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BRIEF REPORT

Factors Associated With Unfavorable Treatment Outcomes Among Persons With Pulmonary Tuberculosis: A Multicentric Prospective Cohort Study From India

Senbagavalli Prakash Babu,[1] Komala Ezhumalai,[1] Kalaivani Raghupathy,[1] Meagan Karoly,[2] Palanivel Chinnakali,[1] Nikhil Gupte,[3,4] Mandar Paradkar,[3,4] Arutselvi Devarajan,[5] Mythili Dhanasekaran,[5] Kannan Thiruvengadam,[6] Madolyn Rose Dauphinais,[2] Akshay N. Gupte,[2] Shrivijay Balayogendra Shivakumar,[4] Balamugesh Thangakunam,[7] Devasahayam Jesudas Christopher,[7] Vijay Viswanathan,[5] Vidya Mave,[3,4] Sanjay Gaikwad,[3] Aarti Kinikar,[3] Hardy Kornfeld,[8] C. Robert Horsburgh,[2] Padmapriyadarsini Chandrasekaran,[6] Natasha S. Hochberg,[2] Padmini Salgame,[9] Amita Gupta,[10] Gautam Roy,[1] Jerrold Ellner,[9] Pranay Sinha,[2,a] and Sonali Sarkar[1,a]; for the Regional Perspective Observational Research for Tuberculosis–India Consortium

[1]Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; [2]Section of Infectious Diseases, Department of Medicine, Boston Medical Center, Boston, Massachusetts, USA; [3]Byramjee Jeejeebhoy Government Medical College and Sassoon General Hospitals, Johns Hopkins University Clinical Research Site, Pune, Maharashtra, India; [4]Center for Infectious Diseases, Johns Hopkins India, Pune, Maharashtra, India; [5]Prof. M. Viswanathan Diabetes Research Centre, Chennai, Tamil Nadu, India; [6]Indian Council of Medical Research, National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India; [7]Department of Pulmonary Medicine, Christian Medical College, Vellore, Tamil Nadu, India; [8]Department of Medicine, University of Massachusetts Chan Medical School, Worcester, Massachusetts, USA; [9]Department of Medicine, Center for Emerging Pathogens, New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark, New Jersey, USA; and [10]Division of Infectious Diseases, Center for Clinical Global Health Education, Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA

In this prospective cohort of 2006 individuals with drug-susceptible tuberculosis in India, 18% had unfavorable treatment outcomes (4.7% treatment failure, 2.5% recurrent infection, 4.1% death, 6.8% loss to follow-up) over a median 12-month follow-up period. Age, male sex, low education, nutritional status, and alcohol use were predictors of unfavorable outcomes.

Keywords. tuberculosis; treatment outcome; risk factors; prospective cohort; epidemiology.

With more than 2.8 million tuberculosis (TB) cases and 0.3 million deaths in 2022, India carried more than a quarter of the global burden of TB disease and mortality [1]. Despite free testing and treatment offered by India's National TB Elimination Programme (NTEP), treatment success was 85% [2]. This is a barrier to the achievement of both the World Health Organization's End TB goals and India's internal TB elimination targets in 2025. Understanding the factors that drive unfavorable outcomes is critical.

Previous studies from India have drawn inconsistent conclusions about the factors that drive unfavorable outcomes and the magnitude of their effect, particularly for factors such as sex and diabetes mellitus (DM) [3–5]. In part, this is because the available studies are often regional, small, and lack follow-up beyond end of treatment. Though the NTEP recommends follow-up of persons with TB (PWTB) for up to 2 years after treatment initiation, it is not routinely implemented, and data on long-term follow-up under programmatic conditions are limited in the Indian setting.

We aimed to address these limitations through our large multicenter prospective cohort study. Our objective was to describe the treatment outcomes of PWTB beyond the treatment phase and identify risk factors of death, failure, relapse, and loss to follow-up.

METHODS

Study Design, Setting, and Population

We collected data at 5 sites that were part of the Regional Perspective Observational Research for Tuberculosis (RePORT)–India consortium as described previously [5]. Briefly, we enrolled participants aged ≥15 years with microbiologically confirmed symptomatic pulmonary TB between May 2014 and January 2019. PWTB who were diagnosed with multidrug-resistant TB, were treated with anti-tuberculosis treatment for ≥1 week, and without a recent human immunodeficiency virus (HIV) result (≤90 days) and unwilling to be tested for HIV or were culture-negative for *Mycobacterium tuberculosis* were excluded from the study. Ethics approval for the study was obtained from the institutional ethics committee of the participating institutions. Written informed consent from the participants was obtained before study procedures were initiated. We collected sociodemographic data, markers of disease severity, behavioral risk factors, and medical comorbidities at enrollment and assigned an outcome at the end of the follow-up period of up to 2 years. The primary outcome was a composite of treatment failure, disease recurrence, loss to follow-up, and death. Operational definitions used in the study are detailed in Supplementary Table 1.

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[a]P. S. and S. S. are co-senior authors.

Correspondence: Prof. S. Sarkar, Department of Preventive and Social Medicine, JIPMER, Puducherry, 605 006, India (prco.manuscript@gmail.com).

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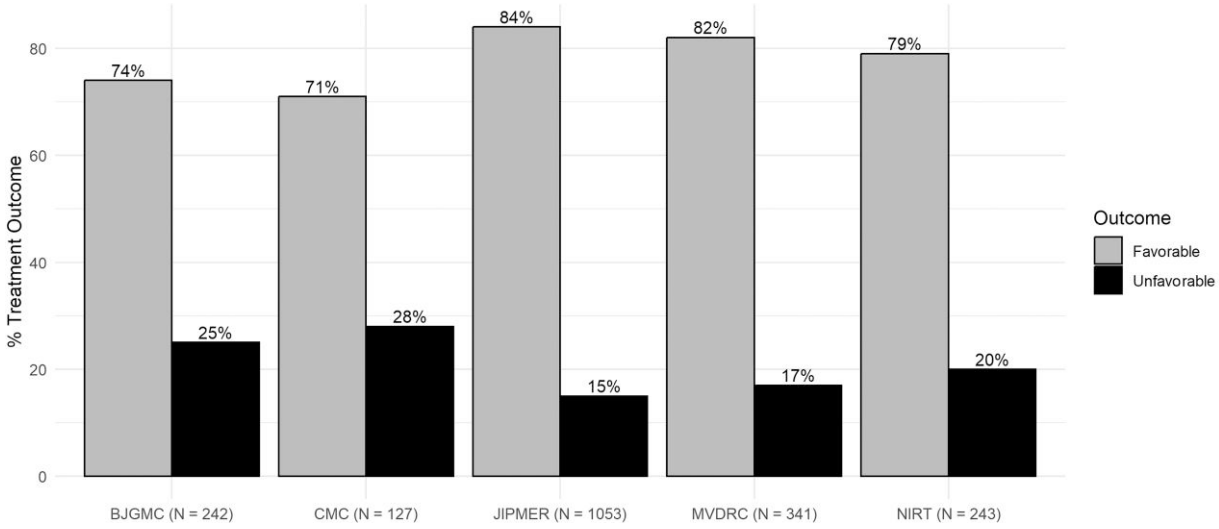

Figure 1. Tuberculosis treatment outcomes of participants with pulmonary tuberculosis by sites enrolled in the Regional Perspective Observational Research for Tuberculosis–India study (2014–2019). Abbreviations: BJGMC, Byramjee Jeejeebhoy Government Medical College; CMC, Christian Medical College; JIPMER, Jawaharlal Institute of Postgraduate Medical Education and Research; MVDRC, Professor M. Viswanathan Diabetes Research Centre (Prof. MVDRC); NIRT, National Institute for Research in Tuberculosis.

Statistical Analyses

We conducted multivariable Poisson regression to calculate incidence rate ratios (IRRs). Factors with a P value up to .20 in the univariate analysis were included in the multivariable generalized linear model. However, for a more comprehensive analysis, diabetes and employment status were included in the model despite univariate $P > .20$, as both are known to influence the TB treatment outcomes. The clustering at the level of study sites was accounted for using the vce (cluster) option in Stata (version 14). Multicollinearity among the independent variables was assessed by examining their standard errors in the regression model. In addition to the primary analysis, we performed an analysis stratified by sex. Additionally, the interaction between body mass index (BMI) and DM was examined in the multivariable analysis by including the interaction term in the multivariable model.

RESULTS

Of 2740 participants enrolled in the parent study, 2006 were eligible for analysis. The mean (standard deviation) age was 42.5 years (14.6), and the majority were male (73%), employed (71%), and had less than 10 years of education (80%). Among these participants, 1144 (57%) were underweight (BMI <18.5 kg/m^2), 627 (31%) had DM, and 37 (2%) were HIV-seropositive. Alcohol use was reported by 53%, and 20% reported current smoking tobacco use (Supplementary Table 2).

The cohort follow-up covered a period of up to 2 years, during which participants were diligently monitored through follow-up visits at predetermined intervals. The median number of follow-up periods was 12 months. During the study period, a subset of participants unfortunately experienced TB recurrence despite initial treatment success.

A total of 1641 (82%) participants had favorable treatment outcomes, 1559 (78%) were cured, and 82 (4%) completed treatment. Of 365 (18%) participants with unfavorable outcomes, 95 (4.7%) had treatment failure, 50 (2.5%) had TB recurrence, 83 (4.1%) died, and 137 (6.8%) were lost to follow-up. There was a significant difference in the rate of unfavorable outcomes (Figure 1) at the 5 sites ($P < .001$).

Table 1 displays the result of the multivariable regression. The risk of unfavorable outcomes increased in a dose-dependent manner with age compared with participants who were aged 15–19 years, a higher risk was found in older age groups; for 40–59 year age range (adjusted IRR [aIRR], 1.49; 95% confidence interval [CI], 1.13–1.96) and for ≥60 years (aIRR, 1.84; 95% CI, 1.33–2.54), with sex; males (aIRR, 1.70; 95% CI, 1.10–2.63), with alcohol use (aIRR, 1.14; 95% CI, 1.04–1.26) and with being underweight (aIRR, 1.87; 95% CI, 1.29–2.73). Education was independently associated with unfavorable treatment outcomes. Lower educational status was a significant predictor of unfavorable outcomes, in particular less than 11 years of education (illiterate: aIRR, 1.73; 95% CI, 1.28–2.33; primary school education only: aIRR, 1.76; 95% CI, 1.39–2.24; and education through high school: aIRR, 1.67; 95% CI, 1.20–2.32). The interaction between BMI and DM was not significant.

In sex-stratified analysis, older age groups, being underweight, and education status were associated with unfavorable outcomes for both males (Supplementary Table 3) and females

Table 1. Risk Factors Associated With Unfavorable Treatment Outcomes of Participants With Pulmonary Tuberculosis Enrolled in the Regional Perspective Observational Research for Tuberculosis–India Study

Characteristic	Category	Total Number of Unfavorable Events[a]	Person-Time, y	Rate/1000 Person-Years (95% CI)	Unadjusted IRR (95% CI)	*P* Value (Unadjusted Analysis)	Adjusted IRR [b,c] (95% CI)	*P* Value (Adjusted Analysis)
Age group, y	15–19	16	171.2	93 (57–153)	1	…	1	…
	20–39	105	744.5	141 (116–171)	1.51 (1.18–1.93)	.001	1.32 (.78–2.24)	.295
	40–59	182	955.2	191 (165–220)	2.04 (1.56–2.67)	<.001	1.49 (1.13–1.96)	.005
	≥60	62	245.4	253 (197–324)	2.70 (1.65–4.41)	<.001	1.84 (1.33–2.54)	<.001
Sex	Female	57	624.0	91 (70–118)	1	…	1	…
	Male	308	1492.3	206 (185–231)	2.26 (1.85–2.77)	<.001	1.70 (1.10–2.63)	.017
Body mass index, kg/m^2	Normal (18.5–22.9)	77	665.2	116 (93–145)	1	…	1	…
	Underweight (<18.5)	257	1166.6	220 (195–249)	1.90 (1.43–2.53)	<.001	1.87 (1.29–2.73)	.001
	Overweight/ Obese (≥23.0)	28	270.5	104 (71–150)	.89 (.70–1.15)	.381	.92 (.68–1.23)	.558
Marital status	Never married	47	389.9	121 (91–160)	1	…	1	…
	Ever married	318	1726.4	184 (165–206)	1.53 (1.22–1.91)	<.001	1.03 (.77–1.38)	.840
Educational status	Illiterate	76	361.8	210 (168–263)	2.62 (1.72–3.99)	<.001	1.73 (1.28–2.33)	<.001
	Primary school (1–5 y)	85	387.0	220 (178–272)	2.74 (1.74–4.30)	<.001	1.76 (1.39–2.24)	<.001
	High school (6–10 y)	172	944.6	182 (157–211)	2.27 (1.55–3.32)	<.001	1.67 (1.20–2.32)	.002
	Junior college (11–12 y)	15	211.1	71 (43–118)	.89 (.53–1.47)	.640	.84 (.51–1.40)	.506
	College (12+ years)	17	211.8	80 (50–129)	1	…	1	…
Household income, USD	<35.7	41	142.7	287 (212–390)	2.18 (1.49–3.21)	<.001	Not included in the model	
	35.7–59.6	79	370.4	213 (171–266)	1.62 (1.38–1.91)	<.001		
	59.7–119.1	122	630.0	194 (162–231)	1.47 (1.16–1.86)	.001		
	>119.1	85	646.0	132 (106–163)	1	…		
Employment status	Unemployed	93	655.4	142 (116–174)	1	…	1	…
	Employed	236	1345.6	175 (154–199)	.81 (.56–1.16)	.249	.87 (.49–1.55)	.631
Smoking	Never smoker	164	1307.3	125 (108–146)	1	…	1	…
	Current smoker	105	393.1	267 (221–323)	2.13 (1.89–2.39)	<.001	1.24 (.98–1.57)	.079
	Former smoker	96	415.9	231 (189–282)	1.84 (1.42–2.38)	<.001	1.14 (.89–1.47)	.303
Diabetes mellitus	No	269	1481.6	182 (161–205)	1	…	1	…
	Yes	96	634.7	151 (124–185)	.83 (0.57–1.21)	.335	.80 (.63–1.03)	.085
Alcohol use	No	124	1048.7	118 (99–141)	1	…	1	…
	Yes	241	1067.6	226 (199–256)	1.91 (1.61–2.26)	<.001	1.14 (1.04–1.26)	.008
Sputum smear grading[d]	Negative	34	282.8	120 (86–168)	1	…	1	…
	1+	145	853.1	170 (144–200)	1.41 (.86–2.33)	.176	1.12 (.63–1.99)	.702
	2+	112	620.1	181 (150–217)	1.50 (.99–2.27)	.053	1.04 (.65–1.67)	.856
	3+	74	358.3	195 (113–336)	1.72 (1.26–2.34)	.001	1.15 (.87–1.54)	.329
Cough	No	10	47.4	211 (113–392)	1	…	Not included in the model	
	Yes	354	2068.8	171 (154–190)	.81 (.39–1.70)	.579		
Fever	No	72	425.4	169 (134–213)	1	…		
	Yes	293	1690.9	173 (155–194)	1.02 (.67–1.56)	.912		
Night sweats	No	188	1236.9	152 (132–175)	1	…		
	Yes	177	879.4	201 (174–233)	1.32 (1.18–1.49)	<.001		
Weight loss	No	35	259.4	135 (97–188)	1	…		
	Yes	313	1773.9	176 (158–197)	1.31 (1.08–1.58)	.005		
Chest pain	No	167	1083.6	154 (132–179)	1	…		
	Yes	196	1022.0	192 (167–221)	1.24 (.98–1.57)	.068		
Fatigue	No	54	453.0	119 (91–156)	1	…		

Table 1. Continued

Characteristic	Category	Total Number of Unfavorable Events[a]	Person-Time, y	Rate/1000 Person-Years (95% CI)	Unadjusted IRR (95% CI)	*P* Value (Unadjusted Analysis)	Adjusted IRR [b,c] (95% CI)	*P* Value (Adjusted Analysis)
	Yes	311	1663.3	187 (167–209)	1.57 (1.11–2.22)	.011		
Cavitation	No	49	419.5	117 (88–155)	1	…		
	Yes	80	435.1	184 (148–229)	1.57 (1.21–2.05)	.001		

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

[a]Unfavorable treatment outcome includes bacteriological or clinical failure/relapse/lost to follow-up during anti-tuberculosis treatment/death.

[b]Age, sex, body mass index (BMI), marital status, educational status, employment status, diabetes mellitus (DM), and sputum smear grading were included in the multivariate model.

[c]Poisson regression analysis was performed with cluster adjustment; DM and BMI were checked for interaction in the model.

[d]Scanty results included in grade 1+.

(Supplementary Table 4). Among females, being employed was significantly associated with a lower risk for unfavorable outcomes (aIRR, 0.66; 95% CI, .45–.97).

DISCUSSION

To our knowledge, RePORT India is among the largest multicenter prospective observational cohorts in India, the country with the largest burden of TB. We found that approximately 1 in 5 PWTB had unfavorable treatment outcomes. This amounts to a 12% shortfall for the targets set by the national strategic plan for TB elimination in India [2]. Age (≥40 years), male sex, being underweight, lower levels of educational attainment, and alcohol use were associated with adverse treatment outcomes. On subgroup analysis by sex, the risk factors for adverse treatment outcomes were similar for men and women except for employment status. These findings of characteristics of those with unfavorable outcomes can be used to prioritize which persons should be provided additional treatment support and monitoring.

We observed that the risk of unfavorable outcomes increased with age in our cohort. Several studies have identified age as a determinant of TB treatment outcome. Among middle-aged adults, a confluence of comorbidities such as DM, increasing alcohol use and smoking use, delays in seeking treatment, and poor treatment adherence may contribute to poorer outcomes [3, 6, 7]. The increasing life expectancy reinforces the need for early diagnosis and treatment support strategies among older persons to reduce the TB disease burden.

As observed in global studies, we also observed that men had a higher risk for unfavorable outcomes, and our findings are consistent with the global studies [4]. Sociobehavioral factors such as alcohol use, smoking, and poorer treatment adherence might explain this discrepancy between sexes. The role of alcohol as a risk factor for TB disease and adverse treatment outcomes is well established [8]; our study adds further evidence to this. Despite the staggering evidence against the effects of alcohol, progress toward control of alcohol use in India has been inadequate.

About three-fifths of our study population were underweight. Recent studies have shown that nutritional interventions can reduce the incidence of TB disease incidence and potentially TB-related mortality as well [9]. Although India's TB program has been providing monetary aid to supplement the participants' nutritional needs since 2018, the aid often arrives too late to affect TB mortality and morbidity [10]. Enhancing the implementation of the scheme and taking appropriate corrective actions are the needs of the hour.

Our study has numerous strengths. This is a large cohort study from 5 sites in India. Further, we were able to achieve 2 years of active follow-up that allowed us to better assess recurrence rates compared with most previous studies. Limitations include lack of data on treatment adherence and glycemic control of study participants. Per NTEP guidelines, we defined death as all-cause mortality not as TB-specific mortality.

Eliminating TB requires a holistic approach. Addressing risk factors such as alcohol consumption, smoking, and undernutrition among persons with TB requires a concerted multisectoral collaboration and a strong political will. These actions will not only further TB elimination efforts but may also have protean benefits on the health of the Indian population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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