Original Article

Survival Analysis of Tuberculosis Patients Registered in a Rural Tuberculosis Unit of Purba Bardhaman District, West Bengal, India

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Abstract

Background. India is still a high tuberculosis (TB) burden country in the world and risk factors of the disease are also highly prevalent. Survival analysis of TB patients had not been adequately studied, especially in this part of the country. The present study was undertaken to estimate overall survival time of TB patients and to find out association of different co-variates with outcome event (death) and survival time of TB patients.

Methods. A record-based retrospective cohort study was conducted in a Tuberculosis Unit of Purba Bardhaman District, West Bengal, India. All registered TB cases in the unit, excluding resistant cases, between October 2010 to March 2016 were included as study subjects (N=3110) and followed up till June 2017 for outcome of interest. Actual data collection and analysis from relevant registers of the Tuberculosis Unit were carried out during June 2017 to November 2017. Descriptive statistics, Kaplan-Meier survival analysis, Log rank test and Cox proportional hazard model for multivariate analysis were applied.

Results. Of 3110 patients, 6.9% (214) had the outcome event of interest (death). The overall mean survival time was 518 days (95% confidence interval 480.9-555.3). Male gender, category II TB, pulmonary TB and TB with human immunodeficiency virus (HIV) were found to be significant risk factors for death due to TB.

Conclusions. Overall survival time was significantly low among males, re-treatment cases, patients with pulmonary TB and patients with HIV co-infection. Awareness generation, adherence to treatment, early diagnosis and treatment are some necessary measures to be properly implemented. **[Indian J Chest Dis Allied Sci 2020;62:127-132]**

Key words: Tuberculosis, Death, Kaplan-Meier survival analysis

Introduction

Tuberculosis (TB) remains a major health problem and the ninth leading cause of death worldwide. It is the leading cause of death from a single infectious agent, ranking above human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS).[1] It claims three lives every minute.[1] Globally, there were estimated 1.4 million TB deaths in 2015[2] and 1.3 million TB deaths in 2016 and an additional 0.4 million and 374,000 deaths among TB with HIV patients, respectively.[1] HIV and TB form a lethal combination. People living with HIV are 20-30 times more likely to develop active TB disease than those without HIV. Without proper treatment, 45% of HIV sero-negative TB patients and all patients of HIV sero-positive TB will die.[3] In 2016, 40% of HIV deaths in the world were due to TB.[3] Globally, about one million cases of pediatric TB are estimated to occur every year with more than 100,000 deaths. Over 95% TB deaths occurred in low- and middle-income countries.[3] India and China have been the top two high TB burden countries in terms of absolute number of incident cases of TB occurring each year.[4] India accounts for 480,000 and 423,000 of deaths due to TB (excluding HIV+TB) in the year 2015 and 2016, respectively.[1] There were 12000 deaths due to TB with HIV in India in 2016.[1] Diabetes is also an independent risk factor for TB and multiple studies suggested that there is 2-3 times higher chance of progression of latent to active TB among diabetics.[5] Tobacco smoking is another risk factor for TB and contributes to half of male deaths in 25-69 years age group from TB in India.[5]

Survival analysis deals with the measurement of survival time (also called disease-free survival time) and different factors affecting survival of the TB patients. In survival analysis, subjects were usually followed-up over a fixed time-period and a particular point of time was noted while the event of interest had

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occurred. Commonly encountered form in survival analysis is censoring, that is about observations where information about their survival time is incomplete. Right censoring is the most commonly encountered form, when the event of interest had not occurred within follow-up period and in left censoring, the beginning time is not known though the end time is known. Several studies have been conducted on various aspects of TB, but there are few studies that focus specifically on survival analysis of TB patients, especially in India which remained as the highest TB burden country in the world for the period of 2000-2015.[6]

The present study was conducted in a rural tuberculosis unit to estimate overall survival time and to find out association of different co-variates with outcome event (death) and survival time of TB patients registered in the tuberculosis unit under Revised National Tuberculosis Control Programme (RNTCP) (now known as National TB Elimination Programme).

Material and Methods

A record-based retrospective cohort study was conducted from June 2017 to November 2017 in a tuberculosis unit located at Chittaranjan Rural Hospital of Bhatar block, Purba Bardhaman District, West Bengal, India. Study patients were all registered TB cases registered between 4th quarter (October to December) of 2010 to Ist quarter (January to March) of 2016. Drug resistant-TB cases and cases with incomplete data regarding outcome or starting of treatment were excluded. A total of 3282 cases were registered in the tuberculosis unit during the reference period, out of them 3110 study patients were included in the study by complete enumeration technique.

Data regarding age, sex (male/female), date of registration, pre-treatment sputum smear, date of diagnosis, date of starting treatment, classification of TB (pulmonary/extra-pulmonary), type of patient (new/relapse/treatment after default/treatment after failure/others), type of TB (category-I/category-II), co-morbidities (HIV and diabetes), treatment outcome [cured/treatment completed/treatment failure/lost to follow-up (defaulter)/death] and date of outcome were collected from RNTCP TB register and laboratory register of the tuberculosis unit. TB treatment related variables were defined according to the RNTCP definitions of TB cases and treatment outcomes (expressed as a percentage of the number registered in the cohort).

Ethical approval from Institutional Ethics Committee, Burdwan Medical College and Hospital and permission from the District Tuberculosis Officer, Purba Bardhaman were obtained before data collection.

Statistical Analysis

The collected data were compiled, re-checked for consistency and completeness and analysed using Statistical Package for Social Sciences (SPSS, version 20). Study analysed the time to event data by following: time of entry point was the point when diagnosis was made and time of outcome was the point when an event occurred or, declared failure or, declared as defaulter. The difference between these two points was regarded as follow-up time. The primary analysis was overall survival, measured from the date of diagnosis of TB to the date of event (*i.e.*, death). Kaplan-Meier survival analysis was used to estimate survival probabilities and mean survival time (median survival time could not be measured). Then, survival function and hazard function of different groups were compared graphically and also by applying Log rank test statistic to test any significant differences between two survival curves. Cox proportional hazard model was also applied by taking all the biologically plausible factors as explanatory variables and death as dependent variable (coded as, 0=no death, 1=death) to find out any association between them. A P-value <0.05 was considered as statistically significant for all tests.

Results

A total of 3110 eligible cases were studied and most of them were adults (95.8%), males (74.4%), category-I (86.6%) and pulmonary TB (83.2%) cases. Out of 3110 cases, 82.3% had successful outcome (cured 52.2%, treatment completed 30.1%), 9.8% were defaulter/lost to follow-up and 6.9% had the event of interest (death) (Table 1). During the reference period, death as an outcome by type of case revealed that among treatment after failure cases, the proportion was 50% (12/24), followed by 29% (29/100) among treatment after default cases but it was as low as 4.8% among new cases (Table 2).

Table 1. Distribution of study patients according to different treatment outcomes (N=3110)

Outcomes	No. (%)
Cured	1623 (52.2)
Treatment completed	936 (30.1)
Defaulter	306 (9.8)
Failure	31 (1.0)
Death	214 (6.9)
Total	**3110 (100)**

Table 2. Distribution of event of interest (death) according to type of tuberculosis (TB) cases (N=3110)

Type of TB Case	Number of Cases	Deaths No. (%)
New	2694	128 (4.8)
Treatment after failure	24	12 (50)
Relapse	195	34 (17.4)
Treatment after default	100	29 (29)
Others	97	11 (11.3)
Total	**3110**	**214 (6.9)**

Kaplan-Meier survival analysis revealed, overall mean survival time of 518 days (95% confidence interals [CI]=480.9 – 555.3) (Table 3, Figure 1), adult had worse cumulative survival experience than children, but the difference was not statistically significant (P>0.05). Category I TB patients had better cumulative survival than category II and the difference is statistically significant (P<0.05) (Figure 2) and mean survival time of category I and category II TB patients were 491.6 days (95% CI=454.4 – 528.7) and 452.8 days (95% CI=406.9 – 498.7), respectively (Table 3), pulmonary TB patients had better cumulative survival than extra-pulmonary TB patients and the difference was statistically significant (P<0.05) (Table 3). The cumulative survival of HIV sero-negative TB patients was better than HIV sero-positive TB patients and the difference was statistically significant (P<0.05) and the mean survival time of TB patients with HIV co-infection and TB patients without HIV co-infection were 164.3 days (95% CI=100.4 – 228.3) and 519.2 days (95% CI=481.8 – 556.6), respectively (Table 3, Figure 3).

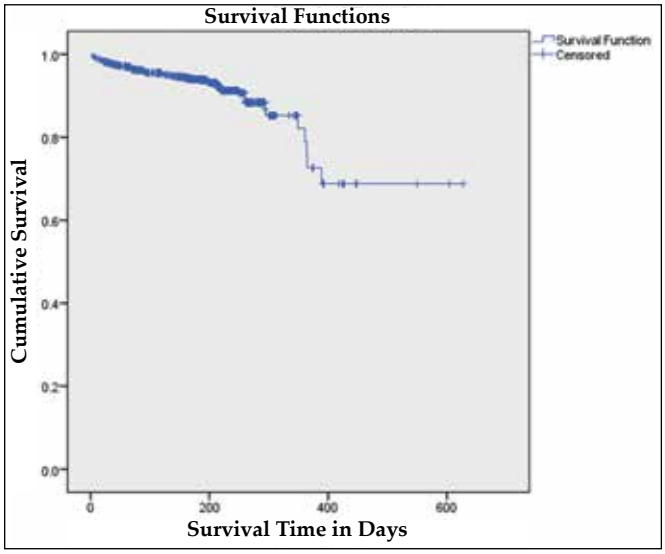


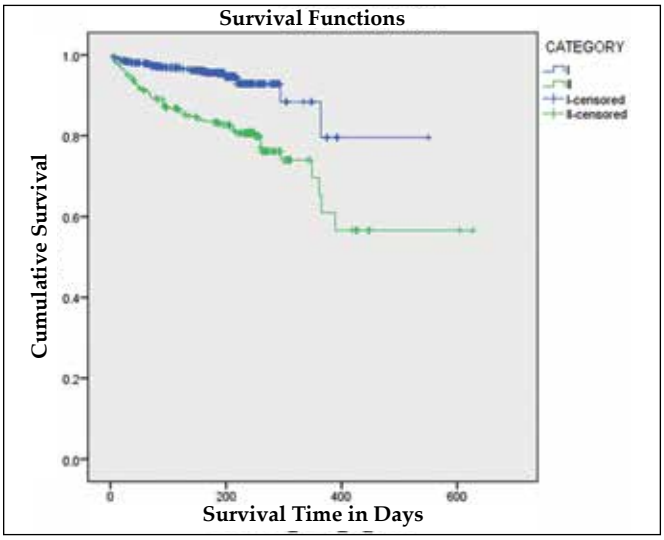
Figure 1. Kaplan-Meier survival curve showing overall survival of the study cases.

Table 3. Mean survival time of study cases according to their certain characteristics (N=3110)

Characteristic	Mean Survival Time (Days)	95% CI	Test of Significance Between Two Survival Curves*
Age (years)			
<15	325.4	317.9 – 332.9	P=0.228
≥15	517.1	479.8 – 554.3	
Gender			
Male	371.2	359.7 – 382.6	P=0.002
Female	512.8	474.5 – 551.1	
Category of TB			
I	491.6	454.4 – 528.7	P=0.000
II	452.8	406.9 – 498.7	
Type of TB			
Pulmonary	513.2	474.9 – 551.4	P=0.000
Extra-pulmonary	370.3	353.9 – 386.7	
TB with HIV			
Present	519.2	481.8 – 556.6	P=0.000
Absent	164.3	100.4 – 228.3	
TB with Diabetes			
Present	542.2	493.6 – 590.7	P=0.664
Absent	496.2	456.1 – 536.2	
Overall	518	480.8 – 555.2	

*Log rank test

Definition of abbreviations: CI=Confidence interval, TB=Tuberculosis, HIV= Human immunodeficiency virus



Log rank test: P=0.000

Figure 2. Kaplan-Meier survival curve of category-I and category-II tuberculosis patients.

All the studied co-variates were biologically plausible, and thus, considered for both univariate and multivariate Cox regression analysis (Table 4). The Cox-model describes the potential association between co-variates and survival time. The dependent variable in this analysis was the 'hazard' (*i.e.*, death). It identified gender (male), category of TB (category II), type of TB (pulmonary TB) and co-infection with HIV as significant risk factors for death of the patients due to TB hazard. TB hazard among males was 1.5 times more than females, 3.2 times more among category II patients than category I, 2.3 times more among pulmonary TB patients than extra-pulmonary TB and 8.8 times more among HIV sero-positive TB patients than HIV sero-negative TB patients (Table 4).

Discussion

The present survival analysis of TB cases registered in a rural tuberculosis unit of West Bengal during a reference period of more than five years revealed useful information regarding survival time, mortality

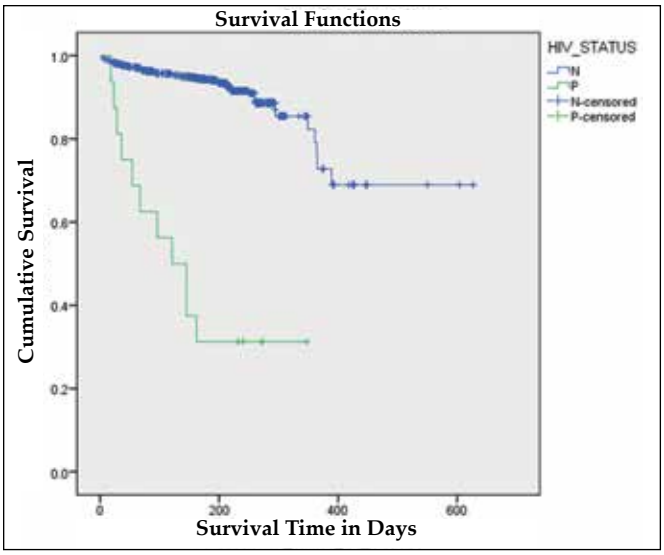


Figure 3. Kaplan-Meier survival curve of tuberculosis patients with human immunodeficiency virus (HIV) and without HIV.

Log rank test: P=0.000

Table 4. Distribution of study cases according to event of interest (death) and co-variates (N=3110)

Co-variates	Total	Deaths No. (%)	Univariate Analysis HR (95% CI)	Multivariate Analysis Adjusted HR (95% CI)*
Age (years)				
<15	132	5 (3.8)	Ref	Ref
≥15	2978	209 (7)	1.714 (0.705 - 4.165)	0.765 (0.302 - 1.933)
Gender				
Female	796	33 (4.1)	Ref	Ref
Male	2314	181 (7.8)	1.803 (1.242 - 2.616)	1.524 (1.047 – 2.219)
Category of TB				
I	2694	128 (4.8)	Ref	Ref
II	416	86 (20.7)	3.57 (2.677 - 4.761)	3.201 (2.395 – 4.278)
Type of TB				
Extra-pulmonary	521	13 (2.5)	Ref	Ref
Pulmonary	2589	201 (7.8)	2.895 (1.650 - 5.080)	2.332 (1.296 – 4.197)
TB with HIV				
Absent	3094	203 (6.6)	Ref	Ref
Present	16	11 (68.8)	11.825 (6.411 - 21.811)	8.804(4.769 – 16.256)
TB with Diabetes				
Absent	2745	190 (6.9)	Ref	Ref
Present	365	24 (6.6)	0.910 (0.595 - 1.392)	0.883 (0.577 – 1.352)

*Cox proportional hazard regression model: The model fitness is good as evident from positive -2 Log likelihood (3265.316).

Definition of abbreviations: HR=Hazard ratio, CI=Confidence interval, TB=Tuberculosis, HIV=Human immunodeficiency virus

experience and few co-relates. According to the present analysis, proportion of total deaths due to TB occurred mostly among the adults (7%), males (7.8%), pulmonary TB (7.8%) and category-II (20.7%) TB patients and 93.1% survived entire follow-up period. Almost similar findings regarding survival ranging from 88.1%[7], 93.7%[8], 94%[9], 94.1%[10], 95.3%[11], 90.4%[12], and 96.6%[13], have been reported.

In the present analysis among 3110 TB patients, besides deaths we found 52.2% were cured, 30.1% completed treatment, 9.8% defaulters, and 1% failed to treatment. Other studies reported different findings as compared to the present study: 40.3%, 38.4%, 14% and 3.8% respectively,[13] and 19% defaulters, 3% failed to treatment.[9]

In the present study, Kaplan-Meier survival analysis showed an overall mean survival time of 518 days (95% CI=480.9 – 555.3). Mean survival time for childhood and adult TB patients was 325.4 days (95% CI=317.9 – 332.9) and 517.1 days (95% CI=479.8 – 554.3), respectively. The difference between them was not statistically significant. This might be due to very small number of childhood TB patients in respect to adults. However, comparable other studies were also lacking.

Present study also observed a high mortality rate among males (7.8%) than females (4.1%), similar to reported in other studies.[10] This might be explained by the fact that, smoking is a risk factor for TB and men smoke more than women; though not assessed in this study.

Out of total 3110 registered patients, survival rate among category I and II patients were 95.2% and 79.3%, respectively, with a lower cumulative survival at the end of intensive phase among category II (91%) patients. The finding is similar to that observed in another study.[11]

Present study showed better cumulative survival among category I TB patients [mean survival time=491.6 days (95% CI=454.4 – 528.7)] than category II [mean survival time=452.8 days (95% CI=406.9 – 498.7)] and the difference is statistically significant as explained from Kaplan-Meier survival analysis. Other reports[3,5] suggested HIV and TB as lethal combination, we also observed the same in the present study and 68.8% of TB patients with HIV died during the period and TB patients without HIV [mean survival time=519.2 days (95% CI=481.8 – 556.6)] had significantly better cumulative survival than TB patients with HIV [mean survival time=164.3 days (95% CI=100.4 – 228.3)]. The findings indicate HIV co-infection as a significant risk factor for the mortality.

The present survival analysis did not reveal any significant difference in mortality experience with diabetes as a co-morbidity. This might be due to use of inappropriate diagnostic criteria for diabetes by the tuberculosis unit as evident from TB register and RNTCP laboratory register. The study identified some risk factors significantly associated with mortality of TB patients: male gender, re-treatment cases (category II), pulmonary TB and presence of HIV co-infection. Some of the risk factors are consistent with the findings reported in other studies (male gender, HIV co-infection and localisation of TB[13], re-treatment cases[9], male gender[7].

Though personal and behavioural characteristics (tobacco smoking, alcohol intake, etc.) have an impact on TB and its outcome, due to non-availability of data, these could not be studied. Another limitation of the study was use of mean survival time, as median survival time could not be calculated. In spite of these limitations, present study could be completed during a period when the treatment and categorisation of TB remained uniform throughout the period as per RNTCP guidelines.

Conclusions

Overall survival time among the tuberculosis patients was quite low and it was reduced significantly among male, re-treatment cases, pulmonary TB patients and patients with HIV co-infection. Awareness generation, adherence to treatment, early diagnosis and treatment are some of the necessary measures to be properly implemented.

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