ijlpr 2023; doi 10.22376/ijlpr.2023.13.1.L281-292

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Anti-Tuberculosis Therapy

Anti-Tuberculosis Therapy in The Drug Resistant Tuberculosis Patients of Kashmir Valley

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Abstract: Drug-resistant tuberculosis (DR-TB) strains are a significant threat to global TB control. Due to a lack of resources and inadequate healthcare infrastructure, it is difficult to identify and monitor drug resistance situations in low and middle-income nations. The study aimed to evaluate the anti-tuberculosis therapy regimen in drug-resistant tuberculosis patients of the mountainous valley of Kashmir. The current study was carried out at Government Medical College, Department of Pulmonary Medicine, Chest Diseases Hospital (CDH), Srinagar, Kashmir. A total of 1100 suspected tuberculosis subjects were included in the study and out of 1100 TB subjects, 195 were documented medication resistance cases. Among 195 drug resistant tuberculosis (DR-TB) cases, 159 (81.5%) had rural dwellings, 6 (3.0%) had household TB contacts, 29 (14.8%) had recurrent tuberculosis (TB), 5 (2.5%) had failure, 94 were women (48.2%) and 101 were men (51.8%). Most of the drug-resistant tuberculosis patients were in the age group of 21-30 years, where 29 were females, and 35 were males. Of the total 1100 Line Probe Assay (LPA) tests done, 69 (6.2%) were such samples the Tuberculosis band (TUB) was absent. Of all the samples tested by LPA, Tuberculosis band (TUB) was present in 1031 samples (93.7%), of which 24 samples (2.3%) were multidrug-resistant (MDR), 121 samples (11.7%) were rifampicin mono-resistant, 42 samples (4.0%) were isoniazid mono-resistant, 8 samples (0.77%) were extensively drug-resistant (XDR) and 836 samples (81%) were pan-sensitive. Regarding the treatment outcome of 195 drug resistant tuberculosis (DR-TB) patients, 112 patients (57.4%) were cured, 15 patients (7.6%) completed treatment, 34 patients (17.4%) died before completing treatment, one patient (0.5%) had failed treatment, 11 patients (5.6%) were lost to follow-up and 18 patients (9.2%) were transferred out. Smoking remained an independent risk factor for poor treatment outcomes in the multivariate analysis (p-value = 0.014, OR = 4.356, 95% CI [1.425–12.45]). This study found a low incidence of Drug-Resistant Tuberculosis (DR-TB). Most of the cases were resistant to first-line anti-tuberculosis drugs. To improve treatment results even further, special attention should be paid to high-risk drug-resistant tuberculosis (DR-TB) patients. Further studies are recommended with a large sample size.

Keywords: Drug Resistant, Tuberculosis, Regimen, Treatment, Kashmir

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Received On 12 September, 2022

Revised On 30 November, 2022

Accepted On 7 December, 2022

Published On 2 January, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Aijaz Nabi Puttoo , Sandeep Tripathi, Naveed Nazir Shah, Ruqeya Nazir, Haamid Bashir, Aaliya Mohi-uD-Din Azad, Rehana Kauser and Inam-Ul-Haq , Anti-Tuberculosis Therapy in The Drug Resistant Tuberculosis Patients of Kashmir Valley.(2023).Int. J. Life Sci. Pharma Res.13(1), L281-292 http://dx.doi.org/10.22376/ijlpr.2023.13.1.L281-292

1. INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is a major threat to control programs worldwide. It is a global health challenge putting an extra burden on the health care system and economies of countries, especially in low- and middle-income countries where there is no advanced and systematic health care system and different cultural ethos are prevalent[1,2]. Tuberculosis is ranked among the ten causes of death worldwide and is one of the leading causes of death from infectious diseases. India accounts for 1/4th of the global tuberculosis burden, and it is reported that approximately 4.8 lakh people died due to TB, of an estimated 28 lakh infected cases in 2015[3, 4]. Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis*, transmitted through the inhalation of aerosolized droplets[5-6]. It mainly attacks the lungs but can also affect other body parts, such as the brain, kidney, and spine [7,8]. TB is highly contagious during the active phase of the disease and can infect an individual through inhalation of as little as ten *Mycobacterium tuberculosis* (MTB) bacteria [9, 10]. After inhalation, these bacteria are mainly apprehended by the alveolar macrophages. Still, they can dodge the host immune system and remain in the dormant phase for a long period, at which point they can reactivate to a virulent form under immune-compromised situations of the host. The bacterium can persist in slow-growing as well as in fast-growing stages, which makes treatment challenging. Almost all antibiotics used to treat TB work when the bacteria actively divide. In the intensive phase of TB treatment, antibiotics mainly kill rapidly growing bacteria, which causes rapid sputum conversion and eradicates clinical symptoms. However, to kill the persistent or slow-growing strains of *Mycobacterium tuberculosis*, the continuation phase of the treatment is essential [11]. TB can be treated effectively using the first-line drugs isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. However, this first-line therapy often fails to cure TB for several reasons [12]. Relapse and the spread of the disease contribute to the emergence of drug-resistant bacteria[13]. The emergence of multidrug-resistant TB (MDR-TB), i.e., which is resistant to at least isoniazid and rifampicin, is of great concern because it requires the use of second-line drugs that are difficult to procure and are much more toxic and expensive than first-line defence drugs[14]. Therefore, the detection and treatment of drug-susceptible or single drug-resistant TB is an essential strategy for preventing the emergence of MDR-TB. *Mycobacterium tuberculosis* strains with extensively drug resistant-TB (XDR-TB), which is resistant to either isoniazid or rifampicin (like MDR tuberculosis), any fluoroquinolone (moxifloxacin, ofloxacin), and at least one of three second-line anti-tuberculosis injectable drugs i.e., capreomycin, kanamycin, and amikacin have also been reported. Tuberculosis is treatable and curable, except for those people who do not receive proper treatment on time, who have a per cent mortality chance. Its mortality rate is associated with the treatment [15]. sometimes some strains show resistance to drugs available in the treatment line, which means that the drug is not sufficiently capable of killing *Mycobacterium tuberculosis*. Resistances are mainly three types reported in tuberculosis, and treatment outcomes are differentiated as per the WHO criteria.

1.1. Initial drug resistance

It was defined as resistance to anti-tubercular drugs in patients who had a history of never having received chemotherapy in the past. It included primary resistance and resistance to previous treatment concealed by the patient or of which the patient was unaware.

1.2. MDR-TB

It was defined as tuberculosis caused by bacilli showing resistance to at least isoniazid and rifampicin. Drug resistance is caused by a mycobacterium resistant to at least one first-line anti-TB drug. Resistance to the strong anti-TB medications, isoniazid, and rifampicin, is classified as multidrug-resistant (MDR-TB),

1.3. XDR-TB

Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB with added resistance to any second-line drugs. Rifampicin resistance (RR) is utilized as a surrogate for MDR-TB, and RR strains should be detected quickly[16]. Different elements in TB control Programmes, such as managerial concerns and patient care, have been linked to the abrupt evolution of medication resistance in *Mycobacterium tuberculosis*. (i) poor holding cases; (ii) defective drugs, insufficient or irregular drug supply, and lack of oversight; (iii) healthcare staff' misunderstanding of epidemiology, treatment, and control; (iv) lack of supervision; (v) availability of anti-TB drugs over the counter, without prescription; (vi) massive bacillary load; (vii) illiteracy and low socioeconomic status of the patients; (viii) laboratory delays in identifying and susceptibility testing of *Mycobacterium tuberculosis* isolates; (ix) use of non-standardized laboratory techniques[17,18]. Drug resistance in *Mycobacterium tuberculosis* develops at a low frequency in large bacterial populations due to random or spontaneous mutation[19]. Rifampicin's probability of drug-resistant mutants is 10-8, while for isoniazid and other regularly used medications, the probability is 10-6. As a result, resistance to isoniazid and rifampicin is significantly more likely to develop than the number of organisms present in a medium-sized cavity in a patient with open pulmonary TB[20, 21].

1.4. Molecular Assays in Tuberculosis

In Tuberculosis patients, the advanced Cartridge Based Nucleic Acid Amplification Test (CBNAAT and Truenat) bridges gaps in detecting mycobacterium drug resistance. Molecular assays like CBNAAT, Truenat, and LPA are transforming the landscape of drug-resistant TB diagnosis and management. They could be a cost-effective solution in a range of contexts. Molecular testing like GeneXpert CBNAAT/ Truenat uses real-time polymerase chain reaction to detect *Mycobacterium tuberculosis* and rifampicin resistance sequences and can enhance established diagnostic methods (such as the old method acid-fast stain technique). Line probe assays are drug susceptibility tests that use PCR and reverse hybridization methods to rapidly detect mutations associated with drug resistance. Line probe assays are designed to identify the *Mycobacterium tuberculosis* complex and simultaneously detect mutations associated with drug resistance. Since the endorsement of molecular assays by the WHO in 2010, over 110 low- and middle-income countries have purchased GeneXpert, many of which have incorporated it into their diagnostic algorithms for TB [22-24]. Preliminary findings have been promising, showing that more cases of TB are being identified (including MDR-TB), there is a shorter time to treatment initiation, and TB diagnosis is

becoming decentralized. Hence, the objective is to evaluate the drug resistance and treatment outcome pattern in tuberculosis patients of the Kashmir Valley.

2. METHODOLOGY

This hospital-based cross-sectional study was conducted in the Department of Pulmonary Medicine, Chest Diseases Hospital (CDH), Govt. Medical College, Srinagar. A study on the ethnic population of Kashmir Valley was undertaken from March 2019 to June 2022 after receiving formal ethical clearance from the institutional ethical committee of Government Medical College Srinagar under Ref No: 138/ETH/GMC/ICMR. Patients of all age groups and sexes were recruited per WHO criteria, and informed consent was taken. The sample size was calculated using the "G" power 3.0 statistical analysis tool. The trial included 1100 patients. A prospective observational analysis of the anti-tuberculosis treatment regimen was conducted on 1100 patients of tuberculosis reported under the NTEP (National Tuberculosis Elimination Programme). In addition, data were collected from patients enrolled for directly observed treatment short-course (DOTS) at the hospital. All registered drug-resistant TB cases were treated with the appropriate dosage of drugs as per the sensitivity panel and followed up regularly. The diagnosis was based on clinical features, chest radiography, smear microscopy, molecular tests, and other supportive laboratory parameters. Among 1100 cases, 195 (17.7%) were drug-resistant, and 836 (76%) were drug-sensitive. Cases were put on the recommended anti-TB treatment regimen. The methodology is described below in the flow chart in figure 1.

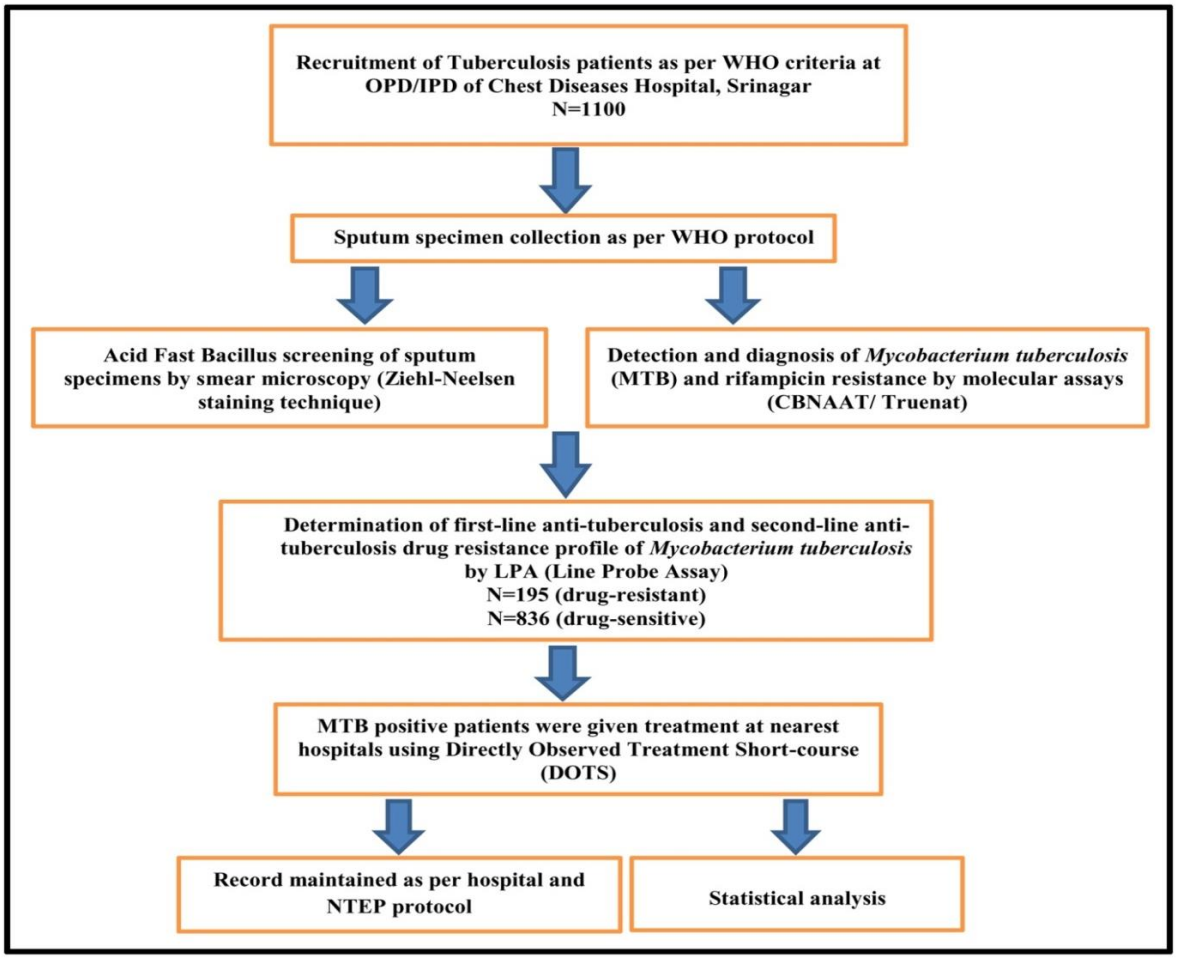

Fig 1: Flow Chart for Diagnosis of Drug-Resistant Tuberculosis

2.1. *Inclusion Criteria*

Patients from Kashmiri ethnicity, Tuberculosis Patients, Patients of all age groups and sexes.

2.2. *Exclusion Criteria*

Non-Tuberculosis Patients.

2.3. *Isolation and identification of Mycobacterium tuberculosis and Drug Susceptibility Testing for Mycobacterium tuberculosis*

The survey tool consists of the patient's socio-demographic details and laboratory examinations. The subjects with symptoms such as cough >2 weeks, hemoptysis, chest pain, loss of appetite, weight loss, night sweating and fever for more than two weeks were taken for sputum examination and were asked to provide two sputum samples as per WHO criteria. Sputum specimens were screened using the Ziehl Neelsen staining technique for identification of *Mycobacterium tuberculosis* and were further confirmed by advanced molecular tests, i.e., Cartridge Based Nucleic Acid Amplification Test (CBNAAT) and Truenat. Patients found to be positive were given treatment at the nearest hospitals using the Directly Observed Treatment Short-course (DOTS). All patients diagnosed with drug-resistant TB during the study were included. Drug Susceptibility Testing (DST) was performed for the first-line anti-tuberculosis therapy regimen and second-line anti-tuberculosis drugs by using the

GeneXpert Cartridge Based Nucleic Acid Amplification Test (CBNAAT) and Line Probe Assay (LPA). These molecular tests determined the pattern of drug resistance and drug sensitivity for the first-line anti-TB drugs rifampicin and isoniazid and the second-line anti-TB drugs fluoroquinolones (FLQ; e.g., ofloxacin and moxifloxacin) and aminoglycosides/cyclic peptides (AG/CP; second-line injectable antibiotics such as kanamycin, amikacin, capreomycin, and viomycin). The GeneXpert CBNAAT and LPA identify *Mycobacterium tuberculosis* (MTB) and simultaneously detect mutations associated with drug resistance. All drug-resistant tuberculosis (DR-TB) patients were tested for HIV at baseline. Sputum cultures and smears were obtained during the treatment period of drug-resistant tuberculosis (DR-TB) patients. The study aimed to detect drug resistance and treatment outcomes in tuberculosis patients of the Kashmir Valley by molecular assays.

2.4. Anti-Tuberculosis Regimen Procedure

Treatment pattern outcomes were defined and classified according to the WHO guidelines[25]. Patients cured of DR-TB completed treatment within eighteen months to over two years, followed by at least two negative sputum cultures. Completed treatment was defined as patients who completed the anti-TB regimen for at least eighteen months. Death was defined as death during treatment, regardless of the cause.

a. Failed Treatment was defined as smear-positive patients who remained positive at the fifth month of treatment or smear-negative turning positive.
b. Lost to follow-up was defined as treated patients who did not return to complete treatment.
c. TB recurrence refers to patients who had previous TB treatment and were cured but were diagnosed again with a new TB infection.
d. Successful treatment outcomes included cured patients and those who completed treatment.
e. Poor treatment outcomes include mortality or death, loss of follow-up and failure to complete the treatment regimen.

2.5. Outcome of interest

The study's main outcome was to observe the drug resistance pattern among drug-resistant tuberculosis (DR-TB) patients. In addition, drug resistance was diagnosed by molecular assays, and the treatment outcome of drug-resistant tuberculosis patients was analyzed concerning the socio-demographic characteristics of an ethnic population of Kashmir Valley.

2.6. Data collection

Data collection in terms of a questionnaire was designed using the medical history of all patients diagnosed with drug-resistant tuberculosis (DR-TB) during the study period. DR-TB was confirmed by drug susceptibility testing (DST) for first-line anti-TB drugs and second-line anti-TB drugs. In addition, all socio-demographic and clinical data were prospectively collected: age, sex, residence, marital status, educational status, employment, co-morbidity, TB drug resistance types, smoking habits, smear-positive pulmonary tuberculosis at baseline, and treatment outcomes.

3. STATISTICAL ANALYSIS

The data were entered into the MS Excel work spreadsheet 2011. The SPSS 2016 (Chicago, IL) program was used for statistical analysis. The clinical information and laboratory data were expressed and analyzed per patient. For comparisons between groups, paired and unpaired Student's t-tests were applied using a significance level of $p = 0.05$. $p<0.05$ was considered statistically significant. In addition, frequency, Chi-square, linear regression, and univariate and multiple variant analyses were performed to analyze the treatment outcomes of DR-TB patients.

4. RESULTS

A total of 1100 subjects were enrolled in this study (Table - 1). The mean ± standard deviation (SD) age of the subjects was 47.5 ± 15.45 years. All the subjects in the study were TB-positive after screening by the acid-fast bacillus staining technique. Out of the 1100 enrolled cases, 195 (17.7%) were drug-resistant to Anti Tuberculosis Therapy (ATT) and 836 (76.0%) were drug-sensitive to ATT. Furthermore, all the 195 drug-resistant cases were taken according to the WHO criteria for drug resistance profiling, among which 94 were women (48.2%) and 101 were men (51.8%) in the study and met the inclusion criteria. In addition, 6 (3.0%) drug-resistant patients had a positive household TB contact history. The socio-demographic and clinical characteristics are elaborated in Table 1.

Table1: Socio-demographic Characteristics of Drug-Resistant Tuberculosis patients

Characteristics	N (%)
Total Number of Subjects	1100 (100)
Patients with drug-resistant TB	195 (17.7)
Patients with drug-sensitive TB	836 (76.0)
Age (mean±SD)	47.5±15.4
Age Group (Years)	
< 40	144 (73.8)
>40	51 (26.1)
Gender	
Male	101 (51.8)
Female	94 (48.2)
Residence	
Urban	36 (18.4)
Rural	159 (81.5)
Occupational status	
Salaried Class	20 (10.2)

Business Class	45 (23.0)
Labour Class	100 (51.2)
Unemployed	30 (15.3)
Educational status	
Educated	50 (25.6)
Illiterate	145 (74.3)
Economic status	
Above Poverty Line (APL)	95 (48.7)
Below Poverty Line (BPL)	100 (51.2)
Marital Status	
Married	155 (79.4)
Un-Married	35 (17.9)
Divorced/Separated	05 (2.5)
Smoking Habits	
Smokers	135 (69.2)
Non-smokers	60 (30.7)
Type of TB	
Pulmonary TB (PTB)	181 (92.8)
Extra-Pulmonary TB (EPTB)	14 (7.1)
TB contact	
Household	6 (3.0)
Any other	189 (96.9)
Type of Baseline Drug resistance	
First Line ATT	195 (100)
Second Line ATT	08 (4.1)

The majority of patients were <40 years of age (n=144, 73.8%) and had rural dwellings (n=159, 81.5%). Most of the patients belonged to the labour class (n=100, 51.2%) and were economically settled below the poverty line (n=100, 51.2%). Regarding educational status and smoking, 145 (74.3%) were illiterate, and 135 (69.2%) were smokers

Table 2: Description of Drug-resistant Tuberculosis Patients concerning age and sex (n=195)

Age (In years)	Female X^2 value	Male X^2 value	Total	P value
11-20	35(2.69)	19(2.60)	54	0.001
21-30	29(0.19)	35(0.19)	64	**0.0031**
31-40	13(0.00)	13(0.00)	26	0.0183
41-50	4(3.0)	15(2.95)	19	0.001
51-60	7(1.0)	9(0.09)	16	0.001
61-70	3(1.2)	9(0.91)	12	0.001
71-80	3(1.4)	1(1.1)	4	0.001
Total	**94**	**101**	**195**	

Chi-square analysis test, the chi-square value= 12.974, p< 0.05, is significant

In Table 2, most drug-resistant TB patients were in the age group of 21-30, where 29 were females, and 35 were males (p=0.003), which was statistically significant. Resistance and sensitivity to anti-tuberculosis Treatment (ATT) drugs are analyzed as described in Table 3 and Table 4.

Table 3: First-line and Second-line Drug Resistance Pattern in Drug-Resistant Tuberculosis (DR-TB) Patients

First-line ATT Drugs	Resistance (n%) N=195	Second line ATT Drugs	Resistance (n%) N=8
MDR* (Rifampicin & Isoniazid)	24 (12.3)	XDR*	8 (4.1)
Rifampicin mono-resistant	121 (62.0)		
Isoniazid mono-resistant	42 (21.5)		

MDR= Multi-Drug Resistant, XDR= Extensively Drug Resistant

Table 4: First-line Drug Sensitivity Pattern in Tuberculosis Patients

First-line ATT Drugs	Sensitivity(n%),N=1031
Rifampicin & Isoniazid	836 (81.0)

Among 195 drug-resistant tuberculosis patients, most were resistant to rifampicin (n=121, 62.0%) vs isoniazid (n=42, 21.5%) vs MDR (n=24, 12.3%) vs XDR (n=8, 4.1%) in our study. Eight patients reported drug resistance to first-line and second-line ATT drugs (Table 3). Among 1031 patients, 836 were drug-sensitive to both rifampicin and isoniazid (Table 4).

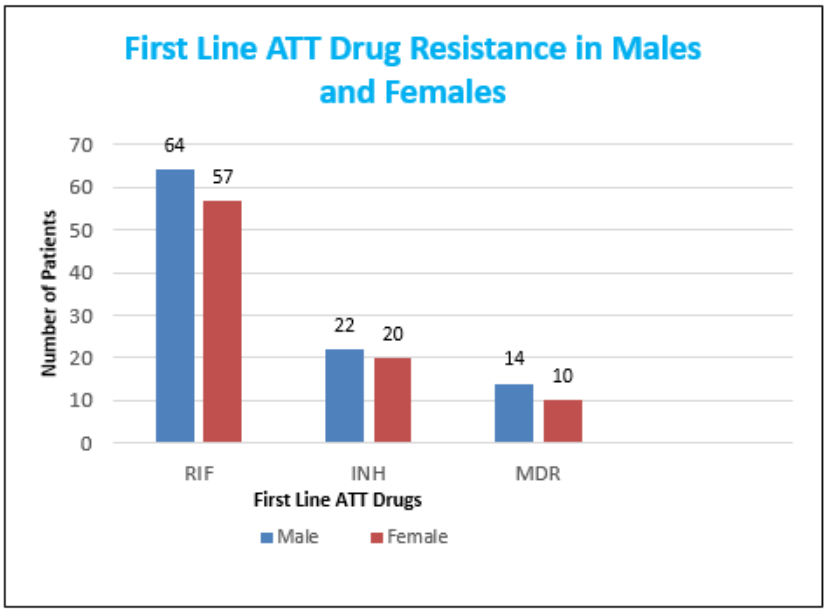

Fig 2 (a): Histogram representing the first-line ATT drug resistance pattern among males and females

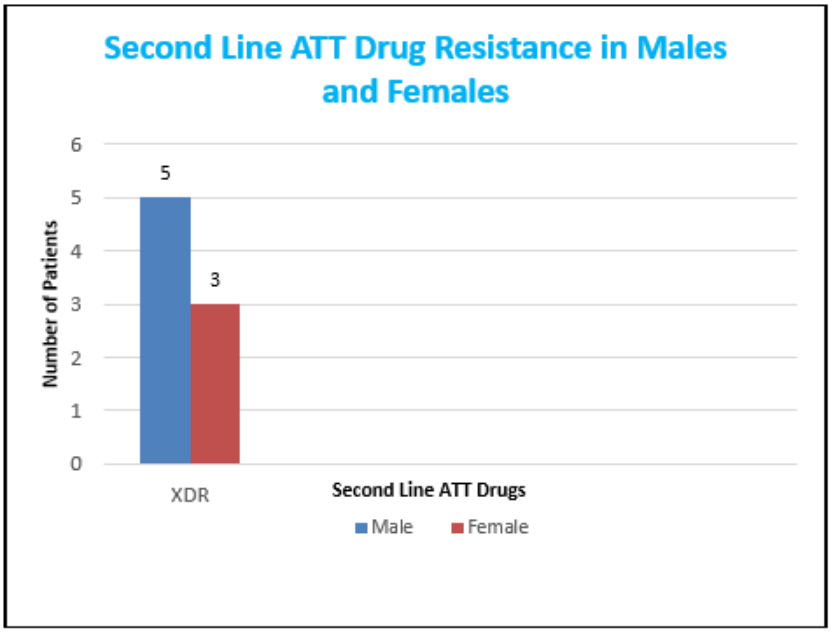

Fig 2 (b): Histogram representing the second-line ATT drug resistance pattern among males and females

Figs 2 (a) and 2 (b) show graphical representations of drug resistance to first-line and second-line ATT drugs in males and females. Compared to Isoniazid and MDR, rifampicin resistance is highly prevalent in both male and female patients in first-line ATT drugs. Whereas males were prevalent in second-line ATT drug resistance

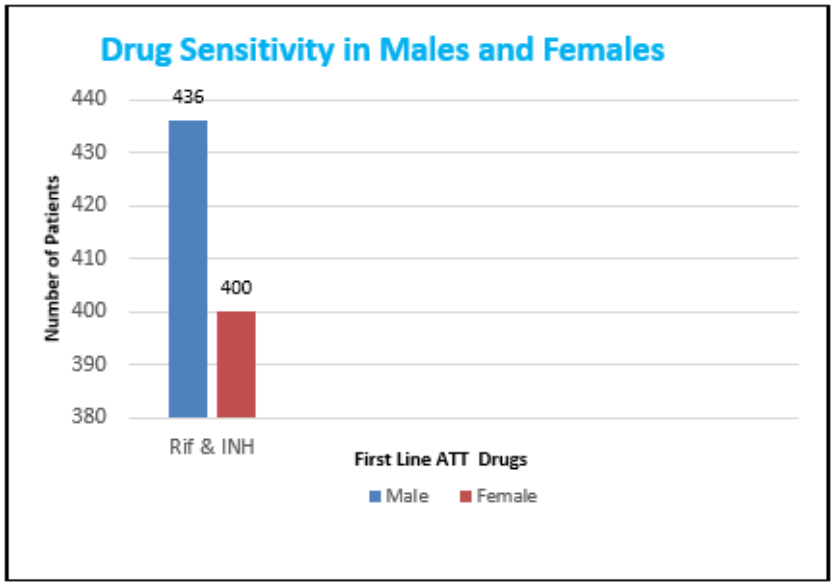

Fig 3 (a): Histogram representing the drug sensitivity pattern among males and females

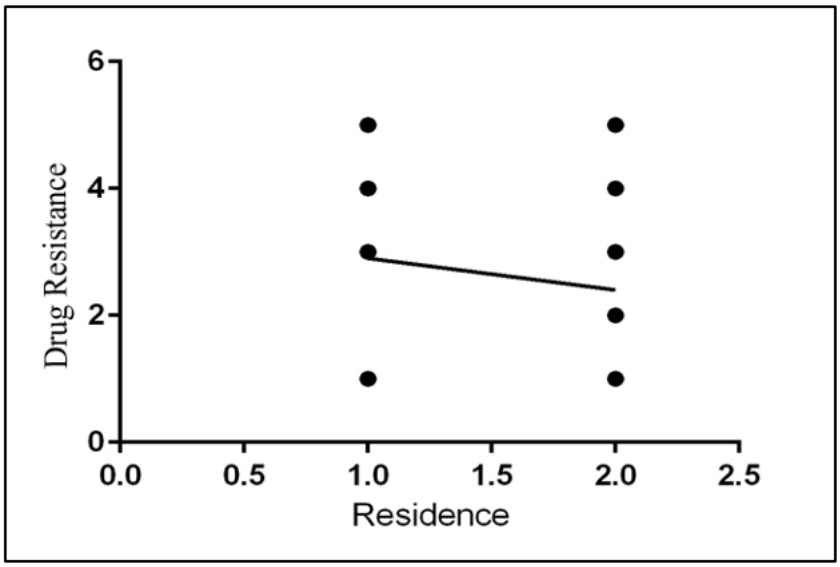

Fig 3 (b): The linear regression analysis of drug resistance pattern among the urban and rural population of Kashmir Valley

Figure 3 (a) represents the drug sensitivity pattern among males and females in our study subjects, and Figure 3 (b) represents the drug resistance pattern among the urban and rural populations of Kashmir Valley. Socio-demographically more rural people were found to be drug-resistant towards tuberculosis disease as compared to the urban population

Table 5: Stratification analysis of the type of drug resistance and treatment pattern in study subjects (N=40)

Type	Frequency N%	INH RESISTANCE	RIF & INH RESISTANCE	RIF RESISTANCE	XDR RESISTANCE
Failure	5 12.5	0 0.00	1 14.29	3 17.65	1 12.50
MDR-Contact	5 12.5	0 0.00	1 14.29	4 23.53	0 0.00
Recurrent	29 72.50	7 87.50	5 71.43	10 58.82	7 87.50
TB-Contact	1 2.50	1 12.50	0 0.00	0 0.00	0 0.00

Table 5 summarizes the stratification analysis of the type of drug resistance prevalent among study subjects as per questionnaire observation. Among 195 drug-resistant tuberculosis (DR-TB) patients, 40 reported these sources of drug resistance, which has been associated with treatment regimens. Among 40 DR-TB patients, 29 had recurrent tuberculosis (TB) and had mostly rifampicin resistance, one had TB contact, 5 had MDR contact and 5 had failure

Table 6: Tuberculosis treatment outcome according to first-line and second-line ATT drug resistance pattern in drug resistant tuberculosis (DR-TB) patients

Outcomes	Isoniazid Resistant	Rifampicin Resistant	MDR*	XDR*	Total
Number of Cases	**n=42**	**n=121**	**n=24**	**n=8**	**N=195**
I. Positive outcomes					
1. Cured	37(88.0)	58(47.9)	15(62.5)	2(25.0)	112(57.4)
2. Treatment Completed	4(9.5)	9(7.4)	2 (8.3)	0 (0)	15(7.6)
Successful Treatment (Cured Completed)	41(97.6)	67(55.3)	17(70.8)	2(25.0)	127(65.1)
II. Negative outcomes					
1. **Failure**	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.5)
2. **Died**	1 (2.3)	22 (18.1)	5(20.8)	6 (75)	34 (17.4)
3. **Lost to follow up**	0 (0)	11 (9.0)	0 (0)	0 (0)	11 (5.6)
4. **Transfer out**	0 (0)	16 (13.2)	2 (8.3)	0 (0)	18 (9.2)
5. **Treatment stopped**	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.5)
6. **On Treatment**	0 (0)	3 (2.4)	0 (0)	0 (0)	3 (1.5)
Poor Treatment (Failure+Death+ Lost to Follow-up+ Transfer out +Treatment stopped+ on treatment)	1 (2.3)	54 (44.6)	7(29.1)	6 (75)	68 (34.8)

MDR= Multidrug Resistant, XDR= Extensively Drug Resistant

It is summarized in Table 6, the treatment outcomes of 195 drug-resistant TB patients were as follows: 127 had successful treatment (65.1%), 112 were cured (57.4%) and 15 completed treatments (7.6%). Poor treatment outcomes were seen in 68 patients (34.8%), 34 patients (17.4%) died before completing treatment, one patient had treatment failure (0.5%), 11 patients were lost to follow-up (5.6%), and 18 patients (9.2%) were transferred out. The univariate and multivariate analyses are summarized in Table 7.

Table 7: Predictors of poor treatment outcomes in drug-resistant tuberculosis patients by univariate and multivariate analyses

Characteristics	Successful Treatment N=127 (65.1%)	Poor Treatment N=68 (34.8%)	Univariate Analysis			Multivariate Analysis		
			OR	95%CI	P	Adjusted OR	95%CI	P
Age								
<40	77	18	1			1		
>40	50	50	0.741	(0.475-2.53)	0.26	0.836	(0.232-2.136)	0.331
Gender								
Male	67	32	1			1		
Female	60	36	3.426	(1.542-11.35)	**0.007**	4.225	(0.732-9.536)	0.671
Residence								
Urban	30	22	1			1		
Rural	97	46	1.586	(0.672-5.314)	0.384	2.943	(0.582-8.546)	0.360
Education								
Literate	70	12	1			1		
Illiterate	57	56	7.12	(2.345-12.41)	**<0.001**	3.856	(1.232-13.24)	**0.013**
Smoking								
Yes	20	51	1			1		
No	107	17	6.11	(2.845-11.556)	**<0.001**	4.356	(1.425-12.45)	**0.014**

In the univariate analysis, poor treatment outcomes were associated with the male sex (p-value =0.007, OR = 3.426, 95% CI [1.542–11.35]) and smoking (p-value < 0.001, OR = 6.11, 95% CI [2.845–11.556]). After adjusting for the effects of potential confounders in the multivariate regression analysis, being a smoker remained an independent risk factor for poor treatment outcomes (p-value = 0.014, OR = 4.356, 95% CI [1.425–12.45]). Additionally, poor treatment outcomes were associated with illiteracy (p value= <0.001, OR=7.12, 95% CI=2.345-12.41)

5. DISCUSSION

This is the study done on drug-resistant tuberculosis (DR-TB) patients of Kashmir concerning anti-tuberculosis therapy regimens and patterns in the mountainous valley. The drastic rise of drug resistance (DR) in tuberculosis (TB) patients is a challenge that burdens the healthcare system and economies of the world and hinders effective TB control programs. Treatment of drug resistance is complex due to prolonged regimens, expensive drugs, and a high incidence of adverse drug toxicities and reactogenicity. These factors contribute directly or indirectly to poor treatment adherence and lead to the exponential magnification of drug resistance, which can have devastating consequences. MDR-TB has been persistently identified in India despite successfully implementing the National Tuberculosis Elimination Program (NTEP)[26,27]. Charan et al. published a recent study in India, where MDR-TB was found in 3% of new cases and 12% of treated patients[28]. Programmatic Management of Drug-Resistant Tuberculosis (PMDT) guidelines was demanded by clinicians treating tuberculosis, warranting successful implementation of PMDT guidelines, which can help us achieve milestones in combating challenging disease. This is the first study in the Kashmir valley that evaluates treatment outcomes of DR-TB and drug resistance and sensitivity in the line of anti-tuberculosis therapy in the ethnic population of Kashmir. Of the 195 DR-TB patients in this study, only 127 (65.1%) were successfully treated; these outcomes were lower than 2019 WHO target for MDR TB of at least 75% treatment success and below the 2020 target of the action plan for the WHO European Region (75%)[29, 30]. In our study, most patients were males (51.8%), which is in accordance with other studies that found DR-TB is more common in males[31,32]. Most of our patients were young, with a mean age of 47.5 years, in agreement with the study of Selim et al., who found a mean age of 39.35 years[33]. Labour class and unemployment were noted in 51.2% and 15.3% of the patients, respectively, in line with the study of Marta Gomes et al., who found that 51.8% were unemployed patients[34]. In our study, we observed that drug-resistant tuberculosis is frequent in patients from low socioeconomic backgrounds who are illiterate/less educated and unaware of the risks to others and themselves. In this study, we studied 195 drug-resistant tuberculosis patients by molecular assays, and we observed that the majority of patients were resistant to rifampicin (n=121, 62.0%) and then to isoniazid (n=42, 21.5%) and MDR (n=24, 12.3%). This is different from the study by Meressa et al., who found that 76.1% of patients with DR-TB were MDR-TB, and WHO reported a global MDR rate of 50%. In our case, the majority were resistant to the drug rifampicin[35]. Moving ahead in, Successful treatment outcomes, we observed and found that there were slightly lower percentages of successful treatment outcomes in our study than those found in studies performed in different populations, such as China, the USA, Shanghai, New York and Hamburg, where they reported (54.9, 64 and 80%, respectively) successful outcomes[36-38]. Some population-based studies, such as those conducted in Ukraine, South Korea and South Africa, reported lower success rates (18, 48.2 and 49%, respectively)[39,40]. Our study reported a much higher success rate in treating drug-resistant tuberculosis than the studies performed by Elmi et al. [41]and Kim et al. [42], who reported success rates of 17.1 and 39%, respectively. The biggest hurdle in controlling tuberculosis is the low rate of treatment success among DR-TB patients, as this might lead to the development of more resistant strains, and the transmission of these more resistant strains to other persons creates havoc in the ethnic population and places a burden on the health care system. The high number of patients lost to follow-up hinders the treatment success rate[43]. In our study, we found a 5.6% loss to follow-up rate, which is a very low rate compared to other studies performed in Pakistan, Spain, South Africa and South Korea, which found the loss to follow-up rates of 1.1, 16, 29 and 32%, respectively[44-47]. Among the possible reasons for the lower rate of loss to follow-up or discontinuation of therapy in our study was the best care given by health workers and continuation therapy adopted by the patients themselves at the DOT centres. The study performed by Holtz et al. [48] highlighted a lack of patient-provider interaction, drug use, and socioeconomic characteristics as the most significant factors associated with loss of follow-up. In our study, we found a failure rate of 0.5% in the drug-resistant tuberculosis patient therapy regimen, which is a good sign for our healthcare system in combating the challenging disease and was lower than the 8 and 8.7% failure rates found in other studies of DR-TB patients[49,50]. In our study, the mortality rate was 17.4% and the findings of Shin et al., who found 5% death among MDR-TB patients[51]. In our study, smoking habits were associated with poor treatment outcomes. These results follow the results of the studies performed by Tachfouti et al. [52] and Albuquerque et al. [53], who evaluated the association between smoking and unsuccessful treatment outcomes among TB patients. After adjusting for the effects of potential confounders in the multivariate regression analysis, being a smoker remained an independent risk factor for poor treatment outcomes (p-value = 0.014, OR = 4.356, 95% CI [1.425–12.45]). Additionally, poor treatment outcomes were associated with illiteracy (p- value= <0.001, OR=7.12, 95% CI=2.345-12.41). Predictive prognostic outcomes in our study reported that smoking and illiteracy are associated with drug resistance among tuberculosis patients, which is in line with studies performed in Uganda, China, and Moroccan ethnic populations[54, 55]. These study findings suggest that MDR and XDR tuberculosis can be treated with a first and second-line ATT regimen for 26 weeks, which is in line with the other studies reported by Gillespie et al[56], Jindani et al[57], and Merle et al. [58]. Our results demonstrate the need for rigorous follow-up of patients receiving Treatment for TB. Just as MDR TB is caused by systemic failures in treatment for drug-susceptible TB, XDR TB develops when MDR TB is inadequately treated. Treatment cure is rare without>4 effective drugs in a TB treatment regimen and consistent adherence to medications. These results and those from Tugela Ferry[59] in 2006 illustrate worst-case scenarios in health systems. When TB infections are inadequately treated, diseases might spread rapidly and have lethal results in the community. If a contagious TB patient refuses treatment and poses a risk to the general population, the patient can be compulsorily isolated according to the health protocol. Moreover, pharmacokinetics/pharmacodynamics modelling has been used for therapeutic drug monitoring (TDM) in the MDR-TB treatment for years[60]. Since the treatment can be up to 24-month treatment, the TDM supported shortening the regimen due to low drug exposure and improving the safety and efficacy of the drugs[61]. The suggestive outcomes are in agreement with our study findings. However, to optimize treatment outcomes among DR-TB patients, special attention should be given to patients with MDR-TB and substance abuse. Admission of these patients to a modern TB DOT centre may be an option to intensify the treatment and monitoring of these high-risk patients. It can also prevent

further drug resistance development and tuberculosis transmission in the community[62]. The treatment management for these patients should not only focus on medical support but also social support. Treatment should not only be seen from the perspective of delivery to the patients. Still, it should also be seen from a comprehensive care perspective that should consider the patient's ability to take medicine to make the right life choice. The treatment should support their circumstances to ensure adherence to the treatment and improve their quality of life [63].

6. CONCLUSIONS

Our findings conclude that, in the ethnic population of Kashmir Valley, the treatment strategy was effective for DR-TB patients. A low incidence of Drug-Resistant Tuberculosis (DR-TB) was also observed in this population. More cases were resistant to anti-tuberculosis drugs in the first line of treatment. Ensuring adherence to effective treatment regimens, especially for patients living in difficult socioeconomic conditions and mountain terrain, is a real challenge. Large multicentric cohort analyses are required to investigate further optimal treatment regimens for MDR-TB and XDR-TB with existing drugs. The evidence of nosocomial MDR-TB transmission emphasizes the paramount importance of infection control in hospitals and of more decentralized and outpatient approaches for treating drug-resistant TB. The incidence of MDR-TB is alarmingly high. The amplification of TB awareness and management programs and rigorous infection control measures are crucial for ending this emerging health concern.

7. ACKNOWLEDGMENT

We thank the Principal/Dean Govt. Medical College Srinagar and Department of Pulmonary Medicine GMC Srinagar for their support in the research. We thank all technical staff of Chest Diseases Hospital, STDC, NTEP, and STO Kashmir for their help and kind support. We are also thankful to all the patients in the study. Along with the screening staff of NTEP, the logistic and procurement section & drug counter of STO Kashmir are doing great work and contributing to the fight against this disease. Special thanks to Dr Inam-Ul-Haq for statistical analysis suggestions and necessary help.

8. AUTHORS CONTRIBUTION STATEMENT

Aijaz Nabi Puttoo conceptualized, Naveed Nazir Shah Supervised and demonstrated, Sandeep Tripathi cosupervised and designed the article idea, Ruqeya Nazir cosupervised and documented, Haamid Bashir and Aaliya Mohi-Ud-Din Azad drafted the article and performed the statistical analysis. Rehana Kauser validated and helped in data documentation. All the authors approved the final draft for publication and equally contributed.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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