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ASSESSMENT OF DEMOGRAPHIC AND CLINICAL PROFILE OF DRUG-SENSITIVE AND MULTIDRUG-RESISTANCE PULMONARY TUBERCULOSIS PATIENTS IN NORTHERN INDIA

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Abstract:

Our study aimed to characterize culture-positive multidrug-resistant tuberculosis (MDR-TB) patients from a center specializing in drug-resistant tuberculosis (DR-TB) in India. We initially performed research on 436 patients and later on we selected 395 patients as subject which was decided on the basis of particular criteria of inclusion and exclusion of subjects. Descriptive statistics were then utilized to analyze the social demographics, clinical features, and associated risk factors among culture-positive TB patients. The mean age of the patients included in our study was 43.6 years, with a majority of 61.5% being males. Notably, 27.3% of patients were smokers, 6.6% of the subject were found to be ex-smokers, and the remaining 66.1% were found to be non-smokers. The most commonly reported symptom among these patients was cough with expectoration, noted in 92.4% of cases, followed by complaints of fever which is 78%, haemoptysis which is 30%, and weight loss which is 63%. Additionally, 21% of the population had a family history of TB, highlighting a potential genetic predisposition. Comorbidities were prevalent among the study population, with 23.8% of patients presenting with other medical conditions. Among these, diabetes was the most common comorbidity, affecting 37 individuals. Regarding TB diagnosis, out of the 395 cases analyzed, 125 were identified as drug-sensitive pulmonary tuberculosis, while the remaining 270 subjects were categorised as MDR-TB. Smear grading revealed that 204 cases showed 2+ or 3+ positivity, while 191 cases exhibited 1+ or scanty positivity. Further analysis of culture-positive samples (364 in total) through drug susceptibility testing (DST) revealed significant resistance patterns. Specifically, 251 cases were resistant to rifampicin (RIF), 243 to isoniazid (INH), and 247 to ethambutol (EMB). Our findings highlight a substantial number of MDR-TB cases in the studied population, largely attributed to poor adherence to anti-TB medications. Consequently, we emphasize the importance of interventions such as reducing alcohol intake, enhancing education, promoting TB advocacy and communication, increasing testing and notification

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efforts, and implementing comprehensive TB control programs to effectively combat this public health challenge.

Keywords: Culture-positive PTB, Risk factors, TB, Comorbidity, Assessment

1. Introduction

In the year 1993, the World Health Organization (WHO) designated tuberculosis (TB) as a 'public health emergency' [1]. Each year, millions of individuals fall ill to TB, and in 2020 alone, 1.5 million people succumbed to the disease (in addition to 214,000 people with HIV) [2]. Tuberculosis ranks as the 13th leading cause of death globally, making it the second most significant infectious killer following COVID-19 [2]. Approximately 86 percent of new TB cases in 2020 were reported in 30 high-burden countries [2]. India takes the lead with two-thirds of the total burden, followed by China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa [2]. According to the Global TB Report 2021, India recorded an estimated incidence of all forms of tuberculosis at 188 per 100,000 population in 2020 (ranging from 129 to 257 per 100,000 population) [3]. The total number of notified incident TB patients in 2021 was 1,933,381, marking a 19% increase from the previous year's figure of 1,628,161 [3]. Ending the TB epidemic by 2030 stands as a crucial health target within the United Nations Sustainable Development Goals (SDGs), as emphasized by the WHO [2]. Conversely, in India, our Prime Minister has set an ambitious goal to eliminate TB from the country by 2025 [4].

TB can affect any organ of the body, but the serious clinical problem is pulmonary tuberculosis (PTB). TB spreads through the air from one person to another person. When a person with lung tuberculosis coughs, or sneeze, the Mycobacterium tuberculosis are released into the air [2]. Only a few of these germs must be inhaled for a person to become infected [2]. About 25% of the global population is infected with tuberculosis (TB), harboring TB bacteria without exhibiting symptoms or being able to transmit the disease. However, the rise of drug-resistant strains of tuberculosis presents a significant challenge for clinicians in effectively treating patients. The main reasons of TB appearance included person-to-person transmission, endogenous relapse, and treatment failure.

In India, drug-resistant tuberculosis (DR-TB) is common. Its presence has been known since anti-TB drugs were first introduced for the treatment of TB. If a person has MDR-TB, it means that patient is resistant to both rifampicin and isoniazid which are the main tubercular drugs. It was thought that the majority of MDR-TB in India resulted from people failing to take their anti-TB medications properly [5]. MDR-TB has a global incidence of 3.4 percent in new cases and 18 percent in previously treated cases. Across the globe, 78% of rifampicin-resistant tuberculosis (RR-TB) cases were multidrug-resistant [6]. From 2014 to 2016, an Indian government survey estimated the incidence of MDR-TB to be 2.84 percent in

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new cases and 11.6 percent in previously treated patients [7]. One of the major impediments to achieving the goal of eradicating TB in India is also this drug resistance TB.

Difficulties in disease diagnosis and preventative methods can result in the spread of tuberculosis, among even people who are not at high risk [8]. TB transmission can extend to social and casual contacts, which are more difficult to track down using traditional epidemiological methods [9,10]. If asymptomatic people go unnoticed for an extended period of time, they can become contagious and become the source of un-recognised TB outbreaks. Among TB cases, MDR-TB is major culprit.

Sputum culture-positive PTB is still a major challenge of tuberculosis transmission, compared with culture-negative or nucleic acid amplification test-negative *Mycobacterium tuberculosis* [11-12]. Clinical characteristics and demographics associated with MDR-TB patients of north India is not clearly understood. The objective of the present study was to determine the socio-demographics and clinical characteristics of MDR-TB cases presenting at drug resistant tuberculosis centre of India.

2. Materials and methods:

This cross-sectional study was conducted within the respiratory medicine department of a tertiary care hospital. Patients who tested positive for sputum smears, regardless of their gender and age, and who were visiting the outpatient department (OPD), were randomly selected for inclusion in the study. The study's protocol received approval from the Institutional Ethics Committee (IEC) of the institution, and informed written consent was obtained from all participants prior to their enrollment.

A total of 436 participants were initially enrolled in the study. However, after applying exclusion criteria and other considerations, 395 patients remained eligible for final analysis. Sputum samples were collected from the purulent portion of the respiratory secretions, and smears were prepared using a wire loop. These smears were then air-dried for 15-30 minutes and fixed by passing the slide over a flame multiple times. Staining using the Ziehl-Neelsen method was performed on all samples, where acid-fast bacilli appeared as pink, straight, or slightly curved rods. Sample processing, including the use of the N-Acetyl L-Cysteine (NALC) Method, was completed within 24 hours. Culture testing was conducted for all 395 cases using the Liquid culture medium-Mycobacterium Growth Indicator Tubes (MGIT). This liquid culture technique aligns with WHO guidelines as the gold standard for rapidly detecting multidrug-resistant tuberculosis (MDR-TB). Culture-positive subjects were further analyzed through Drug Susceptibility Testing (DST) to assess resistance to rifampicin (RIF), isoniazid (INH), and ethambutol (EMB). These steps ensured a thorough assessment of drug resistance patterns among the study population.

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Patients were checked by the chest specialist to confirm the diagnosis of TB.The collected data was analyzed to get significant results with GraphPad Prism 6 (GraphPad Software Inc, San Diego, CA, USA). All the data were presented as mean ± standard deviation (SD), and percentage. Descriptive statistics was employed.

Ethical statement and Patient consent:Study protocol was approved byinstitutional ethics committee. Written informed consent was taken from all the participants prior to enrol in the study.

3. Results

3.1 Demographical characteristics of PTB patients

The mean age of patients was 43.6±12.7 years. Description of demographics was depicted in Table 1. Age of patients ranged from ≤20 to >60 years. Maximum number of cases were aged 51-60 years (n=109; 27.6%) followed by 41-50 years (19.2%), 31-40 years (16.2%), >60 years (14.2%), 21-30 years (13.1%) and ≤20 years (9.6.7%) respectively. Majority of patients were males (n=243; 61.5%). There were 152 (38.5%) females. Out of 395, 12% (n=47) were underweight, and 40.3% have normal body mass index (Table 1). Drinking habit was found in 86 (21.8%) subjects. Married patients (n=260; 65.8%) predominated over unmarried patients (n=112; 28.4%). Rural patients (n=209, 52.9%) predominated over urban patients. Maximum number of patients were farmers/agriculturists/unskilled laborers (n=154; 39%) followed by students (n=66; 16.7%), housewives (n=56; 14.1%), business/shopkeepers and skilled worker/private service (n=48; 12.2% each) and government job/teachers (n=5.2; 20%) respectively (Table 1). Majority of patients were from lower socioeconomic class (n=160; 40.5%, Figure 1).

Fig 1 Socio-economic status of participants

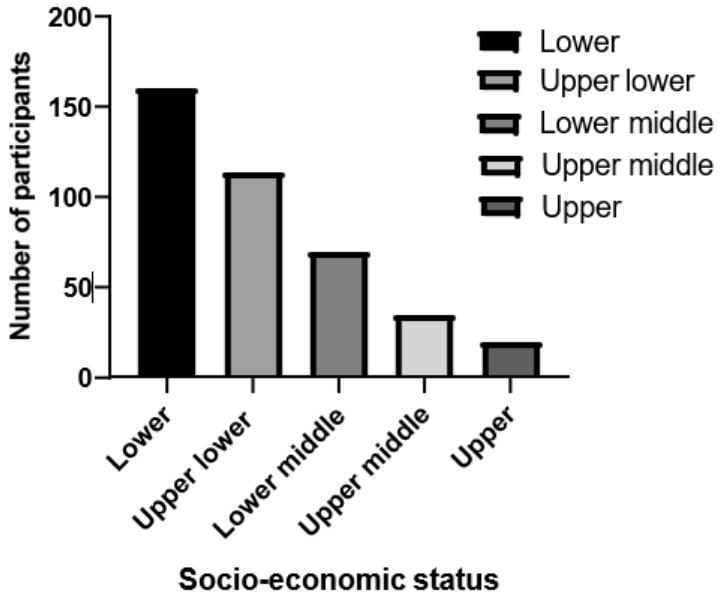

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Table 1 Socio-demographic profile of the studied participants.

S. No.	Characteristics	Number (n=395)	Percentage (%)
1	**Age Group (Years)**		
	≤20	38	9.6
	21-30 Years	52	13.1
	31-40 Years	64	16.2
	41-50 Years	76	19.2
	51-60 Years	109	27.6
	>60 Years	56	14.2
	Age (mean±SD) in Years	43.6±12.7	
2	**Gender (n, %)**		
	Male	243	61.5
	Female	152	38.5
3	**Body Mass Index (n, %)**		
	<18.00 kg/m^2	47	12
	18.0 – 22.9 kg/m^2	159	40.3
	23.0-24.9 kg/m^2	143	36.2
	>25 kg/m^2	46	11.6
4	**Drinking Habit (n, %)**		
	Alcoholic	86	21.8
	Non-Alcoholic	280	70.9
	Unknown	29	7.3
5	**Marital Status (n, %)**		
	Married	260	65.8
	Unmarried	112	28.4
	Widowed/Divorced	23	5.8
6	**Place of Residence (n, %)**		
	Rural	209	52.9
	Urban	186	47.1
7	**Occupation (n, %)**		
	Housewife	56	14.1
	Farmer/Agriculturist/Unskilled Labourer	154	39
	Business/Shopkeeper	48	12.2
	Government Job/Teacher	20	5.2
	Skilled Worker/Private Sector	51	12.9
	Student	66	16.7

3.2 Risk factors and clinical characteristics associated with culture-positive PTB

A total of 108 patients, constituting 27.3% of the study sample, were identified as smokers, while 26 individuals (6.6%) were categorized as ex-smokers. The remainder of the participants, comprising 66.1%, were non-smokers. On average, the pack years among the smokers amounted to 18.56±13.27. Additionally, 38% of the subjects were identified as

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tobacco chewers, while 37% had been exposed to biomass fuel. The most prevalent symptom reported was cough with expectoration, affecting 365 individuals (92.4%). Other complaints such as fever (78%), haemoptysis (30%), and weight loss (63%) were also documented. Furthermore, 21% of the population, totaling 82 individuals, reported a family history of pulmonary tuberculosis (PTB).

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Table 2: Risk factors and clinical characteristics of the participants.

S.No.	Characteristics	Number (n=395)	Percentage (%)
1.	**Smoking history**		
	Smoker	108	27.3
	Ex-smoker	26	6.6
	Non-smoker	261	66.1
	Pack years (mean SD)	18.56±13.27	
2.	**Tobacco chewer**		
	Yes	149	37.7
	No	246	62.3
3.	**Biomass smoke exposure**		
	Yes	146	37
	No	249	63
4.	**Cough with expectoration.**		
	Yes	365	92.4
	No	30	7.6
5.	**Hemoptysis**		
	Yes	118	29.9
	No	277	70.1
6.	**Weight loss**		
	Yes	249	63
	No	146	37
7.	**Fever**		
	Yes	307	77.7
	No	88	22.3
8.	**Family history of TB**		
	Yes	82	20.8
	No	313	79.2
9.	**Diabetes status**		
	Diabetes	37	9
	Non-diabetic	326	82.5
	Unknown	32	8.1
10.	**HIV status**		
	HIV-positive	14	3.5
	HIV-negative	360	91.1
	Unknown	21	5.3
11.	**Smear grading.**		
	3+ or 2+	204	51.8
	1+ or scanty	191	48.2
12.	**Culture report**		
	Positive	364	92.7
	Negative	31	7.3

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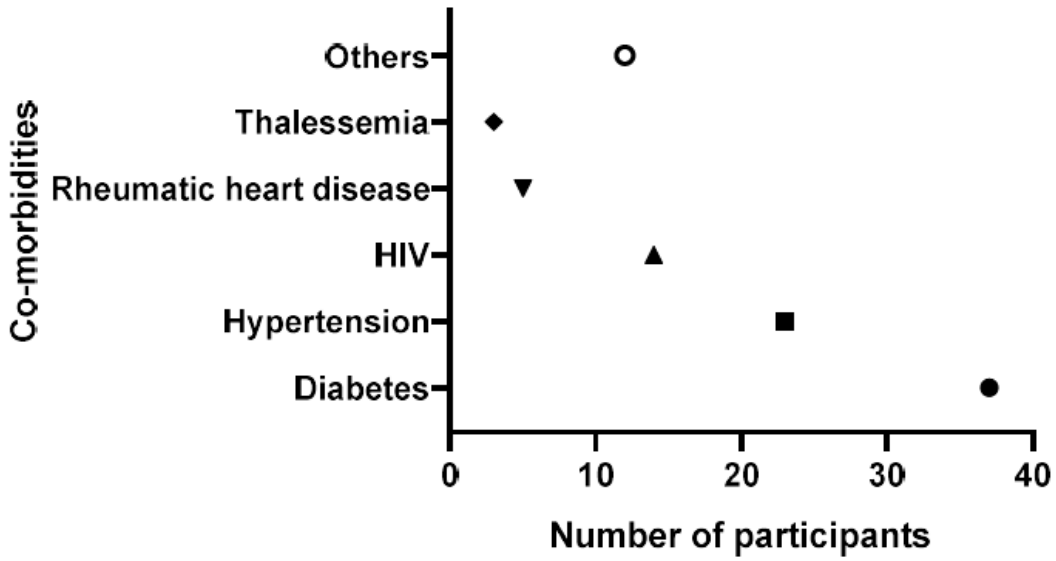
3.3 Associated co-morbidities in PTB patients.

Co-morbidities were present in 94 (23.8%) patients. Diabetes (n=37) was the most common comorbidity followed by hypertension (n=23), HIV (n=14) rheumatic heart disease (n=5), thalassemia (n=3) and others respectively (Figure 2).

Figure 2: Associated co-morbidities with the patients.



3.4 Resistance profile of the culture positive PTB patients

A total of 251 (69%) patients were rifampicin resistant while 113 (31%) were rifampicin sensitive. On the other hand, 243 (66.8%) patients were resistant to NIH and remaining 121 (33.2%) were sensitive to NIH. A total of 247 (68%) patients were EMB resistant while 117 (32%) were EMB sensitive. Resistance profile is presented in Table 3 and Figure 3.

Table 3: Drug susceptibilities of Mycobacterium tuberculosis isolates from all cases

S. No.	Drug	Resistance (n, %)	Sensitive (n, %)
1.	RIF	251(69)	113(31)
2.	INH	243(66.8)	121(33.2)
3.	EMB	247(67.9)	117(32.1)

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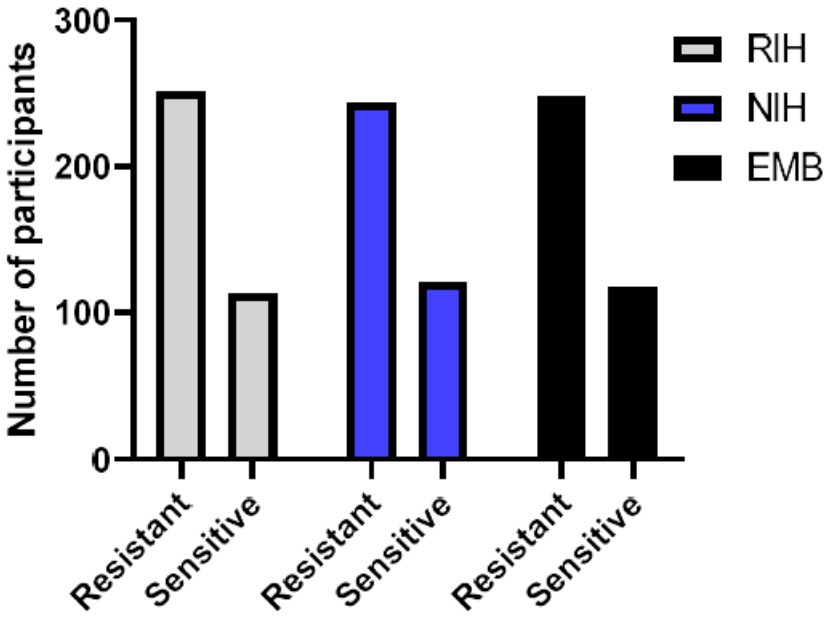
Figure 3: Graphical representation of Drug susceptibilities of Mycobacterium tuberculosis isolates from all cases.



4. Discussion

Roughly half of the global cases of multidrug-resistant tuberculosis (MDR-TB) originate from three countries: India (27%), China (14%), and Russia (9%) [6]. A comparison with the World Health Organization's 2019 report reveals that a survey conducted in India in 2016 showed a lower prevalence of MDR-TB among treated patients (11.6% versus 18%) and new cases (2.84% versus 3.4%). This study focuses on the demographics, clinical characteristics, and risk factors associated with MDR-TB, specifically from a tuberculosis center in northern India. The study identified 125 cases of drug-sensitive pulmonary tuberculosis and 270 cases of MDR-TB. The higher percentage of MDR-TB cases may be attributed to selection bias, as only suspected MDR-TB patients were recruited and investigated.

In India, the age group of 15–24 years exhibits the highest prevalence of tuberculosis, with rates of occurrence among men, women, and children at 60%, 34%, and 6% respectively [13]. In the present study, 9.6% of the population was under 20 years old. Men accounted for 61.5% of the cases, while females comprised 38.5%.

Smoking is a known cause of tuberculosis, which was also found in our study. According to a Ugandan study, 14.7% of men are current smokers [14]. Smoking may be even more prevalent among unemployed youth. A meta-analysis [15] stated an increased risk

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of tuberculosis infection, disease, and mortality with tobacco use. As a result, this provides a point to collectively focus on TB and tobacco control in the study areas. In the present study, most common symptoms were cough with expectoration consistent with another study [14].

The emergence of the HIV pandemic has led to an increase in tuberculosis cases. TB seems to be the most common disease associated with HIV, and it exacerbates HIV, reduces treatment efficacy, and leads to drug resistance. Additionally, drug resistance has resulted from the use of substandard drugs, insufficient or irregular drug supply, and treatment interruption. Out of the total 395 pulmonary tuberculosis patients, 3.5% were HIV positive. A meta-analysis study reported that the co-infection rate of MTB in patients infected with HIV was 14.4% [16].

The association between alcohol consumption and the onset of tuberculosis (TB), particularly smear-positive TB, is widely acknowledged [17-18]. Our findings revealed that 21.8% of the subjects in our study were identified as drinkers, a figure consistent with research conducted across various regions globally [18-20]. Additionally, concerning educational attainment, studies suggest that a less educated population may experience higher mortality rates among adult culture-positive tuberculosis patients, as evidenced in research conducted in Taiwan [21]. In the present study, 14.1% were house- wives, and 39% were unskilled workers. In socio-economic category, 40% patients were belongs to 'lower' status. Other than this, 52.9% of the population belongs to rural areas. In parts of Southern-East Asia, African and Western Pacific regions, the ratio of tuberculosis cases among rural district exceeds 50%.[22] Several tuberculosis characteristics such as age, sex, alcohol users, HIV, and education have been explored in various studies [22-25]. However, there were different characterizations in urban areas, including under-nutrition, indoor air population, and low socioeconomic profile [26-27]. These different characteristics can help local tuberculosis control personnel to manage different tuberculosis population.

In our study, the major percentage was of MDR-TB cases along with greater rural population. The rural patients had higher rate of MDR TB in culture positive tuberculosis, the reason might be due to poor treatment strategy, lack of economic support, and longer duration of disease course. These findings are similar with Mulisa G [28]and Hutchison C[29]. The reasons for multidrug-resistant tuberculosis (MDR-TB) may include poor treatment adherence, a higher prevalence of HIV-positive cases, and the presence of residual pulmonary cavities in rural patients. This finding aligns with similar studies conducted in Southern Africa [30] and the USA [31], indicating a consistency in the factors contributing to MDR-TB across different regions.

India has already completely eradicated major diseases such as smallpox and polio. But the condition with tuberculosis is different. There are several reasons why tuberculosis could not be eradicated till date. The reasons are related to the causative organism, Mycobacterium tuberculosis, as well as social and host factors. Mycobacterium tuberculosis is the causative organism of any infectious disease that infects nearly one-third of the global

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population, making it the single largest organism in terms of numbers infecting the human host. This organism is unique in that it can lay dormant for years without causing any harm while waiting for a favourable situation to multiply and cause disease.Here comes the role of social and host factors, such as malnutrition, HIV, diabetes, repeated and early pregnancy in females, poverty, overcrowding, smoking, alcoholism, and other addictions, poor hygiene, and difficulty accessing health care. These are just a few of the issues that concern us.

There are several limitations to this study, such as it was single centre study. Other than this, confounding factors viz quality of TB drugs, cavity interpretation and categorization of TB, could not be controlled. However, the findings are certain to be useful in establishing a public health priority for the development of actions aimed at preventing and controlling TB transmission in India.

Over the years, Indian government, in collaboration with RNTCP/NTEP, has undertaken numerous initiatives to raise awareness, promote health, and control tuberculosis, and by 2006, the entire country was covered by DOTS. In response to rising drug resistance, the DOTS-PLUS programme for MDR-TB treatment was launched in 2010. Recently, the RNTCP achieved the WHO's preliminary target and entered the second phase of TB control and eradication by enforcing the "Stop TB" strategy by ensuring quality state-of-the-art diagnostic laboratory services such as CB-NAAT, GeneXpert, LPA, and first- and second-line culture and medications. RNTCP has begun to make a difference in the fight against tuberculosis and MDR-TB. The GOI has successfully implemented "Nikshay" – a case-based online software through which more and more cases are being notified and treated as soon as possible. Collaboration with a number of Non-Governmental Organizations (NGOs) has expanded TB care to the periphery. RNTCP has also launched a PPM (Public Private Mix) service to ensure tuberculosis notification, awareness, and proper treatment. Despite all of these precautions, 22 people per lakh people die from tuberculosis each year, amounting to approximately three lakh deaths. This situation compels us to reflect, beginning with the policymakers at the top and working our way down to the microscopists and health visitors at the ground level. Change is required, from the level of political commitment to the level of public awareness of this dreaded disease. The Government of India launched the Nikshay Poshan Yojana in March 2018 [32]. Its main goal is to provide incentives (Rs 500 per month for the duration of treatment) to TB patients for nutritional support. The Nikshay Poshan Yojana is implemented through the use of a smart card that is linked to AADHAR. This ensures that user and account identities are not tampered with. During the Delhi END TB Summit on March 13, 2018, Hon'ble Prime Minister Shri Narendra Modi declared TB-Free India five years ahead of the target date of 2025.

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5. Conclusions

This study offers some evidence that the population distribution of culture-positive MDR-TB and need some specific measures to prevent and control TB transmission. It is understood that multidrug-resistant tuberculosis (MDR-TB) often arises due to inadequate adherence to anti-TB medications. Therefore, implementing strategies such as reducing alcohol consumption, increasing education initiatives, enhancing TB advocacy and communication efforts, expanding testing and notification procedures, and strengthening TB control programs are crucial steps in effectively managing tuberculosis (TB) and mitigating the emergence of drug-resistant strains. As Goethe's saying goes "Knowing is not enough; we must apply. Willing is not enough; we must do." We have to prepare altogether to end the TB by 2030.

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Competing Interest: The authors declare no competing interest.

Ethical statement and Patient consent: Study protocol was approved by institutional ethics committee. Written informed consent was taken from all the participants prior to enroll in the study.

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