonstrated that smear positive patients have a better prognosis regarding mortality than smear negative patients. Indeed, indicators of atypical manifestations, such as smear-negative sputum, were associated with delayed diagnosis and

Table 1. Studies describing in-hospital mortality among pulmonary tuberculosis patients. ADL = activities of daily living; APACHE II = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; DM = Diabetes Mellitus; Hx = history; IHD = ischemic heart disease; TB = tuberculosis; PTB = pulmonary TB; NR = Not reported; WHO = World Health Organization.

| Study     | Year of publication | Definition of TB death | Country | Sample size | No. Deaths (%) | Predictors |
|-----------|---------------------|------------------------|---------|-------------|----------------|------------|
| Alavi-Naini | 2013                | Investigators judgment of TB death | Iran    | 715         | 75 (13.9%)     | Smoking, hepatites, DM, Hx of previous TB, anemia, drug abuse, positive sputum smear |
| Erbes     | 2006                | Investigators judgment of TB death | Germany | 58          | 15 (25.9%)     | Acute renal failure, mechanical ventilation, pneumonia, chronic pancreatitis, sepsis, ARDS |
| Horita    | 2012                | All-cause mortality     | Japan   | 244         | 48 (19.7%)     | Age, oxygen requirement, albumin, ADL |
| Kim 15    | 2010                | Investigators judgment of TB death | Korea   | 156         | 21 (13.5%)     | Male sex, old age, underprivileged, predisposing factors, AFB smear, CRP, lung involvement, high NRS |
| Kim 16    | 2012                | WHO definition          | Korea   | 269         | 82 (30.5%)     | Admission Route, AFB Smear Positivity, albumin, BUN, creatinine, CRP, Drug resistance TB, general weakness, Hb, hx of stopping anti-TB medication, hospital length of stay, initial ICU care, lymphocyte, poor oral intake, severity on chest X-ray, sodium, total cholesterol, under treatment for TB, WBC > 30 days |
| Lee 17    | 2003                | Investigators judgment of TB death | Taiwan  | 41          | 27 (64.8%)     | Multiple organ failure, consolidation on chest X-ray |
| Lin 18    | 2009                | Investigators judgment of TB death | Taiwan  | 59          | 40 (67.8%)     | Acute renal failure, gastrointestinal bleeding, multi-organ dysfunction syndrome, nosocomial pneumonia, treatment delay > 30 days |
| Lubart    | 2007                | Investigators judgment of TB death | Israel  | 461         | 65 (14%)       | Older age, IHD, cachexia, corticosteroid use, low albumin level |
| Okamura   | 2013                | All-cause mortality     | Japan   | 246         | 27 (11%)       | Serum Albumin, total lymphocyte – cat 1, total lymphocyte – cat 2, total lymphocyte – cat 3 |
| Ryu 19    | 2006                | Investigators judgment of TB death | Korea   | 32          | 16 (50%)       | APACHE II, sepsis, tuberculous-destroyed lungs |
| Sun 20    | 2011                | Investigators judgment of TB death | China   | 62          | 36 (58%)       | APACHE II, liver damage, respiratory failure, fungal infection |

Table 2. Newcastle-Ottawa scoring system for cohort studies.
mortality\textsuperscript{2,25}. Recently, a retrospective cohort study from Brazil\textsuperscript{6} reported a high mortality rate during hospitalization (16.1%), and negative sputum smear microscopy was an in-hospital mortality predictor in the population studied. However, patients with pulmonary and extrapulmonary TB were included in this study.

We did not find a significant association between male sex and in-hospital mortality among pulmonary TB patients. Worldwide TB notification data show that far more men than women have TB\textsuperscript{7}. Some studies showed that mortality rates are higher in females during their reproductive years, but after that they are higher in men\textsuperscript{19,20}.

Diabetes was also not associated with mortality in pulmonary TB patients in this study. Only one study\textsuperscript{1} included in this meta-analysis showed that diabetes was a predictor of mortality in TB patients, possibly because they included a larger number of diabetes patients (18% of the enrolled individuals). Some studies\textsuperscript{1,16–18} have found that diabetes increases risk of early mortality during TB treatment. This effect may be explained by impaired TB treatment response\textsuperscript{16}.

Figure 2. Association between AFB smear positive, Diabetes Mellitus, Hx of previous TB, Malignancy, male sex and in-hospital mortality among pulmonary TB patients.

| Predictor/Time/N° of patients | Nº of studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality | Relative effect (95% CI) |
|------------------------------|--------------|--------------|---------------|--------------|-------------|---------|------------------------|
| AFB smear positive/At baseline/1116 patients | 2 | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision | Low | OR 0.99 (0.40–2.48) |
| DM/At baseline/2165 patients | 4 | No serious risk of bias | Serious inconsistency | No serious indirectness | Serious imprecision | Very low | OR 1.31 (0.38–4.46) |
| Hx of previous TB/At baseline/1675 patients | 2 | No serious risk of bias | Serious inconsistency | No serious indirectness | Serious imprecision | Very low | OR 2.66 (0.48–14.87) |
| Male sex/At baseline/1880 patients | 7 | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious imprecision | Low | OR 1.09 (0.84–1.41) |
| Malignancy/At baseline/694 patients | 3 | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | Moderate | OR 1.85 (1.01–3.40) |

Table 3. GRADE Evidence Profile: Predictors of in-hospital mortality among TB patients. *DM = Diabetes Mellitus; Hx = history.
| Predictors                          | OR/HR* | p-value |
|------------------------------------|--------|---------|
| **Sociodemographic factors**       |        |         |
| Age (for 1 year increase)          | —      | 0.007   |
| Old age (>65 years)                | 5.7 (0.8–38.9) | 0.076   |
| Older age                          | —      | <0.001  |
| Underprivileged                    | 4.1 (0.8–21.4) | 0.098   |
| **Substance use**                  |        |         |
| Drug abusers                       | 7.8 (2.4–25.5) | 0.008   |
| Smoking                            | 12.9 (3.9–27.3) | 0.001   |
| **Previous TB**                    |        |         |
| Tuberculous-destroyed lungs        | 6.61 (1.21–36.04)* | 0.029   |
| History of stopping anti-TB medication | 4.58 (0.90–23.38) | 0.068   |
| **Symptoms**                       |        |         |
| General weakness                   | 1.23 (0.35–4.32) | 0.744   |
| Cachexia                           | —      | <0.001  |
| **Chest X-ray**                    |        |         |
| Consolidation                      | 7.73 (1.03–57.68)* | 0.046   |
| Extensive radiographic lung involvement | 5.0 (0.6–42.8) | 0.140   |
| Severity on chest X-ray - Mild     | 1.00   | 0.796   |
| Severity on chest X-ray - Moderate | 1.63 (0.34–7.83) | 0.543   |
| Severity on chest X-ray - Severe   | 1.37 (0.26–7.16) | 0.706   |
| **Laboratorial exams**             |        |         |
| Sputum AFB smear >3                | 2.00 (0.59–6.75)* | 0.264   |
| Multidrug-resistant tuberculosis   | 2.65 (0.28–25.33) | 0.397   |
| Drug resistance TB                 | 2.06 (0.69–6.11) | 0.195   |
| Hb                                 | 1.20 (0.40–1.60) | 0.742   |
| Lymphocyte                         | 1.99 (0.79–4.97) | 0.143   |
| WBC                                | 2.06 (0.89–4.78) | 0.091   |
| Total Lymphocite – cat 1           | 1.00   | —       |
| Total Lymphocite – cat 2           | 0.13 (0.03–0.59) | 0.010   |
| Total Lymphocite – cat 3           | 0.46 (0.13–1.65) | 0.235   |
| Albumin                            | 1.76 (0.68–4.53) | 0.245   |
| Serum Albumin                      | 0.15 (0.06–0.37) | <0.0001 |
| Albumin (for 1 g/dl increase)      | 0.22 (–) | 0.003   |
| Low albumin level                  | —      | <0.001  |
| CRP g/L                             | 1.00 (0.87–1.15) | 0.883   |
| CRP mg/dL                           | 1.62 (0.38–6.95) | 0.517   |
| BUN                                | 3.23 (1.23–8.49) | 0.018   |
| Creatinine                         | 2.00 (0.60–6.64) | 0.256   |
| Sodium                             | 2.48 (0.99–6.21) | 0.052   |
| Total cholesterol                   | 0.87 (0.18–4.11) | 0.857   |
| **Findings during hospitalization**|        |         |
| Admission Route                    | 0.83 (0.33–2.08) | 0.695   |
| Initial admission ward - ICU       | 6.17 (2.08–18.32) | 0.001   |
| Under treatment for PTB at admission | 3.35 (1.12–9.99) | 0.030   |
| APACHE II score                     | 4.91 (1.99–12.11)* | <0.01   |
| APACHE II score >20                | 4.99 (1.43–16.80)* | 0.012   |
| Treatment delay >30 days            | 2.37 (0.49–69.4) | —       |
| Nosocomial pneumonia                | 5.77 (1.33–44.36) | —       |
| Nosocomial pneumonia                | —      | 0.002   |
| Respiratory failure                 | 4.03 (1.56–10.38)* | <0.01   |
| Drug hepatitis                      | 12.3 (6.7–24.7) | 0.001   |
| Liver damage                        | 3.96 (1.23–12.1)* | <0.05   |
| Gastrointestinal bleeding           | 0.5 (0.203–26.18) | —       |
| Acute renal failure                 | 0.6 (0.215–7.15) | —       |
| Acute renal failure                 | —      | 0.001   |
| Continued                           |        |         |
Table 4. Unpooled predictors for in-hospital mortality among TB patients.

| Predictors                          | OR/HR  | p-value |
|------------------------------------|--------|---------|
| Fungal infection                   | 3.44 (1.23–9.62)* | <0.05 |
| Multiple organ failure             | 0.60 (0.14–2.60)* | 0.495 |
| Multi-organ dysfunction syndrome   | 8.59 (1.85–101.27) | —     |
| Multiple organ failure             | 2.65 (1.16–6.04)* | 0.020 |
| Sepsis                             | 5.84 (1.63–20.95)* | 0.007 |
| Hospital length of stay            | 1.51 (0.58–3.91) | 0.395 |
| Anemia                             | 19.8 (5.6–35.5) <0.0001 | |
| Oxygen requirement                 | 2.29 (—) | 0.132 |
| Mechanical ventilation             | —      | 0.002 |
| Chronic pancreatitis               | —      | 0.001 |
| ARDS                               | —      | 0.008 |
| HFD                                | —      | <0.001 |
| Other                              |        |         |
| Poor oral intake                   | 0.94 (0.24–3.71) | 0.930 |
| Activity of Daily living (for 1 point increase) | 0.58 (—) | 0.141 |
| High NRS                           | 23.5 (2.9–194.2) | 0.003 |
| Predisposing factors               | 9.1 (1.5–56.8) | 0.019 |
| Corticosteroid use                 | —      | <0.001 |

In conclusion, the presence of malignancy was significantly associated with in-hospital death in pulmonary TB patients. Other predictors were not associated with in-hospital mortality in TB patients, probably due to the small number of events. Further research should explore promising predictors of in-hospital mortality in large prospective studies.

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Author Contributions
All authors made substantial contributions to conception and design. C.P.B.A. designed the study, collected data, and wrote the manuscript. R.C. designed the search strategy. L.W. designed the study and collected data. P.Z. analyzed data and wrote the paper. J.B. designed the study and wrote the paper. D.R.S. designed the study, collected data, and wrote the paper. All authors provided final approval of the version to be published.

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