**Original Article**

**Risk Factors for Tuberculosis Mortality in a Tertiary Care Center in Oman, 2006–2016**

Zied A. Gaifer

Department of Medicine, Infectious Diseases Division, Sultan Qaboos University Hospital, Sultanate of Oman

**Abstract**

**Background:** Mortality from tuberculosis (TB) remains high despite its declining global incidence. Host risk factors of TB death have not been fully identified. The aim of this study is to explore some of the host risk factors associated with TB mortality. **Methods:** We conducted a retrospective cross-sectional review of patients with TB admitted to Sultan Qaboos University Hospital in Oman from July 2006 to February 2016. Multivariate logistic regression analyses were used to evaluate the risk factors for TB mortality. **Results:** Of the 205 TB cases reviewed, we identified 31 (15%) TB deaths during TB treatment. The median time of death from starting TB drugs was 30 days. Fifty-one percent of the TB deaths occurred in the 1st month of TB diagnosis. The main risk factors for TB mortality were advanced age, low body weight, negative sputum TB smear, pulmonary involvement, human immunodeficiency virus infection, and noncitizen status. **Conclusion:** To improve TB outcome in this high-risk group, abrupt clinical management approaches should be applied when TB is suspected. Public health measures that increase community awareness of TB mortality and reduce barriers to TB care are crucial to reducing TB mortality.

**Keywords:** Death, mortality, Oman, risk factors, tuberculosis

**INTRODUCTION**

Tuberculosis (TB) is one of the top five causes of death worldwide, and in 2015, TB killed 1.8 million individuals.[1] However, the rates of TB mortality are substantially variable between regions, being highest in Africa and South East Asia. This variability in TB death is not merely due to a high incidence of TB and coinfection with human immunodeficiency virus (HIV) in these regions but is also due to limited access to appropriate medical care for TB.

Fortunately, most deaths from TB are preventable, and in the past 15 years, anti-TB drugs reduced TB mortality by 22% and saved 49 million lives. However, this decrease in TB deaths occurred mainly in Eastern Mediterranean and European regions.[1] For instance, Oman, in the past 25 years, achieved significant control of TB as the incidence of TB was reduced by 85%. However, the rate of TB mortality in Oman remained comparable to other Gulf countries.[2]

Recent studies revealed that TB underdiagnosis, coinfection with HIV, and infection with multidrug-resistant *Mycobacterium tuberculosis* are the main risk factors for TB mortality.[3] However, other risk factors for TB death are still unknown. In this retrospective review, we estimate the burden of TB-related death in hospitalized patients in Sultan Qaboos University Hospital (SQUH), and we explore some of the risk factors associated with TB mortality. The identification of such predictors may pave the way to reducing TB-related death by early recognition of patients at risk for death and applying more thoughtful treatment plans.

**METHODS**

This study was conducted at SQUH hospital which is a tertiary hospital in Sultanate of Oman. It was a retrospective cross-sectional mortality survey. Data were collected from the electronic medical record for all TB cases admitted to the hospital from July 2006 to February 2016. A total of 205 TB cases were included in the study.

**Address for correspondence:** Dr. Zied A. Gaifer, Department of Medicine, Division of Infectious Diseases, Prince Mohammed Bin Abdulaziz Hospital, Madinah 41511, Kingdom of Saudi Arabia. E-mail: zgaiferali@gmail.com

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hospital in the period from July 2006 to February 2016. The diagnosis of TB in these cases was established by a positive culture for M. tuberculosis and/or clinical and histological findings compatible with TB.

The primary outcome of the study was death, which was defined as mortality from any cause during or before starting TB treatment. TB patients were followed till they died or were discharged from the inpatient or outpatient hospital care.

Our main exposures variables were sociodemographic parameters, body weight, concomitant comorbidities, and the site of TB infection. We used the World Health Organization (WHO) classification systems to categorize the sites of TB infection into pulmonary and extrapulmonary. Pulmonary TB (PTB) includes cases with TB infection of the lung parenchyma and/or infection of the lung with other organ involvement. Extra-Pulmonary TB (EPTB) cases were those with the other organ TB infection without lung parenchyma involvement. This study is approved by Sultan Qaboos University ethical committee.

Continuous variables are summarized with mean and standard deviation and analyzed using Student’s t-test or Wilcoxon rank-sum test (when applicable). The categorical variables are described as percentages and analyzed with Pearson’s Chi-square test or Fisher’s exact test (when applicable). P < 0.05 was considered significant. Odds ratios and 95% confidence interval (CI) were calculated in multivariable logistic regression model which was applied to control for confounding variables and to identify independent risk factors for TB death. Logistic regression model was built using forward selection method. Initially, we included the variables with P < 0.25 in univariate analysis; then, we added in the model the covariates that often influence TB outcomes such as age, comorbidities, and site of TB infection. In the same model, we checked for interaction between age and comorbidities as well as interaction between TB sputum smear and the site of TB infection. We assessed the model fit using Hosmer-Lemeshow goodness-of-fit test, P > 0.05 is considered as a good fit. We assessed the discriminatory power of the model using area under the curve (AUC). We created receiver operating characteristic curve for all possible cut points from the model values. AUC from 0.7 to 0.8 was considered as acceptable for discrimination. We analyzed the data using STATA version 12 software (STATA Corporation, College Station, TX, USA).

**Results**

Our study included a total of 205 TB cases. The mean age was 42 years and men represented 58.5% of all TB cases. Seventy-five percent of all cases had microbiologically confirmed TB diagnosis while the other 25% had a TB diagnosis based on clinical and histological findings consistent with TB. Table 1 shows the demographic and clinical characteristics of TB patients stratified by their outcomes. Thirty-one TB cases (15%) died during the study period. Of those who died, 7 cases (22%) had an HIV infection, and 28 cases (90%) were classified as PTB (PTB). For our study, PTB includes both PTB and EPTB with concurrent pulmonary involvement. Chronic comorbidities were common among the TB deaths.

The median time for death after starting TB drugs was 30 days (interquartile range, 13–180 days). Fifty-one percent of the deaths occurred within the 1st month of TB diagnosis, and 16% occurred in the 2nd month following the diagnosis. Moreover, 95% of the TB cases were started on TB drugs within 1 week of clinical suspicion of TB. Of those, 75% of patients were started within 24 h of TB sample collection.

| Table 1: Demographic and clinical characteristics of tuberculosis patients stratified by their outcome in Sultan Qaboos University Hospital, Oman (2006-2015) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Characteristics                | All TB (n = 205), n/N (%)       | TB deaths (n = 31), n/N (%)      | Survivals (n = 174), n/N (%)     | P                                |
| Sex (male)                     | 120 (58.5)                      | 21 (67.7)                       | 99 (56.9)                       | 0.259                            |
| Age (year), mean (SD)          | 44 (20.4)                       | 52.33 (23.8)                    | 43.32 (19.4)                    | 0.013                            |
| Age (year), median (IQR)       | 42 (29-61)                      | -                              | -                              | -                                |
| Noncitizen                     | 16 (7.8)                        | 4 (12.9)                       | 12 (6.9)                       | 0.208                            |
| Current smokers                | 40 (19.5)                       | 8 (25.8)                       | 32 (18.4)                      | 0.199                            |
| Alcohol users                  | 16 (7.8)                        | 3 (9.7)                        | 13 (7.5)                       | 0.207                            |
| Weight (kg), mean (SD)         | 61 (22.1)                       | 48.4 (21.9)                    | 63.2 (21.5)                    | 0.007                            |
| Site of TB (pulmonary)         | 124 (60.5)                      | 28 (90.3)                      | 96 (55.2)                      | 0.001                            |
| Alcohol users                  | 16 (7.8)                        | 3 (9.7)                        | 13 (7.5)                       | 0.207                            |
| HIV positive                   | 18 (8.8)                        | 7 (22.6)                       | 11 (6.3)                       | 0.003                            |
| Chronic lung disease           | 23 (11.2)                       | 6 (19.4)                       | 17 (9.8)                       | 0.139                            |
| Immunosuppressive therapy      | 12 (5.9)                        | 1 (3.2)                        | 11 (6.3)                       | 0.499                            |
| Previous TB diagnosis          | 15 (7.8)                        | 4 (15.4)                       | 11 (7.5)                       | 0.191                            |
| Chronic liver disease          | 27 (13.2)                       | 7 (22.6)                       | 20 (11.5)                      | 0.093                            |
| Chronic kidney disease         | 16 (7.8)                        | 6 (19.4)                       | 10 (5.8)                       | 0.009                            |
| Cardiovascular disease         | 27 (13.2)                       | 7 (22.6)                       | 20 (11.5)                      | 0.093                            |
| Malignancy                     | 17 (8.3)                        | 6 (19.4)                       | 11 (6.3)                       | 0.015                            |

SD: Standard deviation, IQR: Interquartile range, TB: Tuberculosis, HIV: Human immunodeficiency virus, SQUH: Sultan Qaboos University Hospital
We found no significant difference between death and survived cases in the time between starting TB drugs and the initial suspicion of TB. All TB cases were treated with first-line TB drugs (e.g. isoniazid, rifampicin, ethambutol, and pyrazinamide), and all discharged patients underwent outpatient follow-up with directly observed therapy.

The sputum smears for TB were positive, negative, or not obtained in 35%, 29%, and 36% of the cases, respectively. Seventy percent of the cases with no available sputum sample results were classified as EPTB. Half of the PTB cases were sputum smear positive. Among the deaths of patients with positive cultures, only two cases had pyrazinamide drug-resistant *M. tuberculosis* strains.

As Table 2 shows, our data suggest that the risk factors for TB deaths were advanced age (odds ratio [OR]: 1.048; 95% CI: 1.014–1.083; *P* = 0.006), low body weight (OR: 0.940; 95% CI: 0.908–0.973; *P* = 0.001), negative sputum TB smear (OR: 3.839; 95% CI: 1.251–11.781; *P* = 0.019), and pulmonary involvement (OR: 4.523; 95% CI: 1.127–18.143; *P* = 0.033). HIV infection was also associated with TB death (OR: 6.161; 95% CI: 1.316–28.851; *P* = 0.021) and non-Omani citizen status appeared to carry a greater risk for TB death when compared to Omani citizens (OR: 7.998; 95% CI: 1.312–48.75; *P* = 0.024). We found no association between TB death and cardiovascular diseases, chronic liver disease, chronic kidney disease, or chronic lung diseases.

**Discussion**

Our study showed that half of TB deaths occurred during the 1st month of TB diagnosis. Poor outcomes in TB patients were often attributed to host factors, mycobacterial microbial factors, and inappropriate TB treatment. Delays in TB treatment may occur if patients seek medical advice late or if the health-care providers do not recognize the TB diagnosis. Many studies demonstrated that late TB treatment was a major factor influencing TB outcomes. In this study, 95% of the TB cases were started on TB treatment at the time of clinical suspicion of TB. This signifies that a delay in TB treatment was not an important cause of TB mortality in our cohort. Our study found no TB deaths occurred before the initiation of TB treatment. This may be because this study was conducted in a tertiary care center, and many of the suspected TB patients had already been started on TB treatment from the primary or secondary care areas before seeking care at the study site. In addition, the in-house availability of rapid molecular TB tests may have shortened the time for TB diagnosis and consequently reduced the time to starting TB drugs.

Consistent with other studies, we found HIV infection was significantly associated with TB mortality. HIV infection debilitates the immune defense against TB and leads to dissemination of TB to the other body organs which often carries an unfavorable prognosis.

Our data suggest that TB mortality was higher in PTB cases than in EPTB cases. Many studies found no difference in TB mortality between those two groups. Moreover, disseminated TB cases are associated with a higher risk of death compared to PTB and EPTB cases. Our findings may be due to combining PTB and disseminated TB cases in the same group. We elected to use the WHO classification to categorize the TB site of infection to make our results comparable those of similar studies using the same WHO classification.

In contrast to other studies, we found a higher TB-related death among non-Omani citizens. Those studies found a higher TB-related death among the country citizen attributed their findings to advanced age and the presence of comorbidities among citizens. In our analysis, we controlled for age and comorbidities. Our findings may be due to a higher incidence of TB meningitis among noncitizens compared to citizens. We believe this may be partially due to the protective effect of bacillus Calmette–Guérin (BCG) vaccine among Omanis. BCG vaccine has been shown to decrease the risk of TB meningitis. We hypothesize that the BCG vaccine may have reduced the risk of TB meningitis in Omani citizens as the BCG vaccination program is well established in Oman compared to the home countries of most of expatriates. Worth mentioning in a study conducted in Gulf countries, Chaabna et al. found that all-cause age-standardized mortality was inversely proportional to national population size. In this study, the decrease in mortality was attributed increase in countries’ population size due to migration of healthy workers.

As with other studies, we found advanced age associated with the risk of TB-related death. As we adjusted for concurrent comorbidities, it is unlikely this finding is related to the

### Table 2: Univariate and multivariate analysis of risk factors for tuberculosis death

| Characteristics          | Unadjusted OR (95% CI) | *P*  | Adjusted OR (95% CI) | *P*  |
|--------------------------|------------------------|------|----------------------|------|
| Age (year)               | 1.022 (1.003-1.042)    | 0.025| 1.048 (1.014-1.083)  | 0.006|
| Weight (kg)              | 0.968 (0.947-0.989)    | 0.003| 0.940 (0.908-0.973)  | 0.001|
| Negative sputum smear for TB | 2.361 (1.077-5.173) | 0.032| 3.839 (1.251-11.781) | 0.019|
| Pulmonary TB             | 7.58 (2.22-25.88)      | 0.001| 4.523 (1.127-18.143) | 0.033|
| HIV positive             | 4.32 (1.52-12.22)      | 0.006| 6.161 (1.316-28.851) | 0.021|
| Noncitizen               | 2.0 (0.60-6.658)       | 0.259| 7.998 (1.312-48.75)  | 0.024|
| Presence of any comorbidity | 3.636 (1.633-8.096) | 0.002| 1.020 (0.282-3.693)  | 0.975|

*Presence of any comorbidity: Any of the following chronic lung disease, chronic liver disease, chronic kidney disease, cardiovascular disease, and malignancy.*

*TB: Tuberculosis, HIV: Human immunodeficiency virus, OR: Odd ratio, CI: Confidence interval*
presence of comorbidities among elderly patients as proposed by some studies.\textsuperscript{[13]} We believe that an aging immune system may have contributed to TB-related deaths in this group of elderly patients.\textsuperscript{[19]} Not surprisingly, we found low body weight was associated with TB-related death, which supports findings in other studies.\textsuperscript{[20,21]} A potential explanation for this association is that body weight is an important indicator of malnutrition, as demonstrated in many studies to be associated with TB death.\textsuperscript{[22,23]} Malnutrition may also occur secondary to severe TB infection, and thus, it is unclear whether low body weight is a cause or a consequence of severe TB infection.

To the best of our knowledge, this first hospital-based study exploring determinates of TB-related mortality in Oman. However, this study has a few limitations. First, we could not assess the time of onset of TB symptoms; therefore, we may have underestimated the effect of TB treatment delay on TB death. However, early detection and of treatment of TB cases remain fundamental prognostic factors for TB outcome.\textsuperscript{[24]} Second, we used all-cause mortality to assess TB-related death as we were unable to find adequate autopsy data to confirm the cause of death. Autopsies are rarely done to confirm the causes of death at the study site. We obtained causes of death from the hospital death records. However, hospital-based studies often are more accurate and have more information than TB surveillance program studies in reporting TB death data.

CONCLUSION

Our study identified that advanced age, low body weight, pulmonary involvement, HIV, and expatriate status were the main predictors of TB-related mortality. When TB is suspected in this risk group, an early clinical management approach should be applied. Implementing public health measures to increase community awareness of TB-related mortality and decrease barriers to TB care are crucial for reducing TB mortality.

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Conflicts of interest

There are no conflicts of interest.

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