International Journal of Infectious Diseases 110 (2021) 385–393

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Long-term Survival of Treated Tuberculosis Patients in Comparison to a General Population In South India: A Matched Cohort Study

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ARTICLE INFO

Article history:
Received 23 May 2021
Revised 25 July 2021
Accepted 27 July 2021

Keywords:
Tuberculosis
Post-treatment
Mortality rate
Potential years of life lost
Standardized mortality ratio

ABSTRACT

Objectives: This study aimed to measure the mortality rate, potential years of life lost, and excess general mortality among individuals treated for pulmonary tuberculosis (TB) in a TB endemic country.
Methods: A retrospective analysis was conducted on a population-based cohort study of 4022 TB patients and 12,243 gender-matched and age-matched controls from prevalence surveys conducted between 2000 and 2004 in the Thiruvallur district of Tamil Nadu, South India.
Results: The mortality rate among TB patients was 59/1000 person-years. The excess standardized mortality ratio was 2.3 (95% CI: 1.7–3.1). The rate of potential years of life lost was 6.15/1000 (95% CI: 5.97–6.33) in the TB cohort compared to the general population of 1.52/1000 (95% CI: 1.46–1.60). Individuals aged >50 years, those underweight (<40 kg), with treatment failures, or lost to follow-up had higher mortality rates when compared with the rest of the TB cohort. The risk of death was significantly higher in the TB cohort until the end of the fourth year when compared with later years.
Conclusion: Mortality in the TB cohort was 2.3 times higher than in the age-matched general population. Most deaths occurred in the first year after completing treatment. Post-treatment follow-ups and interventions for reducing comorbid conditions are necessary to prevent deaths.

Introduction

Between 2000 and 2019, there was a global increase in the success rate of tuberculosis (TB) treatment and a steady decline in TB mortality rate (WHO, 2020). However, treatment outcomes may not reflect the long-term survival in these individuals, given the functional impairment in the lungs secondary to the disease. TB survivors are at increased risk of all-cause mortality and reduced life expectancy, irrespective of adequate TB treatment (Ranzani et al., 2020; Romanowski et al., 2019).

Detailed evaluations of causes of death in cohorts of TB-treated individuals should receive attention, especially in TB-endemic countries. Evaluation of survival after TB treatment and associated causes of death not only enable estimation of the burden of post-TB mortality in the community but also identify the vulnerable population and help plan interventions to reduce post-TB sequelae, including death. There are a few population-based studies focusing on post-TB sequelae that identified some high-risk populations who had a lower survival rate after treatment: smokers; the elderly; individuals with prior TB treatment; and those with diabetes, HIV infection, kidney failure or cancer (Floe et al., 2018; Moosazadeh et al., 2014; Millet et al., 2011; Kolappan et al., 2008).

Risk factors and vulnerable populations may vary from country to country, given the differences in the habits, diet, and ethnicity of the population. This study aimed to estimate the long-term survival, potential years of life lost, and excess mortality among individuals treated for TB under the Revised National TB Control Program (RNTCP) (currently named the National TB Elimination Programme) as compared to the general population in the district. It was hypothesized that patients with TB would have lower survival compared with the general population, and that vulnerable conditions like malnutrition and diabetes would be associated with this excess mortality in this TB-endemic setting.

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https://doi.org/10.1016/j.ijid.2021.07.067

Methods

A population-based matched cohort study was conducted in one TB unit (TU) in Tiruvallur district, consisting of 209 villages and nine urban clusters. The area has 17 governmental health facilities, including seven microscopy centers. The ICMR-National Institute for Research in Tuberculosis (ICMR-NIRT) initiated a Model Direct Observed Treatment Short-course (DOTS) Project in 1999 in the Tiruvallur district after obtaining approval from institutional committees. As part of this, TB cases were routinely detected at health facilities through the RNTCP. The Velliyur TU, with a population of around 580,000, was chosen for close monitoring of the RNTCP-based DOTS implementation from April 1999–2004 by the ICMR-NIRT. Sputum smear examinations were performed for chest-symptomatic patients, and those who were diagnosed with TB were started on anti-TB treatment (ATT) under the supervision of a directly observed treatment (DOT) provider.

TB prevalence survey

In addition to TB case detection at health facilities, the ICMR-NIRT also conducted community surveys every 2.5 years (1999–2009) to estimate the prevalence of TB in the study area. This survey was undertaken to determine the trends in prevalence of TB after implementation of the RNTCP. All available household members aged ≥15 years underwent screening for chest symptoms and had a chest radiograph (CXR). CXR was interpreted by two independent readers and any discrepancy was reviewed by an umpire reader. Two sputum specimens were collected from chest-symptomatic patients who had a cough for >2 weeks or chest pain or fever for ≥1 month, hemoptysis at any time during the previous 6 months, or an abnormal CXR suggestive of TB. Sputum samples were subjected to smear and culture examination. If either the smear or culture result was positive for acid-fast bacilli (AFB), an additional sputum sample was collected. Patients who had two positive smears or were culture-positive were considered to have active TB and were referred to a health facility for ATT.

(i) TB treated cohorts (TBTC): TB patients aged 15–64 years who were registered and categorized as per the RNTCP guidelines were started on treatment in the Government health facilities in Velliyur TU of Tiruvallur district during 2000–2004. Under the RNTCP, the DOTS short-course regimen had a choice of three different categories of treatment: Category I ($2H_3R_3Z_3E_3 + 4H_3R_3$), Category II ($2H_3R_3Z_3 + 4H_3R_3$) and Category III ($2H_3R_3Z_3E_3S_3 + 1H_3R_3Z_3E_3 + 5H_3R_3E_3$) based on a history of previous TB treatment. The non-DOTS regimen that was provided included conventional chemotherapy (2SHT + 10HT/2SH + $1H_2S_2$/18HT/12HT) or short-course chemotherapy (2RHSZ + 4HR/2RHSZ + $4H_2S_2$/2RHZ + 4HR/2RHSZ + $4S_2H_2Z_2$/2RHSZ + 6TH/$6R_3H_3Z_3S_3$). Category I was for new smear-positive patients with pulmonary TB; Category II was for sputum smear-positive patients who had relapsed, had treatment failure, or were receiving treatment after treatment interruption; Category III was for new smear-negative pulmonary TB patients (other than those in Category I) and those with new less-severe forms of extrapulmonary TB. The non-DOTS[7] group included patients with drug toxicity, liver disease, who were immunocompromised on ART, migration, persistent defaulting, and chronic smear positivity.

(ii) Control cohort (CC): Participants who were smear-negative and culture-negative for AFB irrespective of CXR and symptoms during the same period of 2000–2004 formed the comparison or the control cohort. The CC was selected by matching for age (± 3 years) and gender, which was used to determine the 10-year survival rate of TB patients after completion of ATT in comparison with controls who had no TB.

Data collection

After obtaining informed consent, using a semi-structured, precoded interview schedule, data were collected from both TBTC and CC participants by experienced and trained field investigators at the respondents' residence and in the local language. The interview schedule included demographic information (age, gender), general health status, current symptoms, and treatment history including TB, smoking, and alcohol consumption. In case of death, information on the time, date, and cause of death was collected from their closest relative. Data collectors were trained to look for the cause of death from the medical records or death certificates or photographs that had the date of birth and death. Migrated, not traceable, and re-registered TB cases were excluded.

Data analysis

The data was double-data entered using Epi-Data, cross-checked for consistency, and analyzed using STATA 15.1 (StataCorp, Texas, USA). The demographic details were presented using percentages. The mortality rate in person-years for the TBTC was calculated and presented in subgroups by age and gender. The Chi-square test was used to test the differences in the proportion of deaths between the groups and subgroups.

Age-adjusted standardized mortality ratio (SMR) was calculated as a ratio of mortality in the TBTC to mortality in the CC, assuming that the mortality in the CC represents the mortality in the general population. The proportion surviving at every year of follow-up was calculated to understand the time of mortality among TBTC that equaled the mortality of the CC representing the general population.

Potential years of life lost (PYLL) in the TBTC and CC were calculated. The PYLL for each individual is an indicator of premature mortality. It represents the total number of years not lived by an individual who died before age 69 years, which was the estimated life expectancy of the Indian population in 2020 (Menon et al., 2019). PYLL corresponds to the sum of the PYLL contributed for each individual. The rate is obtained by dividing the total PYLL by the total population aged <69 years. Multiple linear regressions were performed to determine the factors that have an effect on the PYLL.

Cox proportional hazard model was used to calculate the hazard ratio (HR) of the factors associated with mortality among the TBTC and CC. Two separate models were performed to calculate the adjusted HR: the first model was adjusted for non-modifiable risk factors (i.e., age and gender), while the stepwise procedure with removal (0.3) and addition (0.1) of risk factors was adopted in the second model. It was adjusted for risk factors that were found to be potentially significant in the estimation of crude HR and in the first model. The population attributable factor was calculated using Levin's equation where the prevalence of risk factors among all individuals and those with event (i.e., mortality along with the crude and adjusted HRs from Cox proportional hazard model) were used (Rockhill et al., 1998). All the tests were two-tailed and conducted at a significance level of 0.05.

Results

A total of 4022 individuals successfully treated for TB were included in the TBTC. Among them, 2181 (54.2%) were on Category I, 316 (7.9%) on Category II, 1476 (36.7%) on Category III, and 49 (1.2%) on the non-DOTS regimen for TB treatment. Of the 4022 TB-treated patients, 2895 (72%) were successfully contacted, among

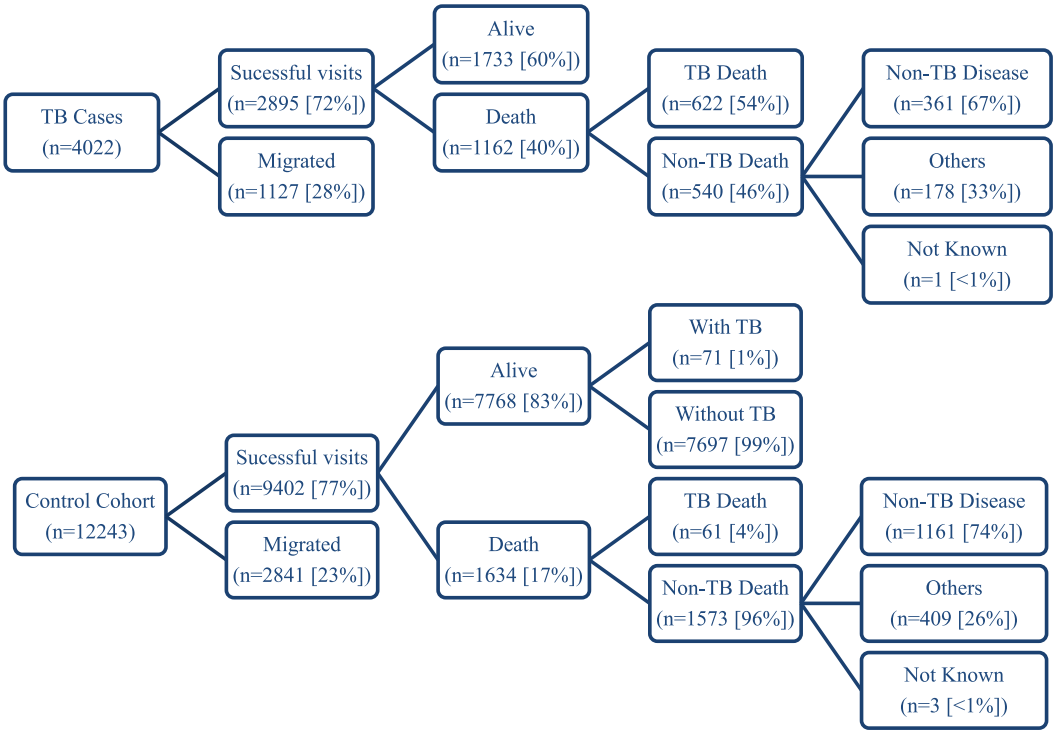

Figure 1. Status of the TB treated patients and controls during follow-up survey in 2014–2015.
In the control cohort, 132 [1.4%] new TB cases were found during these follow-up visits

which 1591 (54.9%) were on Category I, 211 (7.3%) on Category II, 1070 (36.9%) on Category III, and 23 (0.8%) on the non-DOTS regimen for TB treatment. Among those contacted, 1733 (60%) were alive. Similarly, 12,243 age-matched and gender-matched non-TB controls were randomly selected. Among them, 9402 (77%) were successfully contacted. Among the controls, 7768 (83%) were still alive (Figure 1). Death due to TB was recorded in 622 (54%) in the TBTC and 61 (4%) individuals in the CC. Also, 132 (1.4%) individuals in the CC were found to have active TB during the study period. No significant difference in age and gender was observed between the two cohorts. The TBTC was further evaluated based on key TB disease parameters.

Table 1 shows the basic characteristics of the TBTC and the CC. The mortality rate among the TBTC was 5.9 (95% CI: 5.53–6.23) compared with 1.4 (95% CI: 1.3–1.5) among the CC. The mortality rate/1000 years of follow-up in 15–24, 25–40, 41–50, and 51–64 years age groups were 13.4, 38.8, 87.2, and 136.3 versus 5.4, 7.5, 19.5, and 49.1, respectively. The mortality in males in the TBTC was 75/1000 years of follow-up against 24/1000 years of follow-up in the CC. The mortality among females in the TBTC was 37.9/1000 years of follow-up against 11.5 in the CC. The mortality rates for the TBTC and the CC for behavioral risk factors like smoking were 169.1 vs. 48.3 and alcohol consumption 119.5 vs. 39.5. The mortality rates for the TBTC and the CC for various comorbid conditions were: diabetes mellitus (61.8 vs. 28.2), hypertension (48.7 vs. 27.4), heart disease (95.2 vs. 62.7), cancer (150.7. vs. 84.5), arthritis (165.9 vs. 15.4), asthma (272.3 vs. 110.4), and HIV (148.9 vs. 35.6). A higher number of deaths (42%) was observed in those who had the pulmonary form of TB as compared with 18% with extrapulmonary TB and among those who had the non-DOTS form of treatment (66%). Also, those who were lost to follow-up (65.6%) or failed treatment (62.5%) had higher cumulative death rates as compared with those who were cured (32.7%) or completed treatment (32.3%). The mortality rate among those who were lost to follow-up was 15.2 (95% CI: 13.2–17.4) and those who failed treatment 13.2 (95% CI: 10.1–16.9). Mortality rates were higher among those who had non-DOTS treatment [12.3 (95% CI: 6.8–20.4)].

In the TBTC, the major comorbidities were diabetes mellitus (10.8%), hypertension (9.3%), heart disease (1.8%), cancer (2.6%), asthma (4.9%), and HIV (0.5%). The corresponding proportions in the CC were diabetes mellitus (15.2%), hypertension (15.9%), heart disease (3.7%), cancer (2.5%), asthma (0.8%), and HIV (0.1%). Significant differences in death rates between the TB and CC were observed in patients with the following comorbidities: diabetes ($p<0.001$), hypertension ($p<0.001$), and asthma ($p<0.05$).

Table 2 shows the excess mortality among TBTC in comparison with the CC by SMR, PYLL, and the absolute years of life lost attributable to TB. The overall SMR was 2.3 (95% CI: 1.7–3.1). Mortality among the TBTC was twice as high when compared with the CC. The highest SMR was 4.5 among the 30–34 years age group. A similar trend existed for PYLL among the TBTC, it was 6.2 (95% CI: 5.9–6.3) as compared with 1.5 (95% CI: 1.5–1.6) in the CC, stratified by age. The PYLL in the TBTC was 39.1 years and in the CC it was 24.5 years, and the absolute years of life lost due to TB in this cohort were 14.6 years.

Table 3 shows the risk factors for mortality among TBTC based on the Cox Proportional Hazard Model. Risk of mortality among the TBTC increased with age, male gender (aHR: 1.28, 95% CI: 1.08–1.52), smokers (aHR: 2.6, 95% C.I.: 2.27–2.97), illiteracy (aHR: 1.25, 95% CI:1.11–1.41), unemployment (aHR: 1.41, 95% CI: 1.24–1.61), and unfavorable treatment outcomes (aHR: 2.44, 95% CI:2.15–2.76). In the age-adjusted and gender-adjusted model, a weight of <40 kg, drug-resistant TB, re-treatment regimen, unfavorable treatment outcomes, smoking, alcohol intake, past history of TB, unemployed, illiterate, and comorbidities were significantly associated with a higher risk of mortality. Population attributable risk factors in descending order were: aged 51–64 years (16.8%), smoking (13.7%), age 41–50 years (12.8%), alcohol consumption (9.4%), retreatment regimen (6.5%), age 25–40 years (5.4%), <40 kg at admission (4%), illiterate (3.6%), drug-resistant TB (3.1%), male gender (2.7%), pre-

Table 1
Basic characteristics of control and TB-treated cohorts 2000–2004.

	Control				TB				
Factors	Total	Deaths	Person years of follow-up	Mortality rate/1000 person-years	Total	Deaths	Person years of follow-up	Mortality rate/1000 person-years	p-Value[#]
Age group (years)									
15–24	1115	53 (4.8)	9900	5.4 (4.1–7)	399	44 (11)	3300	13.4 (10–18)	<0.001
25–40	3393	225 (6.6)	30,000	7.5 (6.6–8.5)	1081	299 (27.7)	7700	38.8 (34.6–43.4)	
41–50	2336	388 (16.6)	20,000	19.5 (17.7–21.6)	672	337 (50.1)	3900	87.2 (78.4–97)	
51–64	2558	965 (37.7)	20,000	49.1 (46.1–52.3)	743	481 (64.7)	3500	136.3 (124.6–149.1)	
Gender									
Female	2532	253 (10)	22,000	11.5 (10.1–13)	812	223 (27.5)	5900	37.9 (33.2–43.2)	0.010
Male	6870	1378 (20.1)	57,000	24 (22.8–25.3)	2083	938 (45)	12,000	75 (70.3–79.9)	
Residence type									
Rural	5687	986 (17.3)	48,000	20.4 (19.2–21.8)	1774	727 (41)	12,000	61.9 (57.6–66.6)	0.247
Urban	3715	645 (17.4)	31,000	20.7 (19.1–22.3)	1121	434 (38.7)	6600	65.3 (59.4–71.7)	
Category									
Non-DOTS					23	14 (60.9)	106	131.6 (77.9–222.1)	NA
CAT–I					1591	640 (40.2)	10,000	63.5 (58.8–68.6)	
CAT–II					211	124 (58.8)	987	125.6 (105.3–149.8)	
CAT–III					1070	383 (35.8)	7200	53 (48–58.6)	
Type of TB									
Extra-pulmonary TB					255	46 (18)	2000	23.5 (17.6–31.4)	NA
Pulmonary TB					2640	1115 (42.2)	16,000	67.8 (64–72)	
On admission weight									
≥40 kg					1499	660 (44)	9000	72.8 (67.4–78.6)	NA
<40 kg					1396	501 (35.9)	9300	53.8 (49.2–58.7)	
On admission smear status									
NA					69	30 (43.5)	410	70.8 (49.2–101.9)	NA
Negative					1282	473 (36.9)	8500	55.5 (50.7–60.8)	
1+					533	223 (41.8)	3300	67.1 (58.9–76.5)	
2+					331	146 (44.1)	2000	72.8 (61.9–85.6)	
3+					450	196 (43.6)	2600	73.8 (64.1–84.9)	
Scanty					230	93 (40.4)	1500	63.7 (51.9–78)	
Smoking status									
Non-smoker	6747	646 (9.6)	59,000	10.9 (10.1–11.8)	1765	426 (24.1)	14,000	30.3 (27.5–33.3)	0.119
Smoker	2655	985 (37.1)	20,000	48.3 (45.4–51.4)	1130	735 (65)	4300	169.1 (157.3–181.8)	
Alcoholism									
Non-alcoholic	6220	637 (10.2)	54,000	11.7 (10.8–12.7)	1570	429 (27.3)	12,000	34.9 (31.7–38.4)	0.259
Alcoholic	3182	994 (31.2)	25,000	39.5 (37.1–42.1)	1325	732 (55.2)	6100	119.5 (111.2–128.5)	
Diabetes mellitus									
No	7970	1295 (16.2)	67,000	19.2 (18.1–20.2)	2584	1035 (40.1)	16,000	63.3 (59.5–67.3)	<0.001
Yes	1432	336 (23.5)	12,000	28.2 (25.4–31.4)	311	126 (40.5)	2000	61.8 (51.9–73.6)	
Blood pressure									
No	7903	1287 (16.3)	66,000	19.2 (18.2–20.3)	2626	1071 (40.8)	17,000	64.8 (61–68.8)	<0.001
Yes	1499	344 (22.9)	12,000	27.4 (24.7–30.5)	269	90 (33.5)	1800	48.7 (39.6–59.8)	

(*continued on next page*)

Table 1 (*continued*)

Factors	Control				TB				
	Total	Deaths	Person years of follow-up	Mortality rate/1000 person-years	Total	Deaths	Person years of follow-up	Mortality rate/1000 person-years	p-Value[#]
Heart disease									
No	9053	1469 (16.2)	76,000	19.1 (18.1–20.1)	2841	1132 (39.8)	18,000	62.6 (59–66.3)	<0.001
Yes	349	162 (46.4)	2600	62.7 (53.8–73.2)	54	29 (53.7)	305	95.2 (66.2–137)	
Cancer									
No	9168	1493 (16.3)	77,000	19.2 (18.2–20.2)	2820	1111 (39.4)	18,000	61.5 (58–65.2)	<0.001
Yes	234	138 (59)	1600	84.5 (71.4–99.9)	75	50 (66.7)	332	150.7 (114.2–198.8)	
Arthritis									
No	8934	1569 (17.6)	75,000	20.8 (19.8–21.8)	2859	1137 (39.8)	18,000	62.3 (58.8–66)	0.009
Yes	468	62 (13.2)	4000	15.4 (12–19.8)	36	24 (66.7)	145	165.9 (111.2–247.5)	
Asthma									
No	9324	1578 (16.9)	78,000	20 (19–21)	2753	1047 (38)	18,000	58.2 (54.8–61.9)	<0.001
Yes	78	53 (67.9)	480	110.4 (84.4–144.5)	142	114 (80.3)	419	272.3 (226.6–327.2)	
HIV infection									
No	9395	1629 (17.3)	79,000	20.5 (19.5–21.5)	2880	1151 (40)	18,000	62.8 (59.3–66.6)	0.003
Yes	7	2 (28.6)	56	35.6 (8.9–142.4)	15	10 (66.7)	67	148.9 (80.1–276.7)	
TB treatment outcome									
Cured					1214	397 (32.7)	8400	47 (42.6–51.9)	NA
Lost to follow-up					320	210 (65.6)	1400	154.9 (135.3–177.3)	
Expired[*]					123	123 (100)	89	NA	
Failure					96	60 (62.5)	432	138.9 (107.8–178.9)	
Others					8	5 (62.5)	43	117 (48.7–281)	
Treatment completed					1134	366 (32.3)	8000	45.8 (41.3–50.7)	

TB, Tuberculosis, ND, not done, DOTS, Direct Observed Treatment Short-course
[*] Expired, which were documented by the survey team and only considered for the analysis
[#] Chi-Square test was used to test the difference in the proportions of deaths between the groups among the factors

vious history of TB (1.2%), and delay in treatment initiation of >4 weeks (0.9%).

Figure 2 shows that the risk of death among the TBTC was significantly higher until the end of the fourth year compared to later years during follow-up. The HR for mortality in TBTC as compared with the CC was 1.3 (95% CI: 1.2–1.4, p<0.001). The rate of death in the TBTC was 32% higher than the rate in the CC up to the first four years; thereafter, there was no significant difference in the rate of death between the TBTC and CC.

Discussion

This study found that the death rate among individuals successfully treated for TB in a TB-endemic country was higher than their age-matched and gender-matched controls, more so in the early years of the post-treatment period. In a similar study in Brazil where 1459 patients were followed for 6 years post-treatment, the probability of survival after successful completion of ATT was 95.9% (95% CI: 94.8–97.0%) (de Albuquerque et al., 2009). A cohort study in Mexico revisited 305 patients with pulmonary TB after 6 years and again after 10 years of their initial diagnosis and treatment. The mortality was 4.6 in 100 person-years. Of the 78 deaths, 25% died during the 6 months of treatment, 38% died during the first year post-diagnosis, 53% died before the second year, 72% after 3 years, 86% after 4 years, and 92.3% after 5 years (Njera-Ortiz JC et al., 2012). Likewise in Vietnam, 6% of patients died after successful completion of treatment, with a median survival time of 19 months (Vree et al., 2007). Another cohort study in Vietnam among adults treated for pulmonary TB found that 9% of patients died within 2–3 years of treatment initiation: 3.1% during treatment and 5.8% after discharge (Fox et al., 2019).

The current study observed an SMR of 2.3 (95% CI: 1.7–3.1), which was lower than the SMR in a Vietnamese cohort of 4.0 (95% CI: 3.7–4.2) but closer to that observed in a systematic review (Romanowski et al., 2019). A systematic review of 6922 deaths in 40,641,781 TB cases and community controls calculated a pooled SMR of 2.91 (95% CI: 2.21–3.84), which increased to 3.76 (3.04–4.66) when restricted to TB cases with confirmed treatment completion or cure (Romanowski et al, 2019). The population-based longitudinal study of TB survivors in Brazil observed an SMR of 6.47 (95% CI: 6.22–6.73) over 5 years and 3.93 (3.71–4.17) among those who survived the first year (Ranzani et al., 2020).

Table 2
Excess mortality and potential years of life lost among TB patients and controls.

	Mortality in TB patients			Mortality in controls				PYLL in TB	PYLL in controls	Absolute loss of years
Factors	Died (n)	Total (N)	Died (%)	Died (n)	Total (N)	Died (%)	SMR*	(n = 2894)	(n = 9399)	attributable to TB
Age group (years)										
15–19	14	168	8.3%	22	412	5.3%	1.56	49.7	45.3	4.4
20–24	30	231	13.0%	31	703	4.4%	2.95	45.7	39.9	5.8
25–29	52	301	17.3%	40	901	4.4%	3.89	40.6	36.9	3.7
30–34	72	269	26.8%	52	877	5.9%	4.51	35.9	31.4	4.5
35–39	96	317	30.3%	86	1072	8.0%	3.77	30.6	26.4	4.2
40–44	127	308	41.2%	128	1141	11.2%	3.68	26.0	21.2	4.8
45–49	170	354	48.0%	182	1211	15.0%	3.20	20.4	15.9	4.6
50–54	196	333	58.9%	284	1137	25.0%	2.36	15.6	11.7	3.9
55–59	193	321	60.1%	346	1043	33.2%	1.81	11.0	6.6	4.4
60–64	211	293	72.0%	460	905	50.8%	1.42	6.3	3.0	3.3
Gender										
Female	223	812	27.5%	253	2532	10.0%	2.75	22.5	14.6	7.9
Male	938	2083	45.0%	1378	6870	20.1%	2.25	19.1	12.0	7.2
Smoker										
Non-smoker	426	1765	24.1%	646	6747	9.6%	2.52	17.3	12.1	5.3
Smoker	735	1130	65.0%	985	2655	37.1%	1.75	21.2	12.6	8.6
Alcoholic										
Non-alcoholic	429	1570	27.3%	637	6220	10.2%	2.67	17.6	12.1	5.5
Alcoholic	732	1325	55.2%	994	3182	31.2%	1.77	21.1	12.6	8.5
Diabetes										
No	1035	2584	40.1%	1295	7970	16.2%	2.47	20.1	13.3	6.8
Yes	126	311	40.5%	336	1432	23.5%	1.73	17.2	8.8	8.5
Hypertension										
No	1071	2626	40.8%	1287	7903	16.3%	2.50	20.0	13.4	6.6
Yes	90	269	33.5%	344	1499	22.9%	1.46	17.7	8.7	9.0
Heart disease										
No	1132	2841	39.8%	1469	9053	16.2%	2.46	19.7	12.4	7.3
Yes	29	54	53.7%	162	349	46.4%	1.16	21.7	11.9	9.8
Cancer										
No	1111	2820	39.4%	1493	9168	16.3%	2.42	19.8	12.3	7.5
Yes	50	75	66.7%	138	234	59.0%	1.13	19.4	13.3	6.1
Mortality										
No	1137	2859	39.8%	1569	8934	17.6%	2.26	19.8	12.4	7.4
Yes	24	36	66.7%	62	468	13.2%	5.03	18.5	11.0	7.6
Asthma										
No	1047	2753	38.0%	1578	9324	16.9%	2.25	19.8	12.5	7.4
Yes	114	142	80.3%	53	78	67.9%	1.18	19.7	10.3	9.4
HIV infection										
No	1151	2880	40.0%	1629	9395	17.3%	2.30	19.7	12.4	7.3
Yes	10	15	66.7%	2	7	28.6%	2.33	33.6	16.2	17.3
Comorbidity										
No	813	2203	36.9%	874	6481	13.5%	2.74	20.1	14.0	6.1
Yes	348	692	50.3%	757	2921	25.9%	1.94	19.0	10.5	8.5
Total	1161	2895	40.1%	1631	9402	17.3%	2.31	39.1	24.5	14.6
	Rate of YPLL/1000 population							13.5	2.6	10.9

* Standardized mortality ratio (SMR) (% mortality in TB patients/% mortality in control)

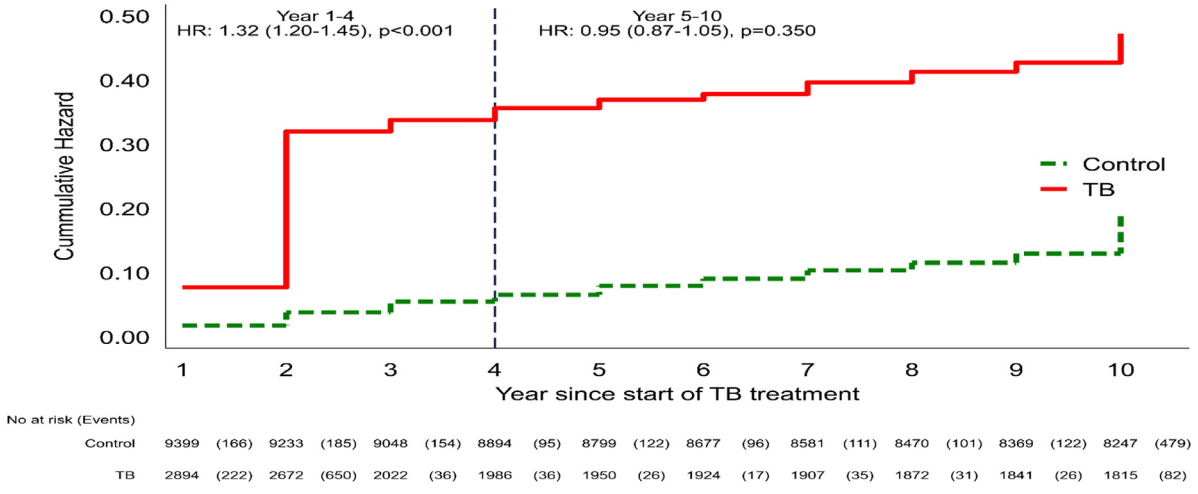

Figure 2. Risk of death among the TB-treated cohort in comparison with the control cohort in long-term follow-up in Thiruvallur.

Table 3
Risk factors for mortality among TB patients.

Factors	Total n	Deaths n (%)	Univariate HR (95% CI)	Significance	Multivariate aHR[1] (95% CI)	Significance	Multivariate aHR[2] (95% CI)	Significance	Population attributable risk (%) Unadjusted[3]	Adjusted[4]
Age in years										
<25	399	44 11.0%	1.00				1.00			
25–40	1081	299 27.7%	2.69 (1.96–3.69)	<0.001			2.05 (1.48–2.83)	<0.001	6.4%	5.4%
41–50	672	337 50.1%	5.45 (3.98–7.46)	<0.001			3.29 (2.38–4.56)	<0.001	13.9%	12.8%
51–64	743	481 64.7%	7.70 (5.65–10.48)	<0.001			4.63 (3.37–6.38)	<0.001	16.3%	16.8%
Gender										
Female	812	223 27.5%	1.00				1.00			
Male	2083	938 45.0%	1.78 (1.54–2.07)	<0.001			1.28 (1.08–1.52)	0.004	5.2%	2.7%
On admission weight										
>40 kg	1720	645 37.5%	1.00		1.00					
≤40 kg	1178	519 44.1%	1.22 (1.09–1.37)	0.001	1.46 (1.3–1.65)	<0.001			1.8%	4.0%
DST pattern										
Sensitive	2646	1038 39.2%	1.00		1.00					
Resistant	249	123 49.4%	1.33 (1.1–1.61)	0.003	1.30 (1.07–1.57)	0.007			2.8%	3.1%
Type of treatment										
CAT–I	2661	1023 38.4%	1.00		1.00					
CAT–II	234	138 59.0%	1.80 (1.5–2.15)	<0.001	1.63 (1.37–1.95)	<0.001			6.4%	6.5%
Delay in treatment initiation										
No delay (≤4 weeks)	2309	910 39.4%	1.00		1.00					
Delay (>4 weeks)	586	251 42.8%	1.12 (0.97–1.29)	0.116	1.09 (0.95–1.25)	0.238			1.0%	0.9%
Smoking										
Non-smoker	1766	427 24.2%	1.00		1.00		1.00			
Smoker	1129	734 65.0%	3.67 (3.25–4.15)	<0.001	3.05 (2.67–3.48)	<0.001	2.60 (2.27–2.97)	<0.001	12.8%	13.7%
Alcoholic										
Non-alcoholic	1573	432 27.5%	1.00		1.00					
Alcoholic	1322	729 55.1%	2.48 (2.2–2.79)	<0.001	2.18 (1.91–2.49)	<0.001			9.0%	9.4%
Previous History of TB										
No History	1581	596 37.7%	1.00		1.00					
Presence of history	1314	565 43.0%	1.17 (1.04–1.31)	0.009	1.12 (1.01–1.26)	0.048			1.3%	1.2%
Education										
Literate	1561	515 33.0%	1.00		1.00		1.00			
Illiterate	1334	646 48.4%	1.60 (1.43–1.8)	<0.001	1.36 (1.21–1.54)	<0.001	1.25 (1.11–1.41)	<0.001	4.5%	3.6%
Occupation										
Employed	1948	737 37.8%	1.00		1.00		1.00			
Unemployed	947	424 44.8%	1.27 (1.13–1.43)	<0.001	1.57 (1.38–1.79)	<0.001	1.41 (1.24–1.61)	<0.001	2.2%	4.9%
Comorbidities										
No	2203	813 36.9%	1.00		1.00					
Yes	692	348 50.3%	1.44 (1.27–1.63)	<0.001	1.10 (0.97–1.25)	0.137			3.6%	1.2%
Outcome										
Favorable	2348	763 32.5%	1.00		1.00		1.00			
Unfavorable	547	398 72.8%	3.39 (3–3.84)	<0.001	2.93 (2.59–3.32)	<0.001	2.44 (2.15–2.76)	<0.001	12.8%	14.0%

R, hazards rate; aHR, adjusted hazards ratio; DST, drug susceptibility pattern
[1] Factors were adjusted for age and gender
[2] Factors that were significant in the univariate and multivariate were considered for the stepwise model
[3] Unadjusted and [4] adjusted population attributable risk factor percentage was calculated

The long-term follow-up of individuals treated for TB in this study area showed that there was an excess of premature deaths among TB patients, even though they were successfully treated in the TB control program with DOTS. This study found that the risk of death was high during the initial 4 years of post-TB treatment. An earlier study in the same area showed overall mortality of 20% during 4 years of follow-up of individuals treated for TB, whereas the current study observed 40% mortality during the follow-up of 10–13 years (Kolappan et al., 2008). The mortality rate in person-years for TBTC was four times higher than the matched control, while it increased to 9–10 times higher for those lost to follow-up or failed to treatment during the 10-year follow-up period. The current study also observed that increasing age, male gender, unemployment, low baseline weight, poor treatment outcomes like lost to follow-up, and those with treatment failures were the risk factors associated with TB mortality in this cohort. Other factors like delay in treatment initiation, smoking, cases of mixed pulmonary and extra-pulmonary forms of TB, resistance to drugs, co-infection with HIV/AIDS, homelessness, and low family income have been shown to be associated with post-TB treatment mortality (Ranzani et al., 2020; Domingos et al., 2008; Low et al., 2009; Faustini et al., 2008). An increase in the mortality rate was also seen in those with a higher smear grading at the time of diagnosis. This could be due to a higher bacillary load in these patients as compared with extra-pulmonary TB, although the durations of TB treatment and dosage were similar.

This study observed premature mortality in terms of PYLL among the TBTC compared with CC. Among the TBTC, every age group had higher mortality leading to premature death. The reason for premature mortality could be due to the impact of TB disease in terms of the structural change in lung parenchyma and bronchial structures leading to pulmonary function impairment along with other comorbid conditions. Also, the increase in mortality among the treatment failures could be because of poor adherence, insufficient dosages, and probably drug resistance. These factors could have led to progression of disease leading to higher death rates.

A major strength of this study was the selection of age-matched and sex-matched controls from the general population, from the same geographical location, and following them longitudinally for 10 years for mortality. A major limitation of this study was that it could not ascertain the cause of death, especially when it had happened at home. There could have been a possibility of recall bias and information bias, which would have led to overestimation of mortality; however, this bias was minimized by using trained investigators. Since a patient had TB, the relatives might have reported it as the cause of death, even if the patient died of some other cause, leading to overestimation of TB as the cause of death. Further, this study did not address the occurrence of EPTB in the control cohort, which might have been a confounding factor for mortality. Previous studies conducted[19] in this same area and population have demonstrated that there is no socioeconomic difference between the surveyed and non-surveyed patients or the patients attending government health facilities for TB treatment; similarly, it is expected that this would not affect the estimates of mortality (Santha et al., 2003). It must be emphasized that public sector health services in India, such as government hospitals and primary health centers, are mostly used by those from the lower socioeconomic stratum; therefore, the findings from this study may be used to compare all public sector health institutions implementing the RNTCP in India.

To conclude, individuals post-TB treatment have a significantly higher risk of mortality as compared with their age-matched general population. This, especially in the younger TB survivors, significantly affects the economy of both individuals and nations. Hence, the National TB Elimination Programs have to prioritize strategies to alleviate post-TB treatment respiratory morbidity, mortality, and TB recurrence, along with ensuring early case detection, treatment initiation, and regularity of treatment. Regular counseling or creating awareness for smokers, alcoholics, and illiterates would also help to reduce mortality. Implementation of long-term follow-up for clinical and/or bacteriological outcomes every 6 months–2 years post-TB treatment and appropriate interventions for comorbid conditions may help in preventing premature mortality (Technical guidelines 2016).

Acknowledgments

The authors thank the patients who took part in the study and the field staff of the Tiruvallur Epidemiology unit for engaging the patients in the field conditions of Tiruvallur, the District TB Officer of Tiruvallur District, and the RNTCP Team in Tiruvallur. We extend our gratitude to the previous Directors, senior scientists, medical officers, and statisticians of ICMR-NIRT (formerly TB Research Centre) for conducting the study and meticulous data collection.

Potential conflict of interest

None.

Financial support

This work was supported by United States Agency for International Development through World Health Organization, SEARO, New Delhi, India through the MODEL DOTS Project.

Ethical Approval

The study was approved by the Ethics committee of the ICMR-National Institute for Research in Tuberculosis.

Authors' contributions

VC, SS and MM designed the study and wrote the study protocol; VC and SS obtained regulatory approvals and conducted the study; TN and BW recruited study patients; VC and TK performed the statistical analysis; VC and TN carried out data cleaning and error checking; SR, VC and CP drafted the manuscript; and SS provided critical inputs and overall guidance.

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