Social Determinants and Risk Factors Associated with Multi-Drug Resistant Tuberculosis Among Tuberculosis Patients in Tamilnadu – A Case-Control Study

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ABSTRACT

Introduction: The emergence of Multi-drug Resistant Tuberculosis (MDR- TB) is a challenge for global control and prevention mainly in developing countries. The objective of the study was to identify independent risk factors for the occurrence of MDR-TB.

Methods: An unmatched Case-control study was conducted among tuberculosis patients registered under NTEP in Kanchipuram district. 'Cases' were consecutive MDR TB patients aged 15 and older. 'Controls' were patients aged 15 and older, diagnosed with drug susceptible TB. Data was collected using pretested semi-structured questionnaire with face-to- face interview. Univariate and multi-variate analysis were used to identify associated determinants of MDR-TB.

Results: A total of 80 subjects, 20 cases and 60 controls (1:3) were recruited. Mean age of 'cases' was 32±9.3 years, and for controls was 31± 8.3 years. Multiple logistic regression analysis identified five significant risk factors such as passive smoking [OR = 8.449, 95% CI (6.791–30.27)], overcrowding [OR= 2.062,95% CI (1.004-3.005)], low socio-economic status [OR=8.000,95% CI (2.362-27.099)] and previous TB treatment [OR =13.72 with 95% CI (8.599-35.118)]. Inadequate ventilation [OR=4.643(4.217-13.906)]

Conclusion: To reduce the burden of drug-resistance, these risk factors can be used as screening tool in identifying individuals with MDR-TB in resource limited settings.

Keywords: Social Determinants, Tuberculosis, Multidrug resistance

INTRODUCTION

MDR-TB is defined as patient with laboratory-confirmed M. tuberculosis and resistance to at least isoniazid and rifampin.[1] A steady increase in drug-resistant tuberculosis (DR-TB) cases threatens global progress towards the United Nations Sustainable Development Goals (SDGs) to End-TB.[2]In 2018 globally an estimated 7.0million patients were diagnosed with Tuberculosis (TB) and TB-related deaths declined from 1.57 million in 2017 to 1.49 million, this remarkable decrease is due to daily regimen of Antimicrobial treatment. But 484,000 persons have been diagnosed multidrug–resistant TB in 2018 globally, representing 4.8% of all persons with TB, 3.4% of persons with a new TB diagnosis, and 18% of persons previously treated for TB and deaths due to MDR-TB was 214,000 persons.[3] India bears 27% of the global burden of multi-drug resistant TB (MDR-TB), with an estimated 124 000 (9.1/lakh population) disease in the country in 2019[2]

One of the major causes is that TB bacilli continues to develop resistance to drugs. For patients with drug

susceptible TB, the standard treatment regimen, which is based on isoniazid and rifampicin, the two most powerful drugs result in marvelous cure rate whereas, patients infected with resistant strains to first line drugs such as isoniazid and rifampicin are practically incurable by standard first line treatment.[4]

Globally Multidrug resistant TB is present in 3.8 %of new TB patients and 20 %with previous history of treatment.[5]Identifying patients who receive inadequate therapy and not being adherent to medications is the main cause of this disease and the need for explaining the factors leading to its existence is highly recommendable. Several studies observed various risk factors leading to the development of MDR-TB such as Treatment failure, Defaulters, Immediate contacts of MDR-TB patients and immunocompromised conditions such as HIV, undernutrition, smoking, and alcohol abuse are at increased risk[6]

However, social determinant factors also play an important barrier for ending TB, WHO reports that key epidemiological social determinants such as poor socioeconomic background, underprivileged working conditions and other contributing factors which include in adequate housing, overcrowding, poor physical environment, and health care needs.[7]Though some studies have quoted social determinants as major risk factor for MDR-TB globally, but exploring such factors is very meagre and limited in Indian subcontinent. Henceforth, exploring social determinant entity in Indian context contributes greatly to eliminating TB epidemic rapidly. With this background, we aimed to identify the independent risk factors including social determinants of MDR-TB among Tuberculosis patients for planning targeted programmatic interventions to reduce burden of multidrug-resistant tuberculosis.

METHODOLOGY

An unmatched Case-Control study was conducted on tuberculosis patients registered under National tuberculosis elimination program (NTEP) in Kanchipuram district of Tamil Nadu from January 2021 to August 2021. Study participants comprised of 20 MDR-TB patients as 'cases' and 60 Drug susceptible TB as 'Controls' in the Ratio of 1:3. The study was approved by institutional ethics committee (SMC/IEC/2021/03/185)

Data Collection Tool: Data was collected using the pretested and semi structured questionnaire. The questionnaire consists of four domains which includes

1) Sociodemographic details such as Age, Gender, Education, occupation, and income were included. Educational qualification was categorized into up to high school and degree holders. Occupation of the study participants were categorized into employed and unemployed. Unemployed category includes housewife, students, and dependent individuals. The

mean income of the participants was Rs.9000. Overcrowding was calculated based on the per capita space norms per person (<50sq feet). Ventilation was assessed by calculation of the door and window area.

2) Behavioural risk factors such as smoking, passive smoking, Alcohol consumption, persistent stress, and persistent sadness were included.

3) Housing conditions such as Overcrowding and poor ventilation were included.

4) Chronic Co-morbid condition like Hypertension, Diabetes, HIV-CO infection, and COPD and defaulter in TB treatment and history of previous TB treatment were included.

The Face and content validation of the questionnaire was done by individual experts from Pulmonology and Community Medicine department, and internal consistency and reliability was seen by using Cronbach's Alpha (0.78), and pilot study was done using 10 % of the study population and were not included in final analysis

Selection of Study Participants By 3 Steps

Step 1) Identifying the study participants; Step 2) Recruitment of cases and controls; Step 3) Data collection

Patients were identified through, NTEP developed a case-based web-based patient TB surveillance called NIKSHAY for both government and private health care facility for monitoring and management of TB control under the National Tuberculosis Elimination Programme (NTEP)[11]located at NTEP Centre in Head Quarters Hospital Kanchipuram. There are a total of 14 tuberculosis units with 27 confirmed MDR-TB cases and 60 drug sensitive Tb patients. Patients who completed intensive phase of treatment were included in the study. Of 27 MDR-TB patients, 20 were included for final analysis.4 Patients who were severely ill, 2 patients who were in out of station and 1 patient who did not give consent were excluded from the study.

For every case, three controls were assigned from the same geographical location(1:3ratio). With the assistance of Senior Treatment Supervisor (STS), recruited patients were interviewed at their homes after obtaining the required approvals from the relevant authorities.

Statistical Analysis: Collected data was entered in MS Excel and analyzed using SPSS Software version 26. To obtain frequency and percentage for cases and controls, we used descriptive statistics analyses. Univariate analysis was performed to identify the crude association between dependent and independent variables. The dependent variable was existence of MDR-TB, and the independent variables are socio demographic, behavioural co-morbid conditions, and housing conditions. Statistical significance was determined using p value <0.005 as a cut-off point and

Mantel-Haenszel Odds ratio was used to measure the strength of association. Those variables which showed significant association at p value < 0.05 in univariate analysis were entered in multinomial logistic regression analyses to find out the independent predictors of MDR-TB among the study subjects

OPERATIONAL DEFINITIONS

Cases: It is defined as patient of either sex, aged 15 years old or older, diagnosed and confirmed by culture of MDR-TB and Mycobacterium tuberculosis strain resistant to at least INH and RMP (two first-line anti-TB dugs)[8]

Controls: It is defined as patient of either sex, aged 15 years old or order, diagnosed and confirmed by culture of non-MDR-TB and M. tuberculosis strain sensitive to first line (Isoniazid, Rifampicin, pyrazinamide, ethambutol, and streptomycin)[8]

Defaulter: MDR-TB patient whose treatment was interrupted for two or more consecutive months. Additionally, the patients who are removed from treatment by clinicians due to persistent, short (< 2 months) interruptions should also receive a default outcome.[9]

Previous Tb Treatment History: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.[10]

Currently smoking: Someone who has smoked more than 100 cigarettes (including hand rolled cigarettes, cigars, cigarillos etc) in their lifetime and has smoked in the last 28 days.[25]

Ex-smoking: Someone who has smoked more than 100 cigarettes in their lifetime but has not smoked in the last 28 days. The international convention is to treat someone as an ex-smoker once they have been smokefree for one month (at least 28 days).[25]

Excessive alcohol: Includes binge drinking, heavy drinking, any alcohol use by people under the age 21 minimum legal drinking age, and any alcohol use by pregnant women.[26]

Persistent sadness: A person with persistent sadness has a sad, dark, or low mood and two or more other symptoms of depression for at least 1-month time[27]

persistent stress: Chronic stress, however, is a consistent sense of feeling pressured and overwhelmed for at least 1 month time.[27]

RESULTS

A total of 80 study participants, 20 were cases and 60 were controls participated in the study. The mean age of the study participants was 32 years. Among the cases 65 % were aged > 32 years, in controls 46.6% were aged > 32 years. Among the study participants males constituted 85% of the cases and 61.6% in controls. In this present study 65% of the cases attended up to high school, whereas in controls 81.7% attended up to high school. Almost 30 % of cases were unemployed and in controls 5% were unemployed. Almost 80% of cases and 5 % of controls had a monthly income of rupees less than 9000. In this study55% of the cases reported overcrowding whereas in controls 68.3% had reported. Almost 70% cases reported inadequate ventilation. Whereas 60% controls were reported. Among the cases, 50% were diabetics, 15% were hypertensives and 30% of patients had COPD, whereas in controls 36.7% were diabetics, 3.3% were hypertensives and 40% of the controls had COPD.

Table 1: Univariate analysis of socio demographic characteristics of the participants

Variables	Case (n=20) (%)	Controls (n=60) (%)	OR (95% CI)	p value*
Age of the participants				
>32years	13(65)	28 (46.6)	2.122 (0.743- 6.0625)	0.159
<32 years	7 (35)	32 (53.3)		
Gender				
Male	17(85)	37 (61.6)	3.522 (.928-13.361)	0.064
Female	3 (15)	23 (38.3)		
Education				
Up to high school	13(65)	49 (81.7)	0.4169(0.1350-1.2878)	0.128
Degree holder	7 (35)	11 (18.3)		
Occupation				
Employed	12(70.0)	54 (95)	0.1111(0.0243-0.5083)	0.0046*
Unemployed	6 (30.0)	3 (5)		
Total income				
<9000	16 (80.0)	20 (25.0)	8.000 (2.362-27.099)	0.000*
> 9000	4 (20.0)	40 (70.0)		
Family size				
>4	11 (55)	41 (68.3)	0.5664(0.2011-1.5950)	0.281
<4	9 (45)	19 (31.7)		
Adequate ventilation at home				
No	14(70)	24(40)	3.5000(1.1804-10.3782)	0.023*
Yes	6(30)	36(60)		

p value* <0.05 is statistically significant using Mantel Hanzal odds ratio

Table: 2 Univariate Analysis of Behavioural risk factors of the participants

Variables	Case (n=20) (%)	Controls (n=60) (%)	OR (95% CI)	p value*
Smoking				
Yes	14 (70)	15 (25)	7(2.282-21.470)	**0.0007***
No	6(30)	45 (75)		
Passive smoking				
Yes	15 (75)	12 (20)	12(3.638-39.585)	**0.000***
No	5 (25)	48 (80)		
Alcohol Abuse				
Yes	8 (40)	11 (18.3)	2 (0.980- 8.994)	**0.054***
No	12 (60)	49 (81.7)		
Persistent sadness				
Yes	14 (70)	19 (31.7)	5.035(1.676-15.130)	**0.004***
No	6 (30)	41 (68.3)		
Persistent stress				
Yes	14 (70)	28 (46.7)	2.667 (0.903-7.872)	0.075
No	6 (30)	32 (53.3)		

p value* < 0.05 is statistically significant using Mantel Hanzal odds ratio

Table 3: Univariate analysis of Co Morbid conditions of the study participants

Variables	Case (n=20) (%)	Controls (n=60) (%)	OR (95% CI)	p value*
HIV co -infection tested				
Positive	7(35)	4(6.7)	7.538 (1.918-29.627)	**0.004***
Negative	13(65)	56(93.3)		
Previous MTB treatment				
Yes	15(75)	4(6.7)	42.000(10.021-176.02)	**0.000***
No	5(25	56(93.3)		
Default TB treatment				
Yes	13(65)	4(6.7)	26.000(6.615-102.185)	**0.001***
No	7(35)	56(93.3)		

p value* < 0.05 is statistically significant using Mantel Hanzal odds ratio

Table 4: Multiple Logistic regression analysis of predictors of MDR-TB

Risk factors	AOR	95% Confidence interval		P value
		Lower Limit	Higher Limit	
History of Overcrowding	2.062	1.004	3.005	**0.040***
Default from treatment	2.496	0.133	46.669	0.540
Previous TB treatment	13.72	8.599	35.118	**0.000***
Low-income status	8.000	2.362	27.099	**0.000***
History of Passive smoking	8.449	6.791	30.27	**0.002***
HIV tested positive	7.845	0.342	19.831	0.197
Smoking history	0.380	0.018	10.954	0.533
Inadequate ventilation	4.643	4.217	13.906	**0.024***

p value* < 0.05 is statistically significant using Mantel Hanzal odds ratio

On univariate analysis of sociodemographic variables, there was no significant difference observed between cases and controls such as age, gender, education and occupation, and significant difference was observed on total income of the family, overcrowding and inadequate ventilation (Table 1).However, only passive smoking and persistent sadness proved to be a significant behavioural risk factor on univariate analysis as shown in (Table 2).Univariate analysis of co-morbid conditions is showed in (Table 3). On multinomial logistic analysis five variables were identified as an independent predictor for MDR-TB, such as overcrowding, previous TB treatment, Low-income status, passive smoking, and inadequate ventilation as shown in (Table:4)

DISCUSSION

This is an unmatched case control study conducted for identifying the social determinants as a risk for MDR-TB, it has provided an appropriate information about risk factors associated with MDR-TB to support and to decrease the TB burden in Northern Tamil Nadu. The identified social determinants and strong predictors were income, overcrowding, previous TB treatment, default treatment, inadequate ventilation, and passive smoking. We observed MDR-TB was most prevalent in age group of more than 32 years. The present study observation is consistent with similar study conducted by Mukati et al (31 to 40 years), Munje et al (25 to 34 years) and contrary, the study conducted by Prakash et al lower age group (15 to 25 years) [12,13,14] In our study we found

that males constituted 85% of the cases and in controls 61.6%. study done in Uganda by Okethwangu D, et al observed men were affected more than the women per 100,000 with p value < 0.01 due to poor adherence to first-line anti-TB treatment were associated with MDR-TB,[15]Alammarietal, similar study conducted in Saudi Arabia which shows that female have high prevalence of MDR-TB[1]

Among the identified sociodemographic factors, low income of <9000 was seen in 80%cases and in 25% controls. Overcrowding was reported by 55% of the cases and in 68.3% controls. Smoking history was seen in 70% of cases and in 25% of controls. Alcohol abuse among cases were 40% and in controls 18.3%. Persistent sadness due to social inactiveness because of the disease was reported in 70% of cases and in 31.7% controls. Cases who reported history of passive smoking were 75% in cases and in 20% of controls. Persistent stress reported among cases were 70% and in controls 46.7% and Inadequate ventilation among the cases reported were 30 % and in controls 40%, so eventually low income with small living space and inadequate ventilation are more likely developed MDR-TB. Because infectious disease and poverty have a high probability of acquiring the infections which often go hand in hand,[16] which shows that the low socio-economic factors are important determinant for acquiring infections, comparative study conducted by Xin-Xu Li et al observed that the risk factors of primary drug sensitive TB and primary MDR-TB more likely happens in the low socio economic group[16]

Among the study participants the Co-morbid conditions such as Diabetes was seen in 50% cases and in 36.7% controls. Hypertension was seen in 15% of the cases and in 3.3% of controls and COPD was seen among 30% cases and in 40% controls. On univariate analysis between socio demographic factors and MDR-TB, income of the family, overcrowding and inadequate ventilation were significantly associated.

Income of the family <9000 with an OR=8 (95% CI;2.362-27.099) P=0.000 it means the cases with lower income has eight times higher risk of developing MDR-TB similar finding observed by Djibut et.[17]

Other socio-demographic factors family size > 4 members in the small living space are significantly associated with MDR-TB with an OR=0.5664 (95%CI; 0.201- 1.5950). Similar study done by Xin-Xu et al on MDR-TB per capita living space < 40 m2 (OR = 4.65; (95% CI = 1.06–20.38)[16]Sachin et al observed MDR-TB to associated with staying in densely in a small living space, those observations suggest the vulnerability of women for MDR-TB.[18]Inadequate ventilation are associated significantly with MDR-TB with an (OR=3.500 (95%CI;1.180-10.378) This similar finding was observed by Venkatesh et al, that 72.7%. of inadequate ventilation which is higher in proportion.[19]

Among the behavioural risk factors passive smoking and persistent sadness is significantly associated with MDR-TB. passive smoking with an (OR=12) (95%CI;3.638-39.585) after an adjustment (AOR=8.449 (95%CI;6.791-30.27), similar study done by Leung et al OR=1.67(95%CI 0.72-3.86) which is not statistically significant. The reason found to be that loss of ciliary motility and immune depression and along with social factors.[20]For persistent sadness (OR=5.035(95% CI;1.676-15.130) and it is statistically significant, similar study conducted by Maja et al OR=3.88 (95% CI:1.63-9.24).[6]

Among co-morbid conditions previous TB treatment, default treatment and HIV co infection is associated with MDR-TB. Previous TB treatment OR=42 (95% CI;10.021-176.02)and AOR 13.72 (95% CI; 8.5999-35.118) A similar study was conducted in South Africa, in which a history of TB treatment failure/completed observed are the main predictor of MDR-TB than newly diagnosed patients, It is also one of the main barriers of TB control.[6]Study done in Georgia resistance is due to repeated and inappropriate way of taking the medication that made the bacteria to mutate and develop resistance against the drugs[21] Among the cases default treatment OR=26 (95% CI:6.615-102.185) and on AOR=2.496 (95% CI:0.133-46.669) it is not statistically significant, similar study done in Uzbekistan OR=3.84(95%CI :1.41-11.11) which is statistically significant. Among the HIV-Co Infection and MDR-TB (OR=7.538 95% CI:1.91-29.627) and AOR=7.845 (95%CI:0.342-19.831) and it is not significantly associated.[22]A systematic analysis and meta-analysis have reported that HIV-positive cases have a 24% higher risk of MDR-TB compared to HIV-negative ones.[23]Another study done by Suchindran et al, observed no significant association between MDR-TB and HIV coinfection.[24]

STRENGTHS AND LIMITATIONS

The study is widely applicable and can inform policy makers which, may help in the rising burden of MDR-TB in Northern Tamil Nadu. We also assessed a wide range of social determinant factors which could be a good addition to the evidence on the risk factors of MDR-B.Ths. study also had some limitations, First, the findings are prone to recall bias that could have potentially reduced the strength of association, however most of the information retrieved from the patient exposure had occurred before disease and the sample size was also less so there is a less possibility of generalization to the whole population.

CONCLUSION

Our study observed some risk factors associated with MDR-TB, based on our various social determinant factors, which is being the barrier for complete cure in MDR-TB patients should be identified by health care workers and manage them by giving proper nutrition support to avoidance of out-of-pocket expenditure. To prevent from mortality,

health education on adequate ventilation, knowledge about the disease, overcrowding and nutrition should be emphasized, to achieve betterment life of MDR-TB patients, early detection of cases based on the updated clinical guidelines and clinical supervision by the health care workers at all levels of system

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