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Prevalence and Factors Associated with Drug Resistance Among Pulmonary Tuberculosis Patients in a District of North Kerala

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ABSTRACT

Background: Drug resistant tuberculosis (DR-TB) remains a major challenge to Tuberculosis (TB) control despite advances in diagnosis and treatment. Although Kerala has achieved better TB control outcomes than many other regions of India, district-level data on the prevalence and determinants of drug resistance are limited. This study estimated the prevalence and pattern of drug resistance among pulmonary TB patients in Malappuram district and explored factors associated with drug resistance.

Methods: This cross-sectional study was conducted among bacteriologically confirmed pulmonary TB patients registered at the District TB Centre, Manjeri, Kerala, during 2024-2025. Information was obtained from the NIKSHAY portal and District TB Centre records after obtaining necessary administrative approvals. Universal sampling was adopted, and 960 patients were included. Drug resistance patterns were described using frequencies and percentages. Associations between clinical or behavioural factors and drug resistance were analysed using the chi-square test.

Results: Among the 960 study participants ,675(70.3%) were males, and most cases were detected through passive case finding (97.1%). Rifampicin resistance was identified in four patients (0.42%), while isoniazid resistance was detected in 49 patients (5.10%). High-level isoniazid resistance (katG mutation) was present in 32 patients (3.33%) and low-level resistance (inhA mutation) was observed in 18 patients (1.88%). Fluoroquinolone resistance was detected in two patients (0.21%). Isoniazid resistance showed significant association with alcohol consumption, tobacco use, and household contact with pulmonary tuberculosis. No significant associations were observed for rifampicin or fluoroquinolone resistance.

Conclusion: The prevalence of rifampicin and fluoroquinolone resistance in this district was considerably lower than national estimates, indicating effective implementation of TB control strategies in Kerala. However, the burden of isoniazid resistance highlights the need for early detection, appropriate treatment, strengthened contact investigation, and behavioural interventions targeting modifiable risk factors.

Keywords: Pulmonary tuberculosis; drug resistance; isoniazid resistance; rifampicin resistance; NTEP; Malappuram; Kerala

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, continues to be one of the leading infectious causes of illness and death worldwide. Despite the availability of effective diagnostic methods and curative treatment, TB remains a major public health concern, particularly in high-burden countries such as India. The emergence and spread of drug-resistant tuberculosis (DR-TB) have further complicated disease control by increasing treatment duration, healthcare costs, and the risk of poor clinical outcomes.

Resistance to first-line anti-tubercular drugs, particularly isoniazid and rifampicin, poses a significant obstacle to achieving global TB elimination targets. Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least both isoniazid and rifampicin, requires prolonged treatment with second-line drugs that are often less effective, more toxic, and considerably more expensive than standard regimens. Although India has strengthened its diagnostic capacity through universal drug susceptibility testing (DST), drug-resistant TB continues to impose a substantial burden on the national TB control programme.

Kerala has consistently demonstrated better TB programme performance than many other Indian states because of its well-developed public health infrastructure and effective implementation of the National Tuberculosis Elimination Programme (NTEP). The widespread use of rapid molecular diagnostic techniques, including Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) and TrueNat, together with universal DST, has improved the early identification of drug-resistant disease. Nevertheless, the epidemiology of drug resistance may vary across districts owing to differences in population characteristics, healthcare access, migration, and behavioural risk factors.

The development of drug resistance is influenced by several biological, clinical, and social determinants. Previous anti-tubercular treatment, delayed diagnosis, inadequate treatment adherence, irrational drug use, diabetes mellitus, HIV infection, tobacco smoking, alcohol consumption, and close contact with patients having drug-resistant TB have all been implicated as potential risk factors. Identifying these determinants at the local level is essential for planning targeted interventions and strengthening TB control strategies.

Although national and state surveillance reports provide an overview of the burden of drug-resistant TB, district-specific evidence remains limited. Such information is particularly important for understanding local epidemiological trends and guiding programme implementation. Therefore, this study was undertaken to determine the prevalence and pattern of drug resistance among bacteriologically confirmed pulmonary tuberculosis patients in Malappuram district, Kerala, and to identify the demographic, clinical, and behavioural factors associated with drug resistance.

MATERIALS & METHODS

Study design and setting

A cross-sectional study was carried out at the District Tuberculosis Centre (DTC), Manjeri, Malappuram district, Kerala, over a 12-month period during 2024–2025. The study was designed to estimate the prevalence of drug resistance among bacteriologically confirmed pulmonary tuberculosis (PTB) patients and to identify factors associated with drug-resistant disease.

Study participants

The study included all bacteriologically confirmed pulmonary TB patients registered at the DTC during the study period, irrespective of age or sex. Universal sampling was adopted, and all eligible patients were enrolled. A total of 960 patients satisfied the inclusion criteria and were included in the final analysis.

Data collection

Data were obtained from the NIKSHAY portal and verified using records maintained at the District Tuberculosis Centre. Information collected included demographic characteristics, mode of case detection, treatment category, drug susceptibility test (DST) results, comorbid illnesses, and behavioural risk factors.

Study variables

The primary outcome was the presence of anti-tubercular drug resistance. Drug resistance patterns evaluated included rifampicin resistance, isoniazid resistance, and fluoroquinolone resistance. Isoniazid resistance was further categorised into high-level resistance (katG mutation) and low-level resistance (inhA mutation).

The explanatory variables included age, sex, treatment history, diabetes mellitus, HIV infection, systemic hypertension, chronic obstructive pulmonary disease (COPD), malignancy, tobacco use, alcohol consumption, and history of household contact with tuberculosis.

Ethical considerations

The study was conducted after obtaining approval from the State TB Officer and the NTEP Core Committee. Patient information retrieved from the NIKSHAY portal and DTC records was handled confidentially, and data were analysed anonymously in accordance with ethical principles.

Statistical Analysis

Data were entered and analysed using standard statistical software. Categorical variables were summarised as frequencies and percentages, while continuous variables were expressed as mean with standard deviation (SD). The association between categorical variables and drug resistance was assessed using the chi-square test. A two-sided p-value of <0.05 was considered statistically significant.

RESULT

Patient characteristics

A total of 960 bacteriologically confirmed pulmonary tuberculosis patients were included in the study. Males constituted the majority of the study population (675/960, 70.3%), while females accounted for 285 (29.7%). Most patients were diagnosed through passive case detection (931, 97.0%), whereas only 29 (3.0%) were identified by active case-finding. The majority of patients were newly diagnosed cases (925, 96.4%).

Comorbidities and behavioural characteristics

Diabetes mellitus was the most frequently reported comorbidity and was present in 432 patients (45.0%). Systemic hypertension was documented in 218 patients (22.7%), COPD in 46 patients (4.8%), and HIV infection in 13 patients (1.4%). Tobacco use and alcohol consumption were reported in 240 (25.0%) and 179 (18.6%) patients, respectively.

Pattern of drug resistance

Among the 960 study participants, isoniazid resistance was the most common form of drug resistance, affecting 49 patients (5.1%). High-level resistance associated with the *katG* mutation was identified in 32 patients (3.3%), whereas low-level resistance associated with the *inhA* mutation was detected in 18 patients (1.9%). Rifampicin resistance was observed in four patients (0.4%), and fluoroquinolone resistance was identified in two patients (0.2%).

Factors associated with isoniazid resistance

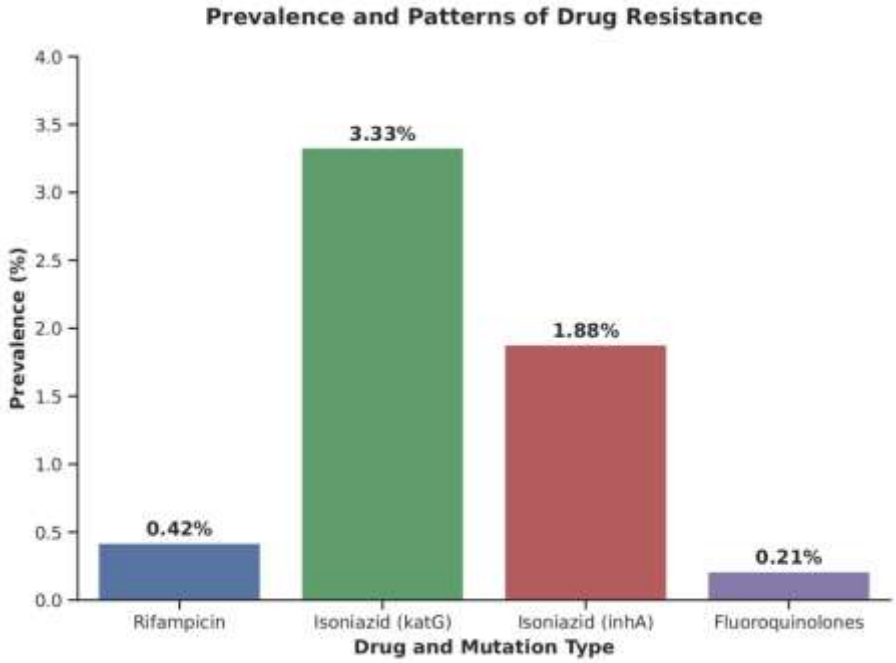
Alcohol consumption, tobacco use, and a history of household tuberculosis contact were significantly associated with isoniazid resistance. Alcohol use was reported in 18 (36.7%) of 49 patients with isoniazid resistance compared with 161 (17.7%) of 911 patients without isoniazid resistance ($p=0.001$). Tobacco use was present in 30 (61.2%) patients with isoniazid resistance compared with 210 (23.1%) patients without

isoniazid resistance (p<0.001). Similarly, household contact with tuberculosis was more frequent among patients with isoniazid resistance than among those without resistance (8.2% vs 1.1%; p<0.001).

No statistically significant association was observed between the evaluated risk factors and rifampicin resistance or fluoroquinolone resistance.

Table 1. Association between selected risk factors and isoniazid resistance

Risk factor	Category	INH-sensitive n (%) (n=911)	INH-resistant n (%) (n=49)	P value
Alcohol use	Yes	161 (17.7)	18 (36.7)	**0.001**
	No	750 (82.3)	31 (63.3)	
Tobacco use	Yes	210 (23.1)	30 (61.2)	**<0.001**
	No	701 (76.9)	19 (38.8)	
Household TB contact	Yes	10 (1.1)	4 (8.2)	**<0.001**
	No	901 (98.9)	45 (91.8)	



Graph 1: Prevalence of drug resistance among pulmonary TB patients

DISCUSSION

This study evaluated the prevalence and determinants of drug resistance among bacteriologically confirmed pulmonary tuberculosis patients in Malappuram district, Kerala. The findings demonstrate a low prevalence of rifampicin and fluoroquinolone resistance, whereas isoniazid resistance was comparatively more common. In addition, alcohol consumption, tobacco use, and a history of household TB contact were significantly associated with isoniazid resistance.

The prevalence of rifampicin resistance observed in the present study (0.42%) was substantially lower than the estimates reported from India. This finding may reflect the effective implementation of the National Tuberculosis Elimination Programme (NTEP) in Kerala, characterised by universal drug susceptibility testing, widespread availability of rapid molecular diagnostic tests, and prompt initiation of appropriate treatment. These programmatic strengths are likely to have contributed to limiting the emergence and transmission of rifampicin-resistant tuberculosis within the district.

Fluoroquinolone resistance was uncommon, being detected in only 0.21% of patients. The low prevalence may indicate judicious use of second-line anti-tubercular drugs and

effective antimicrobial stewardship within the healthcare system. Since fluoroquinolones are essential components of drug-resistant TB treatment regimens, preserving their effectiveness remains an important public health priority.

Isoniazid resistance was identified in 5.10% of the study population, making it the most frequent form of drug resistance. Although this prevalence is lower than that reported in several national and international studies, it remains clinically important because undetected isoniazid mono-resistance can compromise treatment outcomes and increase the risk of subsequent multidrug-resistant tuberculosis. The presence of both katG- and inhA-mediated resistance suggests that multiple molecular mechanisms contribute to isoniazid resistance in this population and highlights the importance of routine molecular drug susceptibility testing for early identification and appropriate treatment selection.

Male patients constituted more than two-thirds of the study population. This observation is consistent with the epidemiology of tuberculosis reported from many high-burden settings, where behavioural, occupational, environmental and healthcare-seeking differences contribute to higher disease occurrence among men. Although sex itself was not associated with drug resistance in the present study, the predominance of male patients reflects the demographic profile of pulmonary tuberculosis in the region.

A notable finding of this study was the significant association between isoniazid resistance and alcohol consumption. Alcohol use may adversely influence treatment adherence, increase the likelihood of treatment interruption, and contribute to poor therapeutic outcomes. In addition, alcohol-related liver disease and drug-induced hepatotoxicity may necessitate treatment modification, further increasing the risk of inadequate drug exposure and the development of resistance.

Tobacco use was also significantly associated with isoniazid resistance. Smoking has been shown to impair pulmonary immune defence mechanisms, reduce macrophage function, and delay sputum conversion, thereby adversely affecting treatment response. Patients who smoke may also have poorer adherence to treatment and follow-up, increasing the likelihood of resistant disease. These findings support the integration of smoking cessation interventions into routine TB care.

Another important observation was the association between isoniazid resistance and household contact with tuberculosis. This finding suggests that primary transmission of resistant *Mycobacterium tuberculosis* strains may contribute to the burden of drug-resistant disease in the community. Strengthening household contact investigation, early screening of exposed individuals, and timely initiation of preventive or appropriate therapeutic interventions may help reduce ongoing transmission.

The present study has certain strengths. It included all bacteriologically confirmed pulmonary TB patients registered during the study period, thereby minimising selection bias and providing a comprehensive assessment of the district-level burden of drug resistance. Furthermore, the use of routinely collected NIKSHAY data reflects real-world programmatic performance under the NTEP.

However, some limitations should be acknowledged. The cross-sectional design precludes causal inference between the identified risk factors and drug resistance. As the study relied on routinely maintained programme records, certain clinical or behavioural variables may have been incompletely documented. In addition, the findings represent a single district and may not be directly generalisable to other regions with different epidemiological characteristics.

Overall, the study demonstrates that the burden of rifampicin and fluoroquinolone resistance remains low in Malappuram district, while isoniazid resistance continues to be an important concern. The significant

association of isoniazid resistance with modifiable behavioural factors and household exposure emphasises the need for comprehensive interventions that combine early diagnosis, universal drug susceptibility testing, behavioural counselling, and strengthened contact investigation to sustain progress towards tuberculosis elimination.

CONCLUSION

This study demonstrated that the prevalence of rifampicin-resistant and fluoroquinolone-resistant pulmonary tuberculosis in Malappuram district was lower than the corresponding national estimates, reflecting the effective implementation of tuberculosis control measures under the National Tuberculosis Elimination Programme in Kerala. Nevertheless, isoniazid resistance emerged as the most frequently encountered form of drug resistance and remains an important programmatic concern because of its potential impact on treatment outcomes and progression to multidrug-resistant tuberculosis.

The significant association of isoniazid resistance with alcohol use, tobacco use, and household tuberculosis contact highlights the influence of modifiable behavioural and epidemiological factors on the development and transmission of drug-resistant disease. These findings support the need for strengthened universal drug susceptibility testing, early identification of isoniazid resistance, comprehensive contact investigation, and integration of tobacco- and alcohol-cessation counselling into routine TB care.

District-level surveillance studies such as the present one provide valuable evidence for local programme planning and resource allocation. Sustained monitoring of drug resistance patterns, together with targeted public health interventions, will be essential for preserving the gains achieved under the NTEP and accelerating progress towards tuberculosis elimination.

Declaration by Authors

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