

Short Communication

Correlates of multi-drug resistant tuberculosis: a case control study from a hilly district of North India

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ABSTRACT

Background: Drug resistance has emerged as a major threat to global TB control efforts in recent years. India, with the highest burden of Tuberculosis worldwide, faces a looming epidemic of drug resistant TB due to initial irrational, irregular and incomplete treatment outside the purview of the robust national programme. Himachal Pradesh, a north Indian hilly state with a population of about 7 million has a considerable burden of Tuberculosis with geographical challenges. The present study envisaged to identify the potential risk factors to the emergence of drug resistance TB in the settings of district Shimla.

Methods: A pilot case control study, all patients (n=11) enrolled for MDR-TB in Tuberculosis Unit Shimla during the period (2013-14) were included. 3 of who died were excluded. Thrice the number of controls (n=24) were selected after matching for age, sex and approximate geographical location.

Results: The univariate analysis showed that, compared with controls, risk factors significantly associated with primary MDR-TB were Socioeconomic status lower than class 3 (OR=13.8; p=0.02), poor ventilation (OR=5; p=0.05), absent BCG scar (OR=23; p=0.002), history of default (p=0.002) and initial treatment from a private practitioner (OR=6.60; p=0.04). The Multivariate analysis showed that the risk factors independently associated with primary MDR-TB were absent BCG scar (OR=28.15; 95% CI=1.51-524.38) and initial irrational and incomplete treatment from a private practitioner (OR=16.77; 95% CI =1.12-319.26).

Conclusions: In our stud, poor ventilation, lower socioeconomic condition and initial default have been found to be significantly associated with the disease whereas absent BCG scar and initial irrational treatment from private practitioners have emerged as independent risk factors for the emergence of drug resistant Tuberculosis further reiterating the need for strengthening Immunization and early diagnosis and treatment aspect of the disease involving private practitioners. Larger and extensive studies on these aspects are further warranted.

Keywords: Tuberculosis, MDR-TB, Case control study

INTRODUCTION

Tuberculosis is a chronic infection mainly caused by *Mycobacterium tuberculosis* and rarely by *Mycobacterium bovis*. The available vaccine is not very promising for the complicated form of disease and there

is no single drug which can be used for shorter duration. RNTCP (Revised National Tuberculosis control programme) relies on a multi-drug therapy to treat tuberculosis.¹ It is very difficult for all diagnosed patients to adhere strictly to the treatment as desired. Non adherence to drug treatment is often difficult to predict

and it is an important reason for multi-drug resistant tuberculosis.

Factors such as poor administrative control on purchase and distribution of the drugs with no proper mechanism on quality control and bioavailability tests is another reason for the emergence of drug resistant Tuberculosis.² There is a considerable risk of amplification of drug resistance if MDR TB is treated with the first line drugs. Resistance can be reduced and prevented with complete, adequate and regular treatment. The study envisaged to find out such factors and will recommend modifications to be implemented in the TB control program.

Multidrug-resistant tuberculosis (MDR-TB) has been defined as the resistance of *Mycobacterium tuberculosis* strains to both isoniazid (INH) and rifampicin (RMP) with or without simultaneous resistance to other drugs.¹ MDR-TB poses a therapeutic and infection control challenge with significantly higher rates of morbidity and mortality.

MDR-TB has substantial economic implications of high treatment cost which is nearly 100 times the cost of treating a susceptible TB case. A worldwide assessment in 35 countries revealed an overall prevalence of MDR-TB as 12.6% for single-drug resistance (range, 2.3–42.4%) and 2.2% for multidrug resistance (range, 0–22.1%) in all the countries surveyed. About 50 million people were infected with multidrug resistant *M. tuberculosis* strains globally, and they account for 14% of the world's total TB cases.¹

India has the second highest burden of MDR-TB cases following China and it is reported that the country has approximately 66,000 MDR-TB cases among notified pulmonary TB cases in 2011 (new cases - 21,000 with a range of 15,000-27,000 and retreatment cases - 45,000 with a range of 40,000-50,000).²

A study conducted by Atre et al on risk factors associated with MDR-TB at the onset of Therapy among the new cases registered with the RNTCP in Mumbai, India revealed that infection with the Beijing strain and Female gender were significant predictors of MDR-TB at the onset of the therapy.³

A study conducted by Balaji et al on risk factors for MDR-TB in a tertiary referral hospital in India revealed that previous treatment with an injectable and Fluoroquinolone was strongly associated with MDR-TB. Smoking and Alcohol were negatively associated with MDR-TB. Residence outside the state showed a trend towards association.⁴ In another study by Kliiman et al conducted in Estonia, a European country with one of the highest MDR-TB and XDR-TB rates in the world, revealed that the risk factors for poor treatment outcome in MDR-TB were HIV infection, previous TB treatment, resistance to Ofloxacin and positive acid-fast bacilli (AFB) smear at the start of treatment.⁵

A study was conducted by Gaude et al at J.N. Medical College and associated hospitals, Belgaum. MDR isolates were obtained in 52.2% of the cases. Illiteracy, low socio-economic status, previous history of TB and alcoholism were found to have statistically significant association for the development of MDR.⁶

A study by Wang et al was conducted in China on factors contributing to the high prevalence of multi-drug resistance Tuberculosis. A multivariate analysis showed that the family annual per-capita income $\leq 7,000$ Yuan (OR =3.238; 95% confidence interval [CI]: 1.270-8.252), no history of fixed dose combinations (FDCs) in anti-TB treatment (OR =4.027; 95% CI: 1.457-11.129), and adverse reactions in the course of TB treatment (OR =3.568; 95% CI: 1.402-9.085) were independent predictors of MDR-TB. Moreover, among the TB patients who had adverse reactions, quitting the treatment was shown as a risk factor for MDR-TB ($p=0.009$). Moreover, among the TB patients who had adverse reactions, quitting the treatment was shown as a risk factor for MDR-TB ($p=0.009$).⁷

Li et al conducted a 1:1:1 matched-pairs case-control study in 2011 to identify predictors associated with primary MDR-TB and primary DS-TB against the control in Jiangsu Province, China. All three groups were geographically matched (by neighbourhood) and matched on sex and age (± 5 years). In total, 110 participants were enrolled in each of three matched groups. Conditional logistic regression analysis showed that predictors independently associated with primary MDR-TB were illiteracy or primary school education, annual per capita income $\leq$ US\$2,000, per capita living space < 40 m², and interval ≥ 7 days of eating fruits; predictors with primary DS-TB were body mass index ≤ 20 and feeling higher life pressure.⁸ In another study conducted by Mittal and Gupta on non-compliance to DOTS in Agra city revealed that more defaulters were in the age group of greater than 45 years (22.8%), male (18.7%), retreatment cases (30.6%) with important reasons being side effects following medication, improvement in symptoms and lack of time.⁹

Objectives of the study

1. To identify the factors associated with MDR-TB in the setting of district Shimla, Himachal Pradesh, India.
2. To recommend modifications, based on the study findings to be implemented in the current TB Control programme.

METHODS

Source of data

Multi Drug Resistance cases were tracked from Drug Resistant TB centre, Dharampur for the period from 1st January 2013 to 30th June, 2014.

Data from tuberculosis patients registered and records at DOTS in TU, Shimla.

Study design

A pilot case-control study.

Study period

All patients registered between 1st January 2013 to 30th June, 2014 in the TU were included in the study. Triple the number of controls was enrolled after matching geographical location, gender and age ± 5 years.

Sample size

Subjects: All patients who fulfilled the inclusion criteria were enrolled for the study i.e. 8 (eight).

Controls: 24 (twenty four) –who have completed DOTS and have been declared cured.

Method of collection of data

After obtaining permission from the District Tuberculosis Officer, all the patients on ATT for MDR-TB in Shimla TU who fulfilled the inclusion criteria were taken as study subjects. They were included in the study after obtaining written informed consent. After the registration of the patient, primary data (socio-demographic profile, medical history) was collected by the investigator from the patient using a semi structured and pretested questionnaire. The secondary data (sputum exam report, category of treatment, DOTS provider details) was collected from the records maintained at the DOTS centres.

Table 1: Socio-demographic characteristics.

Characteristics of primary MDR patients and controls in district Shimla.		
Variables	Primary MDR-TB n (%) / Mean (SD)	Controls n (%) / Mean (SD)
Total	8 (100)	24 (100)
Age	28.63 (8.61)	29.79 (8.75)
Male	4 (50)	12 (50)
Literacy		
Illiterate	2 (25)	0 (0)
<Matriculation	1 (12.5)	3 (12.5)
>=Matriculation	5 (62.5)	21 (87.5)
Marital status		
Single	3 (37.5)	16 (66.7)
Married	5 (62.5)	8 (33.3)
Residential area		
Rural	3 (37.5)	7 (29.2)
Urban	5 (62.5)	17 (70.8)
Occupation		
Unemployed	3 (37.5)	13 (54.2)
Student	1 (12.5)	3 (12.5)
Employed	4 (50)	8 (33.3)
Socioeconomic status		
Class 1	3 (37.5)	12 (50)
Class 2	0 (0)	3 (12.5)
Class 3	0 (0)	4 (16.7)
Class 4	2 (25)	4 (16.7)
Class 5	3 (37.5)	1 (4.2)
Family		
Single	1 (12.5)	2 (8.3)
Nuclear	4 (50)	15 (62.5)
Joint	3 (37.5)	7 (29.2)
House type		
Kutcha	1 (12.5)	0 (0)
Pucca	7 (87.5)	24 (100)
Fuel used		
Only chullah	0 (0)	0 (0)
Mixed	1 (12.5)	2 (8.3)
LPG	7 (87.5)	22 (91.7)
Overcrowding	3 (37.5)	7 (29.2)

Inadequate Ventilation	4 (50)	4 (16.7)
Alcoholism	2 (25)	2 (8.3)
Smoking	4 (50)	11 (45.8)
Exposure to second hand smoke	3 (37.5)	7 (29.2)
Previous drug reaction history	0 (0)	0 (0)
History of initial default	3 (37.5)	0 (0)
Absence of BCG scar	4 (50)	1 (4.2%)
Diabetes mellitus	0 (0)	0 (0)
HIV	0 (0)	0 (0)
History of contact	2 (25%)	4 (16.7)
Initial treatment from private practitioner	3 (37.5)	2 (8.3)

Data analysis

The data was entered in the Microsoft Excel sheet. For descriptive statistics, mean and SD were calculated. Compared with controls, risk factors with crude and adjusted matched ORs and their 95% CIs associated with primary MDR-TB were identified by univariate and multivariate logistic regression models, respectively using Epi-Info v7 software.

Inclusion criteria

All patients registered for treatment for MDR-TB (subjects) and those who have been declared cured (Controls) in TU, Shimla and who gave written informed consent.

Exclusion criteria

Those patients who are not willing to participate in the study and MDR patients who have died before the onset of the study.

RESULTS

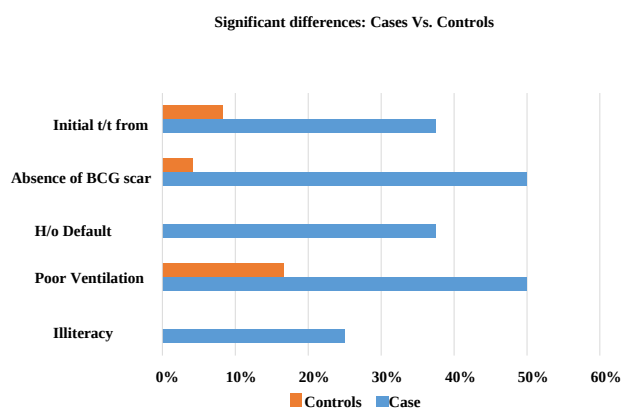
A total of 8 primary MDR-TB and 24 controls were enrolled in the study. The groups were matched for geographical location, gender and age ± 5 years. The overall mean age in the age group 15-45 was 29.5 years (SD =8.6 years) and 50% of the cases and controls were males and females respectively. The mean ages of cases and controls were 28.63 (SD =8.68) and 29.79 (SD =8.75) respectively.

Table 2: Univariate analysis.

Sr. No.	Variable	Chi Square	P value	Crude OR	CI
1.	Gender	0.000	1.00	1.00	0.20-4.95
2.	Illiteracy	6.46	0.01*	-	-
3.	Marital status	2.11	0.14	3.33	0.63-17.60
4.	Residential area	0.19	0.66	1.45	0.27-7.8
5.	Occupation	0.66	0.41	0.50	0.09-2.62
6.	SES –Class 5	6.09	0.01	13.8	1.17-161.7
7.	SES- Less than 3	4.84	0.02*	6.3	1.11-35.99
8.	Staying single	0.12	0.72	1.57	0.12-20.0
9.	House type	3.09	0.07	-	-
10.	Fuel	0.12	0.72	0.63	0.05-8.12
11.	Overcrowding	0.19	0.66	1.4	0.27-7.82
12.	Poor Ventilation	3.55	0.05*	5.0	0.86-28.86
13.	Alcoholism	1.52	0.21	3.36	0.42-31.72
14.	Active smoking	2.46	0.11	0.69	0.53-0.89
15.	Ever smoked	0.42	0.83	1.18	0.23-5.8
16.	Second hand smoke exposure	0.19	0.66	1.47	0.27-7.8
17.	Previous reaction history	-	-	-	-
18.	History of default	9.93	0.002*	-	-
19.	Absent BCG Scar	9.56	0.002*	23.0	2.01-262.56
20.	Diabetes mellitus	-	-	-	-
21.	HIV	-	-	-	-
22.	History of contact	0.27	0.60	0.60	0.087-4.12
23.	Treatment from private practitioner	3.87	0.04*	6.60	0.862-50.54

Table 3: Multivariate analysis

Sr. No.	Variable	Wald Chi square	P value	Adjusted OR	CI
1.	SES <class 3	0.65	0.42	2.55	0.26-25.00
2.	Poor ventilation	1.23	0.26	4.76	0.30-75.14
3.	Absent BCG scar	5.0	0.02*	28.15	1.51-524.38
4.	Initial Treatment from Private practitioner	3.5	0.05*	16.77	1.12-319.26

**Figure 1: Significant difference between cases and controls.**

Amongst the total study subjects, 6.3% (2/32) were illiterate (2 cases vs. 0 controls), 12.5% (4/32) were under-matriculate and 81.3% (26/32) were matriculate or above. Amongst all subjects, 59.4% (19/32) were single (3 cases vs. 16 controls) and 40.6% (13/32) were married (5 vs. 8). 31.3% (10/32) resided in rural (3 vs. 7) and 68.8% (22/32) in urban (5 vs. 17) areas respectively. 50% (16/32) of the total were unemployed (3 cases vs. 13 controls); 12.5% (4) were students (1 vs. 3) and 37.5% (12) were employed (4 vs. 8). The percentage of patients belonging to different socio-economic classes was: Class 5 (12.5%, 4/32; 3 vs. 1), 4 (18.8%, 6/32; 2 vs. 4), 3 (12.5%, 4/32; 0 vs. 4), 2 (9.4%, 3/32; 0 vs. 3) and 1 (46.9%, 15/32; 3 vs. 12). With regards to family status, 9.4% (3/32) lived as single (1 vs. 2), 59.4% (19/32) were part of a nuclear family (4 vs. 15) and 31.3% (10) lived in a joint family (3 vs. 7) respectively.

Age, gender, marital status, residential area, occupation, Socio-economic status, type of family, type of house, type of fuel, overcrowding, alcohol, smoking, exposure to second hand smoke, previous drug reactions, Diabetes, HIV status and history of contact were not significantly different between MDR-TB and non-MDR TB patients.

Significant differences between MDR-TB and non-MDR-TB patients were Illiteracy (25% vs. 0%; $p=0.040$); poor ventilation (50% vs. 16.7%; $p=0.05$), history of default (37.5% vs. 0%; $p=0.002$), absence of BCG scar (50% vs. 4.2%; $p=0.002$) and initial treatment from a private practitioner (37.5% vs. 8.3%; $p=0.04$).

The Univariate analysis showed that, compared with controls, risk factors significantly associated with primary MDR-TB were Illiteracy ($p=0.04$), Socioeconomic status lower than class 3 ($OR=13.8$; 95% $CI=1.11-35.99$), poor ventilation ($OR=5$; 95% $CI=0.86-28.86$), absent BCG scar ($OR=23$; 95% $CI=2.01-262.56$), H/o default ($p=0.002$) and initial treatment from a private practitioner ($OR=6.60$; 95% $CI=0.86-50.54$).

The multivariate analysis showed that the risk factors independently associated with primary MDR-TB were absent BCG scar ($OR=28.15$; 95% $CI=1.51-524.38$) and initial treatment from a private practitioner ($OR=16.77$; 95% $CI=1.12-319.26$).

DISCUSSION

Prevalence of MDR-TB reflects the functional state and efficacy of TB control programmes and realistic attitude of the community towards implementation of such programmes.³

Our study envisaged to explore the different risk factors associated with MDR-TB in this part of the country which has a considerable load of TB patients.

Various studies have found significant association between female gender and MDR-TB. Since our study was matched for gender, age groups and geographical locations, it is not possible to report such associations.

Various studies conducted in China and India, which contribute to a sizeable burden of the disease worldwide, found small living space, poor education and poor nutrition which orient towards a poor socio-economic status, to be associated with the disease.^{7,8} Our study has found illiteracy, low SES and poor ventilation to be associated with MDR-TB as compared to drug sensitive TB.

No significant associations were seen between MDR-TB and habits such as smoking and alcoholism in our study. This might be due to 'reporting biases' associated with these personal issues which respondents may tend to conceal. Many studies in India and abroad have reported different associations with smoking and alcohol.¹⁰⁻¹⁴ In our opinion, there is a need to explore different methodologies regarding such inquiries into behavioural aspects, to retrieve more authentic information.

The present study has found a significant association with the absence of a BCG scar in the patients suffering from MDR-TB which strengthens the version that the vaccine prevents one from the severe form of the disease. It also provides a starting point from which further extensive studies may be carried out to establish the role of the vaccine.

Antimicrobial resistance in the form of multidrug - resistant TB (MDR - TB) has emerged as a major threat to global TB control efforts in recent years.

Various Indian studies have established association of MDR-TB with history of initial defaulting, inadequate initial regimen not conforming to the national guidelines and an initial treatment with an injectable and Fluoroquinolones.¹⁵⁻¹⁷ In our study, initial default has found to be significantly associated with the disease whereas initial treatment from a private practitioner has emerged as an independent risk factor for the emergence of drug resistant tuberculosis further reiterating the need for strengthening early diagnosis and treatment aspect of the disease involving private practitioners which at many times are the first point of contact for the patient, so that the looming epidemic of drug resistance is contained.

The limitations of the present study have been a small sample size with a possible recall bias especially with regards to previous initial treatment history. Hence, large and more extensive studies are called for to examine the role of these risk factors in the emergence of MDR-TB.

CONCLUSION

The pilot Case control study conducted in TU- Shimla identified factors c0-with MDR-TB, which included illiteracy, poor socioeconomic status, poor ventilation, absence of BCG scar, history of initial default and initial treatment from a private practitioner. It can be inferred from these findings that Immunisation services and sensitisation of private practitioners regarding early diagnosis and treatment may be needed to be strengthened for better control of emergence and transmission of MDR-TB. Regulation of unabated sale of Anti-Tuberculosis drugs by private practitioners and chemists needs to be strictly implemented.

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Conflict of interest: None declared

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