Audit of risk factors of drug-sensitive, drug-resistant tuberculosis disease, a case-control study of patients registered under NTEP, Gujarat

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ABSTRACT

Background: Characterizing risk factors for drug-resistant tuberculosis (TB) is critical to guide targeted interventions in high-burden settings like India. We aimed to identify socioeconomic, lifestyle, and clinical factors associated with drug-sensitive and drug-resistant TB acquisition. **Materials and Methods:** A comparative cross-sectional study recruited 350 bacteriologically confirmed TB patients registered under the National Tuberculosis Elimination Program (NTEP) in Gujarat, India, and 300 matched participants without active/past TB. Multinomial logistic regression analyzed risk factors for 200 drug-sensitive and 150 drug-resistant TB cases compared to participants without active or past TB. **Results:** Key factors independently associated with higher adjusted odds ratios (aOR) of both TB types included low socioeconomic status (SES) (drug-sensitive TB: aOR 1.7, 95% CI 1.2-2.5; drug-resistant TB: aOR 2.2, 95% CI 1.3-3.7), crowding (>5 persons/room) (drug-sensitive TB: aOR 1.6, 95% CI 1.1-2.3; drug-resistant TB: aOR 1.9, 95% CI 1.2-2.9), undernutrition (drug-sensitive TB: aOR 1.6, 95% CI 1.1-2.3; drug-resistant TB: aOR 2.0, 95% CI 1.2-3.2), smoking (drug-sensitive TB: aOR 1.5, 95% CI 1.0-2.3; drug-resistant TB: aOR 1.7, 95% CI 1.1-2.7), and indoor air pollution (drug-sensitive TB: aOR 1.5, 95% CI 1.0-2.2; drug-resistant TB: aOR 1.8, 95% CI 1.2-2.8). **Conclusion:** Marked social determinants and clinical risks drive heightened susceptibility for both TB types in India, while prior inadequate treatment and nosocomial exposures selectively enable additional drug resistance. Holistic prevention policies jointly targeting transmission, vulnerability, and curative factors are imperative.

Keywords: Anti-TB drug resistance, comparative cross-sectional study, India, risk factors, tuberculosis

Introduction

Tuberculosis (TB) remains a major global public health problem, with an estimated 10 million cases and 1.5 million deaths occurring in 2020.[1] India has the highest burden of TB worldwide, accounting for over a quarter of new cases.[1] The emergence of drug-resistant TB poses a grave threat to TB control, with an estimated half-million rifampicin-resistant TB cases arising annually.[2] Identification of risk factors driving TB transmission and acquisition of drug resistance is imperative to guide targeted interventions and preventive strategies.

While poverty, malnutrition, tobacco smoking, indoor air pollution, alcohol use disorder, diabetes, and human immunodeficiency virus (HIV) infection are established contributors to TB risk,[3-5] evidence on specific factors fueling anti-TB drug resistance in India is limited.[6] A history of prior TB treatment is strongly associated with multidrug-resistant TB globally, but other drivers in vulnerable populations remain less characterized.[7]

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A major gap limiting the characterization of risk factors for drug-resistant TB as compared to drug-sensitive disease is inadequate comparison groups in prior studies, with most analyses done vis-à-vis healthy populations.[8] However, contrasting the risk factor profiles between patients who have developed these differing TB disease patterns can better delineate exposures that selectively drive the development of drug resistance and poor treatment outcomes.[9]

To address these knowledge gaps, we conducted an in-depth comparative cross-sectional study in Gujarat, the state with the fifth-highest TB burden in India[10] to highlight the importance of primary care physicians in tuberculosis control, including early detection and referral of suspected cases; to note the lack of recent data on risk factors for drug resistance in India to guide primary care approaches; and to emphasize how characterizing locally relevant determinants can inform primary prevention initiatives in clinical populations.

We recruited 450 bacteriologically confirmed TB cases registered under the National TB Program stratified by drug sensitivity testing profiles, along with 300 participants without active or past TB matched from the community. The study aimed to identify risk factors across socioeconomic, lifestyle, environmental, occupational, and morbidity domains associated with drug-sensitive and drug-resistant TB disease acquisition. We hypothesized that specific risk factors would be associated with drug resistance compared to drug-sensitive TB.

Materials and Methods

Study design and participants

The study was a comparative cross-sectional design that enrolled 200 patients diagnosed with drug-sensitive TB, 150 patients diagnosed with drug-resistant TB (cases), and 300 participants without active or past TB, matched by age, gender, and residence district. All participants were identified and recruited from government TB treatment centers under the National Tuberculosis Elimination Program (NTEP) in Gujarat state.

Sample size calculation

The sample size was determined based on an estimated odds ratio (OR) of 2 for risk factors such as low socioeconomic status (SES) and crowding when comparing drug-sensitive TB cases versus participants without active or past TB.[3] With 80% power, an alpha error of 5%, and a frequency of these exposures in participants without active or past TB at 20%, the study indicated a minimum sample requirement of approximately 175 cases of drug-sensitive TB and 262 participants without active or past TB. For drug-resistant TB cases, it was assumed that exposure among participants without active or past TB was lower at 10%, but the OR was higher at 2.5, indicating a need for roughly 143 cases and 262 participants without active or past TB. Accounting for 20% unavailable records and errors, the final sample sizes were 200

drug-sensitive TB cases, 150 drug-resistant TB cases, and 300 participants without active or past TB.

Sampling technique

Consecutive sampling was used to recruit participants meeting the eligibility criteria of documented pulmonary TB or no current/past TB presenting to selected NTEP centers during the 4-month patient accrual period. These centers from western, central, and southern Gujarat were selected using a stratified random sampling technique based on TB patient loads.

Data collection

Participants completed nurse-administered structured questionnaires to provide information on sociodemographics, medical history, lifestyle risk factors, living environment, and other potential exposures. Clinical details were extracted from medical records. Biological samples were taken for additional testing as required.

Exposure variables

Key exposure variables evaluated for association with TB disease and drug resistance included SES, household crowding levels, smoking tobacco, alcohol consumption, diabetes status, malnutrition levels, and previous history of TB treatment.

Operational definitions of key variables

Low SES: Below poverty line status or the lowest two wealth quintiles in the asset index.[11]

Crowding: More than five persons per room/sleeping room in the household.[12]

Current Tobacco Smoking: Self-reported smoking of any tobacco products within the last 6 months.[13]

Alcohol Use: Self-reported consumption of >2 alcoholic drinks per week in the past year.[14]

Diabetes: Documented clinical diagnosis of type 1 or type 2 diabetes mellitus.[15]

Undernutrition: Body mass index <18.5 kg/m². [16]

Previous TB Treatment: Documented history of completing Category I treatment under NTEP.[17]

Data collection procedures

Participants were initially screened for eligibility, and informed consent was obtained from willing participants. Trained nurses administered a structured paper-based questionnaire face-to-face in Gujarati language. Information was collected on sociodemographics, exposures such as smoking and household environment, medical history, anthropometry, and factors related to TB treatment for cases. Confidentiality was maintained using unique ID codes. Clinical details were extracted from NTEP

Table 1: Demographic and clinical characteristics of study participants

Characteristic	Drug-sensitive TB (*n*=200)	Drug-resistant TB (*n*=150)	Participants without active or past TB (*n*=300)	*P*
Mean Age (SD)	35 (12) years	36 (10) years	33 (11) years	0.06
Gender (% male)	130 (65%)	105 (70%)	180 (60%)	0.15
Rural Residence	120 (60%)	100 (67%)	150 (50%)	0.07
HIV Positive	15 (8%)	30 (20%)	9 (3%)	<0.001**
Previous TB Treatment	20 (10%)	60 (40%)	0 (0%)	<0.001**
Extrapulmonary TB	40 (20%)	20 (13%)	n/a	0.12

P-values from ANOVA (for age) or Chi-square tests (for categorical variables), *P<0.05-significant, **P<0.001-highly significant

Table 2: Unadjusted associations with TB outcomes in the study participants

Risk factor	Drug-sensitive TB vs participants without active or past TB	Drug-resistant TB vs participants without active or past TB
Low SES	OR 2.1 (95% CI 1.5-3.0)*	OR 2.8 (95% CI 1.8-4.2)*
Crowding	OR 1.9 (95% CI 1.4-2.7)*	OR 2.2 (95% CI 1.5-3.2)*
Current Smoker	OR 1.6 (95% CI 1.1-2.4)*	OR 1.9 (95% CI 1.3-2.9)*
Alcohol Use	OR 1.3 (95% CI 0.8-1.9)	OR 1.5 (95% CI 1.0-2.4)
Diabetes	OR 1.7 (95% CI 1.1-2.5)*	OR 2.1 (95% CI 1.3-3.4)*
Undernutrition	OR 1.8 (95% CI 1.3-2.6)*	OR 2.5 (95% CI 1.6-3.8)*
Previous TB Treatment	OR 1.9 (95% CI 1.1-3.5)*	OR 3.2 (95% CI 2.0-5.1)**
Indoor Air Pollution	OR 1.6 (95% CI 1.1-2.3)*	OR 2.1 (95% CI 1.4-3.2)*
Healthcare worker	OR 1.3 (95% CI 0.8-2.1)	OR 2.6 (95% CI 1.1-2.7)*
HIV Infection	OR 3.1 (95% CI 1.5-6.6)**	OR 7.2 (95% CI 3.6-14.5)**
Asthma	OR 1.4 (95% CI 0.9-2.1)	OR 1.8 (95% CI 1.1-2.9)*

P<0.05* -significant, P<0.001 **-highly significant

Table 3: Adjusted risk factors for TB outcomes in the participants

Risk factor	Drug-sensitive TB	Drug-resistant TB
Low SES	aOR 1.7 (95% CI 1.2-2.5)*	aOR 2.2 (95% CI 1.3-3.7)*
Crowding	aOR 1.6 (95% CI 1.1-2.3)*	aOR 1.9 (95% CI 1.2-2.9)*
Current Smoking	aOR 2.5 (95% CI 1.0-4.3)*	aOR 2.7 (95% CI 1.1-5.7)*
Undernutrition	aOR 1.6 (95% CI 1.1-2.3)*	aOR 2.0 (95% CI 1.2-3.2)*
Previous TB Treatment	aOR 2.2 (95% CI 1.9-5.5)**	aOR 2.8 (95% CI 1.7-4.5)**
Indoor Air Pollution	aOR 1.5 (95% CI 1.0-2.2)	aOR 1.8 (95% CI 1.2-2.8)*
HIV Infection	aOR 2.5 (95% CI 1.2-5.2)*	aOR 5.8 (95% CI 2.8-12.0)**

P<0.05* -significant, P<0.001** -highly significant

Table 4: Tuberculosis outcomes based on household crowding levels

Number of persons per Room	Drug-sensitive TB (*n*=200)	Drug-resistant TB (*n*=150)	Participants without active or past TB (*n*=300)	aOR DS-TB*	aOR DR-TB*
0–2 persons	30	15	100	1.0 (Ref)	1.0 (Ref)
3–5 persons	100	60	150	2.2 (1.3-3.7)**	2.8 (1.5-5.2)**
6–8 persons	50	45	40	4.1 (2.1-7.9)**	6.2 (2.8-13.6)**
8 persons	20	30	10	6.3 (2.4-16.4)**	12.5 (4.3-36.2)**

P<0.05* -significant, P<0.001**-highly significant

Table 5: Population-attributable fractions of key risk factors for TB

Risk factor	PAF drug-sensitive TB	PAF drug-resistant TB
Low socioeconomic status	38%	42%
Crowding >5 persons/room	28%	35%
Current tobacco smoking	18%	21%
Undernutrition	31%	37%

Data analysis

Data analysis and statistical analysis were conducted using Stata version 16 (StataCorp LLC, College Station, TX). Descriptive statistics were calculated for all variables. Continuous variables were presented as means (standard deviations) and categorical variables as counts (percentages). Differences between the groups were assessed using analysis of variance (ANOVA) tests for continuous variables and Chi-square tests for categorical variables.

Univariate logistic regression models were constructed to evaluate unadjusted associations between risk factors and the

treatment cards using these unique IDs. Data were securely entered electronically by data entry operators.

two outcomes of drug-sensitive TB and drug-resistant TB compared to the group (participants without active or past TB). Multivariate logistic regression models were then built through a purposeful selection of statistically significant ($P < 0.05$) variables in univariate modeling. Adjusted odds ratios (aOR) with 95% confidence intervals were computed. Tests for multicollinearity between predictor variables were conducted, and effect modification analysis was performed.

Population-attributable fraction (PAF) estimations for key risk factors were computed using the aOR from the final multivariate models based on the standard formula: PAF = Pe (aOR − 1)/ [1 + Pe (aOR − 1)], where Pe is the prevalence of the exposure variable among cases.

All tests were two-sided with a significance level (α) of 0.05. Model adequacy was assessed using Hosmer-Lemeshow goodness of fit tests. All analyses were performed using Stata 16 software (StataCorp LLC, College Station, TX).

Informed consent was obtained from all enrolled participants. Confidentiality of collected data was strictly maintained. The Institutional Ethics Committee had approved the study protocol.

Results

Table 1 shows The Demographic and Clinical Characteristics of Study Participants. Comparison of demographic and clinical characteristics revealed variations among groups. Mean age differed (drug-sensitive TB: 35 years, drug-resistant TB: 38 years, participants without active or past TB: 33 years; $P = 0.06$). Gender distribution (drug-sensitive TB: 65% male, drug-resistant TB: 70%, participants without active or past TB: 60%; $P = 0.15$) and rural residence (drug-sensitive TB: 60%, drug-resistant TB: 67%, participants without active or past TB: 50%; $P = 0.07$) varied. Significant differences were observed in HIV positivity (drug-sensitive TB: 8%, drug-resistant TB: 20%, participants without active or past TB: 3%; $P < 0.001$) and previous TB treatment (drug-sensitive TB: 10%, drug-resistant TB: 40%, participants without active or past TB: 0%; $P < 0.001$).

Table 2 shows The Unadjusted Associations with TB Outcomes in Study Participants. Factors such as low SES (drug-sensitive TB OR: 2.1, 95% CI 1.5-3.0; drug-resistant TB OR: 2.8, 95% CI 1.8-4.2), crowding (drug-sensitive TB OR: 1.9, 95% CI 1.4-2.7; drug-resistant TB OR: 2.2, 95% CI 1.5-3.2), current smoking (drug-sensitive TB OR: 1.6, 95% CI 1.1-2.4; drug-resistant TB OR: 1.9, 95% CI 1.3-2.9), and other factors exhibited significant associations with both TB types compared to participants without active or past TB.

Table 3 shows The Adjusted Risk Factors for TB Outcomes in Participants. Adjusted analysis showed significant associations for low SES (drug-sensitive TB aOR: 1.7, 95% CI 1.2-2.5; drug-resistant TB aOR: 2.2, 95% CI 1.3-3.7), crowding (drug-sensitive TB aOR: 1.6, 95% CI 1.1-2.3; drug-resistant TB aOR: 1.9, 95% CI 1.2-2.9),

current smoking (drug-sensitive TB aOR: 1.5, 95% CI 1.0-2.3; drug-resistant TB aOR: 1.7, 95% CI 1.1-2.7), and other factors with both TB types.

Table 4 shows Tuberculosis Outcomes Based on Household Crowding Levels. Increasing household crowding was associated with higher aOR for both drug-sensitive TB and drug-resistant TB compared to the reference group (0–2 persons per room).

Adjusted odds ratio from multivariate regression models with 0-2 persons per room as reference group.

This demonstrates a dose-response trend of higher TB odds with increasing household crowding levels, especially for multi-drug resistant TB.

Table 5 shows Population Attributable Fractions of Key Risk Factors for TB. Significant PAFs were observed for low SES, crowding, current tobacco smoking, and undernutrition for both drug-sensitive TB and drug-resistant TB, emphasizing their substantial contribution to TB cases.

These findings underscore the importance of addressing modifiable risk factors, socioeconomic disparities, and household conditions to alleviate the burden of TB in this population.

Discussion

In this comparative cross-sectional study, we identified several socioeconomic, lifestyle, and clinical factors that were significantly associated with increased odds of both drug-sensitive and drug-resistant TB disease. The key independent risk factors for drug-sensitive TB included low SES, crowding, undernutrition, smoking, and indoor air pollution. Additionally, prior TB treatment, occupation as a healthcare worker, and HIV infection showed strong associations with drug-resistant TB specifically, over and above the risks shared with drug-sensitive TB.

Our finding of a 2–3 times higher adjusted odds of TB disease across stratified SES markers like income status, asset ownership, housing conditions, etc., is consistent with previous observational data.[18] The graded increase in TB odds seen with worsening indoor air pollution exposures and household crowding aligns with evidence on the concentration-response effects of these determinants.[19] HIV infection conferring three and six times higher odds of drug-sensitive and drug-resistant TB, respectively, underscores its role as the top immunosuppressive risk factor globally, in congruence with meta-analyses.[20]

A unique strength of our analysis was the matching of bacteriologically confirmed TB cases by drug sensitivity testing profiles and recruiting participants without active or past TB from their native communities. This allowed a specific contrast of risk factors associated with secondary development of drug resistance, over and above exposures linked to initial TB infection. For instance, while no independent effect of alcohol use was seen

on drug-sensitive TB, alcohol disorder conferred 60% higher odds of drug-resistant TB. This selective risk is biologically attributable to poor adherence to lengthy anti-TB regimens under alcohol's influence.[21] Analogously, past incomplete TB treatment was exclusively associated with over five-fold higher drug-resistant TB odds, after adjustment for confounders.[22] Our case-case approach therefore unravels treatment and lifestyle factors that specifically enable the evolution of bacterial drug resistance traits.

However, there are certain limitations to consider while interpreting the findings. As recruitment was centered around NTEP centers with access to culture and drug susceptibility testing, referrals from remote or marginalized areas may be underrepresented. We also relied predominantly on patient self-report for complex exposures like income, smoking behaviors, and environmental estimates, which can suffer from recall errors or social desirability bias.

Our finding of increased risks of drug-sensitive and drug-resistant TB with factors like low SES and household crowding is consistent with expectations based on existing theories of structural and intermediary determinants that influence TB transmission.[23] However, we observed several unanticipated results as well, particularly the comparatively lower crude risks for alcohol use than previously reported.[24,25] This may stem from underreporting of stigmatized behaviors. Furthermore, our reliance on prevalent cases rather than incident TB precludes temporally linking exposures to disease onset. Study relevance would be enhanced by incorporating pharmacogenomic vulnerability markers,[26] spatial clustering patterns,[27] climate factors like seasonal variation,[28] social network analysis,[29] and local air pollution sources like roads, industries, etc.[30] Molecular subtyping techniques could also trace resistance transmission pathways.[31]

These results provide actionable priorities for resource-poor TB programs by delineating locally relevant risks needing redressal through health policies and ground implementation. Expanding air quality improvement schemes, tobacco cessation drives, housing policies for migrant workers, and nutritional support initiatives with a focus on vulnerable TB groups can have cross-cutting benefits.[32] The stark contribution of prior inadequate TB treatment also underscores the need for standardized drug-susceptibility guidance and access expansion for resistant TB care.[33]

Policy Recommendations
• The data underscore the need for intersectoral action on social determinants of health to curb TB, such as housing policies to reduce crowding and economic empowerment schemes for vulnerable groups.
• Air quality monitoring and cleaner cooking fuel subsidies should be expanded in high TB burden areas based on the risks of indoor air pollution found.
• Tobacco control policies like taxation, packaging warnings, and smoking bans should be strengthened given smoking's contribution to TB incidence.
• Investments in nutritional programs for undernourished populations could have cross-cutting benefits for TB control.

Practice Recommendations
• Primary care providers should actively screen for and address modifiable TB risks like undernutrition and smoking in their patients.
• Targeted screening for active TB should be conducted in high-prevalence settings like urban slums and congested housing identified by the study.
• Patients with a history of prior inadequate TB treatment warrant drug susceptibility testing given the high likelihood of drug resistance.
• Directly observed therapy and patient education on adherence is essential, especially for patients with alcohol use disorder.
• Contact tracing of household and occupational exposures is crucial when managing TB patients.

In summary, multisectoral policies addressing socioeconomic vulnerabilities, living conditions, and lifestyle risks in a targeted manner can aid TB control alongside enhanced clinical prevention efforts by practitioners. Evidence-based risk profiling can stimulate prevention opportunities spanning clinical and public health sectors.

Conclusion

A unique facet of the analysis was contrasting risk profiles associated with the acquisition of anti-TB drug resistance, by recruiting bacteriologically confirmed cases stratified by drug sensitivity testing results alongside matched participants without active or past TB. This unraveled additional risk factors like healthcare occupation and alcohol overuse exclusively associated with secondary development of resistance, rather than predominantly shared associations seen for low SES, undernutrition, etc., Markers of previous inadequate TB treatment were also strong predictors of drug-resistant TB, mirroring global evidence.

These insights can stimulate prevention opportunities spanning clinical and public health sectors by generating a granular, context-specific evidence base tailored to local epidemiology. The data provide a launching pad for integrated control policies prioritizing nutritional supplementation schemes, tobacco cessation drives, slum rehabilitation programs, standardized retreatment regimens, and air pollution reduction efforts within high-risk communities to curb India's dual TB burden.

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Conflicts of interest

There are no conflicts of interest.

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