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# Frequency of Lower Lung Field Tuberculosis in Diabetes Mellitus Patients Attending Tertiary Care Hospital in Bangladesh: A Cross-Sectional Study

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## ABSTRACT

**Background and Aims:** People who have diabetes mellitus (DM) are thought to be more susceptible to pulmonary tuberculosis (PTB). Several published comparative investigations have reported that chest x-ray images from PTB with DM are considered atypical due to their frequent involvement of the lower lung field (LLF). This study aimed to investigate the frequency of lower lung field tuberculosis (LLF-TB) in DM and the risk factor of DM for the development of TB.

**Methods:** This study was a cross-sectional study. PTB was diagnosed by positive sputum acid-fast bacilli (AFB),/Culture,/Gene Xpert MTB/RIF, and DM, which was proven by taking oral hypoglycemic drugs or receiving insulin at the time of hospital admission. Extrapulmonary tuberculosis and seropositive human immunodeficiency virus (HIV) were excluded from this study. A chest x-ray posterior-anterior (P/A) view was done to assess the frequency and patterns of lung involvement. Logistic regression analysis was performed to evaluate the risk factor of DM for the development of TB.

**Results:** A total of 117 PTB-DM participants were studied in this study. The mean age and frequency of isolated LLF-TB were $53.17 \pm 14.38$ years and 20.5%, respectively. The prevalence of LLF-TB and other radiological patterns were statistically significantly correlated with smear positivity (83.3% vs. 20.4%), erythrocyte sedimentation rate (ESR) > 50 mm (95.8% vs. 16.1%), and HbA1c > 7 (79.2% vs. 16.1%). Regression analysis showed that the odds ratio (OR) was 6.81 and 3.93 for DM and age (> 40 years) for the development of LLF-TB ($p < 0.05$).

**Conclusion:** The frequency of LLF-TB among PTB DM patients was around 1/5th. The development of LLF-TB was substantially associated with DM and age greater than 40 years.

## 1 | Introduction

Worldwide, more than two billion people have *Mycobacterium tuberculosis* (MTB) infections, among which more than 11 million have active tuberculosis (TB), and the total number of demises and incident cases that can be attributed to them each year is increasing globally [1]. Patients with diabetes have historically had a high incidence of tuberculosis. At first, the link between diabetes mellitus (DM) and pulmonary tuberculosis (PTB) was described by Howard Root (a physician at the Deaconess Hospital in Boston, MA, USA) in 1934 before anti-mycobacterial medications were developed. The prevalence of DM in urban populations is increasing, and it is associated with an increase in smear-positive PTB (15.2%) compared to rural people [2].

Due to the accelerating rate of globalization, noncommunicable diseases (NCDs) are now contributing to the ailment load in the least developed and developing states, in addition to communicable diseases. The co-existence of NCDs and communicable diseases increases the chance of manifestations of other illnesses and hampers treatment outcomes. TB and DM comorbidity is one inimitable example of this combo.

In 2020, there were an anticipated 10 million new cases of TB worldwide and/or 127 instances for every 100,000 people. Additionally, there were about 1.5 million TB-related deaths [3]. The number of adults with diabetes is expected to climb, accounting for 537 million cases of the disease in 2021 and 783 million by 2045 [4]. The prevalence of DM was 18% in patients with PTB, while the prevalence of DM was 8% in patients with suspected PTB [5].

DM is independently linked with an unfavorable result of PTB. When comparing TB in DM patients to TB in non-DM patients, it has been shown that TB in DM individuals has fewer sputum-positive cases, more cavitary lesions, and fewer symptoms and signs [6]. DM increases the chance of death in tuberculosis patients by two times compared to those who do not have DM [7]. Compared to TB patients with better glycemic control, people with diabetes who have uncontrolled blood sugar have worse treatment results from TB, including treatment failure and mortality [8, 9].

In Southeast Asia, where NCDs account for almost 60% of deaths, the prevalence of DM poses one of the biggest dangers to the least developed and developing nations [10]. In this regard, Bangladesh is no exception. Prior research conducted in Bangladesh reveals that between 2005 and 2011, the prevalence of DM increased (rising from 2% to 8% in rural regions and from 8% to 15% in urban areas) [11, 12]. The fact that the incidence of diabetes has increased so much in just 6 years indicates that there is a greater chance that TB will be more common in the general population because DM increases an individual's vulnerability to developing TB. A systemic review by Jeon and Murray found that the incidence of TB is two to five times higher in DM patients compared to non-DM [13]. According to the World Health Organization's (WHO) Global Tuberculosis Report 2015, TB prevalence in Bangladesh is approximately 404 per 100,000 [14]. Bangladesh is already facing challenges in TB prevention due to an increasing number of MDR-TB patients. Furthermore, as was previously mentioned, a condition like diabetes raises the likelihood of TB, especially MDR-TB. Thus, attempts to control tuberculosis are threatened.

There is controversy regarding patterns of pulmonary involvement in DM. It has been noted that individuals with DM who have PTB have atypical or uncommon radiological characteristics. Several authors have reported an increased frequency of lower lung area involvement in DM [15, 16]. Moreover, PTB DM patients have been reported to have a higher frequency of multilobar involvement. These radiological dissimilarities in DM have been ascribed to cell-mediated immunological abnormalities and polymorphonuclear cell dysfunction [17]. DM declines the function of lymphocytes and a reduction in the number of monocytes and macrophages with abnormalities in their chemotactic and phagocytic actions. Additionally, diabetes also produces a dysfunction of polymorphonuclear leukocytes, with a diminution in their bactericidal activity [18].

Several authors have demonstrated a higher rate of occurrence of cavitation in PTB with DM [15, 19, 20]. Conversely, there were no radiological differences between the PTB with DM and PTB without DM [16, 21]. Although post-primary TB mostly affects the upper zone of the lung, however lower zone involvement is not uncommon. In high TB-burden countries like Bangladesh, lower lung zone TB may create confusion and is frequently misdiagnosed as pneumonia, lung abscess, bronchial carcinoma, and bronchiectasis. This causes delayed diagnosis and treatment, resulting in morbidity and mortality. Therefore, this study was designed to explore the following

**TABLE 1** | Demographic profile of the study subjects ($N = 117$).

| Variables | Isolated lower lung field opacity ($n = 24$) | Other radiological patterns ($n = 93$) | $p$ value |
|---|---|---|---|
| Age (years) | | | |
| ≤ 20 | 0 (0.0) | 7 (7.6) | 0.203 |
| 21–40 | 4 (16.7) | 26 (28.3) | |
| 41–60 | 16 (66.7) | 43 (46.7) | |
| > 60 | 4 (16.7) | 16 (17.4) | |
| Mean ± SD | 53.17 ± 14.38 | 46.42 ± 14.03 | 0.039 |
| Gender | | | |
| Male | 20 (83.3) | 73 (78.5) | 0.601 |
| Female | 4 (16.7) | 20 (21.5) | |
| Duration of DM | | | |
| < 10 years | 16 (66.7) | 65 (69.9) | 0.843 |
| 10–20 years | 7 (29.2) | 26 (28.0) | |
| > 20 years | 1 (4.2) | 2 (2.2) | |
| Smoking history | | | |
| Smoker | 14 (58.3%) | 41 (44.1%) | 0.212 |
| Duration of smoking | | | |
| < 5 years | 1 (7.1) | 6 (14.6) | 0.327 |
| 5–10 years | 2 (14.3) | 12 (29.3) | |
| > 10 years | 11 (78.6) | 23 (56.1) | |
| Treatment of DM | | | |
| Diet and exercise | 0 (0.0) | 5 (5.4) | 0.057 |
| 1 plus OHA | 9 (37.5) | 14 (15.1) | |
| 1 plus Insulin | 13 (54.2) | 57 (61.3) | |
| 1 plus OHA plus Insulin | 2 (8.3) | 17 (18.3) | |

Abbreviations: 1 = Diet and exercise; OHA = oral hypoglycemic agent (including euglycemic drugs).

aims: (1) frequency of LLF-TB in DM and (2) risk factors of DM for the development of TB.

## 2 | Methods

### 2.1 | Study Design, Sample Size, and Population

We conducted a cross-sectional, observational study in the Department of Respiratory Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU) between March 2019 and February 2020. $N = z^2pq/d^2$ equation was used to calculate sample size (Here, $N$ = estimated sample size, $z = 1.96$ [in 95% CI] value of standard normal deviation, $p$ = frequency of lower lung TB in DM-TB patient [19%] according to Perez-Guzman [15], $q = (100 - 19) = 81$, and $d$ = marginal error [5%]). Therefore, the total sample size was 236. Initially, 304 TB-DM patients were evaluated; 117 were finally selected for this study. Diabetic patients were included based on already getting antidiabetic drugs like insulin or oral hypoglycemic drugs. TB patients were included based on positive sputum acid-fast bacilli (AFB) results, positive Gene X-pert results, computed

**TABLE 2** | Chest x-ray findings of the study subjects ($N = 117$).

| Chest x-ray | Frequency ($n$) | Percentage (%) |
|---|---|---|
| Unilateral upper lung field opacity | 8 | 6.9 |
| Bilateral upper lung field opacity | 2 | 1.7 |
| Both upper and lower lung field opacity | 45 | 38.5 |
| Pleural effusion | 4 | 3.4 |
| Opacity plus pleural effusion | 8 | 6.8 |
| Isolated lower lung field opacity | 24 | 20.5 |
| Isolated cavity | 5 | 4.3 |
| Cavity plus opacity | 6 | 5.1 |
| Both upper and lower lung field opacity with cavity with pleural effusion | 10 | 8.5 |
| Cavity and both upper and lower lung field opacity | 2 | 1.7 |
| Inflammatory/bronchiectasis/nodular change | 3 | 2.6 |

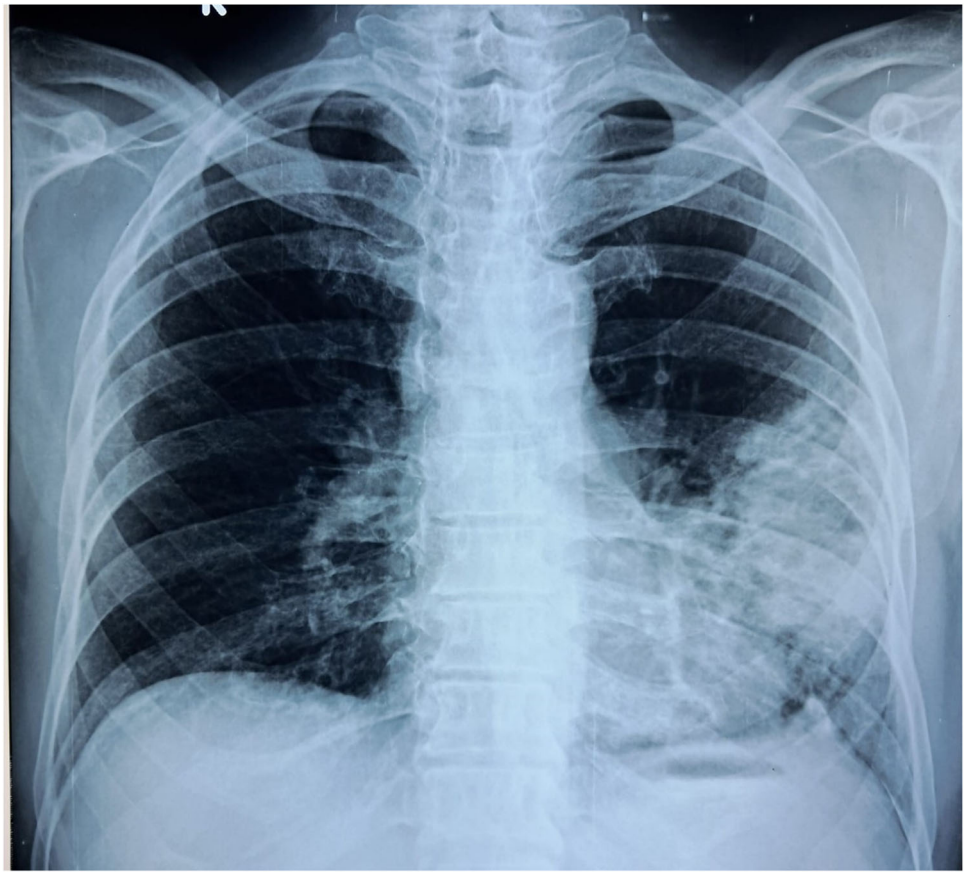

**FIGURE 1** | Chest x-ray P/A view showing consolidation at the left lower lung field.

tomography (CT)-guided fine needle aspiration cytology (FNAC) from lung lesion showed caseating granulomatous inflammation, and positive Gene X-pert on bronchoalveolar lavage (BAL) fluid on Fiberoptic bronchoscopy. An X-ray chest (CXR) posterior-anterior (P/A) view was performed to assess the frequency and identification of radiological patterns. An expert radiologist reviewed the radiological patterns of the chest x-ray.

Lower lung field tuberculosis (LLF-TB) on chest x-ray was defined as an area lying below the horizontal arbitrary line drawn across the hila on chest x-ray P/A view. Radiological patterns of nodular opacity, pleural effusion, bronchiectasis, consolidation, cavitation, and inflammatory change were recorded. Extra-pulmonary TB without pulmonary involvement, and immunocompromised patients other than diabetes (e.g., CKD, malignancy, taking immune-suppressive medicines, or taking corticosteroids for more than 6 weeks recently) were excluded from this study.

## 2.2 | Statistical Analysis

After collection, the data were recorded, and statistical analysis was done on the statistical package for the social sciences (SPSS)-23 version. Demographical variables of age and sex were presented as frequency and percentage. Laboratory variables like chest x-ray, sputum for AFB, Gene X-pert/RIF, erythrocyte sedimentation rate (ESR), and glycated hemoglobin ($HbA_1C$) were expressed as mean and standard deviation. X-ray chest P/A view results and the number of participants with TB-DM were presented as percentage and frequency. ESR and $HbA_1C$ were compared using an unpaired Student's *t*-test; the chi-square test analyzed the duration of diabetes and smoking. The level of significance in the smear AFB status and Gene X-pert status in LLF-TB was assessed using Fisher's Exact test. *p* Values below 0.05 were regarded as statistically significant. Logistic regression analyses were performed to evaluate the risk factor of DM for the development of TB.

## 2.3 | Ethical Approval

The research protocol of this study was submitted to the BSMMU, Dhaka institutional review board before the commencement, and the proposal was approved at the 176th meeting (BSMMU/2019/2229). The study's goals, methods, and purpose were explained to all participants clearly and concisely. Before sample collection, informed consent was obtained from each participant verbally and in writing.

# 3 | Results

Table 1 shows the demographic variables of the participants. In our study, The participants' mean age was $53.17 \pm 14.38$ years,

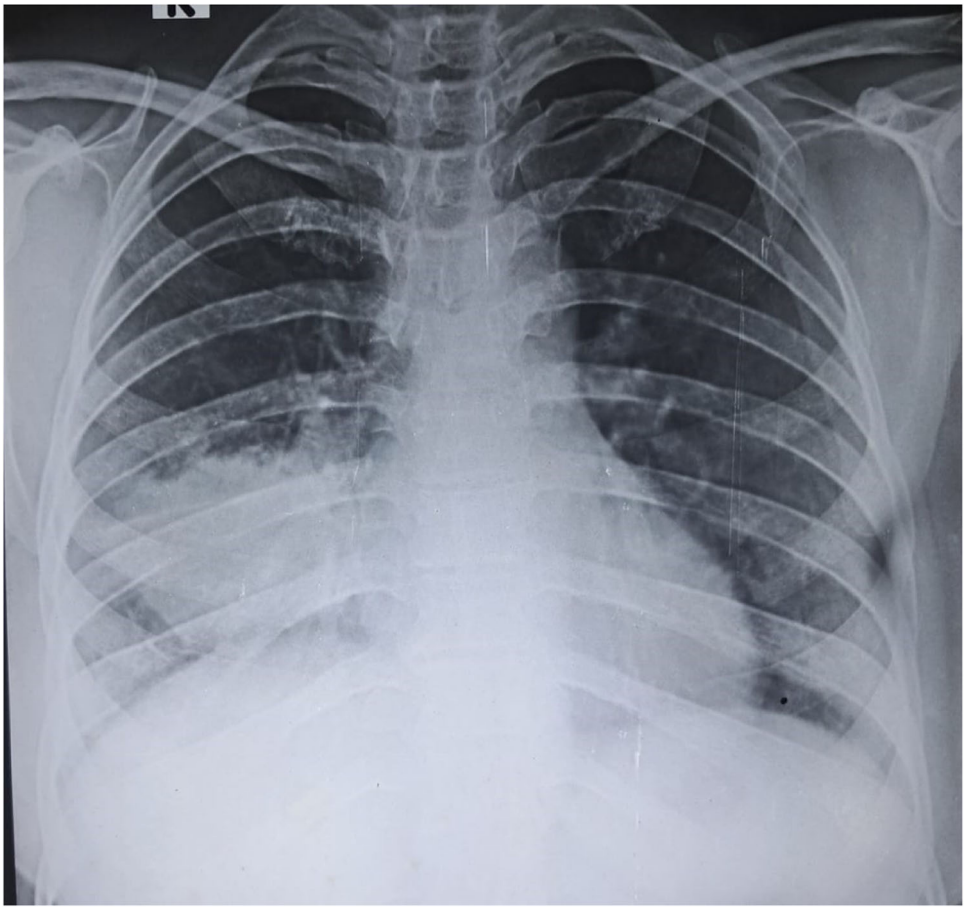

**FIGURE 2** | Chest x-ray P/A view showing cavitation at the right lower lung field.

and isolated LLF-TB among DM patients was more prevalent among patients aged 41–60 ($p = 0.039$). Males had a frequency of 78.5%, and females had a frequency of 21.5%. Isolated LLF-TB was most prevalent among smokers. Among DM patients with more than 10 years of duration and taking only insulin without any oral hypoglycemic agents (OHA), LLF-TB was more prevalent (78.6% and 54.2%, respectively). However, the difference between the different durations of DM and treatment of DM was statistically insignificant ($p$ value = 0.843 and 0.057, respectively).

Table 2 demonstrates the chest x-ray findings of the participants. This study's most prevalent findings were upper and lower lobe involvement (38.5%). The frequency of isolated LLF-TB among DM patients was 24 out of 117 (20.5%). In the present study, cavity was found in 19.6%, and effusion was found in 18.7%. Inflammatory/bronchiectatic/nodular opacity was found in 2.6% of participants (Figures 1–4).

Table 3 demonstrates the frequency of isolated LLF-TB in smear-positive and Gene X-pert-positive patients. In our study, smear positivity was considerably higher in TB DM patients compared to the TB non-DM patients (83.3% vs. 20.4%) ($p < 0.001$). On the other side, gene X-pert positive was notably lower in the TB DM group than in the TB non-DM group (8.3% vs. 68.8%) ($p < 0.001$).

Table 4 illustrates the association of ESR, $HbA_1C$, and MDR-TB with isolated LLF-TB. In this current study, we found that ESR > 50 mm in the first hour (83.9%) and HbA1C > 7% (79.2%) were substantially associated with the development of LLF-TB in DM patients ($p < 0.001$).

Table 5 demonstrates that age (> 40 years) and diabetic condition are significantly associated with the development of isolated LLF-TB. Diabetic patients over 40 years have a 6.8 (1.5–30.3) and 3.9 (1.1–13.9) times risk, respectively, for the development of LLF-TB.

## 4 | Discussion

Individuals with diabetes are seen as having a higher chance of developing PTB [14]. The chest x-ray scans of these patients were deemed “atypical” in multiple published comparison studies, primarily due to their frequent involvement of the LLF and the presence of cavities [17–19]. Polymorphonuclear cell dysfunction and cell-mediated immunological abnormalities have been linked to these radiological differences in DM.

We have studied 117 patients with PTB DM. Among them, male was predominant (75%), and Male: female was 3:1. According to

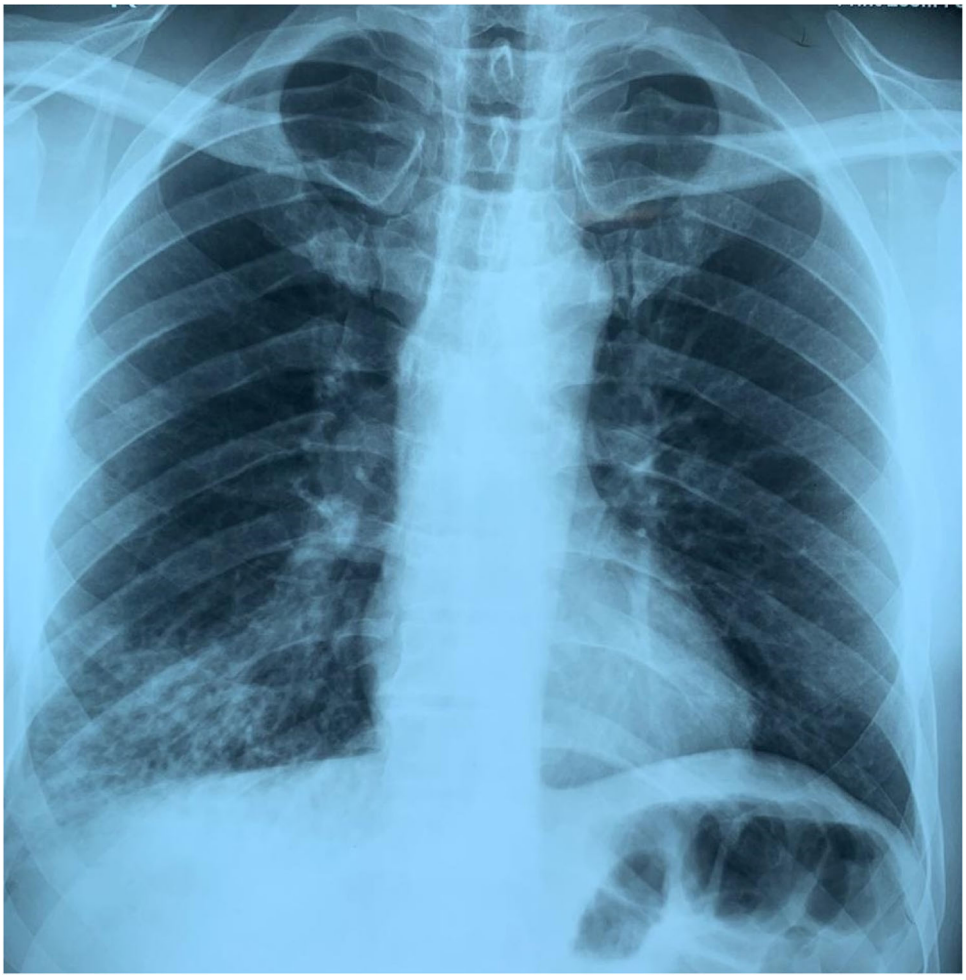

**FIGURE 3** | Chest x-ray P/A view showing patchy inhomogeneous opacities at the right lower lung field.

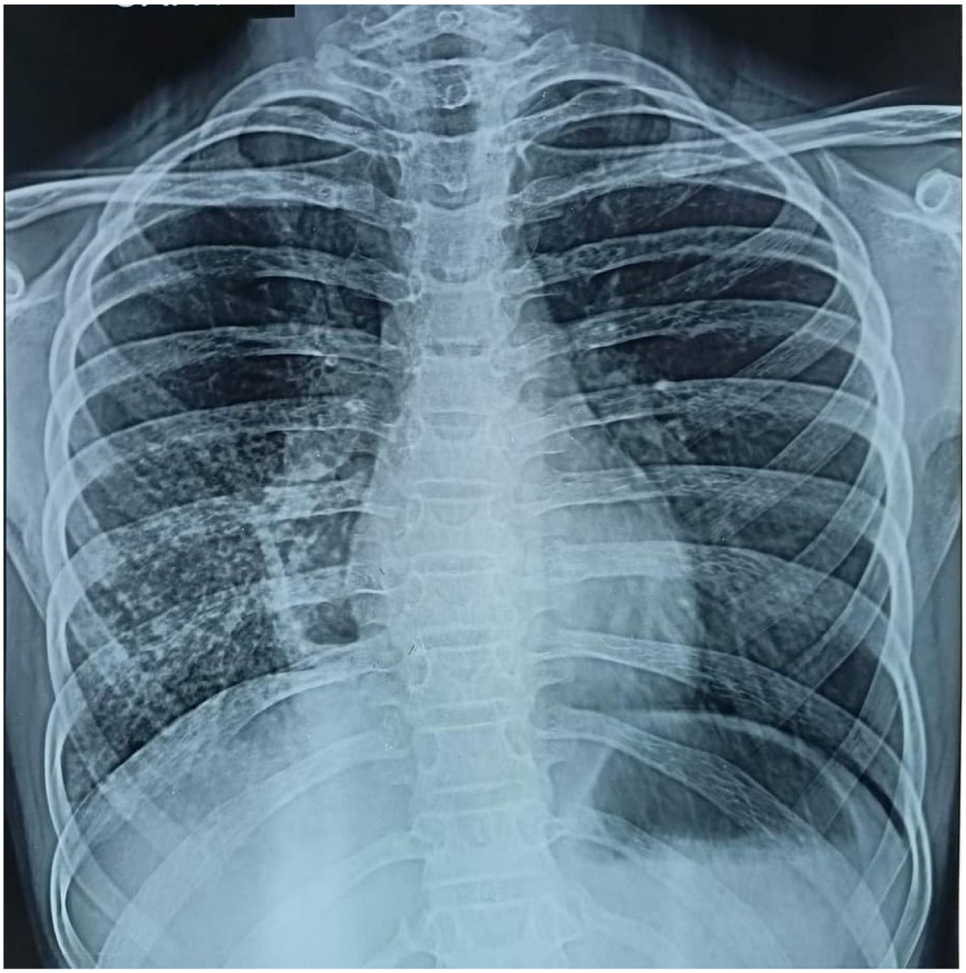

**FIGURE 4** | Chest x-ray P/A view showing patchy inhomogeneous opacities at the right lower lung field.

**TABLE 3** | Frequency of isolated lower lung TB in smear-positive, and Gene X-pert-positive patients ($N = 117$).

| Variables | Isolated lower lung field opacity ($n = 24$) | Other radiological patterns ($n = 93$) | $p$ value |
|---|---|---|---|
| Sputum | | | |
| Positive | 20 (83.3) | 19 (20.4) | < 0.001 |
| Negative | 4 (16.7) | 74 (79.6) | |
| GeneXpert | | | |
| Positive | 2 (8.3) | 64 (68.8) | < 0.001 |
| Negative | 22 (91.7) | 29 (31.2) | |

*Note:* Fisher's Exact test was done to measure the level of significance.

Chaya and Vishwakumar, 72% of the study population were male, and 28% were female [22]. Patel et al. and Qazi et al. also found male predominance [23, 24]. The male predominance might be due to both TB and DM being more prone to males. Another explanation would be that men smoke more and are exposed to dust at work, and men are admitted to hospitals at a higher rate than women. This finding contradicts the study by Mahabalshetti et al., Ahmed et al. and Vidyasagar et al. [25–27]. In these studies, females were more prone to TB. There could be a reason for this, such as the fact that women's coastal breathing causes inadequate ventilation and an increased risk of tuberculosis. According to Meghwani et al., higher incidence was observed in females of the younger age group, which was attributed to early pregnancy [28].

The most prevalent age group among isolated LLF groups was 41–60. This is comparable to the study by Mohammad et al., where the mean age group was $48.2 \pm 12$ years. However, contrary to Mahabalshetti et al. and Ahmed et al., the highest incidence was noted in the 16–40 and 21–40 age groups, respectively. Chaya and Vishwakumar reported that the age categories of 51–60 and 61–70 had the highest incidence.

In this present study, isolated LLF-TB was found in about 20.5% of the participants, which was similar to Saeidi (14%), Singh and Tiwari (23.7%), and Mahabalshetti et al. (10.5%) [25, 29, 30]. Previous studies conducted by Chaya and Vishwakumar observed that 44% of the participants had LLF-TB. The disparity in occurrences can be attributed to ambiguity in the terminology and definition, including terms like lower lobe, LLF, or basal tuberculosis.

According to Perez-Guzman et al., combined upper and lower lung field involvement was 83% [15]. On the other hand, it was 38.5% in our study. This difference might be due to more subdivision of radiological involvement. A prior study by Jabbar et al. and Perez-Guzman found upper lung field involvement was 18% and 19%, respectively, whereas, in the present study, it was 6.9%. The cavity was 26% and 32%, respectively. In the present study, cavity was found in 19.6%, and effusion was found in 18.7%.

A study was led by Shaikh et al. to clarify the association of age, gender, and nationality as variables in the development of isolated LLF-TB in DM, and a positive correlation was found using the Spearman correlation test [31]. Ayuthu et al. demonstrated that isolated LLF-TB was more prevalent among patients with $HbA_1C > 7\%$ (14 vs. 3) [32]. However, this prevalence was much higher in our study than in the previous study (24 vs. 15).

Ahmed et al. and Pandya et al. found that sputum-positive cases were more frequent in isolated LLF-TB (65.38% and 82.35%, respectively) than in other radiological patterns [26, 33]. In our study, sputum positivity was higher (83.3%) than in the previous survey. The higher bacillary load was due to the pulling of mucous in the lower lung field lesions, which could not be efficiently expectorated.

In the present study, it was found that age group (< 40 and > 40 years) and ESR (< 50 and > 50 mm), $HbA_1C$ (< 7% and > 7%), sputum for AFB and Gene X-pert as variables have significant association in the development of LLF-TB among diabetic patients. Regression analysis was done to evaluate the risk factor of DM for the development of LLF-TB and showed that DM has 6.8 times and aged more than 40 years have 3.9 times risk than non-diabetic. Geographical location affects the frequency of tuberculosis among people with DM. It varied from 0.38% in Taiwan [34] to 14% in Pakistan [35] within the Asian area. It was 1.3% in Tanzania [36] and 6.2% in Ethiopia in Africa [37]. Only one study in Europe and North America (Mexico) revealed that PTB prevalence in DM was 1.82% and 4.9%, respectively [38]. However, in this study, the prevalence of LLF-TB in DM is about 20.5%. This discrepancy might be due to endemicity, malnutrition, lack of awareness, and health-seeking behavior.

Our study found that the frequency of lower lung involvement is about one-fifth in DM. Therefore, it is crucial for the clinician involved in managing DM to vigorously investigate and exclude tuberculosis if any patient presents with opacity in the LLF. A person with DM should periodically be evaluated for symptoms and signs of tuberculosis, and if necessary, chest x-ray P/A should be done. The government should take steps to screen for TB in DM patients.

**TABLE 4** | Association of ESR, $HbA_1C$, and MDT-TB with isolated lower lung TB ($N = 117$).

| parameters | Isolated lower lung field opacity ($n = 24$) | Other radiological patterns ($n = 93$) | *p* value |
|---|---|---|---|
| ESR | | | |
| < 50 | 1 (4.2) | 78 (83.9) | < 0.001 |
| > 50 | 23 (95.8) | 15 (16.1) | |
| $HbA_1C$ | | | |
| < 7.0% | 5 (20.8) | 78 (83.9) | < 0.001 |
| > 7.0% | 19 (79.2) | 15 (16.1) | |
| RIF detected | | | |
| Yes | 1 (4.2) | 2 (2.2) | 0.186 |
| No | 23 (93.8) | 91 (97.8) | |

*Note:* Fisher's Exact test was done to measure the level of significance.

## 5 | Limitations of the Study

Most of the studies were done previously using the case-control method, but the present study used the cross-sectional method due to the insufficiency of time. Samples were collected only from one center. So, this study does not represent the whole country. Human immunodeficiency virus screening was not done, which might have been a confounding variable.

## 6 | Conclusion

We found that DM is significantly associated with the existence of LLF-TB. Therefore, it is vital to notice the unusual radiological pattern of tuberculosis while investigating DM patients, and therapy should begin as soon as feasible to lower morbidity and death.

**TABLE 5** | Regression analysis to find out the risk factors for isolated lower lung field TB ($N = 117$).

| Parameters | *B* | *p* value | OR | 95% CI for OR | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| DM | 1.92 | 0.012 | 6.81 | 1.53 | 30.30 |
| Age > 40 years | 1.37 | 0.035 | 3.93 | 1.10 | 13.99 |

### Author Contributions

**Raihan Kamal Galib:** conceptualization, methodology, data curation, investigation, formal analysis, writing–original draft, writing–review and editing. **Susanta Kumar Paul:** conceptualization, methodology, formal analysis, validation, writing–original draft, writing–review and editing. **Khujjista Akter:** data curation, formal analysis, visualization, investigation. **Manzurul Ibrahim Musa:** data curation, methodology, validation, visualization. **Dip Jyoti Sarker:** data curation, investigation, visualization, methodology. **Shah Ashiqur Rahman Ashiq Choudhury:** visualization, validation, writing–review and editing, software. **Shipan Chandra Paul:** writing–review and editing, visualization, software, validation. **Rajashish Chakrabortty:** conceptualization, supervision, project administration, writing–review and editing, validation, visualization, formal analysis.

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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data supporting this study's findings are available on request from the corresponding author.

### Transparency Statement

The lead author Susanta Kumar Paul affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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