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Original Research Article

A Prospective Cohort Study Determining the Characteristics and Patterns of Drug Resistant Pulmonary Tuberculosis

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Abstract:

Aim: The aim of the present study was to determine the characteristics and patterns of drug-resistant pulmonary tuberculosis.

Methods: The present prospective cohort study was conducted for the period of 2 years. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from each patient participating in the study.

Results: A total of 300 drug-resistant pulmonary tuberculosis patients with a median age of 28.2 years comprised the study group. Of them, 200 (66.67%) were males and 100 (33.33%) were females with median ages of 29.1 and 26.4 years, respectively. Most of the patients, 183 (61%), belonged to the age group of 20–44 years. A total of 41.66%, 10%, and 13.33% of MDR/RR-TB, XDR-TB, and H-mono/poly- DR-TB patients, respectively, had treatment outcomes declared as cured. Thus, a higher cure rate was reported for MDR/RR-TB patients than XDR-TB and H-mono/poly-DR- TB patients. It was also noted that 13.46%, 10%, and 80% of MDR/RR-TB, XDR- TB, and H-mono/poly-DR-TB patients, respectively, were declared as having treatment completed. Thus, more treatment outcomes as treatment completed were recorded in H- mono/poly-DR-TB patients. A greater incidence of death was observed in XDR-TB patients in comparison to MDR/RR-TB patients. No death and treatment failure was reported for H-mono/poly-DR-TB patients.

Conclusion: Gender, literacy, co-infection, diabetes mellitus, alcohol intake, smoking habit, low body mass index and poverty have a significant impact on the treatment outcome of drug resistant pulmonary tuberculosis patients. Interventions are needed to reduce the number of treatment failures, deaths, loss of follow-ups and transferred out cases.

Keywords: drug resistance TB; multi-drug-resistant tuberculosis; treatment outcome; adverse drug events

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is caused by bacteria that are resistant to both isoniazid and rifampicin, the most effective anti-TB drugs, or more. MDR-TB presents a major public health concern in many countries and continues to threaten TB control.[1,2] In 2017, there was an estimated 558 000 people developed rifampicin-resistant-TB, and of these, 82% had MDR-TB. The treatment of MDR-TB requires extensive chemotherapy, a WHO recommended regimen in 2016 with at least four effective TB medicines during the intensive phase, including fluoroquinolones

and second-line injections as core drugs, the total course of treatment is 18–24 months, and the intensive period is 6 months. In addition, second-line drugs (SLDs) are very expensive compared with the drugs for standard new TB treatment and can also cause a range of serious side effects.[3-5]

Accelerated tuberculosis (TB) control efforts have been threatened by the emergence of Mycobacterium tuberculosis strains that are resistant to potent first-line drugs (drug resistant tuberculosis or DR-TB).[6-8] In 2015, the World Health Organization (WHO) estimated 480,000 incident multidrug resistant TB (MDR-TB; resistance of both isoniazid and rifampicin) cases globally. With an estimated 79,000 MDR-TB cases, India along with the Russian Federation and South Africa accounted for 45% of the total notified combined MDR-TB and rifampicin-resistant (RR-TB) cases in 2015.[9] The prevalence of DR-TB and MDR-TB varied geographically, and 57% TB patients were resistant to any first-line drugs and 24.1% were resistant to multiple drugs in high-burden regions.[10,11] Studies have been conducted to investigate the prevalence of TB drug resistance across the country in recent years[10,12], but few have evaluated the temporal trend.

Drug-resistant-tuberculosis (DR-TB) patients are classified as rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively-drug-resistant-TB (XDR-TB) patients. The different regimens used for DR-TB treatment are the shorter oral bed aquiline containing MDR/RR-TB; longer oral M/XDR-TB; and isoniazid (H) mono/poly DR-TB. A shorter oral bed aquiline-containing regimen consists of an initial phase (IP) of four months that may be extended to six months, and a continuation phase (CP) of five months; thus, the total duration of the regimen is nine to eleven months. Bedaquiline is used for six months. From the start to the end of the fourth month—bedaquiline (Bdq), levofloxacin (Lfx), clofazimine (Cfz), pyrazinamide (Z), ethambutol (E), high-dose isoniazid (H), and ethionamide (Eto) are used; from the start of the fifth to the end of the sixth month—(if IP is not extended)—Bdq, Lfx, Cfz, Z, and E are used; and from the seventh to the end of the ninth month—Lfx, Cfz, Z, and E are used. The longer oral M/XDR-TB regimen lasts for a total duration of eighteen to twenty months with no separate initial or continuation phases, and the drugs used are levofloxacin (Lfx), bedaquiline (6 months or longer), linezolid (Lzd), clofazimine (Cfz), and Cycloserine (Cs). The H-mono/poly DR-TB regimen lasts for a total duration of six to nine months with no separate initial or continuation phases, and consist of levofloxacin (Lfx), rifampicin (R), ethambutol (E), and pyrazinamide (Z).[13]

The aim of the present study was to determine the characteristics and patterns of drug-resistant pulmonary tuberculosis.

Materials and Methods

The present prospective cohort study was conducted in Department of T.B and Chest , Nalanda Medical College and Hospital ,Patna, Bihar, India for the period of 2 years. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from each patient participating in the study.

Inclusion Criteria

Bacteriologically confirmed, notified, pulmonary tuberculosis cases. Patients of both genders and all age groups were considered.

Exclusion Criteria

The patients of neighboring districts and drug-resistant extra-pulmonary tuberculosis were not included in the study group.

Pre-Treatment Evaluation

Following the diagnosis of the patient as a case of drug-resistant pulmonary tuberculosis, each patient was subjected to

a pretreatment evaluation (clinical and laboratory based). The clinical evaluation included history and physical examinations, and height and weight measurements. Each and every patient was sent to the medicine, ophthalmology, otorhinolaryngology, and cardiology outpatient departments (OPDs) for clinical check ups. A psychiatric evaluation (if needed) of the patients was conducted by the Department of Psychiatry. The Pediatric Department and Department of Obstetrics and Gynecology were also involved as per the requirements. Laboratory-based evaluations included plasma glucose; HIV testing; complete blood count; liver function tests; serum T3, T4, and TSH; urine routine examination; serum sodium; serum potassium; serum magnesium; serum calcium; and urinary pregnancy test (in women of a reproductive age group). Laboratory investigations were conducted in the Department of Clinical Pathology, Department of Pathology, and Anti-retroviral treatment (ART) centre. Chest X-ray/high-resolution computed tomography (HRCT) were conducted in the Radiology Department and an electrocardiogram (ECG) was performed in the Cardiology OPD. The pretreatment evaluations of the patients were conducted to rule out any underlying co-morbid conditions, or radiological, ECG, or bio-chemical derangements.

Follow-Up Monitorings

Treatment follow-up monitoring (clinical, bacteriological, radiological, bio-chemical, and ECG) was conducted at regular intervals throughout the course of the DR-TB-treatment-regimen period. During the monitoring of MDR/RR-TB patients on the shorter oral bedaquiline-containing MDR/RR-TB regimen, a sputum culture was performed at the end of month 3, end of month 6, and/or end of treatment. The follow-up evaluation schedule for patients of the longer oral M/XDR-TB regimen included a monthly sputum culture from month 3 onwards to the end of 6, 7, or 8 months based on the previous month's culture-positive report. Patients on the Hmono/poly DR-TB regimen were monitored by sputum culture performed at the end of month 3, the end of treatment (month 6 and/or 9 if applicable). Follow-up culture results were the basis for declaring the final treatment outcome of all DR-TB patients. All DR-TB patients were clinically evaluated and their weight was measured at monthly intervals.

A urinary pregnancy test; complete blood count; Serum T3, T4, and TSH; liver function tests; X-ray chest PA view; and serum electrolytes (sodium, potassium, magnesium, and calcium) were performed as and when clinically indicated. An electrocardiogram (ECG) was conducted at 2 weeks, monthly in first 6 months, and then as and when clinically required. Post-treatment follow-up monitoring (clinical, radiological, bio-chemical, and ECG) for each treated patient was conducted, with 6 monthly sputum cultures among symptomatic patients, till one year following the completion of the DR-TB-treatment regimen.

Statistics

The data were analyzed and presented as percent, mean, and median. Statistical calculations were conducted by SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1: Age and gender distribution of drug-resistant pulmonary tuberculosis patients

Age Group (in Years)	Male *n* (%)	Female *n* (%)	Total *n* (%)
10–14	2 (1)	8 (8)	10 (3.33)
15–19	30 (15)	20 (20)	50 (16.66)
20–24	60 (30)	10 (10)	70 (23.34)
25–29	30 (15)	10 (4.10)	40 (13.34)
30–34	20 (10)	15 (15)	35 (11.66)
35–39	6 (3)	6 (6)	12 (4)
40–44	16 (8)	10 (10)	26 (8.66)
45–49	8 (4)	7 (7)	15 (5)
50–54	6 (3)	6 (6)	12 (4)
55–59	4 (2)	-	4 (1.33)
60–64	8 (4)	6 (6)	12 (4)
65–69	4 (2)	4 (4)	8 (2.66)
70–74	6 (2)	2 (2)	6 (2)
Total	200 (66.67)	100 (33.33)	300 (100)

A total of 300 drug-resistant pulmonary tuberculosis patients with a median age of 28.2 years comprised the study group. Of them, 200 (66.67%) were males and 100 (33.33%) were females with median ages of 29.1 and 26.4 years, respectively. Most of the patients, 183 (61%), belonged to the age group of 20–44 years.

Table 2: Final treatment outcome of drug-resistant pulmonary tuberculosis

	MDR/RR-TB (*n* = 250)	XDR-TB (*n* = 20)	H-mono/poly DR-TB (*n* = 30)	Total DR-TB Patients (*n* = 300)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Cured	104 (41.66)	02 (10)	04 (13.33)	110 (36.66
Treatment completed	34 (13.6)	02 (10)	24 (80)	60 (20)
Died	68 (27.2)	12 (60.00)	00	80 (26.66)
Treatment failed	25 (10)	00	00	25 (8.34)
Lost to follow up	15 (6)	4 (20)	01 (3.33)	20 (6.66)
Transferred out	4 (1.6)	00	01 (3.33)	5 (1.66)

A total of 41.66%, 10%, and 13.33% of MDR/RR-TB, XDR-TB, and H-mono/poly- DR-TB patients, respectively, had treatment outcomes declared as cured. Thus, a higher cure rate was reported for MDR/RR-TB patients than XDR-TB and H-mono/poly-DR- TB patients. It was also noted that 13.46%, 10%, and 80% of MDR/RR-TB, XDR- TB, and H-mono/poly-DR-TB patients, respectively, were declared as having treatment completed. Thus, more treatment outcomes as treatment completed were recorded in H-mono/poly-DR-TB patients. A greater incidence of death was observed in XDR-TB patients in comparison to MDR/RR-TB patients. No death and treatment failure was reported for H-mono/poly-DR-TB patients.

Table 4: Frequency of adverse events (AEs) among drug-resistant pulmonary tuberculosis patients

Grouped AEs	Specific AEs	Frequency	Offending Anti-TB Drug
Gastrointestinal	Nausea	12 (4)	Pyrazinamide, ethionamide
	Vomiting	6 (2)	Pyrazinamide, ethionamide
	Fullness of abdomen	130 (43.33)	Pyrazinamide, ethionamide
	Abdomen pain	75 (25)	Pyrazinamide, ethionamide
Neurological	Peripheral Neuropathy	65 (21.66)	Linezolid
Psychiatric	Psychosis	40 (13.33)	Cycloserine
	Depression	35 (11.66)	Cycloserine
Skeletal	Arthralgia	44 (14.66)	Pyrazinamide
Ophthalmic	Visual disturbance	7 (2.33)	Linezolid, ethambutol
Endocrinal	Hypothyroidism	2 (1.33)	Ethionamide
Dermatological	Skin discoloration	25 (8.33)	Clofazimine
Cardiological	QTcF prolongation	35 (11.66)	Bedaquiline

Many adverse events (AEs) were observed during the total duration of the DR-TB-treatment regimen.

Discussion

In India, the National Tuberculosis Elimination Program (NTEP) has developed a National Strategic Plan (NSP) 2017–2025 to achieve the milestone of eliminating TB from the country by 2025, and to achieve this target, Universal Drug Susceptibility Testing (UDST) and bedaquiline containing treatment regimens have been rolled out across the country. NTEP has established an efficient system of the targeted delivery of patient support benefits. NIKSHAY (the word is a combination of two Hindi words; Ni = end, kshay = TB), an online tool for monitoring the TB-control program, has been launched and the Public Fund Management System (PFMS) has been established to provide direct-benefit transfer.[13] The WHO has approved molecular assays Xpert MTB/RIF (CBNAAT), Xpert Ultra, and Truenat as initial tests for the diagnosis of tuberculosis (TB) and rifampicin resistance.[14]

A total of 300 drug-resistant pulmonary tuberculosis patients with a median age of 28.2 years comprised the study group. Of them, 200 (66.67%) were males and 100 (33.33%) were females with median ages of 29.1 and 26.4 years, respectively. Most of the patients, 183 (61%), belonged to the age group of 20–44 years. A total of 41.66%, 10%, and 13.33% of MDR/RR-TB, XDR-TB, and H-mono/poly- DR-TB patients, respectively, had treatment outcomes declared as cured. Thus, a higher cure rate was reported for MDR/RR-TB patients than XDR-TB and H-mono/poly-DR- TB patients. It was also noted that 13.46%, 10%, and 80% of MDR/RR-TB, XDR- TB, and H-mono/poly-DR-TB patients, respectively, were declared as having treatment completed. Thus, more treatment outcomes as treatment completed were recorded in H- mono/poly-DR-TB patients. A greater incidence of death was observed in XDR-TB patients in comparison to MDR/RR-TB patients. No death and treatment failure was reported for H-mono/poly-DR-TB patients. For the first line anti-TB drug, the proportion of drug resistance of streptomycin (56.8%) among MDR cases in our study were close to that observed from a previous study in Beijing (51.9%).[15] In 2010, a hospital based study in VietNam, 92% of 188 patients with MDR-TB were resistant to streptomycin. The high proportion of streptomycin resistant cases, especially a high level of resistance to streptomycin in Beijing, Shanghai, Tianjin, indicated that this drug was unlikely to benefit many patients. And this result is consistent with present WHO

treatment strategy that streptomycin is not recommended for MDR-TB cases.[16] Levofloxacin is widely used for respiratory-tract and other infections, and fluoroquinolones are extensively used in people who are later diagnosed with tuberculosis, which might result in a high proportion of resistance to fluoroquinolones in patients with MDR-TB.[17,18] The factors associated with treatment outcomes as failing in patients with drug resistant pulmonary TB were low-body mass index, HIV-DR-TB co-infection, diabetes DR-TB co-infection, bilateral cavities/extensive parenchymal disease on X-ray chest/HRCT chest, poor tolerability of anti-TB drugs, and additional resistance developing during the course of a treatment regimen.

Another meta analysis of the studies conducted in India revealed a worsening trend in DR-TB between the two study decades (decade 1 from 1995 to 2005: 37.7% [95% CI, 29. 0–46.4%] vs decade 2 from 2006 to 2015: 46.1% [95% CI, 39.0–53.2%]); The pooled estimate of MDR-TB resistance was higher in previously treated patients (decade 1: 29.8% [95% CI, 20.7–39.0%]; decade 2: 35.8% [95% CI, 29.2–42.4%]) as compared with the newly diagnosed cases (decade 1: 4.1% [95% CI, 2.7–5.6%]; decade 2: 5.6% [95% CI, 3.8–7.4%]).[19] The high drug resistant rate might be partially due to low economic level and tuberculosis management in the region. It is difficult for a low household income family to cover high MDR treatment costs, which leads to a poor adherence to MDR-TB treatment, and causes the emergence of drug resistance.[20]

Conclusion

Gender, literacy, co-infection, diabetes mellitus, alcohol intake, smoking habit, low body mass index and poverty have a significant impact on the treatment outcome of drug resistant pulmonary tuberculosis patients. Interventions are needed to reduce the number of treatment failures, deaths, loss of follow-ups and transferred out cases. We recommend strengthening of the follow-up monitoring system, timely detection and management of associated co-infection, increased nutritional and economic support to the poor patients for more successful treatment outcomes of drug resistant pulmonary tuberculosis patients.

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