



## Case Report

## Effects of diabetes mellitus on retreatment of Tuberculosis: A multi-centered case-control study from Bangladesh

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## ABSTRACT

**Objectives:** Several studies suggested that diabetes mellitus (DM) worsens the tuberculosis (TB) treatment outcome. But information regarding the association of DM with retreatment of TB is very scarce in Bangladesh. Present study aimed to assess the effects of DM on retreatment of TB.

**Methods:** This case-control study was conducted among 254 patients (127 cases and 127 controls) from January 2022 – December 2022. Patients were recruited by purposive sampling from 92 centers of the Diabetic Association of Bangladesh (BADAS). Data were collected by face-to-face interview and record reviewing with the help of semi-structured questionnaire and checklist respectively. Quality of data was maintained in all stages of the study. Data were analyzed by using IBM SPSS software. Informed written consent was taken from each patient prior to the study. Ethical issues were maintained strictly.

**Results:** Present study matched the age and sex of cases and controls. The study revealed that majority of case (89.0) and controls (97.6) were married. Among cases 78.0 % had DM and among controls 64.6 % had DM. Among diabetic patients, 78.8 % cases' and 64.6 % controls' HbA1C level was not within normal range. The study found that, the number of episodes of previous TB (AOR = 3.088,  $p = 0.019$ ), presence of DM (AOR = 2.817,  $p = 0.012$ ) and uncontrolled HbA1C level (AOR = 2.500,  $p = 0.028$ ) were independently associated with retreatment of TB.

**Conclusion:** The study found that presence of DM, uncontrolled HbA1C level and multiple episodes of previous TB were the risk factors for retreatment of TB. So, a separate guideline for treatment of TB-DM patients should be established to prevent retreatment cases.

## 1. Introduction

As a reemerging disease, tuberculosis (TB) has created its own position high among the communicable disease conditions and in double burden disease situation, TB has poured much burden for the developing countries. According to World Health Organization (WHO), TB is a major public health threat and it is estimated that more than 10 million people fall ill with tuberculosis every year and up to 2022 tuberculosis was the second leading cause of death from an infectious agent [1]. Moreover, the incidence of recurrent TB in those who completed previous treatment can be 30 times higher than the incidence of TB in the

general population [2]. Globally among all TB cases, the majority of cases were reported in the South-East Asia Region of WHO, and Bangladesh is one of the eight countries that accounted for two-thirds of the global burden of TB [3].

Recurrence of active TB after treatment can be due to relapse of infection with the same strain or reinfection with a new strain of Mycobacterium tuberculosis [4]. A host of factors can influence the likelihood of recurrent TB, including the level of adherence to treatment, the severity of the original episode, the patient's immune status, and the risk of reinfection. In a low incidence setting, the majority of cases of recurrent TB would be expected to be due to reactivation (caused by a

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relapse of a previously treated TB episode) [4].

Diabetes mellitus (DM) is considered as a global epidemic of recent times. The total number of people with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030 [5]. Globally, the prevalence of DM is increasing at a dramatic rate; in Southeast Asia, by 2045, 152 million people will be suffering from Diabetes [5]. Bangladesh is, particularly in a daunting challenge. According to IDF diabetic atlas, in 2021, the estimated prevalence of diabetic cases was 12.5 % among 20 – 79 years age-group while 44.4 % of the actual diabetic patients remain undiagnosed [6].

As globalization occurs, the dual burden of communicable and non-communicable diseases occurs simultaneously in low- and middle-income countries [7]. The distinctive example of this dual burden is tuberculosis and diabetes mellitus (TB-DM). Patients who are affected by both TB and DM and whose glycemic control is poor, experience poor TB treatment outcomes, for example, treatment failure and death than those with non-diabetic patients [8,9]. From these, TB patients who fail or default from their first-time treatment therapy, their relapse of TB occur and require retreatment regimen [10]. So, retreatment TB patients are those who are getting treatment again for relapse, failure, or loss to follow up. Retreatment patients have a lower better healing rate than new TB, and experience more side effects in the course of treatment with second-line drugs of TB [11]. Further, TB treatment failure or relapse is associated with drug resistance [12] and interference during treatment is very known for TB retreatment [13]. As a deliberating medical situation, retreatment cases express an immense mortality rate [14,15,16]. Retreatment cases are imposed as a major challenge for the TB control programs. Compared to new cases, retreatment cases require more time and concern; and also complicated treatment regimens. Treatment outcome of retreatment case are poor and have a high risk of death [17,18].

As there is scarce data regarding retreatment TB cases among diabetic patients in Bangladesh, Present study aimed to assess the effects of DM on retreatment of TB.

## 2. Methods

### 2.1. Study design

This case-control study was conducted in 92 centers of the Diabetic Association of Bangladesh (BADAS), from January 2022 – December 2022.

### 2.2. Study population

The study population was all the patients aged  $\geq 18$  years who attended the selected DOTS centres for diagnosis of TB during the data collection period and who had a previous TB registration number or had a history of TB at least one time within the last 15 years.

#### 2.2.1. Retreatment

In this study retreatment cases means all the relapse cases, treatment failure, and loss to follow-up cases

#### 2.2.2. Cases

In this study, patients who were diagnosed as TB patients and who had a previous TB registration number or had a history of TB at least one time within the last 15 years were regarded as cases.

#### 2.2.3. Controls

In this study, patients who attended the DOTS centre for TB testing but were not diagnosed as TB patients and who had a previous TB registration number or had a history of TB at least one time within the last 15 years were regarded as controls. Controls age and sex were matched with cases

### 2.3. Sample size and sampling technique

In this study, 127 retreatment TB patients were included as cases and 127 retreatment presumptive TB patients were included as controls. Each patient was selected by purposive sampling technique according to the inclusion and exclusion criteria of the study. At first cases were identified from the 92 centres of the Diabetic association of Bangladesh and their data were collected. After that controls were selected from the same centres by matching their age and sex.

### 2.4. Data collection methods and instruments

Data were collected by face-to-face interview and reviewing medical records. Information on background characteristics, comorbidities and DM related information were collected by a pre-tested semi-structured questionnaire. A checklist was used to collect information from patients' medical record. All data were collected by trained professionals from the diabetic centers. Total 539 patients were identified as presumptive TB patients who had previous history of TB. Five (5) patients aged  $< 18$  years and 81 patients who were unwilling to participate were excluded from the study. Total 453 patients were selected for evaluation. Among the tested participants, 127 were identified as retreatment TB cases by purposive sampling technique. By matching age and sex another 127 controls were identified, see Fig. 1. After taking written consent from all selected patients, data were collected by face-to-face interview. Other relevant information was collected by reviewing patients' records.

### 2.5. Data management

Data were checked and verified at both field and central levels to ensure quality. Data were kept safely under the control of the principal investigator. All data were checked thoroughly to verify the relevancy and consistency of data. Incomplete and missing data were excluded. Data were coded, categorized, cleaned, and entered into SPSS software (Version 25.0). Double entry of data was performed to control the quality of data.

### 2.6. Statistical analysis

Data analysis was done using SPSS software. Categorical variables were presented as frequencies and percentages. Comparisons between cases and controls were made with the Chi-square test/Fisher's exact test. A conditional logistic regression analysis was done with all significant variables identified by chi-square tests to find the strength of association. Adjusted odds ratios (AORs) and 95 % confidence intervals were estimated, and a  $p$ -value  $< 0.05$  was considered significant. All the statistical tests were two-sided and were performed at significance level of  $\alpha = 0.05$ .

## 3. Results

Present study compared the background characteristics between cases and control. Study found that there was a significant association between marital status and retreatment of TB ( $p$ -value = 0.012). There was no significant association between any other background characteristics (e.g., Highest level of education, occupation, number of family members, monthly family income, BMI, comorbidity and history of tobacco use) and retreatment of TB (Table 1).

Among cases 84.3 % patients and among controls 93.7 % patients had history of only one (1) episode of previous TB. Retreatment of TB was significantly associated with episodes of previous TB ( $p$ -value = 0.016). Retreatment of TB was also found associated with taking TB drugs irregularly ( $p$ -value = 0.007). There was no significant association between retreatment of TB and types of TB in 1st episode and treatment duration in 1st episode (Table 2).

Present study found that 78.0 % cases and 64.6 % controls had DM.

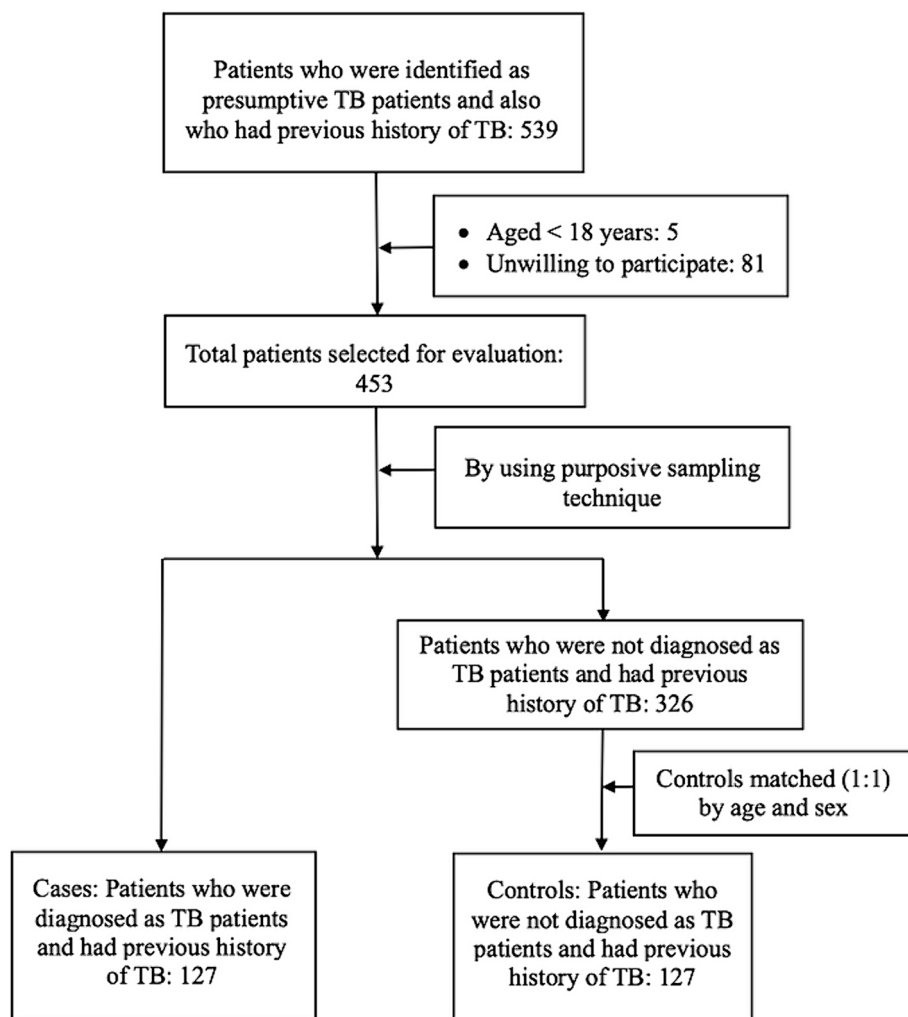


Fig. 1. Selection procedure of cases and controls.

Retreatment of TB was significantly associated with presence of DM ( $\rho$ -value = 0.018). Retreatment of TB was also significantly associated with level of HbA1C ( $\rho$ -value = 0.034) (Table 3).

Conditional logistic regression analysis of factors related to retreatment of TB found that number of episodes of previous TB and presence of DM were two independent risk factors for retreatment of TB. Patients who had more than one (1) episodes of previous TB had 3.088 times higher chance of developing retreatment cases than patients who had only one (1) episodes of previous TB (AOR = 3.088,  $\rho$  = 0.019). Also, diabetic patients had 2.817 times higher chance of developing retreatment TB than non-diabetic patients (AOR = 2.817,  $\rho$  = 0.012).

Univariable logistic regression analysis also found that diabetic patients whose target of HbA1C level was not reached had 2.5 times higher chance of developing retreatment cases than whose HbA1C target was reached (AOR = 2.500,  $\rho$  = 0.028) (Table 4).

#### 4. Discussion

Patient with DM had increased risk of developing TB and also had a higher rate of treatment failure and death even with appropriate TB treatment. But information regarding the association of DM with retreatment of TB is very scarce in Bangladesh. This study aimed to assess the effects of DM on retreatment of TB. In this study, 127 cases were diagnosed as retreatment TB cases and included as cases. On the other hand, another 127 patients with previous history of TB or with a registration number of TB but were not diagnosed as retreatment TB

cases after being tested were considered as controls.

Among cases, majority of the participants' (67.7 %) educational level were illiterate/primary. Among controls, 62.2 % were illiterate or having primary level of education. Present study revealed that there was no significant association between level of education and retreatment cases. But a study conducted in Vietnam found that the level of education was low among the retreatment TB cases [19]. Illiteracy makes the people more vulnerable to develop retreatment TB due to lack of awareness.

Regarding marital status, among both cases and controls, majority were married (89.0 % vs. 97.6 %). Conditional logistic regression analysis found that there was no significant association between marital status and retreatment cases. Another study conducted in Turkey also revealed that there was no association between marital status and retreatment TB cases [20]. So both the studies confirmed that marital status is not a significant risk factor for retreatment of TB.

Among the cases, majority of them (41.7 %) were malnourished or underweight but in controls, majority (42.5 %) were in normal health condition. Though it was not found significantly associated with retreatment TB cases, a study conducted in London [21] found significance and this indicates that BMI might have a strong association of reactivation of TB and might be a potent risk factor for recurrence of TB. Further large-scale studies need to be conducted to verify the result.

Regarding number of episodes of previous TB, among both cases and controls, majority (84.3 % vs 93.7 % respectively) had one episode of TB. Present study found that there was higher chance of retreatment

**Table 1**  
Comparison of cases and controls by background characteristics.

Attributes		Case f (%)	Control f (%)	p-value ( $\chi^2$ test)
Highest level of education	Illiterate/primary	86 (67.7)	79 (62.2)	0.650
	Secondary	26 (20.5)	31 (24.4)	
	HSC and above	15 (11.8)	17 (13.4)	
Occupation	Service	18 (14.2)	21 (16.5)	0.385
	Business	36 (28.3)	23 (18.1)	
	Unemployed	10 (7.9)	9 (7.1)	
	Homemaker	36 (28.3)	40 (31.5)	
	Others*	27 (21.3)	34 (26.8)	
Marital status	Married	113 (89.0)	124 (97.6)	0.012 (Fisher's exact test)
	Unmarried	11 (8.7)	2 (1.6)	
Number of family member (in persons)	Ever married**	3 (2.4)	1 (0.8)	0.277 (Fisher's exact test)
	2–5	91 (71.7)	88 (69.3)	
	6–10	34 (26.8)	32 (25.2)	
Monthly family income (In Tk.)	11–15	2 (1.6)	7 (5.5)	0.383
	5000 – 25,000	99 (78.0)	101 (79.5)	
	26,000 – 50,000	18 (14.2)	21 (16.5)	
	≥ 51,000	10 (7.9)	5 (3.9)	
BMI (Kg/m <sup>2</sup> )***	Underweight (<18.5)	53 (41.7)	35 (27.6)	0.060
	Normal (18.5 – 22.9)	45 (35.4)	54 (42.5)	
	Overweight/Obese (>22.9)	29 (22.8)	38 (29.9)	
		15 (11.8)	20 (15.7)	
Comorbidity	Yes	112 (88.2)	107 (84.3)	0.467
	No	57 (44.9)	53 (41.7)	
History of tobacco use	Yes	70 (55.1)	74 (58.3)	0.612
	No			

f = frequency, % = Percentage, \*Other occupations were farmer, day labourer, student etc. \*\*Ever married: Separated/divorced/widowed/widower. \*\*\*BMI: Body mass index (Asian scale).

**Table 2**  
Comparison of cases and controls by factors associated with retreatment of tuberculosis.

Attributes		Case f (%)	Control f (%)	p-value
Episodes of previous TB	1 episode	107 (84.3)	119 (93.7)	0.016
	>1 episode	20 (15.7)	8 (6.8)	
TB Type (1st Episode)	PTB	112 (88.2)	113 (89.0)	0.844
	EPTB	15 (11.8)	14 (11.0)	
Treatment Duration (1st Episode) (In months)	6 months	111 (87.4)	113 (89.0)	0.697
	≥ 6 months	16 (12.6)	14 (11.0)	
Taking of TB drugs regularly	Yes	119 (93.7)	127 (100.0)	0.007
	No	8 (6.3)	0	

f = frequency, % = Percentage, PTB: Pulmonary Tuberculosis, EPTB: extra-pulmonary tuberculosis.

**Table 3**  
Comparison of cases and controls by Diabetes factors associated with retreatment of tuberculosis.

Attributes		Case f(%)	Control f(%)	p-value
Presence of DM	Yes	99 (78.0)	82 (64.6)	0.018
	No	28 (22.0)	45 (35.4)	
HbA1C (n = 181)	Target Reached	21 (21.2)	29 (35.4)	0.034
	Target not Reached	78 (78.8)	53 (64.6)	

f = frequency, % = Percentage, HbA1C: Glycosylated Haemoglobin, Target reached: <7.0 mmol/L, Target not reached: ≥7.0 mmol/L.

cases among patients who had history of more than one episode of previous TB. Multiple occurrences of TB previously make people immunocompromised and make them more prone to develop TB repeatedly. A study of Turkey had found similar findings [20].

Regarding diabetes mellitus, among both cases and controls, majority patients were diabetic (78.0 % vs. 64.6 %). Present study established DM as an independent risk factor for developing retreatment of TB. In this study, uncontrolled HbA1C level was found significantly associated with retreatment cases of diabetic TB patients. In Taiwan [22], DM was found associated with relapse TB cases.

## 5. Conclusion

This study findings could help to develop more effective strategies to prevent retreatment cases in patients who has diabetes. Identification of the association of diabetes with the risk of retreatment TB can help clinical decision towards the optimal duration of treatment, thereby reducing the risk of retreatment. The study also found that more than one episode of previous TB had higher chance of being retreatment cases. So, the patients who already completed a single regimen of TB treatment should have lifestyle modification and patient with DM should control their blood sugar level within normal range. It would also create a base for further research to better understand the mechanisms by which DM leads to retreatment TB cases.

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## Ethical approval

Ethical approval was obtained from the ethical review committee of the BADAS before commencement of the study. Informed written consent was taken from all patients before data collection. Privacy and confidentiality of data were maintained strictly.

## CRedit authorship contribution statement

**Mohammad Afsarul Habib:** Writing – original draft, Visualization, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Kaniz Afrin:** Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Syeda Sumaiya Efa:** Writing – original draft, Visualization, Formal analysis, Data curation. **Md. Delwar Hossain:** Visualization, Investigation, Data curation. **Md. Rafiqul Islam:** Visualization, Investigation, Data curation. **Md. Mahbubur Rahman:** Visualization, Investigation, Data curation. **Nasreen Islam:** Supervision, Methodology, Conceptualization. **Farhana Afroz:** Supervision, Methodology, Conceptualization. **Muhammad Abdur Rahim:** Supervision, Methodology, Conceptualization. **Mohammad Delwar Hossain:** Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

**Table 4**  
Conditional logistic regression analysis of selected attributes by retreatment of TB.

Attributes		Univariable model			Multivariable model		
		COR	95 % CI	Sig	AOR	95 % CI	Sig
Marital Status	Ever Married*	Reference			Reference		
	Married	0.333	0.035 – 3.205	0.341	0.238	0.023 – 2.491	0.231
	Unmarried	3.333	0.157 – 70.906	0.440	3.629	0.153 – 85.922	0.425
Episodes of previous TB	1 episode	Reference			Reference		
	>1 episode	2.714	1.141 – 6.457	0.024	3.088	1.204 – 7.921	0.019
Presence of DM	No	Reference			Reference		
	Yes	2.133	1.155 – 3.939	0.015	2.817	1.402 – 5.661	0.012
HbA1C	Target Reached	Reference			–		
	Target not Reached	2.500	1.101 – 5.676	0.028	–		

COR: Crude Odds Ratio, CI: Confidence Interval, AOR: Adjusted Odds ratio, Sig: Significance, \*Ever married: Ever married: Separated/divorced/widowed/widower, HbA1C: Glycosylated Haemoglobin, Target reached: <7.0 mmol/L, Target not reached: ≥7.0 mmol/L.

### 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.

### Data availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

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