



# Risk Factors for Death during Pulmonary Tuberculosis Treatment in Korea: A Multicenter Retrospective Cohort Study

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The data regarding risk factors for death during tuberculosis (TB) treatment are inconsistent, and few studies examined this issue in Korea. The purpose of this study was to evaluate baseline prognostic factors for death during treatment of adult patients with pulmonary TB in Korea. A multicenter retrospective cohort study of 2,481 patients who received TB treatment at eight hospitals from January 2009 to December 2010 was performed. Successful treatment included cure (1,129, 45.5%) and treatment completion (1,204, 48.5%) in 2,333 patients (94.0%). Unsuccessful treatment included death (85, 3.4%) and treatment failure (63, 2.5%) occurred in 148 patients (6.0%). In multivariate analysis, male sex, anemia, dyspnea, chronic heart disease, malignancy, and intensive care unit (ICU) admission were significant risk factors for death during TB treatment. Therefore, male sex, anemia, dyspnea, chronic heart disease, malignancy, and ICU admission could be baseline prognostic factors for death during treatment of adult patients with pulmonary TB in Korea.

**Keywords:** Tuberculosis, Pulmonary; Therapeutics; Mortality, Korea

## INTRODUCTION

The incidence and mortality of tuberculosis (TB) remain high worldwide, with 8.6 million incident cases and 1.3 million deaths in 2012 (1). In Korea, TB is a major health problem with no decrease in notified TB cases during the last decade. It has high mortality rate, which is the highest among the infectious diseases and was 4.9/100,000 persons in 2012 (2-6). Thus the incidence and mortality rate of TB must be reduced, and knowledge of risk factors for death during TB is critical.

Several studies have evaluated risk factors for death during TB treatment, and many factors related to age, sex, bacteriological status, co-morbid conditions, the immune and nutritional status of host, and substance abuse have been suggested (7-21). However, the findings are inconsistent due to differences in the enrolled subjects, the burden of TB in the involved countries, human immunodeficiency virus (HIV) infection prevalence, and socioeconomic status (7-21).

In Korea, which has an intermediate burden of TB and a low incidence of HIV infection (22, 23), few studies with few enrolled patients have examined this issue (11, 21). In an effort to clarify this issue, we herein report the risk factors for death during TB treatment in a large multicenter retrospective cohort in Korea.

## MATERIALS AND METHODS

### Study population

All adult patients older than 18-yr-of-age who were diagnosed and treated for pulmonary TB, and were notified in the Korean Tuberculosis Surveillance System at eight hospitals (greater than 500 beds) in Korea between January 2009 and December 2010, were enrolled. We retrospectively collected clinical, radiographic, and bacteriological status data of these patients. In co-morbid conditions, chronic pulmonary disease was

defined as a non-infectious chronic pulmonary disease such as chronic obstructive pulmonary disease and asthma. Chronic kidney disease was defined as a disease causing a progressive loss in renal function. Chronic heart disease was defined as a disease which needed a long term use of cardiac medications such as coronary artery disease, valvular heart disease, cardiomyopathy, and cardiac arrhythmias. Chronic liver disease was defined as a disease causing progressive destruction and regeneration of liver parenchyma such as chronic viral hepatitis, alcoholic liver disease, and liver cirrhosis. Anemia was defined by World Health Organization guidelines as hemoglobin < 13 g/dL (males) or < 12 g/dL (female) at baseline (24).

Of the 4,502 patients with TB, we excluded patients who displayed extrapulmonary TB (n = 1,005), who had unknown sites of infection (n = 21), who had been transferred to another institute before treatment completion (n = 444), whose final diagnosis was changed to another disease than TB (n = 193), who had interrupted TB treatment for 2 or more consecutive months (n = 178), who had unknown treatment outcomes (n = 172), and who had positive HIV antibodies (n = 8). Finally, 2,481 patients with pulmonary TB were included in this study.

In Korea, a 6-month regimen consisting of a 2-month initial phase of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a 4-month continuation phase of isoniazid, rifampicin, and ethambutol has been recommended by the National Tuberculosis Program (25, 26). Alternatively, a 9-month regimen with isoniazid, rifampin, and ethambutol can be administered (25, 26). Therefore, most patients in this study received daily therapy consisting of isoniazid, rifampin, ethambutol, and pyrazinamide. However, the inclusion of pyrazinamide in the initial regimen was made by clinicians based on each patient's clinical situation. TB drugs were self-administered with the support of trained nurses in Public-Private Mix project during treatment (27, 28).

### Treatment outcomes

For these analyses, we used the World Health Organization definitions and recommendations regarding cure, treatment completion, treatment failure, and death (26). Death was defined as dying during treatment irrespective of cause.

### Statistical analyses

Values are expressed as medians and interquartile range (IQR), or as numbers (percentages) in the text and tables. Categorical comparisons of death versus survival were performed using chi-square tests. To evaluate the risk factors for death during TB treatment, we compared selected clinical variables between the death and survival groups using univariate comparison and subsequent multiple logistic regression. In regression, stepwise and backward selection procedures were used to select variables to be maintained in the final model, with a *P* value of < 0.05 as

the criterion for statistical significance. Calculations were performed using SPSS for Windows version 21.0 (SPSS, Armonk, NY, USA).

### Ethics statement

Permission was obtained from the institutional review board of Chonnam National University Hospital to review and publish patient records retrospectively (IRB No. CNUH-2014-057). Informed consent was waived due to the retrospective nature of the study.

## RESULTS

### Patients' characteristics

Table 1 summarizes the baseline characteristics of the 2,481 pulmonary TB patients. The median age was 50.0 yr (IQR 34.0-66.0

**Table 1.** Baseline characteristics of pulmonary tuberculosis patients

Characteristics	No. (%), median (IQR)	Total
Age (yr)	50 (34-66)	2,481
> 65	686 (27.7)	
Sex, male	1,410 (56.8)	2,481
Body mass index (kg/m <sup>2</sup> )	21.2 (19.3-23.5)	1,978
< 18.5	354 (17.9)	
Hemoglobin (g/dL)	13.1 (11.9-14.3)	1,999
Anemia	680 (34.0)	
Symptoms		
Cough	1,210 (48.8)	2,478
Sputum	916 (37.0)	2,479
Dyspnea	431 (17.4)	2,478
Fever	408 (16.5)	2,477
Hemoptysis	243 (9.8)	2,479
Weight loss	295 (11.9)	2,478
Ever smoked	830 (41.8)	1,987
Heavy drinking	212 (13.0)	1,635
Previous TB history	522 (21.0)	2,481
Smear-positive sputum	757 (34.2)	2,211
Culture-positive sputum	1,418 (65.3)	2,172
Cavity (or cavities) on chest radiograph	353 (14.3)	2,477
Bilateral disease	500 (20.2)	2,478
Sites of disease		2,481
Pulmonary TB only	2,090 (84.2)	
Pulmonary and extrapulmonary TB	391 (15.8)	
ICU admission	22 (1.1)	2,036
Co-morbid conditions		
Chronic pulmonary disease	119 (4.8)	2,480
Chronic kidney disease	43 (1.7)	2,480
Chronic heart disease	134 (5.4)	2,480
Diabetes mellitus	366 (14.8)	2,479
Neurologic disease	75 (3.0)	2,479
Chronic liver disease	92 (3.7)	2,480
Malignancy	152 (6.1)	2,481
Initial drug regimen		2,481
HREZ	2,246 (90.5)	
HRE	159 (6.4)	
Others	76 (3.1)	

Data are presented as medians (interquartile range, IQR) for age, body mass index, and hemoglobin and as No. (%) for all other factors. TB, tuberculosis; ICU, intensive care unit; HREZ, isoniazid, rifampin, ethambutol, and pyrazinamide; HRE, isoniazid, rifampin, and ethambutol.

yr), and there were 1,417 males (57.1%). Of 1,551 patients who had drug susceptibility tests, isoniazid-resistant TB, which was defined as resistance to isoniazid alone or isoniazid plus streptomycin (29), and multidrug-resistant (MDR) TB, which was defined as resistant to both isoniazid and rifampin (30), were 61 (3.9%) and 67 (4.3%) cases, respectively. Culture confirmed cases that were positive on a sputum culture for *Mycobacterium tuberculosis* were 1,418 (65.3%) of 2,172 patients who had results of sputum culture.

### Treatment outcomes

Of the enrolled patients, 2,333 (94.0%) had successful treatment, including 1,129 (45.5%) cured patients and 1,204 (48.5%) patients that completed treatment. Unsuccessful treatment occurred in 94 patients, with 85 deaths (3.4%) and 63 treatment failures (2.5%). Of 85 patients who died, TB-related deaths and other causes of deaths were 44 (51.8%) and 41 (48.2%), respectively. All of 63 treatment failure cases had MDR-TB. The median duration between the initiation of TB treatment and death was 41.5 days (IQR 7.0-91.3 days).

### Risk factors for death

In risk factors for all cause of death during TB treatment, advanced age (> 65 yr), male sex, low body mass index (BMI, < 18.5 kg/m<sup>2</sup>), anemia, dyspnea, positive sputum smear, bilateral disease, chronic pulmonary disease, chronic heart disease, diabetes mellitus, neurologic disease, malignancy, different initial drug regimens, and admission to an intensive care unit (ICU) at the start of treatment were significant in univariate analyses. However, in multivariate analyses, male sex, anemia, dyspnea, chronic heart disease, malignancy, and ICU admission were

significant (Table 2).

In risk factors for TB-related death, advanced age, male sex, low body mass index, previous TB treatment, ever smoking, anemia, dyspnea, positive sputum smear, bilateral disease, chronic pulmonary disease, chronic heart disease, diabetes mellitus, neurologic disease, malignancy, and admission to an ICU at the start of treatment were significant in univariate analyses. However, in multivariate analyses, anemia, diabetes mellitus, malignancy, and ICU admission were independent risk factors for TB-related death during TB treatment (Table 3).

## DISCUSSION

The present study is the largest multicenter study in Korea included 2,481 pulmonary TB patients to evaluate risk factors for death during TB treatment. Previous studies included less than 300 patients (11, 21). In this study, independent risk factors for death were male sex, anemia, dyspnea, chronic heart disease, malignancy, and ICU admission.

Old TB patients could have more comorbidities, which alters the presenting symptoms, and atypical radiologic findings compared to young TB patients, which could delay diagnosis and cause high mortality rates (31, 32). Many studies have reported advancing age as a risk factor for death in TB patients (7-10, 12-18, 20). In this study, advanced age was a significant risk factor for death in univariate analyses, but not in multivariate analyses.

Male sex has been reported in other studies as an independent risk factor for death in TB (9, 10, 12-15, 33). Although the reasons for the increased risk of death in males are not well understood, some studies have reported higher rates of treatment default in males, and have suggested that this might be the cause

**Table 2.** Risk factors for all-cause death in pulmonary tuberculosis patients during tuberculosis treatment

Patient characteristics	Survival (n = 2,396)	Death (n = 85)	Univariate analyses		Multivariate logistic regression analyses	
			OR (95% CI)	P value	OR (95% CI)	P value
Age > 65 yr	635/2,396 (26.5)	51/85 (60.0)	4.16 (2.67-6.48)	< 0.001		
Male	1,347/2,396 (56.2)	63/85 (74.1)	2.23 (1.36-3.65)	0.001	3.30 (1.45-7.48)	0.001
Body mass index, kg/m <sup>2</sup> < 18.5	334/1,924 (17.4)	20/54 (37.0)	2.80 (1.59-4.93)	0.001		
Anemia	635/1,944 (32.7)	45/55 (81.8)	9.28 (4.65-18.53)	< 0.001	6.35 (2.84-14.21)	< 0.001
Dyspnea	389/2,393 (16.3)	42/85 (49.4)	5.03 (3.24-7.80)	< 0.001	3.67 (1.82-7.39)	< 0.001
Smear-positive sputum	713/2,133 (33.4)	44/78 (56.4)	2.58 (1.63-4.07)	< 0.001		
Bilateral disease	474/2,393 (19.8)	26/85 (30.6)	1.78 (1.11-2.86)	0.016		
Chronic lung disease	104/2,395 (4.3)	15/85 (17.6)	4.72 (2.61-8.53)	< 0.001		
Chronic heart disease	124/2,395 (5.2)	10/85 (11.8)	2.44 (1.23-4.84)	0.011	2.84 (1.13-7.15)	0.026
Diabetes mellitus	345/2,394 (14.4)	21/85 (24.7)	1.95 (1.16-3.23)	0.010		
Neurologic disease	64/2,394 (2.7)	11/85 (12.9)	5.41 (2.74-10.69)	< 0.001		
Malignancy	127/2,396 (5.3)	25/85 (29.4)	7.44 (4.52-12.27)	< 0.001	11.38 (5.44-23.81)	< 0.001
ICU admission	11/1,981 (0.6)	11/55 (20.0)	44.77 (18.43-108.76)	< 0.001	15.07 (4.47-50.78)	< 0.001
Initial regimen						
HREZ	2,178/2,396 (90.9)	68/85 (80.0)				
HRE	146/2,396 (6.1)	13/85 (15.3)	2.85 (1.54-5.28)	0.001		
Others	72/2,396 (3.0)	4/85 (4.7)	1.780 (0.63-5.01)	0.275		

Data are presented as No. (%). OR, odd ratio; CI, confidence interval; ICU, intensive care unit; HREZ, isoniazid, rifampin, ethambutol, and pyrazinamide; HRE, isoniazid, rifampin, and ethambutol.

**Table 3.** Risk factors for tuberculosis-related death in pulmonary tuberculosis patients during tuberculosis treatment

Patient characteristics	Survival (n = 2,437)	Death (n = 44)	Univariate analyses		Multivariate logistic regression analyses	
			OR (95% CI)	P value	OR (95% CI)	P value
Age > 65 yr	660/2,437 (27.1)	26/44 (59.1)	3.89 (2.12-7.14)	< 0.001		
Male	1,373/2,437 (56.3)	37/44 (84.1)	4.10 (1.82-9.22)	< 0.001		
Body mass index, kg/m <sup>2</sup> < 18.5	343/1,949 (17.6)	11/29 (37.9)	2.86 (1.34-6.11)	0.011		
Previous tuberculosis history	507/2,437 (20.8)	15/44 (34.1)	1.97 (1.05-3.70)	0.040		
Anemia	655/1,968 (33.3)	25/31 (80.6)	8.35 (3.41-20.46)	< 0.001	3.843 (1.27-11.63)	0.017
Dyspnea	408/2,434 (16.8)	23/44 (52.3)	5.44 (2.98-9.92)	< 0.001		
Smear-positive sputum	731/2,169 (33.7)	26/42 (61.9)	3.20 (1.70-6.00)	< 0.001		
Bilateral disease	485/2,434 (19.9)	15/44 (34.1)	2.08 (1.11-3.91)	0.034		
Ever smoking	809/1,952 (41.4)	21/35 (60.0)	2.12 (1.08-4.19)	0.037		
Chronic lung disease	112/2,436 (4.6)	7/44 (15.9)	3.93 (1.71-9.00)	0.004		
Chronic heart disease	128/2,436 (5.0)	6/44 (13.6)	2.85 (1.18-6.86)	0.029		
Diabetes mellitus	352/2,435 (14.5)	14/44 (31.8)	2.76 (1.45-5.26)	0.004	3.64 (1.37-9.68)	0.010
Neurologic disease	71/2,435 (2.9)	4/44 (9.1)	3.33 (1.16-9.56)	0.042		
Malignancy	138/2,437 (5.7)	14/44 (31.8)	7.77 (4.03-15.00)	< 0.001	13.97 (5.30-36.79)	< 0.001
ICU admission	16/2,006 (0.8)	6/30 (20.0)	31.09 (11.20-86.31)	< 0.001	16.16 (3.77-69.35)	< 0.001

Data are presented as No. (%). OR, odd ratio; CI, confidence interval; ICU, intensive care unit; HREZ, isoniazid, rifampin, ethambutol, and pyrazinamide; HRE, isoniazid, rifampin, and ethambutol.

of unsuccessful outcomes (34, 35). However in this study, patients who defaulted were excluded before analysis. Therefore, other factors including differences in treatment adherence, alcohol abuse, smoking behavior, and utilization of health services, between males and females might explain this result.

Anemia has been suggested as a risk factor for death in patients with TB (7, 8, 17, 19). Some authors suggested that it might be influenced by HIV infection because anemia is a well-known risk factor for a poor outcome of this disease (8, 36). However, our study excluded patients with HIV infection and was conducted in a country with a low HIV prevalence (22). Anemia remained an independent risk factor for death in patients with pulmonary TB. A recent study also showed that anemia was a risk factor for death in HIV-negative TB patients (17). This may be a consequence of poor nutritional status in patients with TB (11). In our study, BMI lower than 18.5 kg/m<sup>2</sup> was higher in patients who died compared to survivors; however, it had no significance in multivariate analyses.

Dyspnea was an independent risk factor for death in patients with pulmonary TB in this study. Dyspnea could be caused by respiratory co-morbid conditions and extensive TB lung involvement. Respiratory co-morbid conditions, such as chronic obstructive pulmonary disease, have been suggested as risk factors for death in patients with TB (9, 15, 20). Extensive disease noted on radiologic findings could also be a risk factor for a poor outcome in TB patients (16, 20). In this study, chronic lung disease was a risk factor in univariate analysis; however, it did not reach statistical significance in multivariate analysis. Other comorbid medical conditions have also been suggested as risk factors for death in TB patients (16, 18). In this study, chronic heart disease and malignancy were independent risk factors for death in patients with pulmonary TB and diabetes mellitus was

an independent risk factor for TB-related death. These medical comorbidities may cause more severe disease, impaired recovery, or delayed diagnosis.

ICU admission as a risk factor for death in pulmonary TB patients is not surprising due to the high rate of mortality in these patients (37, 38). The mortality rate due to acute respiratory failure in TB patients has been reported to be 70%-100% (37, 38). In this study, although the incidence of ICU admission was only 1% of enrolled patients, the mortality rate was 50% in these patients.

MDR-TB has been suggested as risk factor for death in previous studies (8). However in this study, death in MDR-TB (4/67, 5.9%) was not significantly different from death in non-MDR-TB (35/1,484, 2.4%,  $P = 0.084$ ). Small number of MDR-TB and absence of results for long term survival might cause the difference in survivals of MDR-TB between this study and previous studies.

This study had several limitations. First, we did not evaluate the socioeconomic status of patients. Some socioeconomic factors, including education level, comprehension difficulties, unemployment, homelessness, and rural dwelling, were reported to be risk factors for death (17). Second, compliance with TB treatment was not evaluated. Third, we did not evaluate long-term outcomes. Fourth, the outcomes of patients who were transferred to another institution were not evaluated. Although the causes were not evaluated, some patients might be transferred to another institution due to worsening conditions during TB treatment, which might have influenced the results of this study. Finally, all patients evaluated in this study were enrolled in Korean hospitals that had more than 500 beds. This may limit the generalizations of our findings for TB patients in Korea.

In summary, the mortality rate of pulmonary TB in Korea was high, at 3.7%. The risk factors for death during TB treatment are advanced age, male sex, anemia, dyspnea, chronic heart disease, malignancy, and ICU admission.

## DISCLOSURE

The authors declare that they have no competing interests.

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