Original Article

Drug Resistance Patterns and Associated Factors Among Patients with Pulmonary Tuberculosis: A Hospital-Based Cross-Sectional Study

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Abstract

Background: Determination of the pattern and prevalence of drug resistance among patients with Mycobacterium tuberculosis and its associated clinical factors. To determine the prevalence and pattern of first-line drug resistance among patients with pulmonary tuberculosis and identify demographic and clinical factors associated with drug resistance. **Material and Methods:** A cross-sectional study from February 2023 to February 2024 was conducted on 85 adults with Mycobacterium tuberculosis confirmed by sputum or bronchoalveolar lavage smear positivity and CBNAAT detection of Mycobacterium tuberculosis were enrolled. Drug susceptibility testing was performed using the BACTEC MGIT 960 system. Demographic, clinical, comorbidity, tobacco-use, and radiological data were recorded and associated with drug resistance. **Results:** The study cohort mean age was 35.27 ± 8.9 years, with 45 (52.94%) males and 40 (47.06%) females. Drug resistance to at least one anti-tubercular drug was detected in 15/85 (17.65%) patients, while 70 (82.35%) were pan-susceptible. Isoniazid monoresistance was observed in 6 (7.06%) patients and rifampicin monoresistance in 1 (1.18%). MDR-TB was identified in 8 (9.41%) patients. Previous tuberculosis history was significantly more frequent among drug-resistant patients than pan-susceptible patients (73.33% vs. 11.43%; p<0.0001). Diabetes mellitus was also significantly associated with drug resistance (40.00% vs. 11.43%; p=0.007). **Conclusion:** Drug resistance was found in 17.65% cases of Mycobacterium tuberculosis patients, with MDR-TB present in 9.41%. Significant associated factors were a history of previous Mycobacterium tuberculosis and diabetes mellitus as a comorbidity. Early drug-susceptibility testing and close monitoring of previously treated and diabetic patients may facilitate timely identification and management of drug-resistant tuberculosis.

Keywords: Antitubercular Agents, Diabetes Mellitus, Drug Resistance, Microbial, Multidrug-Resistant Tuberculosis, Tuberculosis, Pulmonary.

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Introduction

Mycobacterium tuberculosis (TB) stands as a public health challenge, with more than 10.7 million TB cases and approximately 1.23 million TB-related deaths worldwide.[1] with India reporting an estimated incidence of 179 cases per lakh population and approximately 3.42 lakh deaths in 2023.[2]

Pulmonary TB commonly presents with chronic cough, sputum production, fever, night sweats, weight and appetite loss, breathlessness, hemoptysis, chest pain, hoarseness, and anemia.[3] Diagnosis is based on clinical and radiological findings, supported by microbiological confirmation through sputum acid-fast bacilli testing or culture.[4]

The management remains standard with HRZE, however, Drug-resistant TB is an important obstacle to global TB control and develops primarily because of inappropriate treatment, poor adherence, inadequate drug supplies, and insufficient diagnostic facilities.[5]

Multidrug-resistant TB (MDR-TB), a separate entity, shows resistance to isoniazid (H) or rifampicin (R). India bears a substantial proportion of the global drug-resistant TB burden, although reported estimates may underestimate the true magnitude because drug-resistance testing is not universally performed.[5] It requires multiple second-line agents for definitive management wherein Group A drugs include levofloxacin or moxifloxacin, bedaquiline, and linezolid, while Group B includes clofazimine and cycloserine/terizidone; and Group C drugs are used when Group A or B agents are unsuitable.[5]

MDR-TB remains a major challenge, compounded by limited access to culture and drug-susceptibility testing, which can delay detection until treatment failure.6 Data on its prevalence and associated factors, particularly in the Indian population, also remain limited. Owing to this, the present study was initiated to elaborate on the pattern and prevalence of drug resistance among patients with Mycobacterium tuberculosis and its associated clinical factors.

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Materials and Methods

The study was designed as a one-time collection of data from the patient, that is, a cross-sectional study in a medical college of Jaipur, from February 2023 to February 2024. Necessary permission and ethical approval were obtained from the Institutional Ethics Committee and Research Review Board of S.M.S. Medical College, Jaipur (IEC No. 343/MC/EC/2023).

Consecutive patients included were adults over 18 years diagnosed with Mycobacterium tuberculosis on sputum smear positivity or CBNAAT. Specifically, pregnant women and those with extrapulmonary tuberculosis were excluded. A predetermined sample size of 85 was based on the reference of Glasauer et al,7 who reported 12.7% drug resistance.

Demographic and clinical information, including age, sex, residence, previous history of TB, comorbidities such as diabetes mellitus, and tobacco-use history, was recorded using a structured study proforma. A thorough clinical examination and investigations were done to confirm the diagnosis.

Drug susceptibility testing: Drug resistance was assessed using the BACTEC MGIT 960 liquid culture system (Becton Dickinson), following the manufacturer's instructions. For first-line drug susceptibility testing, five tubes were prepared for each isolate: four containing isoniazid (H) 0.1 µg/mL, rifampicin (R) 1.0 µg/mL, streptomycin (S) 1.0 µg/mL, and ethambutol (E) 5.0 µg/mL, and one drug-free control. Drug-containing tubes were inoculated with 0.5 mL of positive broth culture, whereas the control received a 1:100 dilution. Results were interpreted after adequate growth was observed in the control. Pyrazinamide susceptibility testing was performed separately using concentrations of 10, 20, 50, and 100 µg/mL at a pH of 5.7, with results compared with the control tube.

As an outcome, (1) the proportion of isoniazid-monoresistant and multidrug/poly-drug-resistant TB cases was noted; and (2) Associations between relevant demographic, clinical, and treatment-related factors and first-line drug resistance.

Statistical analysis: Data was entered in an Excel spreadsheet and analyzed by advanced Microsoft Excel software. Independent t-test, Chi-square or Fisher's exact test was used as appropriate. A p-value < 0.05 was considered statistically significant.

Results

The mean age of the study cohort was 35.27 ± 8.9 years. Of the 85 patients, 40 (47.06%) were females and 45 (52.94%) were males. Most participants were from Dholpur (41.18%), followed by Sikar (18.82%), Dausa (15.29%), Jaipur (10.59%), Sirohi (8.24%), and Nagaur (5.88%) [Table 1].

Table 1: Demographic and clinical parameters

Parameters	Mean+SD	Number (%)
Age (years)	35.27 ± 8.9	
Gender		
Females		40 (47.06%)
Males		45 (52.94%)
Place of residence		
Dausa		13 (15.29%)
Dholpur		35 (41.18%)
Jaipur		9 (10.59%)
Nagaur		5 (5.88%)
Sikar		16 (18.82%)
Sirohi		7 (8.24%)
Previous history of tuberculosis		
Yes		19 (22.35%)
No		66 (77.65%)
Symptoms		
Diabetes mellitus		14 (16.47%)
History of Tobacco use		55 (64.71%)

Table 2: Association of Parameters with Drug Resistance

Parameter	Category	Pan-susceptible (n=70)	Any drug resistance (n=15)	P value
Age (years)	Mean ± SD	36 ± 8.73	31.87 ± 9.38	0.104‡
Gender	Female	36 (51.43%)	4 (26.67%)	0.095*
	Male	34 (48.57%)	11 (73.33%)	
Place of residence	Dausa	9 (12.86%)	4 (26.67%)	0.637*
	Dholpur	28 (40.00%)	7 (46.67%)	
	Jaipur	8 (11.43%)	1 (6.67%)	
	Nagaur	4 (5.71%)	1 (6.67%)	
	Sikar	15 (21.43%)	1 (6.67%)	
	Sirohi	6 (8.57%)	1 (6.67%)	
Previous history of tuberculosis	No	62 (88.57%)	4 (26.67%)	<0.0001*
	Yes	8 (11.43%)	11 (73.33%)	
Diabetes mellitus	No	62 (88.57%)	9 (60.00%)	0.007†
	Yes	8 (11.43%)	6 (40.00%)	
History of tobacco	No	28 (40.00%)	2 (13.33%)	0.073*
	Yes	42 (60.00%)	13 (86.67%)	

X-ray findings	Cavities	37 (52.86%)	5 (33.33%)	0.170†
	Miliary pattern	14 (20.00%)	4 (26.67%)	0.728*
	Consolidation	35 (50.00%)	7 (46.67%)	0.815†
	Fibrosis	18 (25.71%)	4 (26.67%)	1.000*

* Fisher's exact test; † Chi-square test; ‡ Independent t-test.

Among the culture-positive cases, 70 (82.35%) were pan-susceptible, whereas 15 (17.65%) demonstrated resistance to at least one anti-tubercular drug. Thus, nearly one-fifth of the culture-positive cases showed some form of drug resistance [Figure 1].

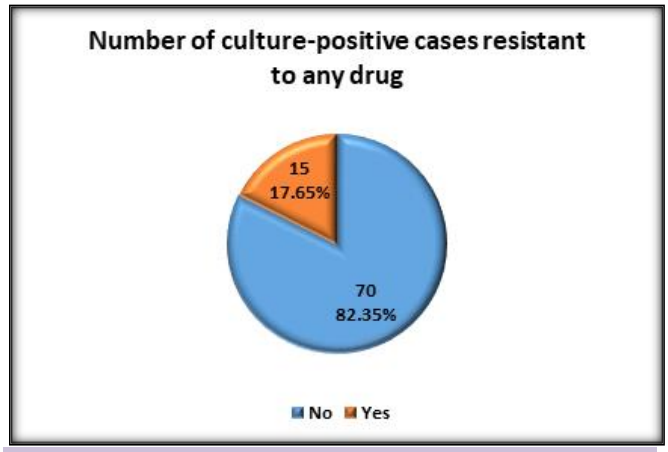


Figure 1: Number of culture-positive cases resistant to any anti-tubercular drug.

Among the 85 patients, drug resistance was detected in 15 (17.65%) cases. Isoniazid (H) monoresistance was observed in 6 (7.06%) patients, while rifampicin (R) monoresistance was present in 1 (1.18%). MDR-TB was identified in 8 (9.41%) patients, including resistance to H+R in 3 (3.53%), H+R+Z in 1 (1.18%), H+R+E in 1 (1.18%), and H+R+Z+E in 3 (3.53%) cases [Figure 2].

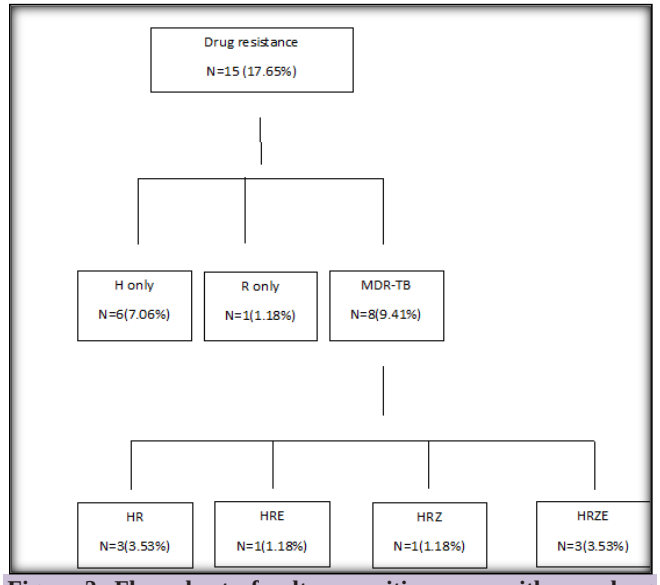


Figure 2: Flow chart of culture positive cases with any drug resistance.

H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol

Patients with any drug resistance were younger than those with pan-susceptible tuberculosis (31.87 ± 9.38 vs. 36.00 ± 8.73 years), although the difference was not significant (p=0.104). Gender and residence were also not significantly associated with drug resistance (p=0.095 and p=0.637, respectively). A significant association was observed with previous tuberculosis history, which was present in 73.33% of drug-resistant patients compared with 11.43% of pan-susceptible patients (p<0.0001). Diabetes mellitus was also significantly more common among drug-resistant patients (40.00% vs. 11.43%; p=0.007). Tobacco use was more frequent in the drug-resistant group but did not reach statistical significance (86.67% vs. 60.00%; p=0.073). None of the chest X-ray findings, including cavities, miliary pattern, consolidation, or fibrosis, was significantly associated with drug resistance. Thus, previous tuberculosis and diabetes were significant predictors of drug resistance [Table 2].

Discussion

Drug resistance was detected in 15 (17.65%) patients; with comparable observations of Glasauer et al,[7] who reported resistance in 12.7% of 26,228 patients, and Nkansah et al,[8] who found drug resistance in 17.4% of 167 sputum samples. Seid G et al,[9] reported a somewhat higher prevalence of 23.52%, whereas considerably higher proportions were observed by Kenaope et al,[10] (49%). Such differences may reflect variations in study populations, geographic settings, inclusion criteria, previous treatment exposure, diagnostic methods, and local patterns of resistance.

Regarding the resistance pattern, mono-drug resistance was observed in seven patients, including six (7.06%) with isoniazid resistance and one (1.18%) with rifampicin resistance. Isoniazid plus rifampicin resistance was observed in three (3.53%) patients, while triple- and quadruple-drug resistance occurred in two (2.35%) and three (3.53%) patients, respectively. The predominance of isoniazid monoresistance in the present study corroborates with previous literature. Nkansah et al,[8] for example, reported monoresistance in 8.4% of isolates and MDR/RR-TB in 13.2% of isolates. Similarly, Sinha et al,[11] reported high levels of resistance to HRSE, with MDR-TB accounting for more than half of resistant cases. These differences reinforce the heterogeneous epidemiology of drug resistance across populations.

Among the factors, age, gender and residence showed no significant association with drug resistance in our study. Rather, previous tuberculosis was reported by 19 (22.35%) participants, and it was significantly more frequent among drug-resistant patients than drug-susceptible patients (73.33% vs. 11.43%; P<0.0001). This observation is consistent with Sinha et al,[11] Goshiye et al,[12] and Glasauer et al,[7] who demonstrated significantly higher resistance among previously treated patients. Previous exposure to antitubercular therapy may promote selection of resistant organisms, particularly when treatment is incomplete, inappropriate, interrupted, or poorly adhered to.

Treatment failure and relapse may further increase the likelihood of acquired resistance.[1]

Diabetes mellitus was another significant factor in the present study. Diabetes was present in 14 (16.47%) patients and was significantly more common among drug-resistant patients than susceptible patients (40% vs. 11.43%; P=0.007) which was replicated in few previous studies.[13,14] The proposed mechanisms can be that cellular immunity is impaired or pharmacokinetic disposal of antitubercular drugs remains altered against a higher burden of mycobacterial tuberculosis, or the patient may have reduced adherence to the treatment (which needs to be further proven in future studies). Poor glycemic control may further impair phagocytic function and T-cell responses, potentially facilitating persistence of resistant strains.[13]

Tobacco use was reported in 55 (64.71%) participants but was not significantly associated with drug resistance (P=0.073). This finding agrees with Baya et al,[15] who found no significant relationship between smoking and MDR-TB. Conversely, Sinha et al,[11] Romo et al,[16] and Vyawahare et al,[17] reported significant associations between tobacco use and drug-resistant TB. Differences in smoking intensity, duration, socioeconomic characteristics, and coexisting risk factors may explain these inconsistent findings.

Also, Radiological findings also did not demonstrate a significant association with drug resistance. Cavitation and consolidation were each observed in 42 (49.41%) patients, while fibrosis and a miliary pattern were present in 22 (25.88%) and,[18] (21.18%), respectively. These findings are consistent with Oriekot et al,[18] who reported no significant difference in chest radiographic findings between drug-sensitive and drug-resistant TB. However, Oladimeji et al,[19] reported significantly greater frequencies of cavitation, consolidation, fibrosis, and other parenchymal abnormalities among drug-resistant or MDR-TB patients. Thus, although radiography provides valuable information regarding disease extent and treatment response, radiological features alone may not reliably predict drug resistance.

The variation in risk factors across studies highlights the heterogeneous nature of DR-TB epidemiology. Early identification of previously treated patients and those with diabetes, together with timely drug-susceptibility testing, appropriate treatment, and close adherence monitoring, may help reduce the emergence and transmission of resistant TB.[13]

Limitations: The findings should be interpreted in light of the study's limitations, particularly its relatively small sample size, single-center, and cross-sectional study design.

Conclusion

In conclusion, drug resistance was observed in 17.65% case of mycobacterium tuberculosis. Drug resistance to one drug only was present in 7 cases, with resistance to H being the most common one and only one case of resistance to R. Drug resistance to two drugs was present in 3 patients, which was for H+R. Triple-drug resistance occurred in two patients and quadruple-drug resistance in three cases. Previous tuberculosis and diabetes mellitus were associated with an increased risk of MDR-TB. Larger multicentric prospective studies incorporating detailed treatment-adherence histories, quantitative measures of glycemic control, and multivariable analysis are warranted to establish independent predictors of drug resistance.

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Conflicts of interest

There are no conflicts of interest.

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