Determinants of Drug Resistance Among Tuberculosis Patients: A Hospital-Based Case-Control Study

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Abstract:

Introduction: Tuberculosis is a public health concern for developing and low-income countries including India. The emergence of drug-resistant tuberculosis has added to the already existing economic and social burden. **Objective:** To assess the determinants of drug resistance among tuberculosis patients attending the tertiary care hospital **Method:** A hospital-based case-control study was carried out with sample size of 220 in a tertiary care institution, Dehradun, Uttarakhand, over the span of one year. Convenient sampling method was used to identify the cases and matched controls were selected with 1:1 ratio from patients visiting the outpatient department of the hospital. Data collection involved face-to-face interviews using a pretested structured questionnaire. The data were analyzed using SPSS for Windows. **Results:** The majority of study subjects belonged to the age group of 15-34 years. Higher numbers of DR-TB cases were found to have Diabetes mellitus (14.5%) as compared to controls (9.1%). The risk involved in development of drug resistance was approximately 4 times higher in TB contacts and it was statistically significant (p-value 0.027). Higher number of DR-TB cases reported having TB in the past (66.3%) as compared to controls (20%). The majority of cases (48.2%) were found to be underweight as compared to controls (10.1%). **Conclusion:** Risk of development of DR-TB among diabetic cases was 1.7 times more in comparison to controls. The risk of development of drug resistance was 7.8 times more in subjects who had TB in the past. Underweight cases were more susceptible to developing DR-TB (OR 4.9; p<0.0001).

Keywords: Case-control study, Determinants, Drug Resistance, Tuberculosis

Introduction:

Globally, Tuberculosis is included in the top ten causes of mortality.[1] It is a public health concern for developing and low-income countries including India. Although the overall mortality rate of TB is decreasing globally, this earlier incurable disease is now becoming curable because of anti-tubercular drugs; however, development of resistance against the anti-tubercular medicines is a big challenge for cure of the DR-TB. Globally, proportion of new cases of tuberculosis with drug resistance decreased from 4.0% (95% UI: 3.14.9%) in 2015 to 3.3% (95% UI: 2.64.0%) in 2022 and proportion of previously treated cases with drug resistance tuberculosis was 25% (95% UI: 1536%) in 2015 and 17% (95% UI: 1123%) in 2022. In 2022 the estimated number of incident cases of drug resistant in India was 110000 (95% UI: 89000-140000).[2] In 2020 in Uttarakhand state the estimated cases of tuberculosis was 275 per lac per year.[3] Emergence of Drug resistance Tuberculosis has added to the already existing economic

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and social burden of countries and thus is a major concern for global TB control efforts.[4] The diagnosis and treatment of the drug resistant TB is a challenge because of the high cost of treatment and poor patient compliance associated with multiple drug therapy.[5] In a country like India, it is difficult to measure the magnitude of the DR-TB because there are only limited laboratories available, which can conduct quality assured drug susceptibility testing.[6] The diagnosis and treatment of the drug resistant TB is a challenge because of the high cost of treatment and poor patient compliance associated with multiple drug therapy.[7] With the aim to assess the determinants of drug resistance among tuberculosis patients attending the tertiary care hospital, this study intends to play an important part in evaluating the risk factors leading to the development of drug resistance among tuberculosis patients to provide newer dimensions for timely intervention and prevention.

Methods:

Study design: A hospital-based case-control study

Place of study: A tertiary care institution, Dehradun, Uttarakhand.

Duration of study: 1 year; from January 2020 to December 2020.

Sample size: The sample size was calculated by using Epi-Info statistical software, considering 1:1 ratio of cases and controls. We assumed that 50% of the control group had been exposed to the risk factor under study. To detect a two-fold increase in risk, we were looking for exposure in the case group is significantly higher at least twice as high (i.e., 100%) compared to control group (50%). This assumption helps in determining the sample size required for the study to detect a meaningful difference between cases and controls with statistical confidence. The level of significance was taken as 5%, power of 80% and confidence level of 95%. Accordingly, the sample size came out to be 220 (110 cases and 110 controls).

Inclusion criteria

Cases: All DR-TB patients & both male and female aged 15 years and above

Controls: All TB patients & both male and female aged 15 years and above

Exclusion criteria

Parents of children aged 15 to 18 years and adult 18 years of age that were not willing to give consent to participate in the study, The patients who were suffering from severe mental illness, Bedridden patients needed emergency or ICU care

Operational Definitions[8]

Cases: Cases were drug-resistant pulmonary tuberculosis (DR-TB) patients, resistant to at least one of the first-line anti-tubercular drugs, diagnosed from an NTEP accredited laboratory during the study period. Cases were selected from the tertiary care hospital by using convenient sampling method.

Controls: Controls were new sputum smear-positive tuberculosis patients (Presumptively Non-resistant), diagnosed from NTEP accredited laboratory during the study period.

- The controls were selected from the same hospital
- One matched control was selected from the same hospital per case (1:1). Matching was done with respect to age, sex and socioeconomic status of the cases.

Study tools and Data collection

After getting the informed written consent or assent from the participants, data were collected using a validated and pretested structured questionnaire as a study tool. The questionnaire included questions about sociodemographic details, concurrent co-morbidities, past exposure to TB patients, and previous TB infections. It was created based on a thorough review of existing literature to ensure it met the studys needs. The study tool was rigorously validated and piloted to minimize information bias, with input from experts such as a chest physician, an epidemiologist, and a public health specialist (Cronbachs alpha = 0.8). After incorporating feedback and making necessary adjustments, the refined questionnaire was used to collect data from participants who met the inclusion criteria of the study.

Data entry and Statistical analysis

Data were entered into Microsoft Excel spread sheet and analyzed using SPSS version 26.0 for windows. Descriptive analysis was done, and proportions were also calculated. Data were compared using cross-tabulation to find strength of association and significance between the study variables. The confidence interval was taken as 95%. The p-value less than 0.05 was considered as statistically significant.

Results:

In this study almost half of the study participants in both the case and control groups belonged to the age group of 15-34 years and the male-female ratio among cases and controls was 1.4:1 and 2.4:1 respectively. Most of the respondents were Hindus (cases-86.4% and controls-90%) followed by Muslims (cases-10.9% and controls-8.2% respectively).

In the present study it was found that 63 cases (53.7%) and 68 controls (61.8%) were educated above high school level (education level above 10th standard/matriculation). Fifty-six cases (50.9%) and 58 controls (52.7%) were found to be unemployed. Most of the cases (97.3%) and controls (95.5%) belonged to the socioeconomic scale of middle class and above (as per modified BG Prasad scale)[9]. It was found that 61 cases (55.5%) and 74 controls (67.3%) had a joint family. The majority of cases (81.8%) and controls (83.6%) were staying with a family size of ≥4. As per the person per room criteria a few cases (21.3%) and controls (14.5%) were found to live in an overcrowded household. (Table 1)

Higher numbers of DR-TB cases were found to have Diabetes mellitus (14.5%) as compared to controls (9.1%) and risk of development of DR-TB among diabetic cases was 1.7 times more in comparison to controls. Similarly, cases with other chronic diseases had higher odds (2.6 times) of development of DR-TB. Co-existence of chronic obstructive pulmonary disease (COPD) was slightly more among the controls (3.6%) as compared to cases (2.7%). However, no statistical significance could be established between any of the coexisting morbidities and development of DR-TB. (Table 2)

Table 1: Distribution of Study Population according to Sociodemographic and Disease Profile (N= 308)

Variables	Cases (N=110)	Controls (N=110)	OR (95% CI)	p-value
Education				
High school or lower	47 (42.7%)	42 (38.2%)	1.2 (0.7-2.07)	0.49
Above high school	63 (57.3%)	68 (61.8%)		
Occupation				
Unemployed	56 (50.9%)	58 (52.7%)	0.92 (0.54-0.57)	0.78
Employed	54 (49.1%)	52 (47.3%)		
Socioeconomic Status (SES)				
Lower	3 (2.7%)	5 (4.5%)	0.58 (0.13-2.52)	0.47
Middle and above	107 (97.3%)	105 (95.5%)		
Family Type				
Joint	61 (55.5%)	74 (67.3%)	0.60 (0.350-1.04)	0.072
Nuclear	49 (44.5%)	36 (32.7%)		
Family Size				
≤3	20 (18.2%)	18 (16.4%)	1.13 (0.56-2.28)	0.72
≥4	90 (81.8%)	92 (83.6%)		
Overcrowding				
Yes	24 (21.8%)	16 (14.5%)	1.6 (0.817-3.291)	0.16
No	86 (78.2%)	94 (85.5%)		

Table 2: Distribution of study subjects according to concurrent co-morbidities

Variables	Cases (N=110)	Controls (N=110)	OR (95% CI)	p-value
Diabetes Mellitus (DM)				
Yes	16 (14.5%)	10 (9.1%)	1.7 (0.73-3.93)	0.21
No	94 (85.5%)	100 (90.9%)		
COPD				
Yes	3 (2.7%)	4 (3.6%)	0.74 (0.16-3.40)	0.70
No	107 (97.3%)	106 (96.4%)		
Any Other Chronic Disease*				
Yes	5 (4.5%)	2 (1.8%)	2.6 (0.48- 13.55)	0.24
No	105 (95.5%)	108 (98.2%)		

* Chronic kidney and liver diseases

Table 3 Distribution of study subjects according to BMI (Asia Pacific classification)[10]

BMI Classification	Cases (N=110)	Controls (N=110)	$\chi 2$, p-value
Underweight (<18.5 kg/m^2)	53 (48.2%)	11 (10.0%)	51.319, <0.0001
Normal (18.5-22.9 kg/m^2)	40 (36.4%)	41 (37.3%)	
Overweight (23.0-24.9 kg/ m^2)	5 (4.5%)	28 (25.5%)	
Obese ($\geq$25 kg/m^2)	12 (10.9%)	30 (27.2%)	

The study subjects having positive history of contact with TB patients were more likely to develop drug resistant TB. The risk involved in development of drug resistance was approximately 4 times higher in TB contacts and it was statistically significant (p-value 0.027).

It was seen that higher number of DR-TB cases reported having TB in the past (66.3%) as compared to controls (20%). The risk of development of drug resistance was 7.8 times more in subjects who had TB in the past.

The majority of cases (48.2%) were found to be underweight as compared to controls (10.1%). Odds ratio was calculated by taking normal as reference category and it was found that cases who were underweight had 4.9 times higher risk of developing DR-TB as compared to controls and it was statistically significant (p-value <0.0001). (Table 3)

Discussion:

A hospital-based case-control study was carried out with equal number of cases and control by involving a total of 220 participants to find out the determinants of drug resistant among tuberculosis patients. In the present study 47 cases (42.7%) and 42 controls (38.2%) were educated up to high school level. Twenty cases (18.2%) and 18 controls (16.4%) had $\leq$3 membered family and a few participants (21.8% cases and 14.5% controls) found to be living under overcrowding condition. The risk of getting drug resistant tuberculosis among participants with education level of high school or lower is 1.2 times as compared with participants with education level of above high school. This finding supports the need of higher education of the people which would help them to be aware and more sensitized about development of drug-resistant tuberculosis.

Odds of staying of participants in the family size of $\leq$3 were 1.13 times among the drug-resistant tuberculosis cases compared with controls. The risk of getting drug-resistant tuberculosis in participants who were residing in a house with overcrowding was 1.6 times as compared with participants not staying in an overcrowded household. No significant difference (p>0.05) between the case and control groups were observed as per education level, occupation, socioeconomic status, family type, family size and

overcrowding. Almost similar findings were reported by various studies.[11-14] In contrast, other studies reported that lower socioeconomic status and family size ≥3 was associated with the development of drug-resistant tuberculosis.[15-17]

Diabetes was present as comorbidity in 14.5% of cases and 9% of the controls in the present study and risk of development of drug-resistant tuberculosis among diabetic cases was 1.7 times more in comparison to controls. Similar findings were also reported by various studies.[14,17] In contrast, a study reported negative association of diabetes with drug-resistant tuberculosis (OR 0.82, 95% CI 0.35-1.91) and this finding would be due to their insufficient data available about the diabetes cases.[18]

In the present study it was found that participants having positive history of contact with TB or DR-TB patients were more likely to develop drug resistant TB. The risk involved in development of drug resistance was approximately 4 times higher in TB contacts and it was statistically significant. Mazta et al.[12] also reported the positive association between contact with TB patients and development of drug resistance. In contrast, a few studies could not establish association between contact with TB patients and development of drug resistance.[13,14] It was found that the majority of DR-TB cases (48.2%) were found to be underweight and risk of development of DR-TB was 4.9 times higher among the cases as compared to controls. In a study by Kumar A et al.[19] almost 69% of DR-TB cases were undernourished. Basu R et al.[20] also reported that majority of DR-TB (56.6%) were underweight. Therefore to reduce the incidence of DR-TB, it is important to prevent and treat undernutrition especially who are suffering from tuberculosis.

Limitations:

This study was done during the covid-19 pandemic and because of this sample size for recruiting cases and control in the ratio of 1:1. The study subjects and their attendants were apprehensive to talk to the investigator due to the pandemic.

Conclusion:

Higher numbers of DR-TB cases were found to have Diabetes mellitus (14.5%) as compared to controls (9.1%). Risk of development of DR-TB among diabetic cases was 1.7 times more in comparison to controls. Participants having positive history of contact with TB or DR-TB patients were more likely to develop drug resistant tuberculosis. The risk of development of drug resistance was 7.8 times more in subjects who had tuberculosis in the past. Underweight cases were found to be more susceptible to develop DR-TB (OR 4.9; $p<0.0001$).

Recommendations:

Early diagnosis and robust treatment of diabetes while diagnosing tuberculosis may reduce the incidence of drug resistance tuberculosis. With proper monitoring of anti-tubercular drug intake among the TB positive patient and reducing the incidence of underweight by providing them good nutrition, cases of DR-TB can be reduced. Further analytical study or randomized trials needed to provide better evidence regarding determinants of DR-TB.

Declaration:

Funding: Nil

Conflicts of interest: Nil

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