Original Article

SURVIVAL OF TUBERCULOSIS PATIENTS TREATED UNDER DOTS IN A RURAL TUBERCULOSIS UNIT (TU), SOUTH INDIA

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Summary

***Objective*:** To estimate survival probabilities and identify risk factors for death of tuberculosis (TB) patients during treatment period.

Methods: TB patients registered during May 1999 to December 2004 from a rural TB unit (TU) with a population of 580 000 in Tiruvallur district, South India, formed study population. Life table and Cox's regression methods were used.

***Results*:** Of the 3818 TB patients who were initiated on treatment, 96, 94 and 97% of category – I, II and III respectively, were surviving after completion of treatment. Higher death rates were independently associated with patient's age (45 years), previous history of treatment, alcoholism and initial body weight (<35 kgs).

Conclusion: The survival probability was found to be similar in all patients irrespective of categorization. Necessary actions need to be initiated in the programme to improve body weight and abstain from alcoholism.

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***Key words*:** Tuberculosis, Death, Cox proportional hazard model, Life table, Risk factors.

INTRODUCTION

Tuberculosis (TB) is an infectious disease. It continues to be a leading cause of death[1]. Globally, there are almost nine million new cases of TB each year, two million of which results in death. More than one-third of these cases and deaths are in India and China[2]. TB incidence in India accounts for one fifth of the global incidence[3]. In India, every year, almost 1.8 million new cases occur, of which almost half are infectious and 370, 000 die[3]. Patients with infectious pulmonary TB disease can infect 10-15 persons in a year[3]. Directly Observed Treatment, Short-course (DOTS), strategy in TB control has considerably improved the quality of diagnosis and treatment outcome globally. In India, DOTS was implemented since 1993 for effective management of TB treatment. The goal of TB control programme is to decrease mortality and morbidity due to TB and cut transmission of TB in the community. For the individual patients and the DOT providers, the treatment outcome is of more interest in particular the probability of surviving the disease. The duration of the treatment is also important in deciding the survival of the patients. In this study, we attempted to estimate survival probabilities and identify risk factors for death of TB patients during treatment period.

METHODS

It is a retrospective study from a rural TB unit (TU) with a population of 580000 in Tiruvallur district, South India. The study area includes 209 villages and nine urban clusters scattered across approximately 200 sq. kms. The DOTS strategy was implemented in this area since May 1999[4]. There are 17 governmental health facilities (HFs) participating in the programme and of these, seven offer diagnostic facilities for sputum examination.

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All the patients diagnosed with TB at one of these Health Facilities (HFs) are given DOT in accordance with RNTCP policies[5]. Every dose of treatment is to be directly observed during intensive phase (IP) and at least first of the three doses is to be directly observed during continuation phase.

During May 1999 – December 2004, 5366 TB patients were registered for treatment under DOTS at the HFs in this area. The data on socio- economic demographic profile was collected within a week of starting the treatment and the treatment profile at the end of the IP. Trained field staff interviewed 3818 (71%) patients at their residence and collected information on socio-economic demographic profile, body weight at initiation of treatment, history of previous treatment, smoking and drinking habits, whether they took treatment under supervision and type of DOT provider using a semi-structured questionnaire. Category and treatment outcome were collected from TB register maintained by TU. Category I is defined as all new cases that are sputum smear positive or seriously ill patients with smear negative or extra-pulmonary disease. Category II patients are cases who have had previous anti-tuberculosis treatment. Category III regimen is prescribed to new patients who are smear negative or extra-pulmonary TB and are not seriously ill. The anti-tuberculosis regimens used for Category I, II and III patients were $2H_3R_3Z_3E_3/4H_3R_3$, $2H_3R_3Z_3E_3S_3/1H_3R_3Z_3E_3/5H_3R_3E_3$, and $2H_3R_3Z_3/4H_3R_3$ respectively (H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin. Numbers before the letters indicate the duration of the treatment phase in months and numbers in subscript indicate the number of times the drug is given each week). Treatment for category I and II patients was extended by another month if the sputum smear remained positive at the end of IP. Standard international definitions were followed to classify TB patients according to outcome[5].

Data were scrutinized and entered twice in order to ensure accuracy, corrected for discrepancy and missing information. Life table method was used to estimate survival and hazard functions of survival times of TB patients for three categories separately. Using this analysis survival curves were constructed for the three categories of patients. Wilcoxon (Gehan) test was used to compare survival times of TB patients between categories. The Life

Table 1: Characteristics of TB patients registered under DOTS in a rural district, South India.

Factors	**Total (%)** n = 3818
Sex	
Female	1048 (27)
Male	2770 (73)
Age (Years)	
<45	2013 (53)
≥45	1805 (47)
Education	
Illiterate	1626 (43)
Literate	2192 (57)
Occupation	
Unemployed	935 (24)
Employed	2883 (76)
Weight (Kg)*	
<35	495 (13)
>35	3054 (80)
Smoking*	
No	2230 (58)
Yes	1586 (42)
Alcoholism*	
No	2619 (69)
Yes	1197 (31)
Category	
I	1944 (51)
II	449 (12)
III	1425 (37)

*The number of patients is less than 3,818 due to the non-availability at the time of interview within a week after treatment began.

Table 2: Estimates of life survival and hazard functions for Categories I, II and III

	Category I					Category II					Category III				
Interval	n_j	c_j	d_j	S(t)	h(t)	n_j	c_j	d_j	S(t)	h(t)	n_j	c_j	d_j	S(t)	h(t)
0	1944	20	4	.9979	.0021	449	18	0	1.0000	.0000	1425	22	1	.9993	.0007
1	1920	48	8	.9937	.0042	431	26	4	0.9904	.0096	1402	43	3	.9971	.0022
2	1864	38	2	.9926	.0011	401	26	6	0.9751	.0156	1356	29	4	.9941	.0030
3	1824	35	14	.9850	.0078	369	24	1	0.9724	.0028	1323	22	5	.9904	.0038
4	1775	50	13	.9776	.0075	344	22	0	0.9724	.0000	1296	25	10	.9826	.0078
5	1712	157	10	.9716	.0061	322	19	0	0.9724	.0000	1261	153	6	.9777	.0051
6	1545	809	8	.9648	.0070	303	20	5	0.9558	.0172	1102	757	3	.9736	.0042
7	728	339	1	.9631	.0018	278	72	3	0.9439	.0125	342	196	2	.9656	.0082
8+	388	378	10	.9147	***	203	198	5	0.8986	***	144	142	2	.9392	***

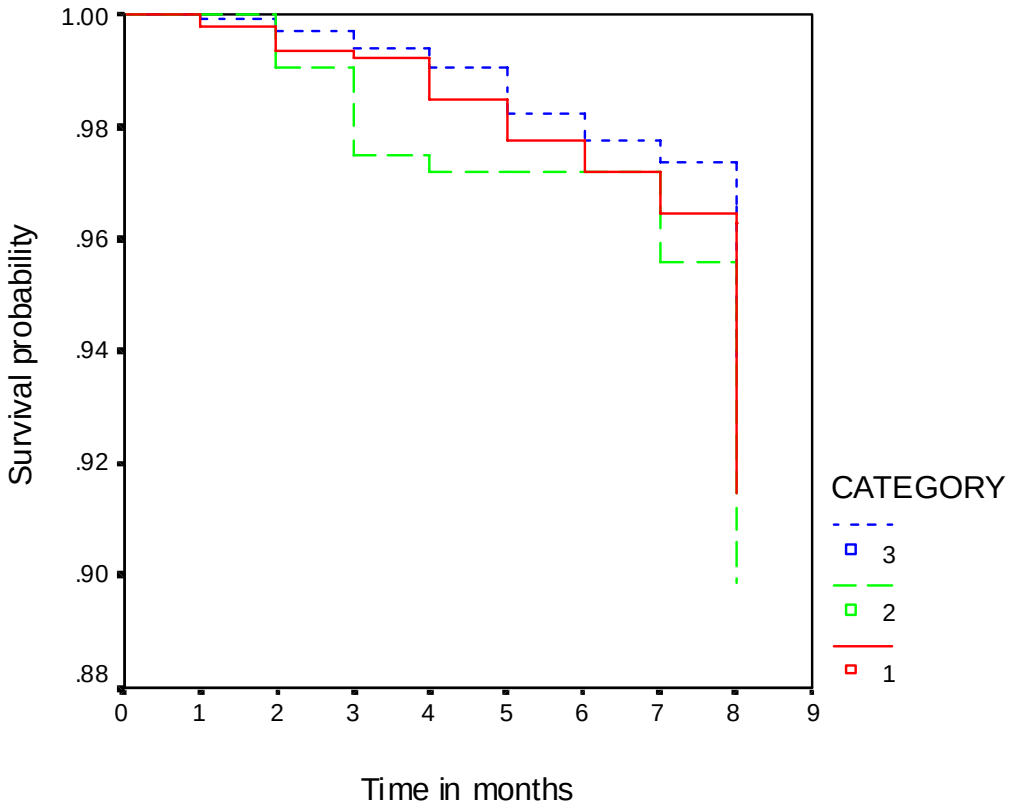

Figure: Survival curves of TB patients under three categories

table estimate of survival function S(t) and hazard function h(t) are given by

$$h(t) = d_j \Big/ (n_j^{/} - d_j / 2)(\tau_j)$$

Where n_j = Number of individual who are alive and therefore at risk of death, at the start of j'th interval
d_j = Number of deaths in the j'th time interval, j =1,2,…,m.
c_j = Number of censored survival time in this interval
$n_j^{/}$ = average number of individuals who are at risk during this interval = $n_j - c_j / 2$
$\hat{o}_j$ = the length of j'th time interval.
Cox's proportional hazards model was performed to identify risk factors for death during treatment period using backward stepwise procedure by SPSS version 10.0. Adjusted hazard ratio and 95% confidence interval (CI) were estimated for the risk factors. The level of statistical significance was defined as $p<0.05$.

RESULTS

Among 3818 TB patients registered under DOTS programme, 2770 (73%) were males, 1805 (47%) were 45 years and above, 3054 (80%) had weight more than 34 kgs, 1626 (43%) were illiterate and 935 (24%) unemployed. The life style indicators for the patients were: 1586 (42%) smokers and 1197 (31%) alcoholics. Of the 3818 patients treated, 1944 (51%) were under category I, 449 (12%) under category II and 1425 (37%) under category III (Table 1). For these patients, the treatment outcomes were as follows: 1538 (40.3%) (Category I- 70.2% and Category II- 38.8%) were cured, 1468 (38.4%) (Category I- 10.0%, Category II-9.8% and Category III- 86.2%) had completed treatment, 535 (14%) (Category I- 11.5%, Category II- 38.5% and Category III- 9.8%) defaulted, 130 (3.4%) (Category I- 3.6%, Category II- 5.3% and Category III- 2.5%) expired, 144 (3.8%) (Category I- 4.7%, Category II- 7.6% and Category III- 1.3%) failed treatment and 3 (0.1%) (Category I- 0.1%, and Category III- 0.1%) were transferred out.

Using Life Table estimate method, survival probabilities of the patients were 99.4%, 99.0% and 99.7% for category I, II and III respectively after the first month of treatment. The corresponding survival probabilities were 98.5%, 97.2% and 99.0% respectively after the three months and 96.3%, 94.4% and 96.6% respectively after seven months of treatment (Table 2). Using Wilcoxon (Gehan) test, there was no significant difference between the survival times of TB patients among the three categories ($p = 0.1$). The survival probability against time in months for category I, II and III is separately shown (Fig). The gap between the three curves distinguishes the difference between survival distributions, where the curve for category II decreases compared to that of category III and I. From this curve, it is understood that the survival probabilities of category III patients is more than category I patients during treatment period but survival probabilities of category II is less than category III and I.

Of the 3818 patients, 305 cases with missing values were excluded for multivariate analysis (Cox proportional hazard model). Of 3513 patients, 109 (3.1%) deaths occurred during treatment period. Duration in months from diagnosis of TB to end of the treatment period and treatment outcomes was measured for 3404 (96.9%) those who were alive at the end of treatment. The variables considered for the model were sex, age, category, education, occupation, body weight at initiation of treatment (<35 kg), history of previous anti TB treatment, smoking and drinking habits, type of DOT providers, whether patient took treatment under supervision in intensive phase and continuation phase. Age (≥45 years), previous history of treatment, alcoholism and body weight at initiation of treatment (<35 kg) were found to be risk factors for death during treatment period. The corresponding adjusted hazard ratios were 2.345 (95% C.I.: 1.557, 3.533), 1.615 (95% C.I.: 1.102, 2.368), 2.015 (95% C.I.: 1.357, 2.992) and 3.709 (95% C.I.: 2.434, 5.652) respectively (Table 3). The other factors namely; sex, category, education,

Table 3: Results of Cox's proportional hazard model of risk factors for death during treatment period.

Factors		No. Registered	No. of Death	p	Adjusted hazard ratio (95% CI)
Sex	Female	965	26		1
	Male	2548	83	0.364	1.317 (0.726, 2.391)
Age	<45Yr	1846	34		1
	≥45	1667	75	< 0.001	2.345 (1.557, 3.533)
Category	I	1784	61		1.189 (0.760, 1.859)
	II	397	17		0.766 (0.390, 1.507)
	III	1332	31		1
Education	Literate	2001	48		1
	Illiterate	1512	61	0.215	1.278 (0.867, 1.883)
Occupation	Employed	2665	72		1
	Unemployed	848	37	0.124	1.375 (0.917, 2.064)
Previous history of treatment	No	2492	64		1
	Yes	1021	45	< 0.05	1.615 (1.102, 2.368)
Smoking	No	2060	57		1
	Yes	1453	52	0.239	0.733 (0.437, 1.229)
Alcoholism	No	2434	59		1
	Yes	1079	50	< 0.005	2.015 (1.357, 2.992)
Type of DOT providers	Government	1388	50	0.379	1.309 (0.718, 2.384)
	Community	1582	45	0.973	0.990 (0.542, 1.807)
Friends, relatives, self and others		543	14		1
Supervision under IP	Always	2619	78		1
	Never	894	31	0.468	1.168 (0.768, 1.778)
Body weight at initial stage of treatment	< 35 kg	488	34	< 0.001	3.709 (2.434,5.652)
	≥ 35	3025	75		1

occupation, smoking, type of DOT providers and supervision under IP were not found to be significant for risk of death during treatment period.

DISCUSSION

Our study findings show that 94-97% of patients were surviving at the end of seven months of anti-tuberculosis treatment, irrespective of categories. A multivariate analysis of the study found that age (≥45), body weight at initiation of treatment (<35 kgs), previous history of treatment and alcoholism were risk factors associated with death during anti-tuberculosis treatment period. A study[6] conducted by our centre in Chennai city showed that 91% patients treated for TB survived the entire follow-up period of 600 days from the date of start of treatment and 9% patients died during the follow-up period. The risk factors identified for TB mortality were young age, male sex, smear postivity, treatment default, treatment failure and the combination of smoking and alcoholism. In the study, survivors were followed up after completion of treatment for a minimum period of 600 days. But our study was confined to the treatment duration and this could be the reason for age (≥45) identified as risk factor. In a study from Netherlands[7], survival probabilities for tuberculosis patients were estimated as 95% after six months of treatment and 6% died within one year while on treatment. The study identified the following risk factors for mortality of tuberculosis patients: male sex, age (>65 years), presence of malignancy, human immune-deficiency virus (HIV) infection, addiction to alcohol or drugs, localization of tuberculosis (pulmonary and extra pulmonary tuberculosis) and type of medical

officer having made the diagnosis (specialist internal medicine). An earlier report from South India[4] showed that 39 (6%) of 676 TB patients died during treatment period and higher death rates were independently associated with weight <35 kgs and history of previous treatment. The study recommended that possible role of nutritional interventions should be explored among underweight patients to reduce mortality. A Russian study[8] reported 183 (9.6%) deaths occurred among 1916 TB patients and older age, previous treatment for TB, multi-drug resistance TB and alcoholism were risk factors for death during treatment period.

In the present study, the survival probability was found to be similar in all patients irrespective of categorization. Age, initial body weight, previous history of treatment and alcoholism were risk factors for higher death rate. Necessary actions need to be initiated in the programme to improve body weight and abstain from alcoholism. The mortality rate was slightly lower compared to that found in other studies. The study population consists of patients registered during 1999-2004, so the average morality would have come down due to patients treated under DOTs over the period of time. The analysis was restricted to study population during the treatment period, so this could be reason for finding similar survival probabilities irrespective of categorization. The deaths reported in this study are those who expired during the treatment period and all the deaths might not be due to TB. In this study other risk factors for deaths, not due to TB, could not be identified. This warrants for a larger study involving patients died due to TB only by evaluation of proper document like death certificate.

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