CLINICAL AND LABORATORY PREDICTORS OF TUBERCULOSIS RECURRENCE

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BACKGROUND

Despite successful completion of therapy for drug-susceptible pulmonary tuberculosis (PTB), a subset of individuals experience an **unfavorable treatment outcome of tuberculosis (TB) recurrence**. India accounts for 26% of the global burden of TB and few data on predictors of TB recurrence exist, especially with a focus on India.

METHODS

Study design: A retrospective analysis of 3 NIH and Indian government funded observational TB cohorts in India (TB-DM, c-TRIUMPh, and eDOTS)

Study population: Adults with newly diagnosed PTB initiated antituberculosis treatment (ATT) and were followed for 18-24 months for TB recurrence (defined as *Mycobacterium tuberculosis* growth on culture or signs –OR– signs/symptoms of TB and AFB smear+ following successful treatment completion)

Predictors:

-A priori selected 8 clinical and laboratory candidate predictors for recurrence: Age, alcohol use, sex, smoking history, culture positivity (month 2 [M2]), smear positivity M2, body mass index (BMI), and chest x-ray cavitation month 6 (M6)

Statistical analyses:

-80% of dataset used for training, and 20% for validation

-We used multivariable logistic regression and bootstrapped backwards selection (repetitions=1000) to identify the best predictors of TB recurrence

-Model accuracy measured by receiver operative characteristic (ROC) curve and area under the curve (AUC)

-Internal validation used on validation dataset to generate model accuracy, sensitivity, and specificity

-Variable importance assessed by the absolute value of the variable's t-statistic within the final model

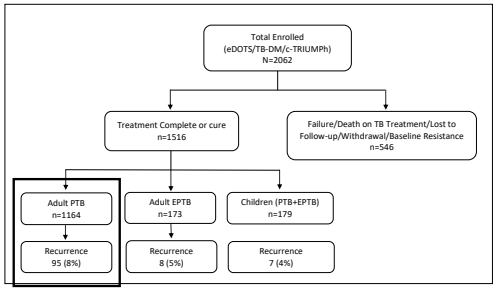


Figure 1. Schema for study participant selection

RESULTS

-*Mycobacterium tuberculosis* **culture positivity** at **month 2** was the most important predictor of TB recurrence

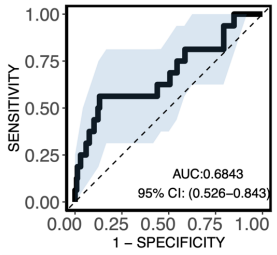
-Additional predictors included female sex, BMI, a history of smoking tobacco, and month 2 smear positivity

Table 1. Characteristics of study population

Characteristic	Categories	No Recurrence N = 1069	Recurrence N = 95	p-value
Study City	Chennai	475 (94%)	31 (6%)	
	Pune	594 (90%)	64 (10%)	0.03
Sex	Male	706 (90%)	75 (10%)	
	Female	363 (95%)	20 (5%)	0.01
Age (Years)	14 – 25	240 (91%)	24 (9%)	
	25 – 45	456 (90%)	53 (10%)	0.004
	> 45	373 (95%)	18 (5%)	
Education (Years)	Illiterate	118 (91%)	12 (9%)	
	0 – 5	157 (89%)	19 (11%)	0.65
	5 – 10	487 (92%)	41 (8%)	
	10 – 12	261 (93%)	20 (7%)	
	> 12	44 (94%)	3 (6%)	
Body Mass Index (kg/m²)	18.5 – 25	453 (94%)	27 (6%)	
	< 18.5	536 (89%)	65 (11%)	0.003
	> 25	78 (96%)	3 (4%)	
Smoking History	Never	736 (92%)	63 (8%)	
	Ever	266 (91%)	25 (9%)	0.71
Alcohol Use	None	639 (93%)	45 (7%)	
	Any	395 (90%)	44 (10%)	0.04
History of Diabetes	Absent	630 (91%)	65 (9%)	
	Present	439 (94%)	30 (6%)	0.19
Baseline Smear	Negative	245 (95%)	14 (5%)	
	Positive	823 (91%)	81 (9%)	0.07
Baseline Culture	Negative	112 (96%)	5 (4%)	
	Positive	951 (91%)	90 (9%)	0.11
Baseline Chest X-ray Cavity	Present	297 (93%)	24 (7%)	
	Absent	528 (92%)	43 (8%)	> 0.95
Month 2 Smear	Negative	824 (94%)	57 (6%)	
	Positive	94 (85%)	16 (15%)	0.01
Month 2 Culture	Negative	779 (94%)	50 (6%)	
	Positive	101 (85%)	18 (15%)	0.001
Month 6 Chest X-ray Cavity	Present	63 (86%)	10 (14%)	
	Absent	389 (94%)	23 (6%)	0.02
Antituberculosis Treatment Regimen	Daily	170 (94%)	11 (6%)	
	Thrice Weekly	894 (92%)	82 (8%)	0.37

Table 2/Figure 2. Results from final model using bootstrapped backwards selection including ROC curve and AUC

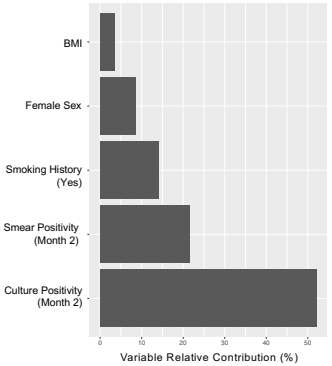
Predictor Variable for TB Recurrence	Coefficient	Standard Error
Intercept	**-2.10**	**0.70**
Culture Positivity (month 2)	**0.73**	**0.35**
Smear Positivity (month 2)	**0.64**	**0.40**
Smoking History (Yes)	**-0.51**	**0.37**
Female Sex	**-0.56**	**0.30**
Body mass index	**-0.02**	**0.04**
Age	--	--
Alcohol Use	--	--
Chest X-ray Cavitation (month 6)	--	--



RESULTS

- Among 1164 adults diagnosed with PTB who completed antituberculosis treatment and achieved cure, 95 (8%) subsequently experienced TB recurrence.
- Based on a priori selected candidate predictors, variables highlighted in bold in Table 2 were significant in our model (selected by bootstrapped backwards regression). The model exhibited a c-statistic of 0.68 (95% CI 0.52-0.84) and a Kappa statistic of 0.23 (Figure 2).
- Internal validation revealed an accuracy of 90% (95% CI 0.86-0.93), a sensitivity of 0.94 and a specificity of 0.31.

Figure 3. Variable importance plot demonstrating the relative contribution of each selected variable to the model



- Culture positivity at month 2 had the highest relative contribution to the model followed by smear positivity at month 2

CONCLUSIONS

- Recurrence following clinical cure from tuberculosis occurs relatively frequently
- Our prediction modeling revealed female sex, BMI, smoking history, month 2 smear positivity, and month 2 culture positivity as the most important predictors to discriminate TB recurrence from sustained cure.
- A TB recurrence prediction model could enable clinicians to identify patients at risk for recurrence during ATT and may be used to alter patient care strategies, such as enhanced monitoring post treatment for high-risk individuals.

ADDITIONAL KEY INFORMATION

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