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Clinico-demographic profile of pre-extensively drug-resistant pulmonary tuberculosis patients in India

Bella Devaleenal Daniel [a,*], Muthuvijayalakshmi M [a], Vikas Oswal [b], Chetan Kumar Jain [c], Neeta Singla [d], Santosh Kumar [e], Anuj Bhatnagar [f], Vikram Vohra [d], Jigna Dave [g], Namrata Kaur Bhui [h], Rajesh Solanki [i], Rathinam Sridhar [j], Parul Vadgama [k], Suryakant [l], Rathinam Prabhakaran [m], Paranchi Murugesan Ramesh [n], Bharathi Jeyadeepa [a], Shanmugapriya Kumaravadivelu [a], Balaji Ramraj [a], Jyoti Jaju [o], Chandrasekaran Padmapriyadarsini [a]

[a] ICMR –National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India
[b] Shatabdi Centenary Hospital, Mumbai, Maharashtra, India
[c] Sarvodaya Charitable Trust Hospital, Mumbai, Maharashtra, India
[d] National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India
[e] SN Medical College, Agra, Uttar Pradesh, India
[f] Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi, India
[g] Government Medical College, Bhavnagar, Gujarat, India
[h] Group of T.B. Hospitals, Sewri, Mumbai, Maharashtra, India
[i] BJ Medical College, Ahmedabad, Gujarat, India
[j] Government Hospital of Thoracic Medicine, Stanley Medical College, Chennai, Tamil Nadu, India
[k] Government Medical College, Surat, Gujarat, India
[l] King George Medical University, Lucknow, Uttar Pradesh, India
[m] Government Rajaji Hospital, Madurai Medical College, Madurai, Tamil Nadu, India
[n] Government Thiruvatteeswarar Hospital of Thoracic Medicine, Kilpauk Medical College, Chennai, India
[o] International Union Against Tuberculosis and Lung Disease, New Delhi, India

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ABSTRACT

Drug-resistant tuberculosis (DR TB) is a major public health problem and an important area of research. Identification of various risk factors is essential for its prevention and management. Adults weighing more than 30 kg, aged 18 years or more diagnosed with pre extensively drug resistant TB (pre-XDR TB) were initiated on bedaquiline and linezolid based regimens along with pretomanid/delamanid as part of two multicentric clinical trials in India. Pre-XDR TB was defined as patients infected with *M. tb* strains resistant to rifampicin (may or may not be resistant to isoniazid) with additional resistance to fluoroquinolones and/or second line injectable as per the existing World Health Organization (WHO) definitions during the trial period. We describe here the baseline demographic and clinical profile of patients with pre-XDR TB and enrolled in those two trials. Of 554 Pre-XDR TB patients, 297 (54 %) were males. Median age (IQR) was 27 years [22.0–36.3] and body mass index was 17.4 [15.7–20.1] kg/m^2. Of all, 326 (59 %) had BMI <18.5 kg/m^2. History of previous episodes of TB was reported by 415 (75 %) patients. Among them, 142 (34 %) had taken treatment more than once, 279 (67 %) had treatment failure during the previous episodes. Persons with a known history of diabetes were 67 (12 %). Cough, cough with expectoration, fever and weight loss were the presenting complaints in 539 (97 %) and 487 (88 %), 337 (61 %) and 314 (57 %) respectively. Sputum smear microscopy showed more than ++ acid-fast bacilli in 264 (48 %). Chest x-ray showed bilateral lung involvement in 329 (60 %) with more than two zones involvement in 304 (55 %) and presence of cavities in 264 (48 %) patients. Persons in the younger age group, those with malnutrition and previous history of TB treatment were observed to be more in these cohort of patients with PreXDR TB. High rates of treatment failure during the earlier episodes of TB with increased disease severity and drug resistance during the current episode is a matter of grave concern. Improved treatment success during the management of

* Corresponding author. ICMR-National Institute for Research in Tuberculosis, Chennai, 600031, India.
E-mail address: belladevalleenal.d@icmr.gov.in (B.D. Daniel).

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drug sensitive TB, addressing the nutritional challenges are some of key areas of focus in the prevention of DRTB burden.

1. Introduction

India has achieved highest level (>80 %) of treatment coverage in spite of its higher tuberculosis (TB) burden.[1] Prevention, early diagnosis and management of drug resistant tuberculosis (DR TB) is a vital area in TB control. Drug resistance to *Mycobacterium tuberculosis (M.tb)* is caused by mutation/s in particular gene/s which make TB drugs ineffective against the mutant bacilli. The various factors that could lead to drug resistance include inadequate or inappropriate treatment regimen, poor compliance to treatment and delay in diagnosis and initiation of treatment for DR TB. In addition, failure to achieve optimal therapeutic drug levels in spite of appropriate treatment and compliance could be a factor for the development of drug resistance. Identification of risk factors for DR TB helps in planning appropriate interventions for its prevention. Pre extensively drug resistant tuberculosis (Pre XDR TB) is a TB disease in which *M. tb* from any biological specimen is resistant to rifampicin with additional resistance to any fluoroquinolone.[1] Evidences regarding risk factors that could predispose to multidrug resistant tuberculosis (MDR TB) i.e *M.tb* resistant to rifampicin and isoniazid and its effects on treatment are largely known. However, literature regarding risk factors for Pre XDRTB are largely limited. We describe here the baseline clinical characteristics of patients with pulmonary pre-XDR TB who were eligible and managed with shorter oral bedaquiline and linezolid DR TB regimens as a part of two clinical trials in India.

2. Methods

Adults aged 18 years and above diagnosed with pulmonary PreXDR TB were recruited as part of two multicentric pragmatic clinical trials [BEAT study CTRI/2019/01/017310 and modified BPaL (mBPaL) study CTRI/2021/03/032189] in India. The objectives were to assess the effectiveness and safety of oral shorter bedaquiline and linezolid based regimens given along with delamanid (DLM), clofazimine in BEAT and pretomanid (Pa) in mBPaL trials. These two trials are described in detail elsewhere.[2,3] Pre XDR TB definition used for BEAT study was MDR TB plus resistance to either fluoroquinolones (FQ) and/or second line injectable (SLI).[2] As per the World Health Organization (WHO) revision of PreXDR TB definition in 2021, TB disease in which *M.tb* was resistant to rifampicin with or without isoniazid resistance plus additionally resistant to any FQs (second line anti TB drug) was used for mBPaL trial eligibility.[1,3] Appropriate ethical and regulatory clearances were obtained for conducting those trials. Rifampicin resistance was confirmed by Cartridge based Nucleic Acid Amplification Test (CBNAAT) in sputum samples. Mycobacteria Growth Inhibitor Tube (MGIT) drug susceptibility testing (DST) and line probe assay were the additional tests done to identify resistance to rifampicin, isoniazid, FQ, SLI and other newer drugs in the sputum samples. Case record forms were used to collect baseline demographic details, clinical characteristics and laboratory results.

Data was entered in REDCap electronic data capture tools and analysis was performed using SPSS version 25 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). The continuous variables were presented as median with interquartile range (IQR) or mean with standard deviation. The categorical values were presented as frequency with percentage.

3. Results

Of 554 Pre-XDR TB patients, 257 (46 %) were females. Median age (IQR) was 27 years [22.0–36.3]. Median body weight was 45.5 [40.0–52.5] kg and Body Mass Index (BMI) was 17.4 [15.7–20.1] kg/m^2. Of the total, 326 (59 %) patients had BMI <18.5 kg/m^2. Among them, 164 had BMI less than 16.5 kg/m^2 and 162 had BMI between 16.5 and <18.5 kg/m^2. Those who reported as ever smoked were 62 (11 %) and smoked for more than 10 years were 44 (8 %). Around 68 (12 %) mentioned as ever consumed alcohol.

Of all, 78 had one or more comorbidities at baseline and persons with history of diabetes were 67 (12 %). Baseline demographic, past TB treatment and current illness characteristics were presented in Table 1. Cough (539, 97 %) and cough and expectoration (487, 88 %) were the most common presenting symptoms followed by fever (337, 61 %), loss of weight (314, 57 %) and loss of appetite (286, 52 %). Breathlessness and chest pain were reported by 230 (42 %) and 159 (29 %) respectively. Regarding the duration of symptoms, cough with expectoration for more than four weeks was present in 358/487 (74 %). Among those with fever, 94 (28 %) had less than two weeks, 95 (28 %) had between two and four weeks and 148 (44 %) had more than four weeks. Duration of weight loss was more than 4 weeks in 201 (64 %) patients, between 3 and 4 weeks in 79 (25 %). Median (IQR) duration of both cough and

Table 1
Demographic and clinical characteristics of Pre XDR TB patients enrolled in clinical trials across different sites in India (N = 554).

Characteristics	Numbers (n)	%
Age in years		
18-30	354	64
31-45	124	22
46-60	71	13
>60-65	5	1
Weight		
≤45 Kg	267	48
>45 Kg	287	52
BMI (Mean ± SD) kg/m^2		
<18.5	326	59
18.5–24.9	198	36
25.0–29.9	26	4
30.0–34.9	4	1
Previous TB treatment		
H/O previous TB diagnosis or ATT		
No	139	25
Yes	415	75
If yes, frequency (N = 415)		
Once	273	66
>Once	142	34
If yes, Place of TB Diagnosis/treatment (N = 415)		
Public health centre	278	67
Private Health centre	130	31
Others	7	02
Previous treatment outcome (N = 415)		
Treatment success (Cure + completed)	47	11
Treatment failure	279	67
Lost to follow up	89	22
Sputum smear status		
Scanty	36	7
1+	215	39
2+	112	20
3+	152	27
Negative	39	7
Sputum Culture		
MGIT positive	534	96
MGIT Negative	20	4
Smear Negative and MGIT positive	33	6
X-ray		
Normal	6	1
Abnormal	548	99
Bilateral involvement	329	60
>2 zones	301	55
Presence of Cavities	264	48

fever was 8 (4–12) weeks. Almost 60 participants had at least one episode of haemoptysis during the current illness. Patients without cough at baseline (n = 15), presented with loss of weight (4), loss of appetite (5), fever (5), breathlessness (3), chest pain (2) and haemoptysis (1).

Regarding the symptom complex, 196 (35 %) presented with cough, expectoration, fever and weight loss, 109 (20 %) with cough, expectoration and fever, 97 (18 %) with only cough, expectoration, 84 (15 %) with cough, expectoration and weight loss, 20 (4 %) with cough, fever and weight loss. Around 10 (2 %) presented with cough and weight loss, 15(3 %) had only cough.

4. Discussion

In this cohort of Pre-XDR TB, unlike the general gender distribution for TB, almost equal proportion of females were affected. Most of them (64 %) were in the most productive years of their life; less than 30 years of age and 22 % were in the age group between 31 and 45. This is similar to other studies reported from Ethiopia (15–34 yrs)[4] and India (18–41 yrs).[5] The extensive and differing duration of presenting symptoms such as cough and expectoration enabling the transmission of DR TB is a matter of grave concern. Almost 9 % of our cohort did not have cough for more than 2 weeks. Weight loss was observed in more than half. Melissa S Sander et al. showed that the sensitivity of screening for cough >2 weeks alone was 61 %, and specificity was 84 %. Screening for at least two symptoms had sensitivity and specificity of 77 % and 70 % respectively, while combination of either cough >2 weeks and/or at least 2 symptoms had sensitivity of 87 % and specificity of 63 % for TB detection.[6]

More than half of our cohort were malnourished and 30 % were severely malnourished. BMI less than 18.5 kg/m2 was observed among 65 % of DR TB patients in Republic of Guinea.[7] Poor nutritional status is not only a risk factor for DR TB but also affects the treatment success. It is often associated with longer time to sputum culture conversion posing the threat of transmissibility and poor treatment outcomes.[8]

DR TB could be due to primary resistance (transmission of resistant strains) or secondary (acquired) resistance during treatment. Three fourth of our study population had previous history of TB diagnosis or treatment and closer to one-tenth of them had treatment success during that episodes. Almost one fourth of the patients did not complete their earlier TB treatment. Retreatment was also observed among one third of the previously treated patients. Previous TB treatment was observed among 65 % of DR TB patients in Ethiopia.[4] Previous unsuccessful treatment is a risk factor for poor treatment outcomes in DR TB patients.[9]

More than half of our cohort had bilateral lung involvement and almost half had cavitary lung disease in chest X-ray. Extensive lesions and cavitation in chest X-ray are risk factors for delayed sputum culture conversion and death in XDR TB patients.[10]

The treatment outcome and the factors influencing it in this cohort were not presented here. There could be selection bias as the studied population included set of PreXDR TB patients with predefined inclusion and exclusion criteria for clinical trial participation. As the criteria were set to simulate field conditions, the results could be generalizable.

5. Conclusion

Younger age group, malnutrition and previous TB treatment failure were some of the factors observed more in this cohort of Pre-XDR TB patients. Addressing the nutritional requirements of DR TB patients is an important element in management. Management of drug sensitive TB with appropriate regimen, dosage and duration, treatment compliance and completion is key for prevention of drug resistance. Early diagnosis to prevent extensive lung damage and improved treatment outcomes are key priorities in PreXDR TB management.

Authors contribution

BD, CP,: Design, conceptualization, data analysis, interpretation of data, draft and review the manuscript, MV: Data analysis, draft and review the manuscript, VO, CK, NS, SK, AB, VV, JD, NB, RS, RS, PV, SK, RP, PM: Data acquisition, interpretation of data and review of the manuscript, BJ, SK, BR, JJ: data analysis, interpretation of data and review of the manuscript. All authors approve the manuscript and agree to be accountable for all aspects of the work.

Ethical statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the ICMR National Ethical guidelines for biomedical and health research involving human participants. All procedures were performed in compliance with relevant laws, institutional guidelines and had been approved by the IEC/IRB of the participating Institute(s). All participants of BEAT and mBPaL trial provided written informed consent for participation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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