FACTORS ASSOCIATED WITH MORTALITY AMONG TUBERCULOSIS PATIENTS IN SOUTHEAST TURKEY

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ABSTRACT

Introduction: Tuberculosis (TB) is a disease caused by bacillus mycobacterium tuberculosis. Tuberculosis is a preventable and treatable disease that, despite the rapid advances in active therapy, continues to cause global mortality. In this study, we investigated the risk factors associated with mortality in patients undergoing treatment for TB.

Materials and methods: Records of 2,450 tuberculosis patients who were followed-up with in tuberculosis dispensaries in the city of Diyarbakir, southeast Turkey, between January 2005 and December 2011 were reviewed retrospectively. Case definitions and treatment outcomes were classified according to WHO criteria.

Results: Of the 2,450 registered TB patients, 1,339 were male (54.7%) and 1,111 were female (45.3%). Their mean age was 32.15±17.87 years, and 51 (2.1%) of them died. Mortality rates were higher in pulmonary TB (PTB) patients, males, relapse patients, category 2 patients, those >65 years old, TB meningitis patients, and patients who self-administered their therapy. According to Kaplan-Meier analysis, the mortality rates were significantly higher in patients aged >65 years, in those with Category II and in those TB meningitis. The significant independent risk factors for mortality during anti-TB treatment were advanced age, TB meningitis and gastrointestinal TB.

Conclusion: Mortality was increased in the elderly, males, those with relapse, and in category II and extrapulmonary TB patients. Based on these data, we suggest that tuberculosis control programs should pay more attention to the high-risk groups determined in the current and previous studies. Treatment regimens for these risk groups should be considered for revision.

Key words: Tuberculosis, extrapulmonary tuberculosis, mortality, Southeast Turkey, category II, relapse.

Received January 30, 2014; Accepted March 30, 2015

Introduction

Tuberculosis (TB) is an infectious disease that is caused by Mycobacterium tuberculosis. M. tuberculosis mostly affects the lungs, but it also can spread and cause damage in other organs. Tuberculosis is a preventable and treatable disease that, despite the rapid advances in active therapy, continues to cause global mortality.

The 2013 report from the World Health Organization (WHO) indicated that there were 8.6 million tuberculosis patients identified internationally and that TB caused 1.4 million deaths1). Nevertheless, the global TB mortality has decreased by 41% since 1990; the WHO aimed to reduce this rate to 50% by 20152).

There was a serious epidemic of TB in Turkey at the beginning of this century. At that time, TB mortalities ranked first among all causes of death. This continued into the 1950s, as the TB mortality rate was 262 per hundred thousand in 1945 and 204 per hundred thousand in 19503). A total of 15,879 new cases were reported in Turkey in 2010, and the mortality rate that year was reported to be
3.1/100,000 (approximately 2,200 people died due to TB). The dramatic decrease in the annual mortality rate can be attributed to the directly observed therapy (DOT) strategy, which was implemented in Turkey in 2006.

In the present study, we aim to investigate the risk factors associated with mortality among 2,450 tuberculosis patients who were seen at the tuberculosis dispensaries in the province and districts of Diyarbakir between 2005 and 2011.

Materials and methods

Patients
We performed a retrospective cohort study of TB patients in the city of Diyarbakir, southeast Turkey, who were seen between January 2005 and December 2011. This study included 2,450 tuberculosis patients. Patient data were collected from the records of the Diyarbakir province/district tuberculosis dispensaries. The patients consisted of all age groups including both the pediatric and the elderly. Tuberculosis exclusively determined mortality. The demographic characteristics of the patients, including age, gender, diagnosis date, date of death, site of TB disease (pulmonary, extrapulmonary, or both), case definitions and categories, acid resistant bacillus (ARB) smears and cultures, type of therapy, and outcomes of therapy were reviewed. Smears were examined for acid-fast bacilli in 1,281 of the 1,531 patients with pulmonary TB or both pulmonary and extrapulmonary TB. Since 250 patients could not give or did not wish to give sputum samples, their treatment was prescribed clinically or radiologically (assuming they had pulmonary tuberculosis). Directly observed therapy was begun in patients in Diyarbakir after June 2006.

No patient identifiers were included in the study database. The study protocol was approved by the Ministry of Health Tuberculosis departments, Turkey Republic.

Definitions
Case definitions were made according to the records of the tuberculosis dispensaries and the patient statements. Case definitions and treatment results were classified based on WHO definitions. The cases were classified and treated according to the treatment categories suggested by the WHO as follows:

Category I: New smear positive pulmonary TB (PTB) patients; new smear negative PTB patients with extensive parenchymal involvement; severe concomitant human immunodeficiency virus (HIV); or severe forms of extra pulmonary TB (EPTB).

Category II: Previously treated sputum smear positive PTB; relapsed cases; patients who resumed treatment after interruption; and patients whose treatment failed.

Category III: New smear negative PTB (except category I); less severe forms of EPTB.

Category IV: Chronic and multi-drug resistant (MDR) TB cases (still sputum positive after observed retreatment). These patients were sent to advanced centers.

Statistical analysis
Data analyses were performed using Statistical Package for Social Sciences (SPSS) Version 18.0 for Windows (SPSS Inc., Chicago, IL). Univariate and multivariate analyses were used to determine the characteristics of the TB patients that were associated with an increased risk of mortality. Descriptive statistics were determined for the patients’ demographic and clinical characteristics. Survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate COX regression analysis was performed to analyze variables associated with mortality. The parameters that were identified as risk factors for TB mortality in previous studies, as well as variables with p values<0.05 in univariate analysis were included in the model. Independent variables predicting adjusted hazard ratio (AHR) and the corresponding 95% confidence interval (95%CI) were estimated for potential risk factors. A two tailed p<0.05 was considered statistically significant.

Results
Over the 7-year study period, 2,510 TB suspects were reported in the city of Diyarbakir, southeast Turkey. Of these, 60 were excluded from the study because their TB diagnosis was eliminated upon follow-up. The remaining 2,450 patients were included in the analysis, including 1,484 pulmonary TB patients (60.6%), 919 extra-pulmonary TB patients (37.5%), and 47 TB patients (1.9%) with both pulmonary and extrapulmonary TB. The characteristics of the study population are presented in Table 1.

The study population consisted of 1,339 males (54.7%) and 1,111 females (45.3%) with a mean
age of 32.15±17.87 years (range: 1-103 years). The majority of the patients were younger than 35 years (65.1%). Among the EPTB patients, 34.8% (n = 320) were diagnosed with TB lymphadenitis and 32.3% (n = 297) with TB pleurisy. In terms of case definition, 2,172 (88.7%) were new TB patients and 176 (7.2%) were relapse TB patients. Treatment was administered as a DOT in 1,852 patients (75.6%) and 598 patients (24.4%) self-administered therapy (24.4%).

Table 1: Characteristics of the 2,450 study participants with tuberculosis diagnosed in Diyarbakir, southeast Turkey from January 2005 to December 2011.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N (%)</th>
<th>Survived N (%)</th>
<th>Died N (%)</th>
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<tr>
<td>Gender</td>
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<tr>
<td>Female</td>
<td>1111 (45.3)</td>
<td>1093 (98.6)</td>
<td>18 (1.6)</td>
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<td>Male</td>
<td>1309 (54.7)</td>
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<td>New</td>
<td>2172 (88.7)</td>
<td>2162 (95.0)</td>
<td>10 (0.5)</td>
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<td>Relapse</td>
<td>176 (7.2)</td>
<td>176 (100.0)</td>
<td>0 (0.0)</td>
</tr>
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<td>Treatment after interruption</td>
<td>43 (1.8)</td>
<td>42 (97.7)</td>
<td>1 (2.3)</td>
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<tr>
<td>Treatment after failure</td>
<td>13 (0.5)</td>
<td>13 (100.0)</td>
<td>0 (0.0)</td>
</tr>
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<td>Chronic</td>
<td>3 (0.1)</td>
<td>3 (100.0)</td>
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<td>From transport</td>
<td>4 (0.2)</td>
<td>4 (100.0)</td>
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<td>TB category</td>
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<tr>
<td>Category 1</td>
<td>944 (38.5)</td>
<td>929 (98.3)</td>
<td>15 (1.7)</td>
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<td>Category 2</td>
<td>217 (9.3)</td>
<td>207 (95.6)</td>
<td>10 (4.4)</td>
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<td>Category 3</td>
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<td>1290 (99.1)</td>
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<td>22 (0.9)</td>
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<tr>
<td>Pulmonary</td>
<td>1464 (60.6)</td>
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<tr>
<td>Extra pulmonary</td>
<td>914 (37.5)</td>
<td>909 (99.3)</td>
<td>5 (0.7)</td>
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<tr>
<td>Both</td>
<td>47 (1.9)</td>
<td>44 (93.6)</td>
<td>3 (6.4)</td>
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<td>Age Group</td>
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<tr>
<td>&lt;35 years</td>
<td>1599 (65.5)</td>
<td>1596 (98.0)</td>
<td>3 (0.6)</td>
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<td>36-65 years</td>
<td>704 (28.7)</td>
<td>671 (95.2)</td>
<td>33 (4.8)</td>
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<td>&gt;65 years</td>
<td>151 (6.2)</td>
<td>139 (92.2)</td>
<td>12 (7.8)</td>
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<td>Major site of disease</td>
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<tr>
<td>Pulmonary</td>
<td>1496 (61.1)</td>
<td>1487 (98.1)</td>
<td>9 (0.6)</td>
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<td>Lymph node</td>
<td>320 (13.2)</td>
<td>317 (99.1)</td>
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<td>Pleura</td>
<td>209 (12.1)</td>
<td>207 (99.5)</td>
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<td>Gentamicin</td>
<td>42 (1.7)</td>
<td>40 (95.2)</td>
<td>2 (4.8)</td>
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<tr>
<td>Gentamicin (pot)</td>
<td>37 (1.8)</td>
<td>35 (94.6)</td>
<td>2 (5.4)</td>
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<td>Streptomycin</td>
<td>39 (1.8)</td>
<td>37 (94.9)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Isoniazid (extra pot)</td>
<td>37 (1.5)</td>
<td>35 (94.6)</td>
<td>2 (5.4)</td>
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<tr>
<td>Others</td>
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<td>95 (98.9)</td>
<td>1 (1.1)</td>
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<td>Therapy type</td>
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<td>Self-administered therapy</td>
<td>598 (24.4)</td>
<td>591 (99.2)</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Directly observed therapy</td>
<td>1182 (75.6)</td>
<td>1180 (99.2)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

Table 2: Treatment outcomes of 2450 study participants with tuberculosis.

### Results

- **Cure**: 597 (15.8%)
- **Treatment completion**: 1,774 (72.4%)
- **Treatment failure**: 14 (0.6%)
- **Leaving treatment**: 109 (4.4%)
- **Case of transported**: 115 (4.7%)
- **Death**: 51 (2.1%)

### Figures

**Figure 1**: Kaplan-Meier analysis of tuberculosis related mortality in different age groups (log-rank test, P<0.001). The mortality rates were significantly higher in patients older than 65 years.

In the multivariate COX regression analysis for death due to TB (Table 3), the risk of death was significantly increased in TB patients between the ages of 36 and 65 years (AHR = 12.04, 95% CI: 5.00-29.01) and those older than 65 years (AHR = 21.15, 95% CI: 7.81-57.24) compared to patients between the ages of 0 and 35 years. Moreover, patients with TB meningitis (AHR = 6.26, 95% CI: 0.55-0.45) had a significantly increased risk of death.
1.76-22.25) and patients with gastrointestinal TB (AHR = 5.06, 95% CI: 1.86-13.76) were more likely to die compared to PTB patients.

The median follow-up time was 63 months (range: 1-101 months). According to Kaplan-Meier analysis, the mortality rates were significantly higher in patients older than 65 years (p<0.001), Category II patients (p=0.006) and in patients with TB meningitis (p<0.001) (Figure 1-3).

Of the 1,281 patients whose smear was examined, 923 (72.0%) had a positive smear for acid-fast bacilli, while 358 (28.0%) had a negative smear. There were 22 MDR patients, which constituted 0.9% of all patients.

Discussion

While tuberculosis was an important health issue in the 19th century, morbidity and mortality due to TB have decreased with effective therapy. However, several factors, such as economic difficulties in developing countries, increment in HIV prevalence, and insufficient implementation of control measures have hampered the decline of TB incidence to the desired levels. Mortality from TB was 3 million per year in the 1990s. According to the 2013 WHO report, 8.6 million TB patients were identified globally, and there were 1.4 million associated deaths. According to this report, TB mortality rate has decreased 45% since 1990, and should be reduced another 5% (to 50%) by 2015.

Since TB is an important cause of mortality worldwide, we also performed a mortality study for the TB patient population in our region. In the present study, the TB mortality rate in our region (2.1%) is slightly lower than that of Addis Ababa (4%), which is part of Ethiopia; however, our mortality rate is slightly higher than that found in a study from Switzerland (1.6%) and similar to that from a study from Taiwan (2.1%). A plausible reason that the mortality rate of our region is lower than that of Addis Ababa might be that MDR TB and HIV infection are observed less frequently in our region. In spite of efficient anti-tuberculosis treatment and advanced microbiological analyses, TB-induced mortalities are still a considerable problem in our era.

Various factors, including aging and comorbidities such as chronic obstructive pulmonary disease, cardiovascular disease, diabetes mellitus, gastrectomy, and malignity might change the clinical features of TB. Previous studies have shown that elderly patients have poor treatment outcomes, slightly lower success in treatment, and higher mortality rates compared with youth. Also, it has been reported that pulmonary TB in the elderly is characterized by atypical symptoms, more extensive radiological lesions with lower zone preponderance, higher sputum positivity, more frequent comorbidity, and more frequent side-effects. Lee et al. found that mortality associated with pulmonary TB was higher in the elderly than in younger patients (11.1% vs. 1.3%, p<0.05, respectively). In another study, the success of a nine-month treatment regimen was 87% in the young and 71% in the elderly, while mortality was found in 3% of the young and 21% of the elderly in that study.

In accordance with the findings of previous studies, in our current study, we found that advanced age was strongly associated with TB-related death. Multivariate analysis revealed that the risk of death was increased 12-fold in TB patients between the
ages of 36-65 years and increased 21-fold in TB patients older than 65 years compared to patients with between the ages of 0-35 years. We suggest that higher mortality risk in elderly patients can be attributed to increased comorbidities, higher frequency of malnutrition, weak cellular and humoral response, more common drug side effects, and that elderly persons are more likely to be living in public places, such as nursing homes, which can cause delays in diagnosis and treatment.

It is known that TB mortality is higher in males than in females\(^{14}\). In addition, TB is also more frequently also observed in males\(^{15}\). Consistent with previously published results, we observed that the frequency (54.7% vs. 45.3%) and mortality (2.5% vs. 1.6%) of TB disease was higher in males than females. The increased frequency of TB disease in men is most likely due to their increased environmental exposure risks and higher admission rates to tuberculosis dispensaries for diagnosis and treatment. Also, another reason for higher mortality rate in males may be a consequence of lower compliance to completing TB treatment than women.

Other factors associated with mortality are categories and the case definitions of TB patients. In a retrospective study including 2,674 TB patients, Kolappan et al reported that Category II patients had a higher mortality rate than those in Category I and Category III\(^{16}\). In that study, patients with treatment failure had a higher mortality than patients who defaulted on treatment. Another study by Furin et al. evaluated the outcomes of Category II patients treated between 2007 and 2009 in Georgia; they found that 366 of 6,633 Category II patients (5.5%) receiving treatment died\(^{17}\). Mehra et al. observed that Category II patients have a significantly lower success rate of therapy as compared to relapse patients\(^{18}\). Further, Shen et al. reported that relapse cases were associated with mortality during anti-TB treatment\(^{19}\). In the current study, we observed higher mortality rates in relapse (5.1%) and Category II patients (4.6%). According to Kaplan-Meier analysis with log-rank test, the mortality rates were significantly higher in Category II patients (p=0.006) than in the other category groups. It seems that the treatment regimen for Category II and relapsed patients needs to be re-evaluated.

In a study by Zhang et al., the death rates of pulmonary positive, pulmonary negative, and extra pulmonary TB patients were 2.7%, 3.6%, and 4.3%, respectively\(^{20}\). Similarly, in our current study, PTB and EPTB mortality rates were 2.0% and 2.3%, respectively. Among all EPTB cases, lymph nodes were the most common site of involvement, followed by pleural effusion\(^{21}\). In an important epidemiological research study conducted in the USA, 253,299 cases were analyzed, and EPTB (18.7%), lymphatic (40.4%) and pleural (19.8%) involvement were the most common sites of EPTB\(^{22}\). Of the 2,450 patients included in our current study, 60.6% were PTB, 37.5% were EPTB, and 1.9% had both. In accordance with the results of previous studies, we also observed that TB lymphadenitis (34.8%) and TB pleurisy (32.3%) were the most common manifestation of EPTB.

Tuberculosis meningitis is the most severe manifestation of EPTB; it has a high mortality rate and may be fatal if not treated\(^{23}\). Also, the long term mortality of TB meningitis is significantly high despite standard TB therapy\(^{24}\). Although TB meningitis was a rare manifestation of EPTB in our current study, we found a significant association between it and increased mortality risk. Kaplan-Meier analysis with log-rank test revealed that the mortality rates were significantly higher in those with TB meningitis (p<0.001). In addition, multivariate COX regression analysis for TB related death revealed that the risk of death was increased 6-fold in patients with TB meningitis and increased 5-fold in patients with gastrointestinal TB compared with PTB patients. Since TB meningitis is strongly associated with increased mortality risk, more vigorous clinical management, earlier suspicion and diagnosis, and novel treatment strategies are required.

Our study had several limitations. First, HIV status, which was associated with mortality among TB patients in other studies, was not available in our study cohort. TB patients were not routinely tested for HIV in Turkey until 2012. On the other hand, HIV prevalence is <0.1% in Turkey\(^{25}\). Therefore, we assumed that HIV infection was not significantly associated with mortality among TB patients in our region. Second, the retrospective nature of this study is a methodological limitation.

**Conclusion**

Data from the current study suggest associations between increased TB-related mortality risk and advanced age, TB meningitis, gastrointestinal TB, and receiving Category II treatment. In addition, TB-related mortality was more frequent in males and relapse patients. We suggest that tuberculosis control
programs should pay more attention to the high-risk groups determined in the current and previous studies. Treatment regimens for these risk groups should be considered for revision.

References