Mortality of tuberculosis patients in Chennai, India

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Objective We aimed to measure the mortality rate and excess general mortality as well as identify groups at high risk for mortality among a cohort of tuberculosis patients treated in Chennai Corporation clinics in south India.

Methods In this retrospective cohort study we followed up 2674 patients (1800 males and 874 females) who were registered and treated under the DOTS strategy in Chennai Corporation clinics in 2000. The follow-up period from the date of start of treatment to either the date of interview, or death was 600 days.

Findings The mortality rate among this cohort of tuberculosis patients was 60/1000 person-years. The excess general mortality expressed as standardized mortality ratio (SMR) was 6.1 (95% confidence interval (CI) = 5.4–6.9). Younger patients, men, patients with Category II disease, patients who defaulted on, or failed courses of treatment, and male smokers who were alcoholics, all had higher mortality ratios when compared to the rest of the cohort.

Conclusion The excess mortality in this cohort was six times more than that in the general population. Young age, male sex, smear-positivity, treatment default, treatment failure and the combination of smoking and alcoholism were identified as risk factors for tuberculosis mortality. We suggest that mortality rate and excess mortality be routinely used as a monitoring tool for evaluating the efficiency of the national control programme.

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Introduction

Tuberculosis (TB) is a major public health problem in India and most of the disease burden is due to premature mortality among TB patients.[1] Mortality is measured either as true rate (person-time rate) or as risk of death within a specific time period of follow-up (case-fatality rate). The case-fatality rate is the more commonly used mortality measure of the two. However, case-fatality rates among TB patients reported in the literature range from 12% to 44% and are not comparable because they were measured as cumulative incidence for different follow-up periods.[2–8] Risk factors such as smoking, alcoholism, irregular and incomplete anti-tuberculosis treatment as well as HIV infection are known to increase the mortality associated with TB.[2,4,5,7,9]

WHO defines TB mortality as the number of TB cases dying during treatment, regardless of the cause.[10] This definition, however, does not reflect the actual TB mortality rate because it includes deaths due to co-morbidities and accidents, excludes deaths among treatment defaulters who have a high risk for mortality and presupposes that TB mortality does not occur after the completion of treatment. A better, though indirect, measure of mortality would be the computation of excess mortality (or standardized mortality ratio (SMR)) occurring among TB patients and comparing it to the mortality among the standard population (or the estimated national population for a certain year).

Since 1999, the Chennai Corporation has been implementing the Revised National Tuberculosis Control Programme (RNTCP), applying the principles of DOTS, in Chennai city through its network of clinics and hospitals. We measured the mortality rate and excess general mortality among TB patients registered with Chennai Corporation clinics in 2000 and identified the groups at high risk of mortality in this cohort.

Methods

Setting and study population

Chennai city consists of ten zones and each zone has a sub-district supervisory unit known as a Tuberculosis Unit covering a population of 500 000. Our study population consisted of all TB patients aged ≥15 years, who were registered under the RNTCP in 2000 in all Chennai Corporation clinics. We included deaths only among TB patients who were registered and treated at the Corporation's clinics.

Definitions

In the RNTCP, treatment of patients is classified into three categories. Category I includes all new sputum smear-positive and seriously ill smear-negative and extra-pulmonary patients. Category II includes all previously treated sputum smear-positive patients, treatment after default, relapses and treatment failures. Category III includes sputum smear-negative patients, such as those with abnormalities on chest X-ray and extra-pulmonary patients.

Data collection

We collected data, such as the name, age, sex, residential address, category of treatment and date of registration of each patient from the RNTCP Tuberculosis Register. A health worker visited the households of all registered patients at least once during the study period

(August 2002–December 2003) and interviewed the patients or their close relatives living in the same household to ascertain the patients' current living status (either alive or dead) and to collect documentary evidence of death (death certificate or burial-ground record of death) for those reported dead. In addition, for seven of the ten zones, information on history of tobacco smoking and alcoholism was collected from male patients only. Females were excluded in these zones because the investigators considered that it was impolite to question women about smoking and alcoholism.

Follow-up

We retrospectively followed-up all patients from the date of start of treatment in their respective RNTCP treatment centres, to either the date of interview (for the survivors) or the date of death (for the dead). Since all the survivors were followed up for a minimum period of 600 days (20 months), the follow-up

period for analysis for all survivors was set at 600 days and for those who were dead the follow-up period was until the date of death within 600 days. The outcome "death" occurring within 600 days from start of treatment was used to measure the mortality in this cohort.

Data analysis

We measured mortality by age, sex, category of treatment and treatment outcome in two ways: (1) excess mortality (or SMR) among TB patients compared to the mortality rate in the standard population (the standard population

for this study was the estimated national population for 1998 obtained from the Sample Registration System for 1998); and (2) risk of death (or case-fatality rate) at 6, 12 and 20 months from start of treatment, calculated as the number of deaths divided by the total number of TB patients. We performed a step-wise multivariate analysis to identify the variables significantly contributing to the risk of death. These selected variables alone were used by the Cox's proportional hazards model to obtain the adjusted hazard ratio. The survival probability from the date of start of treatment until the end

Table 1. **Study population: distribution by age and sex**

Age group (years)	Male n (%)	Female n (%)	Total n (%)
15–44	1137 (42.5)	697 (26.1)	1834 (68.6)
45–59	467 (17.5)	125 (4.7)	592 (22.2)
⩾ 60	196 (7.3)	52 (1.9)	248 (9.2)
Total	**1800 (67.3)**	**874 (32.7)**	**2674 (100)**

Table 2. **Excess mortality among tuberculosis patients**

Group	No. of cases	Person-years follow-up	Observed deaths	Mortality rate per 1000 person-years	Expected deaths[a]	SMR[b] (95% confidence interval)
All patients	2674	4203	252	60.0	41.0	6.1 (5.4–6.9)
Age group (years)						
15–44	1834	2921.8	127	43.5	8.4	15.1 (12.5–17.9)
45–59	592	915.4	77	84.1	10.5	7.3 (5.8–9.1)
⩾ 60	248	365.5	48	131.3	22.1	2.2 (1.6–2.8)
Sex						
Male	1800	2801.9	207	73.9	32.0	6.5 (5.6–7.4)
Female	874	1400.8	45	32.1	9.1	5.0 (3.6–6.6)
Treatment category						
Category I	1370	2133.3	159	74.5	20.6	7.7 (6.5–9.0)
Category II	209	318.7	32	100.4	2.9	11.0 (7.5–15.2)
Category III	1095	1750.7	61	34.8	17.5	3.5 (2.7–4.4)
Treatment outcome						
Cured	1207	1954.3	68	34.8	18.7	3.6 (2.8–4.6)
Completed	1077	1751.6	36	20.6	17.7	2.0 (1.4–2.8)
Defaulted	241	368.9	43	116.6	3.0	14.3 (10.3–19.0)
Failed	27	38.5	8	207.9	0.4	18.2 (7.6–33.4)
Behavioural factors						
Non-smokers and non-alcoholics	410	662.2	16	24.2	7.0	2.3 (1.3–3.6)
Smokers	200	314.2	15	47.7	4.1	3.7 (2.0–5.8)
Alcoholics	97	151.7	10	65.9	1.7	6.0 (2.8–10.4)
Smokers and alcoholics	370	555.8	66	118.8	6.2	10.7 (8.2–13.5)
Information not available	723	–	–	–	–	–

[a] Based on standard mortality rates (from sample registration system of 1998).
Males: 15–44 years: 3.0/1000 person-years (p-y); 45–59 years: 12.2/1000 p-y; ⩾60 years: 63.0/1000 p-y.
Females: 15–44 years: 2.7/1000 p-y; 45–59 years: 8.7/1000 p-y; ⩾60 years: 52.1/1000 p-y.
[b] Standardized mortality ratio.

Research
C Kolappan et al.
TB mortality in India

Table 3. **Case-fatality rates among tuberculosis patients for different periods of follow-up**

Group	Patients at risk	Number of patients dead (case-fatality rate %)		
		at 6 months	at 12 months	at 20 months
All patients	2674	71 (2.7)	130 (4.9)	252 (9.4)
Age group (years)				
15–44	1834	32 (1.7)	62 (3.4)	127 (6.9)
45–59	592	22 (3.7)	40 (6.8)	77 (13.0)
⩾ 60	248	17 (6.9)	28 (11.3)	48 (19.4)
Sex				
Male	1800	57 (3.2)	104 (5.8)	207 (11.5)
Female	874	14 (1.6)	26 (3.0)	45 (5.1)
Treatment category				
Category I	1370	43 (3.1)	79 (5.8)	159 (11.6)
Category II	209	8 (3.8)	17 (8.1)	32 (15.3)
Category III	1095	20 (1.8)	34 (3.1)	61 (5.6)
Treatment outcome				
Cured	1207	0 0	15 (1.2)	68 (5.6)
Completed	1077	0 0	11 (1.0)	36 (3.3)
Defaulted	241	6 (2.5)	19 (7.9)	43 (17.8)
Failed	27	0 0	6 (22.2)	8 (29.6)
Behavioural factors				
Non-smokers and non-alcoholics	410	3 (0.7)	8 (2.0)	16 (3.9)
Smokers	200	8 (4.0)	11 (5.5)	15 (7.5)
Alcoholics	97	3 (3.1)	6 (6.2)	10 (10.3)
Smokers and alcoholics	370	17 (4.6)	38 (10.3)	66 (17.8)
Type of disease				
Extra-pulmonary	364	4 (1.1)	8 (2.2)	12 (3.3)
Pulmonary	2310	67 (2.9)	122 (5.3)	240 (10.4)
Initial smear status				
Smear-negative	1211	31 (2.6)	53 (4.4)	90 (7.4)
Smear-positive	1286	37 (2.9)	73 (5.7)	150 (11.7)

of the follow-up period was measured using the Kaplan–Meier method.

Results

Of the 2674 registered patients, 2422 (91%) survived the entire follow-up period of 600 days from the date of start of treatment and 252 (9%) patients died during the follow-up period. The cohort consisted of 1800 (67.3%) males and 874 (32.7%) females; and 1834 (68.6%) belonged to the younger age group of 15–44 years (Table 1).

The standardized mortality ratios (SMR) for the study cohort are shown in Table 2. Overall, the cohort had an SMR of 6.1 (95% confidence interval (CI) = 5.4–6.9). Among the three age groups, the 15–44 years age group had the highest SMR of 15.1 (95% CI = 12.5–17.9). Males had a higher SMR than females. Category II patients had a higher SMR, than those in Category I and Category III. Patients with treatment failure had a

higher SMR than patients who defaulted on treatment. Male patients with a history of both smoking and alcoholism also had a high SMR.

The case-fatality rate for the cohort was 2.7% at 6 months 4.9% at 12 months and 9.4% at 20 months (Table 3). At six months, patients aged ⩾60 years had the highest case-fatality rate (6.9%). At 12 months, treatment failures had the highest case-fatality rate (22.2%) followed by patients ⩾60 years (11.3%) and males who were both smokers and alcoholics (10.3%). At 20 months follow-up, the case-fatality rate was highest among treatment failures (29.6%) followed by patients ⩾60 years (19.4%), defaulters (17.8%) and males who were smokers and alcoholics (17.8%).

The risk of death increased with age, with adjusted hazard ratios for the 45–59 years and ⩾60 years age groups being 1.6 (95% CI = 1.0–2.6) and

3.0 (95% CI = 1.7–5.3), respectively (Table 4). The adjusted hazard ratios for treatment failures, defaulters and treatment completed were 7.7, 3.3 and 0.6, respectively, compared to cured patients. The adjusted hazard ratio for males who were smokers and alcoholics was 2.9 (95% CI = 1.8–4.7), compared to non-smokers and non-alcoholics. The adjusted hazard ratios were significantly higher for the oldest age group, treatment defaulters, failures and male smokers who were also alcoholics.

The survival probabilities for 20 months follow-up for age groups 15–44, 45–59 and ⩾60 years were 93.1%, 87% and 80.6%, respectively (Fig. 1).

Discussion

Our analysis has shown that the mortality among this cohort was six times (SMR = 6.1) in excess of the mortality in the standard population. This is similar to the overall SMR of 8.3 for TB

Table 4. **Risk factors for mortality among tuberculosis patients[a]**

	No. registered	No. of deaths	% of deaths	Hazard ratio		
				Crude	Adjusted[b] (95% confidence interval)	P-value
Age groups (years)						
15–44	1204	46	4	1.0	1.0	
45–59	372	26	7	1.8	1.6 (1.0–2.6)	0.061
≥ 60	148	17	11	3.0	3.0 (1.7–5.3)	0.000
Total	**1724**	**89**	**5**			
Treatment outcome						
Cured	837	41	5	1.0	1.0	
Defaulted	134	22	16	3.4	3.3 (1.9–5.5)	0.000
Failed	21	7	33	6.8	7.7 (3.4–17.5)	0.000
Treatment completed	732	19	3	0.5	0.6 (0.3–1.0)	0.048
Total	**1724**	**89**	**5**			
Behavioural factors						
Non-smokers and non-alcoholics	1127	36	3	1.0	1.0	
Smokers	182	8	4	1.4	1.1 (0.5–2.3)	0.861
Alcoholics	86	5	6	1.8	1.3 (0.5–3.4)	0.583
Smokers and alcoholics	329	40	12	3.8	2.9 (1.8–4.7)	0.000
Total	**1724**	**89**	**5**			

[a] Subjects with incomplete data on behavioural factors, initial smear status, and treatment outcome of expired, transferred out and others were excluded (950 subjects) from this analysis.

[b] Based on step-wise analysis, the hazard ratio was adjusted for patients with respect to age, treatment outcomes and behavioural factors. The remaining factors were found to be not significant by step-wise analysis method.

patients reported from the Netherlands, using mortality rates among the general population as the standard[11] as was done in our study.

In this cohort, TB was a major cause of death among the 15–44 years age group than in those belonging to the ≥60 years age group. This was probably due to the very few competing causes for mortality in the younger group compared to the older group. Male patients had a higher SMR than female patients reflecting the likelihood of majority of treatment defaults occurring among men[12] possibly due to additional risk factors such as smoking and alcoholism. Smear-positive patients had a higher mortality than smear-negative patients because smear-positivity is related to severity of the disease.

The risk of mortality between the treatment and post-treatment periods was the same for all subgroups of patients, except male smokers who had a significantly higher risk during the treatment period than in the post-treatment period.

Our results have shown that the risk of mortality increased substantially among almost all subgroups from the second six months to the final eight months — 4.9% at the end of 12 months to 9.4% by the end of 20 months. Although it is difficult to explain this increase in mortality after 12 months from the start of treatment, it is likely that these deaths were due to drug-sensitive or drug-resistant relapse cases.

In our cohort, mortality continued to occur even after the completion of treatment emphasizing that the definition of TB mortality should not be restricted to the treatment period alone as this may result in underestimation of mortality.

While few studies have shown the association between smoking and TB and between alcoholism and TB,[7,9,13–15] none of these had simultaneously collected data on both smoking and alcoholism. We found that male patients who were both smokers and alcoholics had a higher SMR (10.7) than those who were either only smokers (3.7) or only alcoholics (6.0) demonstrating that smoking alone and alcoholism alone were not risk factors but smoking and alcoholism in combination became a risk factor. To draw a valid conclusion, however, about the effect of smoking and alcoholism separately on mortality among TB patients, a larger sample of

patients with sufficient number of deaths in the smoking alone or alcoholism alone groups would be required.

We suspect that excess mortality rates may differ for cohorts selected from different areas or at different time points from the same area due to variations in the relative proportions of subgroups of patients with high SMRs, such as younger patients, smear-positive patients, male smokers who are also alcoholics, irregularly treated patients and most importantly the efficiency of implementation of the treatment programme. We suggest that all these factors be considered while interpreting mortality data.

Our study had two limitations. Although the RNTCP treatment services were accessible to the entire population living in the Chennai Corporation area, the services were mostly used by people from the lower socioeconomic stratum. We would like to emphasize that in India, public sector health services, such as government hospitals and primary health centres, 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.

The second limitation was that we did not ascertain the human immuno-deficiency virus (HIV) status of the patients. Interestingly, however, we found an indirect evidence of HIV prevalence in this cohort. HIV prevalence may be safely assumed to be very low in this population because of the very low case-fatality rate among the high-risk age group of 15–44 years (1.7% and 3.4% for 6 and 12 months of follow-up, respectively). It is known that mortality among TB patients in high HIV-prevalent regions occurs within the first few months of starting anti-tuberculosis treatment and is more among smear-negative and extra-pulmonary TB patients.[2,5,16] In a region of low HIV prevalence, such as this study cohort, mortality is not restricted to any time period and occurs more among smear-positive and pulmonary TB patients. Thus, we suggest that the pattern of mortality among TB patients be used as a proxy indicator for the level of HIV prevalence in a region.

We conclude that the mortality among this cohort of TB patients was six times higher than the mortality rate in the standard population. The excess mortality rate was very high among treatment failures, treatment defaulters, younger patients, smear-positive patients (Categories I and II) and male smokers who were also alcoholics. Ensuring regularity of treatment by strictly adhering to the DOTS strategy would reduce

Fig. 1. **Kaplan-Meier survival curves for different age groups**
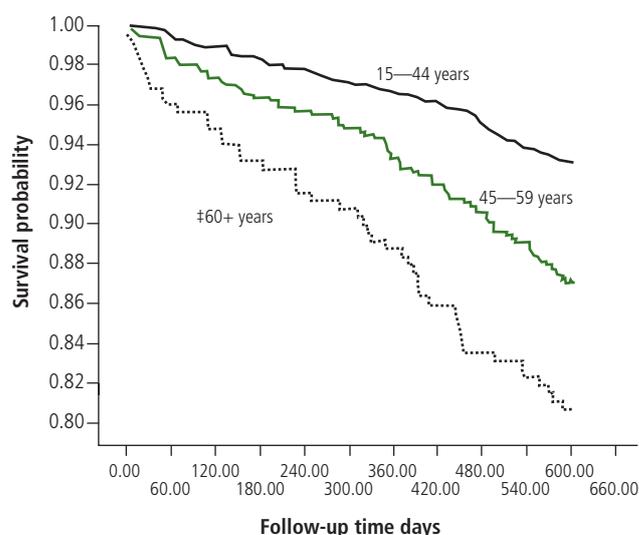
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mortality by minimizing treatment defaulters and failures. The SMR is a better measure of TB mortality than general mortality (in accordance with the current WHO definition) among TB patients during treatment. Our analysis proves that mortality rate is an important health index to monitor TB control programmes. We suggest that mortality rate and excess mortality be routinely used, along with cure rates and conversion rates, as a monitoring tool for evaluating programme efficiency. ■

Résumé

Mortalité chez les tuberculeux à Chennai, en Inde

Objectif La présente étude a pour objectif de mesurer le taux de mortalité et la surmortalité générale, ainsi que d'identifier les groupes à haut risque parmi une cohorte de tuberculeux traités dans le dispensaire tenu par Chennai Corporation, au sud de l'Inde.

Méthodes Dans le cadre de cette étude rétrospective de cohorte, on a suivi 2674 malades (1800 hommes et 874 femmes) enregistrés et traités selon la stratégie DOTS dans le dispensaire de la Chennai Corporation en 2000. Le suivi, depuis la date de début de traitement jusqu'à la date de l'entretien ou du décès, a duré 600 jours.

Résultats Le taux de mortalité parmi la cohorte de tuberculeux était de 60/1000 personnes-années. La surmortalité générale, exprimée sous forme de taux-type de mortalité (SMR), était de 6,1 [intervalle de confiance à 95 % (IC) = 5,4 - 6,9]. Les malades jeunes, de sexe masculin, atteints de tuberculose de catégorie II, n'ayant pas pris correctement leur traitement ou dont le traitement avait échoué, ainsi que les fumeurs de sexe masculin et alcooliques, présentaient tous des taux de mortalité plus élevés que le reste de la cohorte.

Conclusion La surmortalité dans cette cohorte était six fois plus élevée que dans la population générale. Les malades jeunes, de sexe masculin, à frottis positif, n'ayant pas pris correctement leur traitement ou présentant un échec thérapeutique, ou encore associant tabagisme et alcoolisme, ont été identifiés comme des sujets à risque à l'égard de la mortalité par la tuberculose. Il est donc proposé d'utiliser systématiquement le taux de mortalité et la surmortalité comme outils de surveillance pour évaluer l'efficacité des programmes nationaux de lutte contre la tuberculose.

Resumen

Mortalidad de los pacientes tuberculosos en Chennai (India)

Objetivo Decidimos medir la tasa de mortalidad y el exceso de mortalidad general, así como identificar los grupos con alto riesgo de mortalidad en una cohorte de enfermos tuberculosos tratados en consultorios de Chennai Corporation, en el sur de la India.

Métodos En este estudio de cohortes retrospectivo seguimos a 2674 pacientes (1800 hombres y 874 mujeres) que se registraron y trataron en el marco de la estrategia DOTS en consultorios de Chennai Corporation en 2000. El periodo de seguimiento desde la fecha de comienzo del tratamiento hasta la fecha de la entrevista o la defunción fue de 600 días.

Resultados La tasa de mortalidad en esa cohorte de pacientes con tuberculosis fue de 60/1000 años-persona. El exceso de mortalidad general expresado como razón de mortalidad normalizada (RMN) fue de 6,1 (intervalo de confianza (IC) del 95% = 5,4–6,9). Los

pacientes más jóvenes, los hombres, los pacientes con enfermedad en la fase II, los pacientes perdidos o que dejaron el tratamiento y los fumadores varones alcohólicos presentaron todos ellos razones de mortalidad mayores en comparación con el resto de la cohorte.

Conclusión El exceso de mortalidad en la cohorte considerada fue seis veces superior al de la población general. La edad temprana, el sexo masculino, la baciloscopia positiva, el abandono del tratamiento, el fracaso terapéutico y la combinación de tabaquismo y alcoholismo se revelaron como factores de riesgo de mortalidad por tuberculosis. Sugerimos que la tasa de mortalidad y el exceso de mortalidad se utilicen de forma sistemática como instrumentos de seguimiento para evaluar la eficiencia del programa nacional de control.

ملخص

وفيات السل في شيناي، الهند

الهدف: هدفنا لقياس معدلات الوفيات والزيادة في الوفيات العامة مع التعرُّف على المجموعة المعرَّضة لأخطار مرتفعة للوفاة من بين أترابٍ مسلولين يعالجون في عيادات مؤسسة شيناي جنوب الهند.

الطريقة: هذه دراسة استعادية تابعنا فيها 2674 مرض (منهم 1800 رجلاً و874 امرأة) ممن سجلوا كمسلولين وعولجوا باستراتيجية المعالجة القصيرة الأمد تحت الإشراف المباشر في عيادات مؤسسة شيناي عام ألفَيْن. وقد استمرت المتابعة 600 يوم بدأت بتاريخ البدء بالمعالجة وانتهت بيوم المقابلة أو يوم الوفاة.

الموجودات: بلغت معدلات الوفيات بين 5.4 و6.9. وقد كانت معدلات

الوفيات لدى المسلولين الصغار والرجال ومن هم في الفئة الثانية من المرض ومن قصَّر في اتباع دورة المعالجة أو فشل منها والمدخنين من الكحوليـين أعلى مما كانت عليه لدى بقية الأتراب.

الاستنتاج: بلغت الزيادة في الوفيات لدى هؤلاء الأتراب ستة أضعاف ما لدى عامة السكان. ويتعرَّض كل من الصغار والذكور وإيجابيي اللطاخة والمقصِّرين في المعالجة ومن فشلت لديه المعالجة ومن يدخن ويتعاطى المسكرات لأخطار الوفاة أكثر من غيرهم. واقترحنا أن من الممكن استخدام معدل الوفيات وزيادة الوفيات بشكل روتيني كأداة رصد لتقيـيم فعالية برنامج المكافحة الوطني للسل.

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