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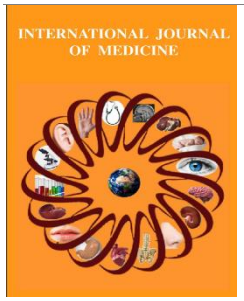

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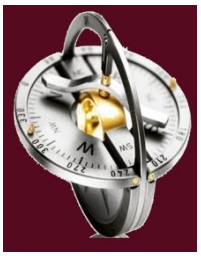

Research Article

From Rifampicin Resistance to XDR-TB: A Profile from the Sub-Himalayan Region

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Abstract

Background: Drug-resistant tuberculosis (DR-TB) poses a major challenge to India's National Tuberculosis Elimination Program, particularly in resource-limited regions like Himachal Pradesh. While rifampicin resistance and multidrug resistance (MDR-TB) are widely reported, data on advanced resistance patterns and treatment outcomes in the sub-Himalayan region remain scarce. ***Objectives***: To describe the demographic and clinical characteristics of DR-TB patients, delineate resistance patterns, assess treatment outcomes and identify predictors of mortality. ***Methods***: A retrospective observational study was conducted at Indira Gandhi Medical College, Shimla, analyzing 212 bacteriologically confirmed DR-TB cases registered between January 2018 to July 2025. Data on demographics, comorbidities, microbiological resistance patterns, and treatment outcomes were retrieved from programmatic records and analyzed using descriptive statistics and chi-square testing. ***Results***: The mean patient age was 39.1 ± 17.2 years; 60.8% were male. Pulmonary TB accounted for 82% of cases. Rifampicin resistance was most frequent (79%), followed by isoniazid resistance (47%); MDR-TB was observed in 23%, pre-XDR in 14%, and XDR in 0.9%. Overall, 70.3% achieved favorable outcomes (cure or treatment completion), while 9.9% died and 5.7% were lost to follow-up. Younger patients (<30 years) showed better outcomes (>80% success), whereas older adults (≥50 years) had higher mortality (71%). Age above 41 years was a significant predictor of death ($p<0.001$). ***Conclusion***: DR-TB in the sub-Himalayan region predominantly affects young adults but carries high mortality in older patients and those with advanced resistance patterns. Strengthening early detection, expanding drug susceptibility testing, and tailoring geriatric-sensitive interventions are critical to improve outcomes and achieving India's End TB targets.

Keywords: Pulmonary TB , Rifampicin Resistance , MDR-TB , XDR-TB, Sub-Himalayan Region.

Introduction:

Tuberculosis (TB) continues to remains as one of the worlds infectious diseases, despite being both preventable and curable. According to World Health Organization (WHO) global tuberculosis report 2023, an estimated 10.6 million people developed TB and 1.3 million people died of the disease worldwide in 2022, making TB the second leading infectious killer globally after COVID-19 [1].

India contributes the largest share of the global burden, accounting for nearly 28% of global TB cases [2]. Within India, the National Tuberculosis Elimination Program (NTEP) has prioritized early detection, universal drug susceptibility testing (DST), and timely initiation of appropriate regimens. However, the rapid emergence of drug-resistant TB (DR-TB) threatens the achievement of the End TB Strategy and India's target of TB elimination [2,3].

Drug-resistant TB encompasses a spectrum of resistance patterns, with rifampicin resistance (RR-TB) and multidrug resistance (MDR-TB, defined as resistance to at least isoniazid and rifampicin) being the most clinically significant. More advanced forms include pre-extensively drug-resistant TB (pre-XDR, defined as MDR with additional resistance to either a fluoroquinolone or a second-line injectable) and extensively drug-resistant TB (XDR, defined as MDR with additional resistance to any fluoroquinolone and at least one Group A drug such as bedaquiline or linezolid, according to the 2020 WHO classification) [4,5]. The presence of such resistant strains complicates treatment by necessitating the use of longer, more toxic, and costlier regimens with lower success rates [6]. Globally, the treatment success rate for MDR/RR-TB remains only around 60%, compared to 86% for drug-susceptible TB [1].

India bears the world's largest burden of MDR/RR-TB, with an estimated 124,000 incident cases annually [2]. Within India, the epidemiology of DR-TB varies considerably by region, influenced by socio-economic conditions, healthcare access, prior treatment practices, and surveillance capacity [7]. The sub-Himalayan region, including Himachal Pradesh, presents unique challenges for TB control. Its mountainous terrain, scattered population distribution, and difficulties in transportation delay diagnosis and limit continuity of care [8]. Seasonal migration of workers across state and international borders further complicates programmatic management [9]. Despite these challenges, there are relatively few published studies focusing on the clinical and microbiological profile of DR-TB in Himachal Pradesh, and existing literature on DR-TB is predominantly from metropolitan centers such as Delhi, Mumbai, and Chennai [10-12].

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Treatment outcomes in DR-TB remain suboptimal in India. National data indicate that loss to follow-up, treatment failure, and mortality are all significantly higher among patients with MDR and pre-XDR TB than in drug-susceptible TB cohorts [2]. Risk factors for poor outcomes include advanced age, male gender, comorbidities such as diabetes, HIV infection, smoking, alcoholism and the presence of extensive radiological

diseases [13,14]. In particular, diabetes mellitus has emerged as an important driver of adverse TB outcomes in India, given its high prevalence in northern states [15]. The interplay between aging, comorbidity, and resistance pattern is especially relevant for Himachal Pradesh, where an increasing elderly population and lifestyle transitions are contributing to a changing TB epidemiology [16].

Globally, a growing body of literature has highlighted the significance of molecular diagnostic tools such as cartridge-based nucleic acid amplification tests (CBNAAT) and line probe assays (LPA) in early detection of resistance [17]. Their deployment has improved detection of rifampicin and isoniazid resistance, yet gaps remain in comprehensive testing for fluoroquinolones and second-line injectable drugs [18]. In India, the expansion of DST facilities under the NTEP has increased testing coverage, but implementation in hilly and rural regions lags behind urban centers. This disparity has implications for both patient-level outcomes and programmatic TB control.

The state of Himachal Pradesh, situated in the northwestern Himalayas, contributes to India's TB burden with an incidence higher than the national average [19]. Limited research has characterized the epidemiology of DR-TB in this region. A few smaller studies have reported high prevalence of MDR-TB among retreatment cases and suggested that delayed diagnosis, lack of adherence, and inadequate treatment supervision are critical contributors [20]. However, comprehensive hospital-based studies examining patient demographics, resistance profiles, and treatment outcomes are lacking. Such evidence is essential for tailoring state-specific policies, strengthening diagnostic infrastructure, and improving patient management strategies.

Against this background, the present study was undertaken at a tertiary care referral hospital in Himachal Pradesh with the following objectives:

1. To describe the demographic and clinical characteristics of patients with drug-resistant TB.
2. To delineate the patterns of resistance observed (rifampicin, isoniazid, MDR, pre-XDR, and XDR TB).
3. To assess treatment outcomes of patients initiated on appropriate regimens under programmatic conditions.
4. To identify clinical predictors of mortality among patients with DR-TB.

The finding of this study aims to provide evidence-based State specific TB control strategies, for implementation of diagnostic and treatment protocols and ultimately strengthen the fight against DR-TB in resource -limited, geographically challenging settings of the Sub-Himalayan region.

Materials and Methods

Study Design and Setting

This retrospective observational study was conducted at Department of Microbiology, Indira Gandhi Medical College Shimla, a tertiary care referral hospital in Himachal Pradesh, situated in the Sub-Himalayan region of northern India. The hospital functions as the nodal center for the Programmatic Management of Drug-resistant Tuberculosis (PMDT) under the National Tuberculosis Elimination Programme (NTEP). It caters not only to the local population but also to patients referred from peripheral health centers across the State. Given the hospital's position as the State's PMDT facility, the patient population analyzed in this study represents a wide catchment area encompassing both rural and semi-urban regions.

Study Population

The study included patients with bacteriological (Mycobacterium tuberculosis) confirmed drug-resistant tuberculosis (DR-TB) cases registered at the DR-TB center between January 2018 and July 2025. Inclusive criteria were:

1. Patients with bacteriologically confirmed Mycobacterium tuberculosis using either Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Tru-NAT, Line Probe Assay (LPA), or culture with drug susceptibility testing (DST).
2. Patients initiated on DR-TB treatment under programmatic conditions.
3. Patients of all ages and both sexes.

Exclusion criteria were:

1. Patients with incomplete laboratory data or missing treatment outcome records.
2. Patients transferred out of the state before treatment initiation.
3. Patients later confirmed to have non-tuberculous mycobacterial (NTM) infection misclassified initially as TB.

Data Collection

Data was extracted retrospectively from patient treatment cards, hospital case sheets, laboratory registers, and NTEP electronic records (Nikshay portal). Following Variables were collected:

- Sociodemographic variables: age, sex, residence.
- Clinical variables: type of TB (pulmonary vs extrapulmonary), comorbidities (diabetes, HIV, chronic obstructive pulmonary disease), history of prior TB treatment, and nutritional status (BMI where available).
- Microbiological variables: results of CBNAAT, Tru-NAT, LPA, and culture-based DST for first-line and second-line drugs.
- Treatment-related variables: regimen initiated duration, and adherence records.
- Outcomes: classified according to WHO/NTEP definitions (cured, treatment completed, treatment failure, died, lost to follow-up, not evaluated, or still on treatment).

All data were entered into a predesigned Microsoft Excel sheet, checked for accuracy, and anonymized before analysis.

Laboratory Procedures

All patients underwent baseline testing for drug susceptibility using a combination of molecular and culture-based methods as per NTEP guidelines.

1. CBNAAT (Xpert MTB/RIF)/ Tru-NAT: Used for initial diagnosis and rifampicin resistance detection.
2. Line Probe Assay (LPA): Performed on smear-positive samples to detect resistance to isoniazid, rifampicin, fluoroquinolones, and second-line injectable agents.
3. Culture and DST: Performed on solid (Löwenstein-Jensen) or liquid (MGIT) media for patients where molecular results were inconclusive or further drug resistance profiling was required.

Definitions for drug resistance, treatment regimen, outcome and other parameter were taken as per NTEP/WHO guidelines

Statistical Analysis

Data were analyzed using Epi-info version 7.4.4. Descriptive statistics were applied to summarize baseline characteristics. Continuous variables (e.g., age) were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using Chi-square test and p value = < 0.05 was taken as significant.

Ethical Considerations

Since this was a retrospective study of programmatic data, informed consent was waived. All patient records were anonymized prior to analysis, and confidentiality was strictly maintained.

Results

A total of 212 microbiologically confirmed drug-resistant tuberculosis (DR-TB) patients were included in the study. Their demographic profile, resistance patterns and treatment outcomes are described as below and summarized in **Table 1**.

Table 1:

Resistance category (n)	Age group involved years (%)	Sex (%)	BMI (%)	Site of Tuberculosis (%)	Comorbidity
Mono resistance TB (132)	21-40 (47%)	Male (61%)	Underweight (49%)	Pulmonary (74%)	Diabetes 64%, (9 out of 14), HIV 1
MDR-TB (49)	21-40 (61%)	Male (55%)	Underweight (57%)	Pulmonary (94%)	Diabetes (21%, 3 out of 14)
Pre-XDR TB (29)	21-40 (52%)	Male (72%)	Underweight (55%)	Pulmonary (93%)	Diabetes (14%, 2 out of 14)
XDR TB (2)	21-40	Male (50%)	Normal	Pulmonary	

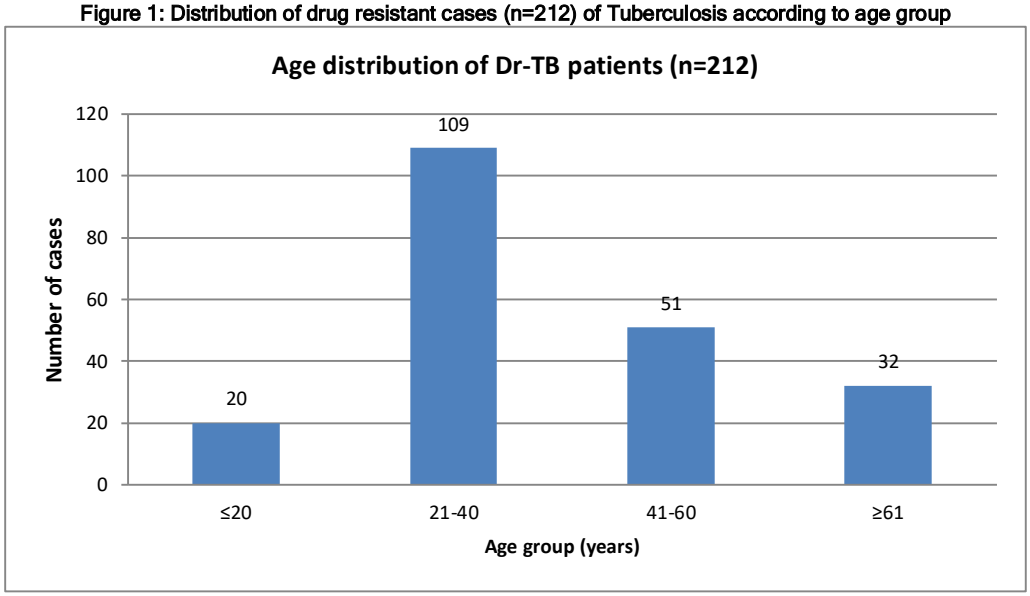
Demographic and Clinical Profile:

The mean age of patients was 39.1 years ±17.2, (range 13 to 85 years). The majority (52%) belonged to 21-40 years of age group (Figure1). Overall 60.8% (n=129) of the cohort were males, while 39.2% (n=83) were females, giving a male-to-female ratio of 1.6:1.

Pulmonary tuberculosis was the predominant (82%) while extrapulmonary Tb constituted 18% involving lymph nodes, pleural and skeletal sites. Diabetes mellitus was documented in 6.6% (14) of the patients, whereas HIV co-infection was seen in one case only.

Complete prior TB treatment details were not available for all patients, but review suggested that the most patients had been previously exposed to first-line therapy, consistent with acquired resistance trends.

Figure 1: Distribution of drug resistant cases (n=212) of Tuberculosis according to age group



Drug Resistance Patterns

The drug resistance patterns are detailed in **Table 2**. Among the 212 patients rifampicin resistance was the most frequent, detected in 167 (79%) of patients, either as isolated resistance or as part of more extensive resistance profiles. Isoniazid resistance was documented in 100 (47%) cases. Multidrug-resistant TB (MDR-TB) was present in 49 patients, accounting for 23% of the entire cohort.

Table 2: Resistance patterns detected by Line Probe Assay (n=212)

	Drug Resistance	Gene involved	Number of cases (percentage)
First Line LPA	Rifampcin	Rpo-B	167 (79%)
	Isoniazid	Kat-G	100 (47%)
		inh-A	25 (12%)
		Combined	42(20%)
Second Line LPA	Fluoroquinolones	Gyr-A(3A)	29(14%)
		3B 3C 3D	
	Second line injectable drugs	Eis	1(0.47%)
		Rrs	3(1.42%)

A subset of 29 patients (13.6%) met criteria for pre-extensively drug-resistant TB (pre-XDR), characterized by additional resistance to either a fluoroquinolone or a second-line injectable. Only two patients (0.94%) had extensively drug-resistant TB (XDR-TB).

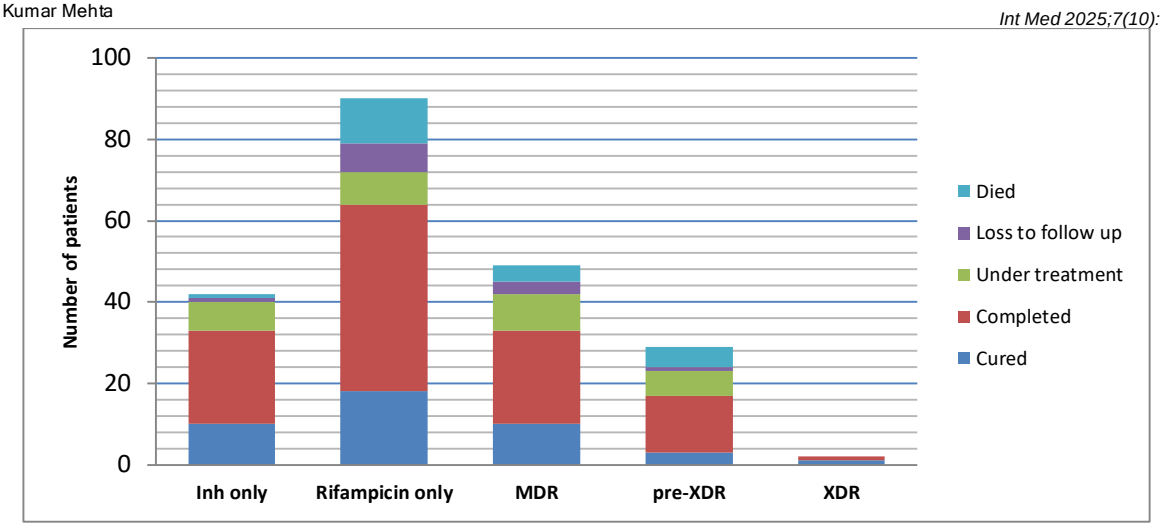
Resistance patterns showed age related trends with younger patients (<30 years) more likely to have isolated rifampicin resistance, while older patients (≥30 years) tended to harbor more complex resistance patterns, including MDR and pre-XDR TB.

Treatment Outcomes

Treatment outcomes for the cohort are summarized in **Table 3 and Figure 2**. Of the 212 patients, 42 (19.8%) were declared cured, while 107 (50.5%) completed treatment. Together, these favorable outcomes accounted for 149 (70.3%) of all cases. At the time of data cutoff 30 (14.2%) were under treatment, 12 (5.7%) were lost to follow-up and 22 (9.9%) had died.

When outcomes were stratified by resistance, patients with rifampicin resistance alone had the highest probability of cure or treatment completion, while those with MDR-TB had comparatively poorer outcomes, with higher proportions of treatment failure, loss to follow-up, and death.

Figure 2: Distribution of treatment outcome of the patients according to drug resistance type:



Among the 29 patients with pre-XDR TB cases 58.6% (17) achieved favorable outcomes, with 17.2% (5) deaths and one was lost to follow-up and 20.6% (6) were under treatment. Both the XDR Tb cases had favorable outcome.
Age also strongly influenced the outcomes. Patients <30 years of age had a favorable outcomes in more than 80% of cases, while in patients ≥50 years, had success rate below 62% with disproportionately high mortality (71%).

Predictors of Mortality
Final outcomes (survival or death) were available for 80% (170) of the resistant cases. Higher mortality (83%) was observed among patient above 41 years of age which was statistically significant (Chi square= 16.1, and p <0.001). Male patients had higher mortality (62%) as compared to females though was statistically not significant (OR=1.1, p=0.8). Rifampicin resistance showed a non significant association with higher (90%) mortality (OR=2.9, p=0.14). Among the pre XDR patients mortality was observed among 24% of the cases though not statistically significant.
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Discussion
This study provides a comprehensive characterization of drug-resistant tuberculosis (DR-TB) in a tertiary care hospital in Himachal Pradesh, a state situated in the Sub-Himalayan region of India, by evaluating demographic features, resistance patterns, and treatment outcomes among 212 patients. In our study there was a predominance of younger and middle-aged adults in our cohort, which is consistent with global and Indian data, where TB disproportionately affects the economically productive age group [1,2] thereby highlighting the significant socio-economic burden of DR-TB in this region.
However, the finding that mortality clustered in elderly patients (≥41 years) underscores the dual burden of TB and aging in India. This parallels observations from European and East Asian cohorts, where elderly patients are at higher risk of death due to comorbidities, delayed diagnosis, and impaired immunity [3,4].

The prevalence of MDR-TB in this study (23%) is comparable to estimates from northern India but higher than some southern Indian states [5,6]. A meta-analysis by Prasad et al. reported MDR prevalence of 2-3% among new cases and 12-17% among retreatment cases nationally [7]. Our higher proportion likely reflects a referral bias, since the hospital functions as a nodal center for complex cases, and also indicates possible ongoing transmission of resistant strains in the community.
Pre-XDR TB constituted 14% of our cases, aligning with reports from Delhi and Mumbai where fluoroquinolone resistance is increasingly common [8,9]. The two XDR cases detected highlights diagnostic limitations, as advanced DST is not universally available in this region. True XDR prevalence may therefore be underestimated. With WHO-recommended regimens increasingly reliant on bedaquiline and linezolid, surveillance for resistance to these drugs is critical [10].

Treatment Outcomes in Context
Our overall favorable outcome rate (88%) compares favorably with the national average of 60% for MDR/RR-TB [2], but mortality (9.9%) remains significant. Studies from metropolitan centers in India report mortality ranging from 10-20% [11,12]. The lower figure in our cohort may reflect diligent programmatic supervision in a smaller population base, but it is still unacceptable given India's End TB targets.
Loss to follow-up (5.7%) was lower than national averages (~12%), suggesting that adherence support mechanisms may be relatively effective in Himachal Pradesh. Nonetheless, each patient lost represents a potential source of ongoing transmission and amplification of resistance. Interventions such as digital adherence technologies, community health worker follow-up, and psychosocial support could further reduce default rates [13].
The poorer outcomes in pre-XDR patients in our study echo findings from other regions [14]. Current pre-XDR regimens are lengthy, toxic, and less effective. Incorporation of all-oral, shorter regimens including bedaquiline, pretomanid, and linezolid (BPaL) is urgently needed in India to improve outcomes in this subgroup [15].

Risk Factors and Mortality
In our study older patients had more complex resistance patterns and higher death rates. This is consistent with studies from Europe, South Africa, and India [16-18], which consistently highlight age as a key determinant of poor outcomes. Elderly patients often present late, have comorbidities, and face difficulties tolerating prolonged multidrug regimens. Geriatric-sensitive TB care, including early screening, comorbidity management, and modified adherence strategies, is therefore a priority.
Rifampicin resistance showed a non-significant trend toward increased mortality. Prior studies have consistently demonstrated that rifampicin resistance, particularly in combination with fluoroquinolone resistance, predicts poor outcomes [20]. Our finding likely reflects limited sample size and heterogeneity in treatment regimens.

Strengths and Limitations
The strengths of this study include its sample size, systematic analysis of resistance patterns, and integration of treatment outcome data. However, limitations include its retrospective nature, single-center design, and incomplete data on prior TB treatment history and comorbidities. Therefore, generalizability to the entire Sub-Himalayan region should be made with caution.

Conclusion
This study reinforces that DR-TB remains a formidable challenge in Himachal Pradesh. While programmatic efforts have achieved relatively good treatment completion, mortality remains unacceptably high, especially among older adults and patients with pre-XDR TB however to achieve India's ambitious End TB target stringent efforts are to be implemented.

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