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Predictors of tuberculosis treatment outcomes among a retrospective cohort in rural, Central India

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ABSTRACT

Introduction: Programmatic design affects access to healthcare and can influence tuberculosis treatment outcomes. Potential predictors of tuberculosis treatment outcomes in one rural Indian setting were examined to improve outcomes with a focus on access to care.

Methods: Routinely collected tuberculosis treatment data from Jan Swasthya Sahyog, a community based healthcare system in rural Chhattisgarh, India were examined from 2003–2015. Predictors were analyzed for associations with death, loss to follow-up or failure in multivariable logistic regression models. The effect of distance from treatment on outcomes was graphed and Pearson's correlation coefficients (r^2) calculated. Descriptive time to event analyses were performed for all deaths and loss to follow-up from January 2010 to September 2015.

Results: 4979 patients with active TB were treated during the study period. Patients were mostly male, malnourished, diagnosed with pulmonary disease and many travelled lengthy distances. Positive treatment outcomes improved from 55% to 80% from 2003 to 2015 for all patients though positive treatment outcomes have been above 80% in the primary care setting since 2012. The annual case fatality rate was 4.4% with small yearly variation.Gender and site of treatment (primary versus secondary care facility) and also season of treatment initiation and travel time to care best predicted outcomes in both the complete model and model which included only patients with initial BMI data. No differences were found between primary and secondary care patients for initial BMI, percentage of sputum positivity among those with pulmonary disease and grade of sputum positivity among the sputum positive. Those who traveled the furthest to access care achieved the worst outcomes during the summer and, to a lesser degree, the monsoon. Distance from care was associated with treatment outcomes in a dose-response manner out to substantial distances. From 2010 to 2015, most patients who died or were lost to follow-up did so in the first week of treatment.

Conclusions: The provision of care through local facilities improves the treatment of tuberculosis in rural India. Interventions addressing death or loss to follow-up should focus on the newly diagnosed. Rural Indian physicians should be aware of how access issues affect TB treatment outcomes.

1. Introduction

The WHO mandates successful TB treatment outcomes of greater than 90% in developing nations and lower resource settings [1]. High proportions of successful TB treatment reported in higher resource settings [2,3] that serve TB patients from all over the world argue such goals are possible. Nonetheless, the realities of differences in public health resources to burden of TB patients can make such targets difficult to attain [4].

In 2017, India reported an incidence of 2.8 million new TB cases, accounting for approximately one-quarter of the world's new cases [5]. This includes 147,000 new cases of multi-drug resistance TB (MDRTB), also approximating a quarter of the world's total [5]. Excluding Human Immunodeficiency Virus (HIV), India reported 423,000 deaths due to TB. This number approximates a third of the world's total [5]. In India, TB care is coordinated by the Revised National Tuberculosis Control Programme (RNTCP). The RNTCP reports impressive treatment outcomes both nationwide [6] and in Chhattisgarh and Madhya Pradesh, the states from which the majority of our patient's live [5]. Independently published RNTCP data also estimate successful outcomes in about 85% of patients [7,8], though concerns exist about data inaccuracies [9]. Non-RNTCP Indian data report success in only

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50%–75% of diagnosed or enrolled patients [10–13]. While much is known about patient demographic and microbiologic data that affect TB outcomes in India [7,8,11,13–23], less studied are measures of healthcare access such as location of treatment [4], distance from care [24] and loss-to-follow-up before and during the treatment course [8,25–27].

At Jan Swasthya Sahyog, a team of health care providers treat rural Indian TB patients. In this retrospective cohort study, the objectives were to determine characteristics correlated with treatment outcomes, understand the effects of distance from care and season of treatment initiation on treatment outcomes and ascertain timing of deaths or loss to follow-up on treatment.

2. Methods

2.1. Setting

JSS is a community-based health care system operating in rural Chhattisgarh since 1999. JSS runs a secondary care hospital and three primary care clinics. TB care has been performed at all JSS sites since 1999 though has undergone multiple systems based modifications during that same time period. JSS primarily serves the rural Indian poor including tribal populations.

2.2. Design and data collection

JSS has maintained a database for all enrolled TB patients from early 2003, which includes demographic and clinical information recorded at diagnosis and throughout treatment. For most analyses, patient data were retrospectively reviewed from January 2003 to September 2015. For time-to-event (a) loss to follow-up and (b) death outcomes, a subset of patients from January 2010 to September 2015 were analyzed.

For distance from care analyses, patients provided their village name at treatment start. Community health workers (CHWs) serving each region provided information about each village's distance from care in both absolute distance (kilometers) and travel time (hours).

For data on loss to follow-up and death, patient charts were reviewed. For 2010 and 2011, data were extracted from paper charts and single entered in an Excel database. For 2012–2015, the Electronic Medical Record (Bahmni, ThoughtWorks, Bengaluru, India) was mined. The time from date of diagnosis to date of last clinical follow-up or death was recorded among those whose outcome was coded as 'loss to follow-up' or 'death' respectively.

2.3. Inclusion/exclusion criteria

All children and adults treated for active TB disease in both primary care clinic and secondary care hospital settings were included. Due to staffing shortages, there were periods (most of 2004 and September–December 2008) during which patient data were not collected.

2.4. Variable and outcome classification

Treatment outcomes were classified as follows: 'ongoing treatment' (at time of database closure), 'cured', 'completed', 'died', 'failed', 'lost to follow-up' or 'not evaluated/transferred care' (with unknown clinical endpoint). With the exception of 'ongoing treatment,' these definitions exactly mirror published WHO definitions [28]. The sum of cured and completed was defined as 'treatment success/positive outcomes,' also as per WHO definitions [28]. Cured referred to negative microscopy or culture (sputum or, if patient no longer producing sputum, saliva) at the end of treatment. Completed denoted patients who completed at least six months of consecutive treatment. Negative outcomes included patients who died, failed or were lost to follow-up. Patients who were still ongoing treatment at database closure or who were not evaluated/transferred care were considered uncertain outcomes and were not included in analyses.

Electronic scales were used to measure weight to the nearest tenth of a kilogram while height was measured to the nearest centimeter to calculate BMI. Analyses were performed using $< 16\ kg/m^2$, 16 to $< 18.5\ kg/m^2$ and $\geq 18.5\ kg/m^2$ as categories (based on WHO definitions [29]) due to the low number of patients who were normal weight, overweight or obese. Modifications in BMI cutoffs for Asian populations were not used because this population was predominantly underweight.

Site of disease was categorized as either pulmonary disease or extrapulmonary/disseminated disease. The former category included all patients with pulmonary TB; the latter category included all individuals with extrapulmonary disease and all disseminated disease. Those patients with both pulmonary and extrapulmonary involvement were categorized as pulmonary disease per WHO definitions [28]. AFB staining was graded per the standard 1+, 2+, and 3+ system [30]. For each patient, date of treatment start, site of treatment (secondary care hospital or primary care clinic), and previous treatment history ('new,' 'relapse,' 'treatment after failure,' and 'treatment after loss to follow-up') were recorded. Date of treatment start was categorized into season as monsoon (June–September), winter (October–February) or summer (March–May). Primary care clinics included three village-based clinics specializing in preventive and chronic care. The secondary care hospital was a single facility performing acute and emergency care and referrals.

The following data were recorded via patient self-report: gender, age and caste. For analyses, age was quantified as < 49 and ≥ 50 years old. Pediatric patients were defined as those individuals ≤ 18 years old at treatment start [31]. Data about human immunodeficiency virus (HIV) infection and diabetes status were not available for the duration of our retrospective analysis due to a period of systems optimization and so were not included in analyses.

2.5. Data analysis

All data were combined and transferred from Excel to STATA SE 14.1 for analyses.

Demographic characteristics were examined using descriptive techniques. Missing data were excluded from the calculation of all descriptive statistics and models.

A step-wise, multivariable analysis was conducted to determine relationships between demographic and clinical variables and treatment outcomes. Initially, univariate analyses of all variables of clinical interest were performed using Chi-squared testing. Variables demonstrating statistical significance ($p < 0.05$) in unadjusted analyses were checked for interactions. For significant interactions, a cutoff of $p \leq 0.15$ was used via analysis-of-variance (ANOVA) testing. Multiple significant interactions (all as dichotomous variables) were noted including gender and site of treatment, gender and absolute distance from care, site of treatment and season of treatment initiation, site of treatment and absolute distance from care, and season and both absolute distance and travel time from care. Finally, regression analyses were performed via generalized linear models including the following selected variables and interactions: gender and site of treatment (interaction), age (variable), treatment history (variable) and season of treatment initiation and travel time from care (interaction). Travel time from care was deemed more relevant than absolute distance from care (in the setting of longitudinal patient care) and was the variable of choice for regression analyses. Variables and interactions were removed from each model unless their removal demonstrated a significant likelihood ratio test for the reduced model compared to the full model ($p < 0.05$). Sensitivity analyses were also performed including BMI in these same models as BMI was not recorded for every patient at treatment initiation.

All patients commuting from similar absolute distances from care were aggregated into 25 km blocks while all patients commuting from similar travel times to care into one hour blocks to eliminate outliers. These aggregated outcome proportions were graphed for both loss to follow-up and positive outcomes and Pearson's correlation coefficients (r^2) determined.

For patients enrolled in care from January 2010 to September 2015