Long-term survival of patients treated for tuberculosis: a population-based longitudinal study in a resource-poor setting

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Abstract

OBJECTIVE We assessed the long-term survival of TB patients belonging to the Saharia tribe, a high TB burden community in Shivpuri district, Madhya Pradesh, central India.

METHODS Population-based, longitudinal study conducted among 9756 Saharia population in 2013, and a resurvey done 2 years later in 2015 using the same methods. The status of the individuals during resurvey was recorded as non-TB, relapse and death. The deaths recorded in this period were used to measure the mortality among TB-affected population and the non-TB population in this cohort.

RESULTS The standardised mortality ratio for the study cohort was 122.9 per 1000 population; males had higher mortality than females (129.9 *vs*. 96.8). The expected mortality among the non-TB population was 30.2, and the observed mortality among TB-affected population was 122.9 per 1000 population.

CONCLUSION In the Saharia tribe, post-treatment mortality in the TB-affected population is significantly higher than in the general population. This highlights an urgent need for implementation of effective public health strategies to prevent disproportionate deaths among TB-affected individuals in resource-poor settings, and the importance of periodic follow-up of patients after cure/completion of treatment, especially in vulnerable populations.

keywords India, mortality, Saharia, tribal, tuberculosis

Sustainable Development Goal: Good health and well-being.

Introduction

Tuberculosis (TB) is a major public health problem worldwide and is a leading cause of death due to a single infectious agent. The burden of the disease varies enormously among countries ranging from 5 to 500 with a global average of around 130 per 100 000 population. Global TB report reveals that countries are making progress in tuberculosis (TB) control with a reduction in TB-related mortality [1]. India has an uneven burden of TB with an estimated 2.8 million TB cases in a global total of 10.4 million, thus contributing to about 27% of the global burden. The Revised National TB Control Programme of India (RNTCP; now National Tuberculosis Elimination Programme – NTEP), the flagship public health programme, was launched in 1997 and was extended gradually to other parts of the country. It was implemented in the current study area in the year 2004, and full nationwide coverage was done in 2006. This programme achieved a 42% TB mortality reduction by 2018 as compared to 1990 mortality levels [2].

The majority of studies describe TB patient survival either during the course of treatment or immediately post-treatment [3-8]. Long-term survival among patients post-TB treatment is rarely described [9-12]. We attempted to assess the long-term survival of TB patients in a population-based longitudinal study in the Saharia tribe of central India (a community with a high TB burden) [13]. We hypothesised that treated TB patients have a lower survival rate than the general population without TB.

Methods

Study area and population

Saharia is a particularly vulnerable tribal group (PVTG) in Shivpuri district, Madhya Pradesh, India. In general,

such tribes dwell in small groups of hamlets known as 'Saharana' that lie adjacent to the villages. A community survey for TB case detection was conducted in the study area as an epidemiological investigation by the ICMR-National Institute of Research in Tribal Health.

Study design

The population-based, longitudinal study in Saharia was undertaken in Pohri Block of Shivpuri district in 2013. The resurvey was done in 2015 in the same population. We describe the 2 years' survival of bacteriologically positive TB patients diagnosed and treated under NTEP in 2013.

Sample size and sampling

The required sample size was estimated as 9225 population aged 15 years and older considering the reported prevalence of 1518/100 000 pulmonary TB in the Saharia tribe. Considering village as the sampling unit, 53 villages were randomly selected to cover the estimated sample size. All households in the selected villages were included in the survey. A list of all eligible household members was prepared and each member was assigned an unique identification number. The details of sampling design and procedure are discussed in detail elsewhere [14].

Data collection

Trained field investigators conducted a door-to-door community survey to collect household information and to identify presumptive TB cases through screening of eligible individuals (15 years and above) through a specifically designed individual schedule. All available eligible individuals (≥15 years) were examined for symptoms suggestive of TB. Individuals remaining absent for symptom inquiry were revisited the same day or on subsequent days. A coverage of >90% was achieved during both the surveys. Those missing were unavailable during the visits, had temporarily migrated to other places in search of livelihood, or declined to participate or provide written consent.

Two sputum specimens were collected for smear and culture examination from presumptive TB cases and examined in the laboratory by Ziehl–Neelsen smear microscopy and solid media culture methods. All detected TB cases were referred to the nearest health facility for anti-tuberculosis treatment as per NTEP guidelines. All TB cases were periodically followed for 2 years for treatment completion, relapse/recurrence of TB and death. However, after 2 years, all households included in the baseline survey were resurveyed using the same methodology and the information about all eligible individuals (≥15 years) was updated and people were re-screened for the symptoms of TB. The TB status of individuals included in the follow-up (end line) survey was recorded as non-TB cases, new TB cases, relapsed TB cases and death.

Data management and analyses

The schedules and laboratory reports were examined for correctness and later computerised using Census and Survey Processing System (CSPro) and analysed using IBM-SPSS software Version 25.0. Baseline and end-line survey data were matched using a unique identification number. Stratification was done on mortality among TB-affected population and non-TB population. The mortality rates were observed and estimated per 1000 population. Mortality rates were compared between the TB-affected Saharia population and the non-TB Saharia population. Excess mortality among TB patients was compared to the expected mortality rate of the non-TB Saharia population. The expected mortality for the non-TB population was estimated based on age-specific mortality rates for the rural population of Madhya Pradesh (SRS-based abridged life tables, 2013–17) (Census of India, 2019) [15]. Statistical tools, univariate analysis, Chi-square test of significance were used to test differences in the distribution of mortality. Trend Chi-square was used to test the mortality among different age groups. The *p value of* <0.05 was considered significant.

Ethical issues

The study was approved by the Ethics Committee of ICMR-National Institute of Research in Tribal Health. Informed written consent was obtained from all individuals. All individuals positive for TB were referred to NTEP, and free counselling was provided throughout the treatment.

Results

TB disease among the study population

Of the total 10 300 Saharia tribal population eligible for screening, 9756 individuals (94.7%) were screened and 293 had TB. During the 2 years of follow-up (end line) survey, 269 deaths (233 in 9463 non-TB population and 36 in 293 TB-affected population) were recorded. 195 TB cases (155 new and 40 recurrent cases) were detected during follow-up (Figure 1).

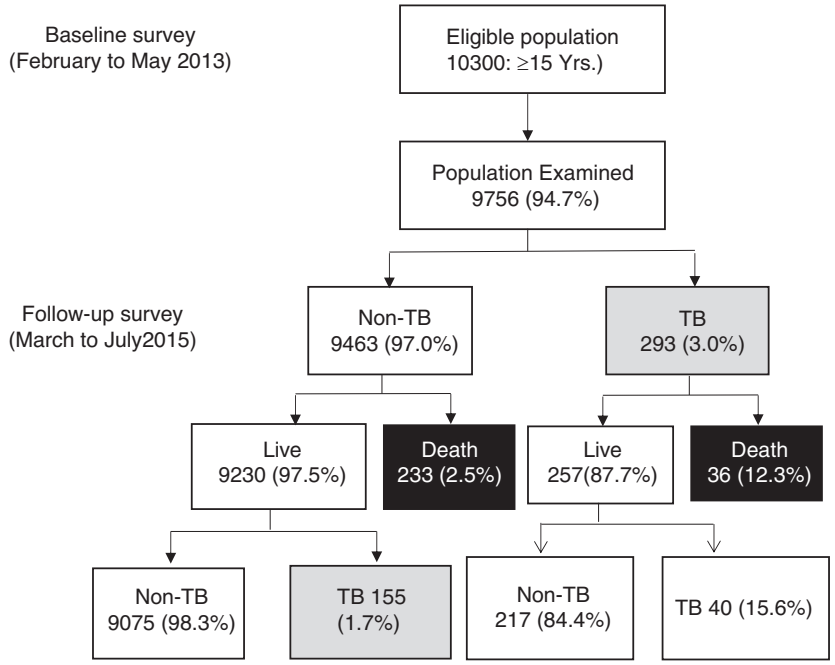

Figure 1 Process of 2-year follow-up of Saharia tribal population.

Mortality during 2-year follow-up survey

The observed mortality rates for the study cohort are shown in Table 1. Overall, the observed mortality among TB-affected population and the non-TB population was 122.9 and 24.6 per 1000 population respectively. Mortality was significantly higher among the TB-affected population than those not affected, and it was higher among males than females in both groups (134 *vs*. 99 non-TB population and 129.9 *vs*. 96.8 in TB-affected population). Age-specific mortality among the TB-affected population was higher in the 15- to 24-year age group (200), whereas among the non-TB population, it was higher in the age group of 55 years and older (135.7).

Expected and observed mortality rate

The estimated mortality rate among the non-TB population using the SRS-based life tables was compared with observed mortality among TB-affected population (Table 2). Overall, expected mortality among the non-TB population was estimated to be 30.2 per 1000 population. In contrast, the mortality among TB-affected population was 122.9 per 1000 population. This mortality among the TB-affected population is significantly higher than the expected mortality among the non-TB population (122.9 *vs*. 30.2). Notably, mortality was higher among males in both the TB-affected and non-TB populations (129.9 *vs*. 96.8 and 34.9 *vs*. 26.1). The age-specific mortality revealed higher number of deaths among TB-affected individuals in the 15- to 24-year age group (200/1000). However, death among the non-TB population was more common in those aged 55 years and older (135.7/1000) (Figure 2).

Discussion

The salient finding from this study is the higher mortality observed among TB-affected population *vs*. the non-TB population: our analyses have shown a fourfold higher death rate among the TB cohort. This corroborates the findings of a cohort study done in a rural setting that estimated a 4.2 times higher mortality among TB patients [16]. Similarly, a study from southern India reported six fold higher mortality among TB affected population as compared to the mortality among the general population [17]. The same study also reported that mortality continued to occur even after the completion of treatment, emphasising that the definition of TB mortality should not be limited to the treatment period, as this may result in underestimation of mortality rates. A retrospective cohort of 3357 smear-positive patients initiated on anti-TB treatment and completed 80% or more of their treatment, reported overall mortality of 28% in 3 years [18]. Excess mortality in successfully treated TB

Table 1 Mortality among TB-affected population and non-TB population during 2-year follow-up

	Baseline popn.	Non-TB popn	Mortality in non-TB popn.	Mortality rate/1000	TB patients	Mortality in TB popn	Mortality rate/1000	Mortality difference
Sex								
Male	4781	4550	134	29.5	231	30	129.9	100.4
Female	4975	4913	99	20.2	62	6	96.8	76.6
Age								
15–24	2853	2818	24	8.5	35	7	200.0	191.5
25–34	2616	2553	16	6.3	63	7	111.1	104.8
35–44	1783	1717	36	21.0	66	6	90.9	69.9
45–54	1391	1314	55	41.9	77	9	116.9	75.0
55+	1113	1061	102	96.1	52	7	134.6	38.5
Total	9756	9463	233	24.6	293	36	122.9	98.2

Table 2 Expected mortality rate among the non-TB population and observed mortality in tuberculosis affected population

	Population†		Mortality‡		Mortality rate/1000		Total popn.	Total expected mortality‡	
Age groups	Female	Male	Female	Male	Female	Male	(F + M)	(F + M)	Rate/1000
Population									
15–24	1518	1300	14	14	9.2	10.8	2818	28	9.9
25–34	1243	1310	13	18	10.5	13.7	2553	31	12.1
35–44	877	840	11	20	12.5	23.8	1717	31	18.1
45–54	664	650	19	34	28.6	52.3	1314	53	40.3
55+	611	450	70	73	114.6	162.2	1061	144	135.7
Total	4913	4550	128	159	26.1	34.9	9463	286	30.2
Observed mortality among TB patients									
15–24	5	30	1	6	200.0	200.0	35	7	200.0
25–34	18	45	2	5	111.1	111.1	63	7	111.1
35–44	12	54	2	4	166.7	74.1	66	6	90.9
45–54	15	62	1	8	66.7	129.0	77	9	116.9
55+	12	40	0	7	0.0	175.0	52	7	134.6
Total	62	231	6	30	96.8	129.9	293	36	122.9

†Age-group-wise non-TB population.
‡Expected mortality based on age-specific mortality rates for the rural population of Madhya Pradesh (SRS-based abridged life tables, 2013–17).

patients has also been reported from other countries, *viz.* 2.5% in Ethiopia [19], 6.47 in Brazil [10], 6.6% in Vietnam [20], and 8.3 times in Netherlands [21]. A systematic review and meta-analysis showed an estimated post-treatment case fatality rate of 2.69% among Indian patients with TB [22]. Similarly, Kamila Romanowski *et al.* (2019) showed significantly increased mortality post-treatment among TB-affected individuals as compared to the general population [23].

The current study also identified significantly higher survival probabilities in females than males. This could be due to higher risk factors associated with men and their higher likelihood to lost to follow-up or take a longer time to complete the treatment, which may contribute to higher mortality post-completion of treatment. The other fact is that globally males have a lower life expectancy than females. Tobacco smoking and alcoholism which are highly prevalent among males in this community may be considered as other important factors for higher mortality among males in this cohort [24]. Intervention strategies that can lower lost-to-follow-up rates, smoking and alcohol cessation should be enhanced to increase survival probabilities.

The general mortality rate among TB patients includes deaths due to co-morbidities and other external causes. TB mortality should include deaths only due to TB;

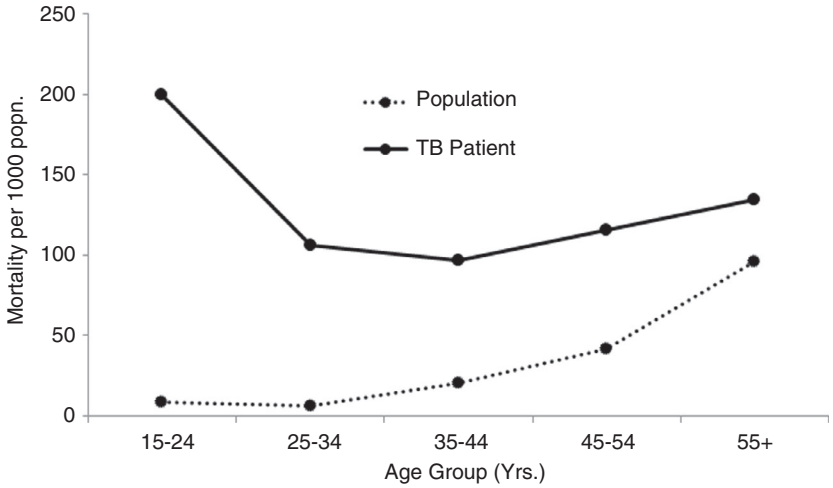

Figure 2 Mortality rate among TB-affected population and non-TB population.

unfortunately, ascertaining the exact cause of death is difficult, especially when deaths occur at home and in remote areas. It has been suggested that the excess mortality over a standard general mortality rate can be used as an indirect measure of TB mortality [17]. Although it is difficult to explain this increase in mortality in TB-affected populations, it is likely that these deaths were due to lung impairment due to TB. Studies in different settings reported lung impairment at TB treatment completion and persistent impairment several years post-completion of treatment [25-27]. Pulmonary impairment, ranging from mild malfunction to severe chest symptoms, may increase the risk of death in individuals after successful TB treatment [28,29]. These results highlight the importance of the history of pulmonary tuberculosis as a risk factor for long-term lung dysfunction that generally goes unnoticed. Though specific host factors causing lung impairment are not clearly understood, host immune responses might be playing an important role in the lung impairment. The severity of lung impairment might be dependent on the variability in host genes that modulate immune responses [30]. Further, studies on genetic predisposition to pulmonary impairment post-cure for TB disease will be helpful in understanding the higher death rates in these tribal groups post-TB treatment.

The mortality in TB-affected individuals during and after the successful treatment highlights quality of TB care. Reduction in the mortality rate is an important indicator of the success of NTEP. Indeed, the success of TB control programmes all over the world is measured by the number of lives saved and the number of deaths prevented. The global TB case fatality rate of below 5% is one of the top ten indicators for monitoring implementation of the End TB Strategy [1]. However, no reliable data on TB mortality are currently available. Our findings show higher mortality in successfully treated TB cases than in the general population. These findings underscore the need for monitoring the long-term survival of persons successfully treated for TB in a programmatic setting. They also emphasise the need to devise appropriate strategies to reduce long-term mortality due to TB. The evidence suggests that the policymakers may consider this as one of the important indicators for programme evaluation.

The findings of the present study provide an assessment of the long-term survival of TB-affected population in a high TB burden setting, highlighting the prominent contribution of TB to excess mortality in this vulnerable population. The Saharia tribe is a marginalised tribal group living in small, remote hamlets. Transport facilities are practically non-existent. Due to peoples' poverty, the loss of wages for attending health facilities becomes a critical restraining factor. These are only some of the vital issues faced by the community in accessing health facilities in their area. The Tribal Action Plan of NTEP provides for additional diagnostic and treatment services along with special incentives to the health staff working in tribal areas [31,32]. There is a gradual improvement in the programme performance since its implementation in the area as seen from an increase in the cure rate from 67% to 83% during the year 2005 and 2017 [33]. This emphasises a need to address the socioeconomic and environmental factors that are responsible for TB spread and prevalence in this vulnerable population [34]. Policymakers and other stakeholders need to make coordinated efforts to address TB and its associated factors for

controlling TB and reducing mortality due to TB in this tribal group.

Strength and limitations

We used a population-based cohort, conducted house-to-house baseline and end-line surveys, notified under NTEP, and followed up for treatment adherence, and hence, it is unlikely that we missed a significant number of cases that were started on treatment. As a result, no or minimal bias is expected. Despite >90% coverage achieved during both surveys, a few individuals could not be contacted during multiple field visits, as a result disease outcome of these individuals could not be ascertained. Although it is a shortcoming of the study, it is unlikely to affect the mortality rates in TB-affected and non-TB individuals. Moreover, the mortality data on TB-affected and non-affected populations obtained do not identify the actual cause of death. Furthermore, no data on other risk factors in this population are available. Lastly, there is no report suggesting a high prevalence of HIV infection and MDR-TB in the Saharia tribe. The study findings therefore may not be generalised or applied to other areas, particularly to populations/groups with high HIV/MDR-TB prevalence and for non-tribal populations.

Conclusion

In the Saharia tribe, post-treatment mortality in the TB-affected population is significantly higher than in the general population. This highlights an urgent need for implementation of effective public health strategies to prevent disproportionate deaths among TB-affected individuals such as Saharias living in resource-poor settings, and the importance of periodic follow-up of patients after cure/completion of treatment, especially in vulnerable populations. Further studies are essential to identify and to address the biomedical and social factors leading to post-treatment mortality in this population.

Acknowledgements

The authors are grateful to the Indian Council of Medical Research for funding the project; to the Director, ICMR-National Institute of Research in Tribal Health for supporting the study; to the state and district officials, Government of Madhya Pradesh for their constant support in undertaking this work in the Saharia tribe. The contributions of the Block Medical Officers and peripheral field staff are acknowledged. Sincere thanks are also due to the study participants and the field, laboratory, data entry operator and secretarial staff involved in the study. The funding agency had no role in the design, collection and interpretation of data and writing the manuscript.

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