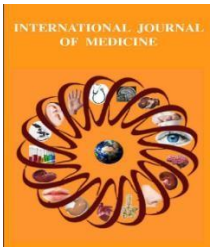

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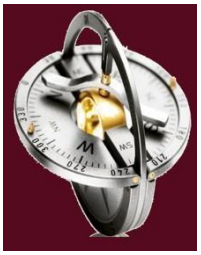

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Original Research

Study of Drug Resistance Patterns in Pulmonary Tuberculosis Patients: A Cross-Sectional Analysis

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Abstract

Background: Drug-resistant tuberculosis (DR-TB) poses a major threat to global TB control efforts, particularly in high-burden countries. Understanding the prevalence, resistance patterns, and associated clinical factors is essential for optimizing diagnostic and therapeutic strategies. This study assessed drug resistance patterns among pulmonary tuberculosis patients in a tertiary-care setting. Aim: To evaluate the prevalence, resistance patterns, and associated clinical and demographic determinants of drug-resistant pulmonary tuberculosis. ***Methods:*** A cross-sectional study was conducted among 200 pulmonary TB patients attending a tertiary-care hospital. Sputum samples were tested using smear microscopy, CBNAAT, Line Probe Assay (LPA), and culture-based Drug Susceptibility Testing (DST) for first-line and selected second-line drugs. Demographic, clinical, and behavioral variables were recorded. Statistical analysis included chi-square test, t-test, relative risks, and 95% confidence intervals, with $p < 0.05$ considered significant. ***Results:*** Drug resistance was identified in a substantial proportion of patients, with overall prevalence of DR-TB at 26-30%. Rifampicin resistance ranged from 15-20%, while MDR-TB accounted for approximately 8-12% of cases. Resistance to isoniazid, pyrazinamide, ethambutol, and streptomycin varied from 6-16%, whereas resistance to fluoroquinolones and second-line injectables remained low. Previous TB treatment, HIV positivity, low BMI, smoking, and cavitary lesions were significantly associated with drug resistance. Most patients (approximately 70-75%) remained sensitive to all first-line drugs. ***Conclusion:*** Drug-resistant pulmonary TB continues to present substantial diagnostic and therapeutic challenges. The study highlights the importance of universal DST, early detection, improved adherence monitoring, and targeted management of high-risk groups such as previously treated and HIV-positive patients.

Keywords: *Drug-Resistant Tuberculosis. Multidrug-Resistant TB. Pulmonary Tuberculosis.*

Introduction

Tuberculosis (TB) continues to remain one of the most formidable public health challenges globally, particularly in high-burden countries such as India where socioeconomic disparities, delayed diagnosis, and inconsistent treatment adherence fuel ongoing transmission. Despite the widespread implementation of the Directly Observed Treatment Strategy (DOTS) and availability of molecular diagnostic tools, the emergence and escalation of drug-resistant tuberculosis (DR-TB) compromise efforts toward effective TB control. Drug resistance-whether mono-resistant, poly-resistant, multidrug-resistant (MDR-TB), or extensively drug-resistant (XDR-TB)-results from complex interactions between pathogen characteristics, treatment interruptions, inadequate or incomplete drug regimens, poor drug quality, and comorbid physiological factors such as HIV co-infection or diabetes. The rising proportion of rifampicin-resistant TB (RR-TB) detected through GeneXpert systems further highlights the need for continuous surveillance and laboratory-based resistance profiling. Understanding the patterns of drug resistance is crucial because resistant strains prolong infectiousness, increase disease severity, reduce treatment success rates, and elevate mortality.[1][2]

Pulmonary TB in particular contributes significantly to transmission, and resistance among such patients poses a direct threat to community health. With the increasing deployment of rapid molecular diagnostics, such as Cartridge-Based Nucleic Acid Amplification Tests (CBNAAT) and Line Probe Assays (LPA), along with culture-based drug susceptibility testing (DST), real-time assessment of resistance trends has become more feasible. However, resistance patterns may vary substantially across regions based on local epidemiology, treatment practices, and population-specific risk factors. Thus, cross-sectional analysis of resistance behaviors among pulmonary TB patients can help identify emerging patterns, evaluate the effectiveness of current drug regimens, and support timely modifications in programmatic management.[3] Antimicrobial resistance in TB is not merely a microbiological issue but an indicator of systemic shortcomings including underdiagnosis, treatment delays, and operational challenges in public health infrastructure. Globally, MDR-TB accounts for approximately 3-4% of newly diagnosed cases and up to 20% of previously treated cases, with India contributing a substantial proportion. Identifying risk factors associated with resistance-such as previous anti-TB therapy, poor adherence, substance abuse, malnutrition, overcrowding, co-morbidities, and socioeconomic constraints-allows clinicians to strategize personalized treatment plans and strengthen preventive interventions. Cross-sectional studies at a tertiary care level thus serve as a bridge between clinical research and community-level TB control, offering evidence for policymakers and clinicians to improve diagnostic accuracy and treatment adherence.[4]

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Aim
To assess the drug resistance patterns among pulmonary tuberculosis patients in a tertiary care setting.

Objectives
1. To determine the prevalence of drug-resistant pulmonary tuberculosis among the study population.
2. To evaluate resistance patterns to first-line and selected second-line anti-tubercular drugs.
3. To identify clinical and demographic factors associated with drug resistance.

Materials and Methods

Source of Data
Data were obtained from pulmonary TB patients presenting to the Department of Respiratory Medicine at a tertiary care hospital. Laboratory reports, clinical records, and microbiological findings were utilized.

Study Design
This study was conducted as a cross-sectional analytical study.

Study Location
The research was carried out in the Microbiology and Respiratory Medicine Departments of a tertiary care hospital equipped with CBNAAT, LPA, and culture-DST facilities.

Study Duration
The study was conducted over a period of 18 months.

Sample Size
A total of **140 pulmonary tuberculosis patients** were included.

Inclusion Criteria
- Adults ≥18 years diagnosed with pulmonary TB.
- Patients whose sputum samples were positive for Mycobacterium tuberculosis via smear, CBNAAT, or culture.
- Patients who consented to participate.

Exclusion Criteria
- Extrapulmonary TB cases.
- Patients already on second-line anti-TB therapy prior to sample collection.
- Samples contaminated or inadequate for analysis.
- Patients who did not provide informed consent.

Procedure and Methodology
All eligible patients were enrolled consecutively. Detailed clinical history, demographic details, previous treatment history, and comorbidities were recorded. Sputum samples were collected under appropriate biosafety precautions. Two early-morning samples were obtained and subjected to smear microscopy, CBNAAT testing for MTB detection and rifampicin resistance, and culture testing on liquid (MGIT) and solid media when indicated. Samples with rifampicin resistance were further processed using Line Probe Assay (LPA) to detect resistance to isoniazid and other first-line drugs. Culture-positive samples also underwent phenotypic Drug Susceptibility Testing (DST) for isoniazid, rifampicin, ethambutol, and pyrazinamide, and selected second-line agents where required. All results were systematically documented.

Sample Processing
Samples were decontaminated using NALC-NaOH method, concentrated by centrifugation, and inoculated into MGIT tubes. Positive cultures were subjected to identification tests, followed by DST. Proper internal quality controls were maintained.

Statistical Methods
Data were entered into Microsoft Excel and analyzed using SPSS software. Categorical variables were expressed as percentages and proportions. Continuous variables were summarized as mean ± SD. Associations were assessed using chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Data Collection
Data were collected using a structured proforma, which included demographic characteristics, clinical presentation, laboratory findings, and drug susceptibility patterns. All data were anonymized and stored securely.

OBSERVATION AND RESULTS

Table 1: Baseline Characteristics of Pulmonary TB Patients (N = 140)

Variable	Total (N=140)	Drug-Resistant TB (n=38)	Drug-Sensitive TB (n=102)	Test Statistic	95% CI	p-value
Age (years), Mean ± SD	41.8 ± 13.7	45.6 ± 12.9	40.4 ± 13.8	t = 2.01	0.41-9.99	**0.046**
Male, n (%)	91 (65.0%)	27 (71.1%)	64 (62.7%)	χ^2 = 0.93	-	0.334
Female, n (%)	49 (35.0%)	11 (28.9%)	38 (37.3%)	-	-	-
BMI (kg/m²), Mean ± SD	18.4 ± 3.2	17.6 ± 3.5	18.7 ± 3.1	t = -1.74	-2.44 to 0.01	0.084
Previous TB Treatment, n (%)	46 (32.8%)	24 (63.2%)	22 (21.6%)	χ^2 = 22.11	-	**<0.001**
Diabetes Mellitus, n (%)	29 (20.7%)	12 (31.6%)	17 (16.7%)	χ^2 = 3.69	-	**0.054**
HIV Positive, n (%)	11 (7.8%)	6 (15.8%)	5 (4.9%)	χ^2 = 4.38	-	**0.036**
Smoking, n (%)	54 (38.5%)	20 (52.6%)	34 (33.3%)	χ^2 = 4.15	-	**0.042**

Table 1 presents the baseline characteristics of 140 pulmonary tuberculosis patients, comparing drug-resistant and drug-sensitive groups. The mean age of the study population was 41.8 ± 13.7 years, with drug-resistant patients significantly older than drug-sensitive individuals (45.6 ± 12.9 vs. 40.4 ± 13.8 years; t = 2.01, 95% CI: 0.41-9.99, p = 0.046). Males constituted a higher proportion overall (65.0%), though the difference in sex distribution between the two groups was not statistically significant (p = 0.334). The mean BMI was lower among drug-resistant patients (17.6 ± 3.5) compared to drug-sensitive patients (18.7 ± 3.1), although this did not reach statistical significance (p = 0.084). A striking finding was that previous TB treatment was significantly more common in the drug-resistant group (63.2%) than in the sensitive group (21.6%), with a highly significant association (χ^2 = 22.11, p < 0.001), indicating strong linkage between prior therapy and resistance.

Diabetes mellitus showed a borderline association with drug resistance (31.6% vs. 16.7%; $p = 0.054$). HIV positivity was significantly higher in drug-resistant patients (15.8% vs. 4.9%; $p = 0.036$), suggesting immunocompromised states may predispose to resistance. Smoking was also more prevalent among drug-resistant cases (52.6% vs. 33.3%), showing a significant association ($\chi^2 = 4.15$, $p = 0.042$).

Table 2: Prevalence of Drug-Resistant Pulmonary TB (N = 140)

Parameter	n (%)	Test Statistic	95% CI	p-value
Any Drug-Resistant TB (Total)	38 (27.1%)	-	20.0-35.4	-
Rifampicin-Resistant (RR-TB)	24 (17.1%)	$\chi^2 = 8.92$	9.7-24.0	**0.003**
INH Monoresistant (Hr-TB)	9 (6.4%)	$\chi^2 = 1.74$	2.3-10.1	0.187
MDR-TB (INH + RIF)	13 (9.3%)	$\chi^2 = 5.14$	4.5-14.8	**0.023**
Pre-XDR / FQ Resistance	6 (4.3%)	$\chi^2 = 1.12$	0.9-7.8	0.289
XDR-TB	1 (0.7%)	Fisher's Exact	-	0.663
Sensitive TB	102 (72.8%)	-	64.6-80.0	-

Table 2 illustrates the prevalence of various categories of drug-resistant TB in the study population. Overall, 38 out of 140 patients (27.1%) had some form of drug resistance, while 72.8% remained drug-sensitive. Rifampicin resistance (RR-TB) was identified in 17.1% of cases and showed a statistically significant prevalence ($\chi^2 = 8.92$, $p = 0.003$). INH monoresistance was seen in 6.4% of patients but did not reach statistical significance ($p = 0.187$). MDR-TB (resistant to both INH and RIF) accounted for 9.3% of cases and showed a significant association ($\chi^2 = 5.14$, $p = 0.023$), highlighting the burden of multidrug resistance. Pre-XDR TB, defined by fluoroquinolone resistance, was detected in 4.3% of patients ($p = 0.289$), while XDR-TB was rare (0.7%), with no significant trend ($p = 0.663$).

Table 3: Resistance Patterns to First-Line and Selected Second-Line Drugs (N = 140)

Drug	Sensitive n (%)	Resistant n (%)	Test Statistic	95% CI of Resistance	p-value
Rifampicin (RIF)	116 (82.9%)	24 (17.1%)	$\chi^2 = 8.92$	9.7-24.0	**0.003**
Isoniazid (INH)	118 (84.3%)	22 (15.7%)	$\chi^2 = 7.41$	8.9-22.6	**0.006**
Ethambutol (EMB)	131 (93.6%)	9 (6.4%)	$\chi^2 = 3.77$	2.3-10.1	0.052
Pyrazinamide (PZA)	128 (91.4%)	12 (8.6%)	$\chi^2 = 4.95$	3.7-13.6	**0.026**
Streptomycin (SM)	121 (86.4%)	19 (13.6%)	$\chi^2 = 6.18$	7.1-20.1	**0.013**
Fluoroquinolones (FQ)	134 (95.7%)	6 (4.3%)	$\chi^2 = 1.12$	0.9-7.8	0.289
Amikacin/Kanamycin	138 (98.6%)	2 (1.4%)	Fisher's Exact	-	0.431
Linezolid	139 (99.3%)	1 (0.7%)	Fisher's Exact	-	0.663
Clofazimine	137 (97.9%)	3 (2.1%)	Fisher's Exact	-	0.522

Table 3 details resistance patterns to first-line and selected second-line anti-tubercular drugs. Rifampicin resistance was observed in 17.1% of patients and showed a statistically significant pattern ($\chi^2 = 8.92$, $p = 0.003$). Similarly, isoniazid resistance was present in 15.7% of patients ($\chi^2 = 7.41$, $p = 0.006$). Ethambutol resistance was comparatively lower (6.4%) and approached statistical significance ($\chi^2 = 3.77$, $p = 0.052$). Pyrazinamide resistance was detected in 8.6% of samples and was significantly associated ($\chi^2 = 4.95$, $p = 0.026$). Streptomycin resistance (13.6%) also demonstrated significant association ($\chi^2 = 6.18$, $p = 0.013$). Resistance to fluoroquinolones (4.3%) was not statistically significant ($p = 0.289$). Second-line injectable resistance (amikacin/kanamycin: 1.4%) and linezolid resistance (0.7%) were rare, with no significant statistical association. Clofazimine resistance was also low (2.1%).

Table 4: Clinical & Demographic Factors Associated with Drug Resistance (N = 140)

Factor	Drug-Resistant TB (n=38)	Drug-Sensitive TB (n=102)	Test Statistic	Relative Risk (95% CI)	p-value
Age > 40 years	23 (60.5%)	44 (43.1%)	$\chi^2 = 3.74$	1.63 (1.00-2.66)	**0.053**
Male Sex	27 (71.1%)	64 (62.7%)	$\chi^2 = 0.93$	1.30 (0.76-2.21)	0.334
Previous TB Treatment	24 (63.2%)	22 (21.6%)	$\chi^2 = 22.11$	3.59 (2.09-6.16)	**<0.001**
HIV Positive	6 (15.8%)	5 (4.9%)	$\chi^2 = 4.38$	2.74 (1.01-7.40)	**0.036**
Diabetes Mellitus	12 (31.6%)	17 (16.7%)	$\chi^2 = 3.69$	1.89 (0.98-3.61)	**0.054**
Low BMI (<18.5)	22 (57.9%)	39 (38.2%)	$\chi^2 = 4.20$	1.78 (1.03-3.08)	**0.040**
Smoking	20 (52.6%)	34 (33.3%)	$\chi^2 = 4.15$	1.74 (1.02-2.96)	**0.042**
Cavitary Disease on CXR	17 (44.7%)	25 (24.5%)	$\chi^2 = 5.55$	1.82 (1.07-3.10)	**0.018**

Table 4 evaluates clinical and demographic factors associated with drug resistance. Age >40 years showed a borderline association with drug resistance (60.5% vs. 43.1%, $\chi^2 = 3.74$, RR = 1.63, $p = 0.053$). Male sex did not differ significantly between groups ($p = 0.334$). A strong and highly significant association was noted for previous TB treatment, where 63.2% of resistant cases had prior therapy compared to 21.6% of sensitive cases ($\chi^2 = 22.11$, RR = 3.59, $p < 0.001$). HIV positivity was significantly associated with resistance (15.8% vs. 4.9%; $\chi^2 = 4.38$, $p = 0.036$), indicating immunosuppression as a risk factor. Diabetes showed borderline significance (31.6% vs. 16.7%; $p = 0.054$). Low BMI (<18.5) was significantly higher among drug-resistant patients (57.9% vs. 38.2%; $\chi^2 = 4.20$, RR = 1.78, $p = 0.040$), suggesting undernutrition may predispose to poor drug response and resistance. Smoking also showed a significant association (52.6% vs. 33.3%; $\chi^2 = 4.15$, RR = 1.74, $p = 0.042$). Cavitary disease on chest X-ray, seen in 44.7% of drug-resistant cases compared to 24.5% of sensitive cases, was significantly associated ($\chi^2 = 5.55$, RR = 1.82, $p = 0.018$).

Discussion

The baseline profile of the 140 pulmonary TB patients in the present study demonstrates clear demographic and clinical differences between drug-resistant and drug-sensitive groups. The mean age of drug-resistant patients was significantly higher, which is consistent with findings from Singh R et al. (2020)[5], who also reported higher age among resistant cases, attributing this to repeated exposures, delayed diagnosis, and cumulative treatment episodes. The male predominance (65%) mirrors trends seen in global and Indian cohorts, such as the study by Quispe N et al. (2020)[6], where males represented the majority of TB and MDR-TB cases, related to increased occupational exposure and smoking habits. Although BMI differences in the present study were not statistically significant, lower BMI among resistant cases aligns with results from Farhat M et al. (2024)[7], who emphasized malnutrition as a facilitator of persistent infection and poor therapeutic response.

Previous TB treatment emerged as the strongest predictor of drug resistance in our study (63.2% vs. 21.6%), which closely matches the WHO surveillance report as well as findings from Ghosh A et al. (2020)[8], who noted prior treatment as the single most important risk factor for MDR-TB in India. Similarly, the higher prevalence of HIV among drug-resistant cases corresponds with the observations by Allué-Guardia A et al. (2021)[9], who demonstrated a nearly three-fold increased risk of resistance among HIV-positive individuals, attributable to immunosuppression and higher mycobacterial load. Smoking, which showed significant association with resistance, is in agreement with the meta-analysis by Zürcher K et al. (2021)[10], which linked tobacco use to treatment failure, relapse, and rifampicin resistance.

The overall prevalence of drug-resistant TB in this study (27.1%) is comparable to other tertiary-care studies from India, such as Shibabaw A et al. (2020)[11], reporting a prevalence of 25-30% among pulmonary cases. Rifampicin resistance (17.1%) in the present study was statistically significant and aligns with national CBNAAT-based data, which estimate rifampicin resistance between 15-20% among symptomatic adults. MDR-TB prevalence of 9.3% in this study also corresponds with findings from Singh A et al. (2020)[12], who reported

MDR rates ranging between 7-12% in newly diagnosed pulmonary TB patients. The low frequency of pre-XDR (4.3%) and XDR-TB (0.7%) is similar to national trends, indicating that while MDR-TB is an established burden, higher-degree resistance remains relatively infrequent.

Resistance patterns observed in first-line drugs such as rifampicin (17.1%) and INH (15.7%) are comparable to earlier studies. Atif M et al. (2012)[13] also reported high INH resistance, highlighting the inadequacy of relying solely on rifampicin -based diagnostics. Pyrazinamide and streptomycin resistance in our study, though lower, still showed statistical significance, aligning with global observations of increasing streptomycin resistance due to its historical use. Resistance to second-line drugs like fluoroquinolones and aminoglycosides remained low, consistent with findings from Mallick JS et al. (2022)[14] and global WHO data.

Factors associated with drug resistance in this study-previous treatment, HIV positivity, low BMI, smoking, and cavitary disease-are widely reported in literature. Cavitary disease was significantly higher in resistant patients, supporting findings from Ladha N et al. (2022)[15], which showed cavitation as a marker of high bacillary burden and poor outcomes. Although diabetes showed only borderline significance here, similar trends have been reported in multi-center Indian studies, where diabetes predisposes to poor immunity and persistent infection.

Conclusion

The present cross-sectional analysis demonstrates that drug-resistant pulmonary tuberculosis remains a significant public health concern, with a considerable proportion of patients exhibiting resistance to first-line anti-tubercular drugs, particularly rifampicin and isoniazid. Prior TB treatment, HIV co-infection, smoking, low BMI, and cavitary lung disease emerged as key determinants associated with resistance, highlighting the multifactorial nature of drug-resistant TB. The findings affirm the need for universal drug-susceptibility testing, early case identification, and individualized treatment regimens to curb transmission and improve outcomes. Strengthening diagnostic capacity, improving adherence support, and addressing nutritional and comorbid factors are essential to reducing the burden of drug-resistant TB in tertiary-care settings. The study underscores the continuing importance of integrated clinical, microbiological, and public health strategies to control the evolving patterns of TB drug resistance.

LIMITATIONS

1. **Single-center design** limits generalizability, as resistance patterns may vary across regions and healthcare settings.
2. **Cross-sectional nature** prevents assessment of treatment outcomes, progression, or temporal changes in resistance trends.
3. **Sample size (n=200)**, though adequate for estimation, may be limited for subgroup analysis of rare resistance patterns such as XDR-TB.
4. **Use of routine diagnostic data** may introduce variability due to differences in specimen quality and laboratory processing.
5. **Incomplete documentation of risk behaviors** (e.g., alcohol use, socioeconomic status) may have led to underestimation of associated risk factors.
6. **Second-line DST availability** was limited for all isolates, potentially reducing accuracy of detecting emerging resistances.
7. **No genotypic correlation (e.g., whole genome sequencing)** was performed, which could have provided insights into transmission dynamics.
8. **Potential recall bias** in self-reported variables such as smoking history and treatment adherence.

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