



# Survival and Predictors of Death after Successful Treatment among Smear Positive Tuberculosis: A Cohort Study

Mahmood Moosazadeh, Abbas Bahrampour, Mahshid Nasehi<sup>1</sup>, Narges Khanjani<sup>2,3</sup>

Department of Biostatistics and Epidemiology, Faculty of Health, Kerman University of Medical Sciences, Kerman, Iran, <sup>1</sup>Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran, <sup>2</sup>Environmental Health Engineering Research Center, Kerman University of Medical Sciences, Kerman, Iran, <sup>3</sup>Monash Centre for Occupational and Environmental Health, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

#### Correspondence to:

Dr. Narges Khanjani, Faculty of Health, Kerman Medical University, Kerman, Iran. E-mail: n\_khanjani@kmu.ac.ir

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#### ABSTRACT

**Background:** Tuberculosis (TB) can affect patients' life even after successful treatment. In this study, we aimed to determine the survival rate of patients with smear positive TB after successful treatment and identify the predictors of mortality.

**Methods:** This was a prospective study. The source of data was the TB registry system in Iran and 964 patients were eligible for the study. The life table was used to determine the annual survival rate. Survival curves were estimated using Kaplan–Meier and were compared using the log-rank test. In order to determine the predictors of survival, four models of Cox regression, exponential, Weibull and log-logistic fitted and finally exponential model with minimum akaike information criteria and Bayesian information criterion values were selected. Then, variables with significant levels <0.2 in univariate analysis were entered into the multivariate model. Hazard ratios with a confidence interval of 95% were used to measure the association.

**Results:** A total of 149 patients (15.5%) died during the follow-up period. The median of survival time after successful treatment was 10.5 years and survival probability for 11 years after successful treatment was 70%. Furthermore, previous TB treatment, high age, suffering from kidney failure and cancer were predictors of mortality after successful treatment.

**Conclusions:** This study showed that positive smear pulmonary tuberculosis even after successful treatment has an adverse effect on the patients' survival and leads to a decrease in their survival rate in the long run. Furthermore, individuals with a history of previous TB treatment had much lower survival rates.

Keywords: Successful treatment, survival, tuberculosis

# **INTRODUCTION**

Despite the availability of effective therapy, tuberculosis (TB) is one of the main problems in the most countries. Based on available statistics, about one-third of the world's population are infected with *Mycobacterium* TB and approximately nine million of those died due to TB.<sup>[1-4]</sup> Nevertheless, it can be

declared that this disease is one of the main reasons of death among infectious diseases worldwide.<sup>[4]</sup> According to one of the recent reports, 75% of people with TB belong to the economically active age group (15-54 years) and 95% of the cases and 99% of deaths occur in developing countries.<sup>[5]</sup> Also, TB is the cause of 25% of preventable deaths all of which are in the economically active age groups.<sup>[6]</sup>

In a study in Brazil, Albuquerque *et al.* followed-up 1459 patients from May, 2001 to June 30, 2007. The mean follow-up time was 1753.7 days (the range was 4-2371). At the end of the follow-up period, the probability of survival after anti-TB treatment was 95.9% with confidence intervals (CI) of (94.8-97.0%).<sup>[7]</sup> In a study in Vietnam with the survival median of 19 months, 6% of patients died after the completion of treatment.<sup>[8]</sup>

In a cohort study in Mexico, 305 patients with pulmonary tuberculosis (PTB) diagnosed in 1998, were visited during 2004-2006 and 2008-2009. The average and the median follow-up time of each patient for the entire cohort were 2032 and 2137 days, respectively. The incidence of mortality was 4.6 in 100 person-years. Of the 78 deaths from PTB, 25% died during the 6 months treatment, 38% died until the end of the 1<sup>st</sup> year of diagnosis, 53% died before the 2<sup>nd</sup> year, 72% after 3 years, 86% after 4 years, and 92.3% after 5 years; only one of the 78 patients survived for 7 years and over.<sup>[5]</sup>

It has been recommended that the treatment outcome may not reflect final patient status, in part due to pulmonary impairment after TB disease.<sup>[5,9,10]</sup> Identifying the characteristics of TB patients who died after successful treatment led to recognition of vulnerable populations and exploration of interventional designs for improving public health.<sup>[11]</sup>

There are little documentations on mortality after successful treatment in patients with smear positive PTB at the international level. Also, the authors' knowledge indicates that, no such studies have been done in Iran and there is no evidence of any published articles. Based on the above-mentioned importance, in this study, the rate of survival and predictors of mortality after successful treatment were determined in patients with positive smear PTB in northern Iran (Mazandaran).

# **METHODS**

The present study is a prospective study. The source of data was the TB registry in Iran. The eligibility criteria included smear positive TB patients with Iranian nationality who received a period of 6 months treatment and who were recorded in the group of successful treatment. Time of diagnosis and start of treatment of these patients were between 2002 and 2009. The sampling method was census and all of the cases entered the study. The number of eligible patients who entered the cohort were 997 cases. Samples were followed-up until the end of year 2012.

In order to extract the basic data of patients, a check list was designed based on variables in the TB recording software. The instrument for data collection included variables of sex (male, female), age (year), place of residence (urban, rural), suffering from HIV/AIDS (yes, no, not tested), history of TB treatment (yes, no), result of sputum smears at the beginning of treatment (1-9 Bacilli, 1 positive, 2 positive, 3 positive), result of sputum smears at the end of the 2<sup>nd</sup> month of treatment (negative, 1-9 Bacilli, 1 positive, 2 positive, 3 positive), suffering from diabetes (yes, no), renal failure (yes, no), cancer (yes, no), smoking (yes, no), treatment outcome (cure, completion of treatment), vital status at the end of follow-up (alive, dead, missing) and the date of death by initiation of the study. Data were recorded in a checklist by the interviewers. The content validity of this check list was confirmed using opinions of experts and available papers. Due to the objectivity of variables included in the checklist, determining its reliability was not necessary; however, in order to ensure the reliability, data of 20 patients were extracted by two interviewers whose agreement coefficient was 100%.

After entering the study, each patients' vital status was actively evaluated. If after successful treatment the patient with TB died for any reason (since the exact cause of death had been unclear), it would be considered as an event and his date of death was considered as time of the event. The survival time was measured from the date of recording the successful treatment to the date of the latest information received from the patient's condition. If there was no access to the patient for determining their vital status, they were considered as missing and any patient who did not suffer from event until the end of follow-up, was considered as censored. The demographic and clinical variables of missing cases were compared with those whose vital status has been determined. In order to compare the distribution the of data between the two groups of deceased and survived patients, Chi-square test or Fisher's exact test was used for classifying variables and performing independent *t*-tests. The data had a normal distribution) and was used for comparing the mean age between the two groups.

The mortality incidence rate was expressed in terms of cases per 1000 person-years of follow-up. Life table was used to calculate death and survival rate. In the bivariate analysis, survival curves were estimated using the Kaplan–Meier curves and were compared using the log-rank test.

To determine factors affecting survival and to study the confounding epidemiological and clinical variables, four models of Cox regression, exponential, Weibull and log-logistic were first fitted and then based on the lowest values of akaike information criteria (AIC) and Bayesian information criterion (BIC) the best regression model was selected. Before using these models, prerequisites for using the models were examined. First, the constant proportional hazards assumption over time was tested in terms of the studied variables using graphic methods and goodness-of fit analysis using Schoenfeld residuals. Then, the condition of constant risk over time was studied in order to use the exponential model. After univariate analysis, variables with the significant level <0.2were entered into the multivariate model in order to determine the predictors of mortality after successful treatment for patients with positive smear PTB. Hazard ratios with their 95% CI were used to measure association. All tests were two-tailed and P < 0.05 was considered to be significant levels.

The current project was approved at the Research and Technology Deputy of Kerman University of Medical Sciences with Code No. 92-136. In addition, the authors obtained the informed consent from all participants in the study. Meanwhile, the name of the patients was not recorded in the check list and each patient was identified through a specific number, the name of the city and the diagnosis year. Also, researchers considered all aspects of patients' privacy during and after the implementation of the study.

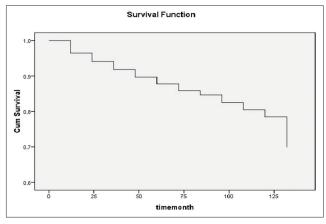
# RESULTS

In this cohort, 1158 cases with smear positive PTB were recorded, but 133 patients were excluded because their treatment outcome was not successful. They suffered from treatment failure or their treatment was discontinued due to death during the treatment, wrong diagnosis and absence of treatment. Also, 27 cases were excluded because of nonIranian nationality. Ultimately, 997 patients with smear positive PTB were enrolled in the cohort.

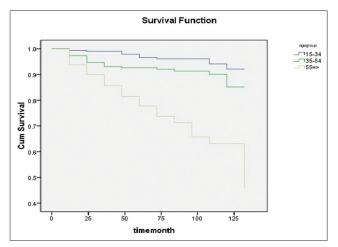
Among patients with successful treatment, 33 cases (3.3%) were missing, but their survival status was not significantly different when determined in terms of gender (P = 0.2), mean age (P = 0.9) and previous TB treatment (P = 0.1), the result of sputum smear before treatment (P = 0.2) and the result of sputum smear at the end of the 2<sup>nd</sup> month of treatment (P = 0.9). Due to the minimum number of missing and the proper sample, the missing cases were not estimated and the survival analysis was performed on 964 cases with positive smear PTB.

The entire of follow-up time period was 5756 person-years. The median survival time was 10.5 years. The mean survival time, the probability of survival at the end of the 1st year of follow-up and the probability of survival at the end of follow-up time period was 9.2 (standard error[SE] = 0.196% (SE = 0.16) and 70% (SE = 0.8)respectively [Figure 1]. In the age group of 55 years and older, the probability of survival was 46% (SE = 0.6) [Figure 2]. Also, the cumulative survival rate at the end of the follow-up period (the  $11^{\text{th}}$  year and more) was 62% (SE = 1.3) in the group with previous TB treatment and 70% (SE = 0.8) in the group without previous TB treatment. It should be noted that the highest mortality rate was (11%) in the last follow-up year (11 years and above) and (4%) in the first follow-up year, respectively.

A total of 149 patients (15.5%) with positive smear PTB died during the follow-up period. This means that the mortality incidence rate in patients with positive smear PTB was 25.9/1000 person-years. The mean age of all patients was  $20.6 \pm 48.6$  and the mean age was  $63.8 \pm 17.9$  in the death group and  $45.8 \pm 19.9$  in the survival group and this difference was statistically significant (P > 0.001). Table 1 illustrates the distribution of demographic and clinical variables among survived and expired patients with PTB.



**Fisgure 1:** Survival curves of smear positive tuberculosis after successful treatment



**Figure 2:** Survival curves of smear positive tuberculosis after successful treatment by age group

According to this table, the majority of expired patients was male (16.3% vs. 14.4%) and the death rate in the age group of 55 years and over was more than that in the age groups of 35-54 and 15-34 years. Also, the frequency of patients with a history of TB treatment, a sputum smear result of 2 positive and over, diabetes, kidney disease, cancer, smoking and HIV/AIDS is more in the deceased group than in the survival group.

To investigate factors affecting mortality, assumptions of applying Cox regression tests were assessed and the results indicated that the risk of the event over time had no significant difference among the studied variables (P = 0.1). Also censorship during cohort had been random and had no connection with the investigated event. It should be noted, the risk value has been a constant value over time and has not depended on time and it

**Table 1:** Distribution of clinical and demographic

 characteristics among successfully treated smear positive

 TB patients

Variables	ables n n (%)			Р
		Death	Survived	
Total	964	149 (15.5)	815 (84.5)	-
Gender				
Male	540	88 (16.3)	452 (83.7)	0.2
Female	424	61 (14.4)	363 (85.6)	
Age group				
15-34	303	13 (4.3)	290 (95.7)	$\leq 0.001$
35-54	261	24 (9.2)	237 (90.8)	
55≤	400	112 (28)	288 (72)	
Previous TB treatment				
No	909	131 (14.4)	778 (85.6)	0.001
Yes	55	18 (32.7)	37 (67.3)	
Treatment result				
Cured	816	117 (14.3)	699 (85.7)	0.01
Complete treatment	148	32 (21.6)	116 (78.4)	
The result of sputum				
smear before treatment				
1-9 bacile and	353	48 (13.6)	305 (86.4)	0.1
one positive				
2 and 3 positive	611	101 (16.5)	510 (83.5)	
The result of sputum				
smear at the end of				
2 months treatment				
Negative		136 (15.5)		0.5
Positive	85	13 (15.3)	72 (84.7)	
Diabetes				
No		123 (14.9)	· · · · ·	0.1
Yes	140	26 (18.6)	114 (81.4)	
Renal disease				
No	944		805 (85.3)	≤0.001
Yes	20	10 (50)	10 (50)	
Cancer				
No		139 (14.9)		0.01
Yes	30	10 (33.3)	20 (66.7)	
Smoker				
No	784	· ,	665 (84.8)	0.3
Yes	180	30 (16.7)	150 (83.3)	
HIV/AIDS				
No	38	9 (23.7)	29 (76.3)	0.3
Yes	12	4 (33.3)	8 (66.7)	

TB=Tuberculosis

was feasible to use Cox, Weibull, exponential and log-logistic (P = 0.7). According to Table 2, the lowest AIC and BIC was in the exponential model and among the four regression models of Cox, exponential, Weibull and log-logistic and accordingly, to determine factors affecting the survival, the exponential model was used.

Results of univariate survival analysis indicated that the mortality rate in females was 20% less than that in males and in the age group of 55 years and older, it was 7.9 times higher than the age group of 15-34 years. In patients with a history of TB treatment it was 2.5 times higher than those without previous TB treatment and in patients with complete treatment results, it was 20% more than that in patients with the cured treatment results. In patients with sputum smear of 2 positive and 3 positive, it was 30% more than that in patients with 1-9 Bacillus and 1 positive, in patients with positive sputum smears at the end of the 2<sup>nd</sup> month of treatment, it was 20% more than patients with negative smears. In diabetic patients, it was 40% more than that in nondiabetic patients, in cancerous patients; it was 2.7 times more than that in noncancerous patients. In patients with renal failure, it was 5 times more than that in patients without renal failure and in smokers: it was 20% more than that in nonsmokers. It should be noted that since the data related to the variable of HIV/AIDS was accessible only in 50 cases and other cases were missing; it was not entered into the model [Table 3].

Then, for removing the effect of confounding factors affecting survival of patients with positive smear PTB; results of variables with a significant level of <0.2 were entered into a multivariate model. The findings of the exponential regression multivariate test showed that the mortality rate in patients with a history of TB treatment was 2.9 times higher than that in patients without the history of previous TB treatment, and in patients with positive sputum smear at the end of the  $2^{nd}$  month of treatment, it was 40% more than in patients with negative smear. In diabetic patients, it was 30% lower than that in nondiabetic patients and in patients with renal failure it was 4.1 times higher

Model	AIC	BIC
Cox regression	1813.5	1842.7
Weibull regression	1042.8	1081.7
Exponential regression	1040.9	1075
Log-logistic regression	1043.5	1082.5

AIC=Akaike information criteria, BIC=Bayesian information criterion

than that in nonrenal failure, and in cancerous patients it was 90% more than that in noncancerous patients. It should be noted that the role of diabetes and sputum smears at the end of the 2<sup>nd</sup> month of treatment was not statistically significant [Table 4].

#### DISCUSSION

In this study, the survival rate after successful treatment of patients with positive smear PTB and its influential factors were investigated, it was shown

**Table 3:** Univariate exponential regression model of factors associated with death among successfully treated smears positive TB patients

Variables	HR	CI	Р
Gender			
Male	-	-	-
Female	0.8	0.6-1.2	0.36
Age group			
15-34	-	-	-
35-54	2.2	1.1-4.4	0.01
55≤	7.9	4.5-14.1	< 0.001
Previous TB treatment			
No	-	-	-
Yes	2.5	1.5-4.1	< 0.001
Treatment result			
Cure	-	-	-
Complete treatment	1.2	0.8-1.8	0.28
The result of sputum			
smear before treatment			
1-9 bacile and one positive	-	-	-
2 and 3 positive	1.3	0.9-1.8	0.53
The result of sputum smear at			
the end of 2 months treatment			
Negative	-	-	-
Positive	1.2	0.7-2.1	0.15
Diabetes			
No	-	-	-
Yes	1.4	0.9-2.1	0.12
Renal disease			
No	-	-	-
Yes	5	2.6-9.5	< 0.001
Cancer			
No	-	-	-
Yes	2.7	1.4-5.1	0.003
Smoking daily			
No	-	-	-
Yes	1.2	0.8-1.8	0.35

TB=Tuberculosis, HR=Hazard ratio, CI=Confidence interval

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Table 4: Multivariate exponential regression model of			
factors associated with death among successfully treated			
smear positive TB			

Variables	HR	CI	Р
Age group			
15-34	-	-	-
35-54	2.3	1.2-4.5	0.01
55≤	8.3	4.6-14.8	< 0.001
Previous TB treatment			
No	-	-	-
Yes	2.9	1.8-4.8	< 0.001
The result of sputum smear at			
the end of 2 months treatment			
Negative	-	-	-
Positive	1.4	0.8-2.5	0.22
Diabetes			
No	-	-	-
Yes	0.7	0.4-1.1	0.09
Renal disease			
No	-	-	-
Yes	4.1	2.1-8.1	< 0.001
Cancer			
No	-	-	-
Yes	1.9	1.03-3.8	0.04

TB=Tuberculosis, HR=Hazard ratio, CI=Confidence interval

that the survival rate in 11 years after successful treatment was 70% and the survival rate in male patients, age group of 55 years and over, in patients with a history of previous TB treatment, in patients with the completion of treatment, in patients with sputum smear of 2 positive and 3 positive, patients with positive sputum smear at the end of the 2<sup>nd</sup> month of treatment, diabetic patients, patients with kidney failure, cancerous patients and smoking patients was lower. Also, variables of TB treatment, high age, simultaneous kidney failure and cancer were predictors of mortality after successful treatment in patients with smear positive PTB.

In a study by Albuquerque *et al.*, the survival rate of 1459 patients identified from 2001 to 2003 was studied in 2007. In this study, the possibility of survival 7 years after anti-TB treatment was 95.9%, which is more than the survival rate in the current study. This might be due to the difference in the follow-up period. The follow-up period in the study by Albuquerque *et al.* was 7 years while in the present study, it was 11 years. Also, variables of age, delay in treatment, and simultaneous HIV/AIDS

infection, losing weight and history of previous TB treatment determined the mortality in patients with TB<sup>[7]</sup> that except for the synergetic impact of TB and HIV/AIDS which was not examined in this study, in other cases, they are consistent with the results of the present cohort.

In an 11 year follow-up period in a Spanish cohort, 762 recorded TB patients from the years 1995 to 1997 with successful treatments were followed-up to 2005. Among them, 173 patients (22.7%) died and the death rate was 3.4/100 person-years. From all TB patients, 178 (23.4%) cases were HIV-positive, 134 (17.6%) were injection drug users (IDU) and 208 (27.3%) were alcohol users. Also, predictors of death included age of 41-60 years, age of >60 years, alcohol consumption and HIV-infected IDU.<sup>[11]</sup> According to the present study, the death rate is higher than that in the present cohort, the probable reason of this difference might be the features of patients in two cohorts and the risk of death which has been higher in the cohort of Spanish patients.

In a cohort in Mexico,<sup>[5]</sup> the survival rate of 305 patients with PTB recorded from 1998 to 2005 from the diagnosis time until 2009 were studied. Age of 45 years and older and the treatment period <6 months were considered as factors contributing to low survival of patients. Also, out of them, 78 patients (25.6%) died with a death rate of 4.6/100 person-years. At least two reasons might explain higher death rate compared to the present study. First, in Mexican cohort,<sup>[5]</sup> the patients who died during treatment were entered into the study and 25% of 78 deaths occurred during the treatment period. Another reason might be that patients with inappropriate treatment (absence and failure of the treatment) were part of the cohort population and most likely had a higher mortality risk and 92.3% of the deaths occurred in the first 5 years after diagnosis and as a result, the person-year of people at risk has been at lower.

Vree *et al.* studied the survival status of 304 patients with positive smear PTB in the cohort until 2 years after the completion of treatment. The median survival after the completion of treatment was 19.4 months. Also, 15 patients (6%) died<sup>[8]</sup> and the mortality rate was lower than that in the present study and its possible cause is probably the longer study period.

In a retrospective cohort, in order to evaluate the effect of diabetes on the result of

treatment and long-term survival, patients with multidrug-resistant (MDR)-TB were followed for 8-11 years. Of 1407 patients with MDR-TB, 239(17%) suffered from diabetes. The mean survival time in patients with MDR-TB and diabetes was lower than that in patients with MDR-TB without diabetes (102 months vs. 114 months, P = 0.001).<sup>[12]</sup> In a retrospective cohort in Maryland, Dooley et al. studied the effect of diabetes on the treatment of patients with TB. Out of 297 patients with TB, 42 patients (14%) had diabetes mellitus. The risk of death in patients with diabetes mellitus was twice of that in patients without diabetes. After adjusting based on HIV virus infection status, age, weight and nonindigenous nationality, the risk of death in diabetic patients was 6.5 times more than that in nondiabetic patients.<sup>[13]</sup> In this study, in a univariate model, the death of cases with smear positive PTB in diabetic patients has been higher than that in diabetic patients, while the differences between the two groups have not been significant. Also, after the modification of the effect of other variables in the multivariate model, the mortality rate in diabetic patients has become nonsignificantly lower than that in nondiabetic patients. Diabetes has been reported as an important risk factor in activating latent TB in various studies due to weakening the immune system. In some studies among diabetic patients, the prevalence of TB is 2-3 times more than that in nondiabetic patients<sup>[1,14-18]</sup> and in this cohort, a significant percentage of patients with positive smear PTB had diabetes too. Also, studies showed that the rate of successful treatment in diabetic patients with TB is lower than that in nondiabetic patients with TB, therefore, among diabetic TB patients with a higher risk of death, some cases failed treatment and were excluded from the cohort and the remaining cases had a healthier clinical status which can be one of the reasons for the lack of consistency of these results.

In a cohort, Oursler *et al.* indicated that the strongest predictors of mortality in patients with positive smear PTB included diabetes mellitus, renal transplant failure and chronic destructive diseases of the lungs and AIDS.<sup>[19]</sup> In another cohort, the survival status of 333 HIV-infected patients treated for TB was evaluated. The mortality rate has been 5.25/10000 person-years. The survival probability at 30 months was 74%. The mortality risk factors of TB included female sex, age equal to or older than

30 years, having anemia and lack of using retroviral therapy during treatment. Also, the protective factors for survival included CD4 lymphocyte count >200 and anti-TB treatment.<sup>[20]</sup> Also, in a study, it was reported that 2 years after treatment, the survival status in patients with negative smear PTB and HIV is significantly more than that in patients with positive smear PTB and HIV.<sup>[21]</sup>

In this cohort, due to the large number of missing's, the HIV/AIDS variable has not been entered into the model while due to its clinical effect; it was examined without considering the time impact using Chi-square test and showed that the mortality of patients with smear positive PTB in patients with HIV/AIDS has been more than that in patients without HIV/AIDS; however, this difference has not been statistically significant and this lack of significance is probably due to the low sample size in terms of HIV/AIDS. Also, some cases with TB and simultaneous HIV/AIDS who had a higher chance of premature death were excluded from the cohort most likely due to the absence of treatment, treatment failure or death during treatment.

One of the strengths of this study is that it provided valid evidence and documentations for long-term survival of patients with positive smear PTB. One of the limitations of this study is that a large number of patients with smear positive PTB were not examined in terms of HIV/AIDS and the sample size was not adequate for studying the relationship between death under the effect of positive smear PTB and HIV/AIDS.

# **CONCLUSIONS**

The present study showed that after successful treatment the positive smear PTB has an adverse effect on the patients' survival and caused a decrease in their survival rate in long-term. Also, individuals with the history of previous treatment for TB have much lower survival rates.

Given the predictors of mortality after successful treatment in patients with smear positive PTB, it has been suggested that an appropriate strategy be adopted for active prognosis in individuals with diseases weakening the immune system and also their immediate treatment be conducted. Also, in order to make the treatment efficient in patients with positive smear PTB and in order to reduce the recurrence and cutting off the treatment, the directly observed short course treatment should be strengthened.

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