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The association between type 2 diabetes and pulmonary cavitation revealed among IGRA-positive tuberculosis patients

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The co-occurrence of tuberculosis (TB) and diabetes mellitus (DM) presents a significant obstacle to TB eradication. Pulmonary cavitation can occur in severe cases of TB, particularly in patients with DM. From 1 May 2014 through 30 June 2019, we conducted a cross-sectional study of 1,658 smear- or culture-confirmed pulmonary TB (PTB) patients at the Second Department of Pulmonary Medicine and Tuberculosis, Shenzhen, China. A total of 861 participants who satisfied the criteria (chest CT scan for cavitation, interferon-gamma release assay (IGRA), diagnosis of diabetes mellitus), with the median age of 36.7 years, 63.6% of male, 79.7% IGRA positive, 13.8% with diabetes, and 40.8% with pulmonary cavitation, were included in the study. The association between diabetes and pulmonary cavitation was confirmed in these TB patients (adjusted OR, 2.54; 95% CI, 1.66–3.94; $p < 0.001$). No associations were observed between diabetes and IGRA, as well as between lung cavitation and IGRA. Based on the criteria of IGRA+/-, pulmonary cavitation+/-, and DM+/-, the further analysis with univariate and multivariate logistic regression were conducted in six subgroups. The significant association between diabetes and pulmonary cavitation was further confirmed in the IGRA+ subgroup (adjusted OR, 3.07; 95% CI, 1.86–5.16; $p < 0.001$) but not observed in IGRA- individuals. This observation suggests that different immunological mechanisms of pulmonary cavitation/DM may be employed in IGRA+ TB patients from IGRA- TB patients.

KEYWORDS

tuberculosis, diabetes mellitus, pulmonary cavitation, interferon-gamma, risk factor

1 Introduction

Tuberculosis (TB) remains a major global health challenge, particularly in low- and middle-income countries. According to the World Health Organization, there were 10.6 million new TB cases and 1.6 million deaths from TB in 2021 (1). China has the world's second largest population of TB patients, with approximately 1 million new TB cases reported each year.

Diabetes, as a metabolic disorder disease, is associated with innate and adaptive immune dysfunctions and alterations in specific cytokines and chemokines (2). Previous studies have

reported a paradoxical hyperinflammatory response in TB patients with DM, such as IFN- γ , IL-2, and TNF- α (3–5). There were studies indicating that diabetes mellitus (DM) is associated with an increased risk of TB (6–8). It was reported that individuals with DM have a 2- to 4-fold higher risk of active TB, and up to 30% of individuals with TB are likely to have DM (9).

As a key pathological feature and a dangerous consequence of clinical TB, pulmonary cavitation is associated with poor treatment outcomes, relapse, higher transmission rates, and the development of drug resistance (10). Previous studies proved that the incidence of cavitary TB is higher in diabetic patients compared to non-diabetic patients (11–14). TB individuals with DM experience persistent hyperglycemia, leading to a compilation of aberrant metabolic changes and increased superoxide production, which activates inflammatory pathways and leads to immune system dysfunction, indicating an abnormal and progressive immune response that favors cavitation in diabetic TB individuals (15).

Interferon- γ serves as a crucial lymphokine for the protective immune response to *M. tuberculosis* (16, 17). Reduced sensitivity of IFN- γ release has been demonstrated in humans with physiologically and pathologically immunocompromised factors (18). The interferon- γ release assay (IGRA), measuring early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) to indicate a specific cellular immune response to *M. tuberculosis*, has been routinely used in clinical screening for TB infection. Additionally, it serves as an adjunct diagnostic biomarker for active TB (19). In this study, we assessed whether cavitary or DM is associated with MTB-stimulated interferon- γ secretion in clinical TB patients.

2 Materials and methods

2.1 Ethics statement

This study was approved by the ethics committee of the Third People's Hospital of Shenzhen (IRB No.: 2021-014-02). All patients' private information was deleted, and each case was coded with a pathology accession number to protect patient privacy. The ethics committee waived the requirement for written informed consent from patients. The study was conducted in accordance with the ethical standards and confidentiality principles outlined in the Helsinki Declaration.

2.2 Study population

From 1 May 2014 to 30 June 2019, a total of 1,658 patients with microbiologically confirmed pulmonary TB were recruited in the Second Department of Pulmonary Medicine and Tuberculosis, the Third People's Hospital of Shenzhen. A positive sputum smear or culture was indicative of microbiologically confirmed pulmonary TB, excluding non-mycobacterium pulmonary diseases.

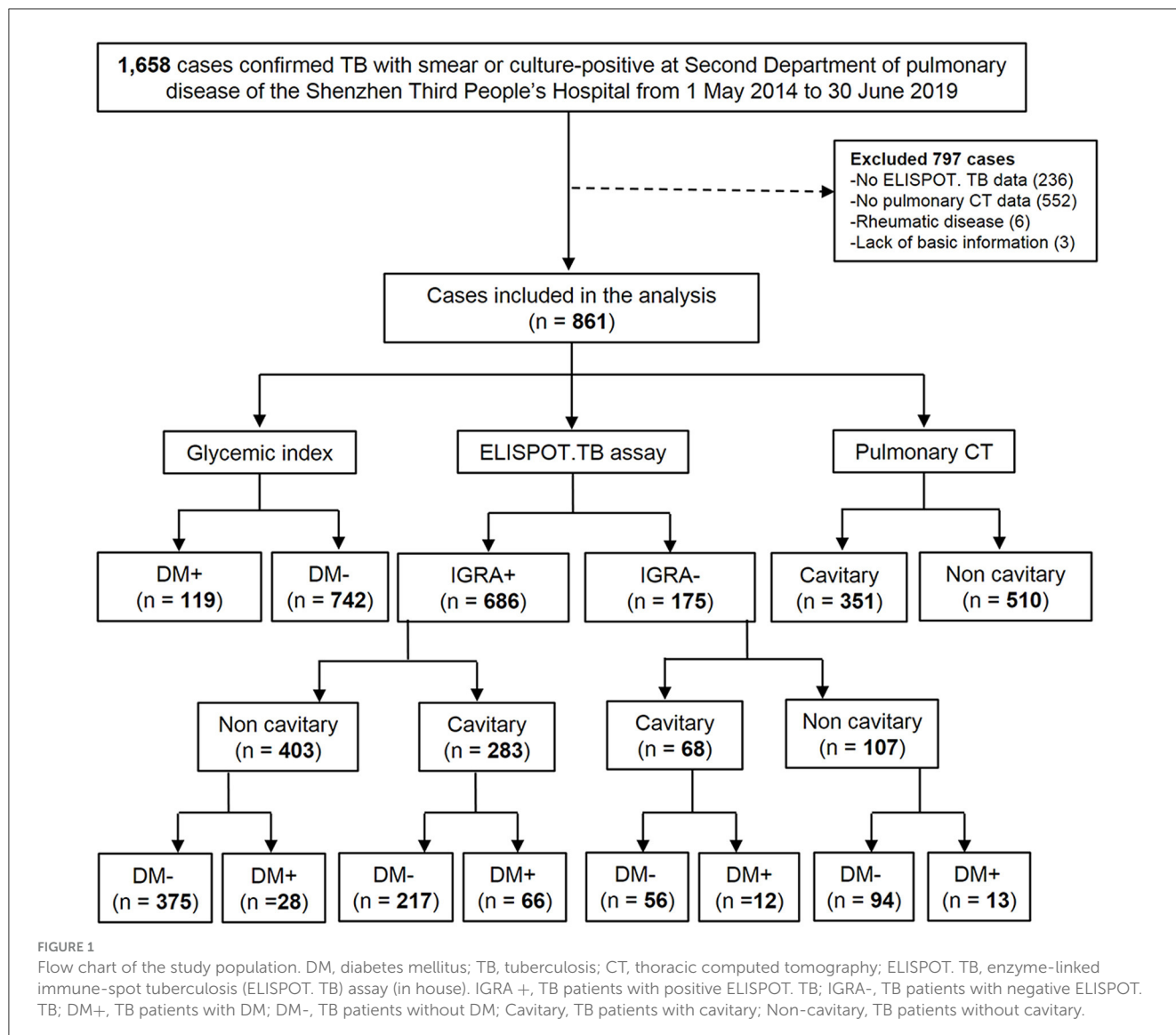
Sociodemographic characteristics, outpatient characteristics, outpatient and inpatient clinical encounters, medication prescriptions and fills, medical conditions, procedures, and laboratory results. Among the 1,658 patients, the exclusion

criteria for this study included (1) absence of IGRA results ($n = 236$); (2) lack of CT images ($n = 552$); (3) onset of the rheumatic disease ($n = 6$); and (4) absence of basic information ($n = 3$). Ultimately, 861 patients were enrolled in this study (Figure 1).

2.3 Methods

The enzyme-linked immune-spot tuberculosis (ELISPOT.TB) assay was used for screening the interferon-gamma release. Blood glucose and glycated hemoglobin (HbA1c) tests along with chest high-resolution computed tomography (CT) were performed at the patient's first admission. The IGRA assay was performed according to previously published research methods (20) and briefly described as follows: Panel A (peptides of ESAT-6 aa 21 to 40, aa 51 to 70, and aa 71 to 90) and Panel B (peptides of CFP-10 aa 21 to 40, aa 51 to 70, and aa 66 to 85) were used as antigens at a concentration of 10 μ g/ml. Peripheral blood mononuclear cells (PBMCs) were freshly isolated from 10 ml of anticoagulated blood samples using the Ficoll density gradient centrifugation method. A total of 2×10^5 cells/well were seeded in duplicate in 96-well plates pre-coated with an anti-IFN-capture monoclonal antibody. The cells were then stimulated with different antigens for 24 h at 37°C, 5% CO₂. PBMCs in medium alone or stimulated with phytohemagglutinin were used as negative or positive controls. Biotinylated anti-IFN-detection monoclonal antibody was added for 4 h, followed by the addition of streptavidin-alkaline phosphatase conjugate for 1 h. Subsequently, nitroblue tetrazolium-BCIP (5-bromo-4-chloro-3-indolylphosphate) chromogenic substrate was added for staining. The spots were counted using BioReader 4,000 Pro-X (Biosys, Germany). The test result of ELISPOT.TB assay was considered positive if either or both of Panel A had 18 or Panel B had 11 or more spots than the negative control.

Diabetes mellitus was defined according to the diagnostic criteria established by the WHO, and patients with HbA1c \geq 6.5% were commonly diagnosed with DM (21). The baseline information on demographic variables (for e.g., sex, age, ethnicity, marital status, and work status), behavioral risk factors (for e.g., smoking and alcohol use) and paraclinical data [for e.g., hemoglobin (HGB)] along with serum albumin (ALB), white blood cell count (WBC), lymphocyte count (LYN), neutrophilic granulocyte count (GRA), monocyte count (MONO), and C-reactive protein (CRP) were considered as confounders. The CT scanners used in this study included CT64 (China), Light Speed 16 and General Electric (GE) Revolution CT256 from United Imaging. The machine (Toshiba Asteion; Toshiba, Tokyo, Japan) parameters were as follows: 1.15-mm section thickness, 3-mm gap, 1- or 2-s scanning time per section, 120 kV, and 200 mA. The images were photographed at the lungs (window width, 1,800 HU, window level, 400 HU). Two experienced radiologists reviewed the CT images and reached a consensus decision at the Third People's Hospital of Shenzhen. The definition of pulmonary cavitation can be referred in this article (3), and a representative CT image is displayed in Supplementary Figure 1.



2.4 Statistical analysis

The study data were entered into a spreadsheet and analyzed using the statistical software R (version 4.1.2) (22). Bioinformatic analysis was performed using the OmicStudio tools at <https://www.omicstudio.cn>.

Bivariate associations were analyzed using chi-square tests for categorical variables and the Wilcoxon rank sum or Kruskal-Wallis tests for continuous variables. A two-sided *p*-value < 0.05 was considered statistically significant. To identify the risk factors associated with the presence of pulmonary cavitation in TB patients, univariate and multivariate logistic regression models were developed. The baseline information on demographic variables (for e.g., sex, age, ethnicity, marital status, and work status), behavioral risk factors (for e.g., smoking and alcohol use), and paraclinical data (for e.g., HGB, ALB, WBC, LYN, GRA, MONO, and CRP) were considered as confounders. The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were also calculated to estimate the degree of association

between different variables and pulmonary cavitation. Variables with a *p*-value ≤ 0.20 on the univariate analysis were initially offered to a saturated multivariate logistic regression model. The optimized model was generated using a “both” stepwise process, and the most appropriate model was determined by assessing the likelihood test and the minimum Akaike information criterion (AIC) value (23). The variance inflation factor (VIF) was used to detect multicollinearity in the regression analysis. A variable with VIF >5 was considered to have multicollinearity, and variables with multicollinearity were manually removed step by step until it was eliminated. The model was further assessed using the Hosmer-Lemeshow goodness-of-fit test. A receiver operating characteristic (ROC) curve was produced to display the predictive accuracy of the model using the R package “pROC.” The “lme4” and “gtsummary” packages were used to build and display the univariate and multivariate logistic regression models (24). The “tidyverse” package was used for data import, manipulation, and visualization (25). Additionally, we adopted a similar approach as above to explore the potential association of predictors with IGRA

and the relationship between predictors and pulmonary cavitation depending on the IGRA results.

3 Results

3.1 Study population and clinical characteristics

The study sample comprised 861 microbiologically confirmed pulmonary TB patients. The mean (SD) age of the patients was 36.7 (13.0) years, with 548 (63.6%) being male. Among them, 351 (40.8%) were diagnosed with cavitory PTB as determined by CT findings, and 119 (13.8%) had diabetes mellitus (DM+). Additionally, 686 (79.7%) were tested positive ELISPOT.TB (IGRA+). The baseline characteristics, include marital status, work, ethnicity, smoking and alcohol use, white blood cell count, neutrophilic granulocyte count, lymphocyte count, monocyte count, hemoglobin, albumin, and C-reactive protein, were shown in [Supplementary Table 1](#).

3.2 Univariate and multivariate logistic regression analyses of risk factors for cavitory, DM, and IGRA in TB patients

We first tested the risk factors for the lung cavitation. The analysis data in [Table 1](#) suggest that gender (adjusted OR, 0.65; 95% CI, 0.46–0.92; $p = 0.016$), work status (adjusted OR, 20.60; 95% CI, 0.44–0.82; $p = 0.001$), ethnicity (adjusted OR, 3.00; 95% CI, 1.92–7.38; $p = 0.013$), recent alcohol use (adjusted OR, 1.79; 95% CI, 1.10–2.94; $p = 0.019$), and smoking cigarettes (adjusted OR, 1.58; 95% CI, 1.05–2.40; $p = 0.030$) were significantly associated with pulmonary cavitation. Among the clinical characteristics, diabetes and WBC count (adjusted OR, 1.10; 95% CI, 1.05–1.16; $p < 0.001$) were significant risk factors for pulmonary cavitation. The significant association between cavitory and diabetes was identified in the TB group (adjusted OR, 2.54; 95% CI, 1.66–3.94; $p < 0.001$). Univariate and multivariate logistic regression analyses found no statistical significant differences between cavitory and IGRA in these TB patients (OR, 1.10; 95% CI, 0.79–1.56; $p = 0.60$).

We then tested the risk factors for diabetes mellitus. As shown in [Table 2](#), the gender (adjusted OR, 0.43; 95% CI, 0.24–0.72; $p = 0.002$), age (adjusted OR, 1.08; 95% CI, 1.06–1.10; $p < 0.001$), marital status (adjusted OR, 3.87; 95% CI, 1.75–9.81; $p = 0.002$), and WBC count (adjusted OR, 1.10; 95% CI, 1.02–1.17; $p < 0.001$) were significantly associated with diabetes. Furthermore, no statistical significant difference between diabetes and IGRA was found (OR, 0.95; 95% CI, 0.60–1.56; $p = 0.842$).

We also tested the risk factors for the IGRA and the results are presented in [Table 3](#). It can be observed that age is a significant risk factor (adjusted OR, 0.98; 95% CI, 0.97–1.00; $p = 0.008$). Moreover, significant associations between IGRA and two clinical characteristics were observed: one was WBC (adjusted OR, 0.92; 95% CI, 0.86–0.98; $p = 0.008$) and another one was HGB (adjusted OR, 1.01; 95% CI, 1.00–1.02; $p = 0.046$). No statistically significant difference between IGRA and diabetes was found (OR, 0.95; 95% CI, 0.60–1.56; $p = 0.80$), nor was there a significant difference

between IGRA and cavitory findings (OR, 1.10; 95% CI, 0.79–1.56; $p = 0.60$) in these TB patients.

3.3 Univariate and multivariate logistic regression analyses of risk factors in the specific subgroup of TB patients

According to the pulmonary cavitation+/-, diabetes+/-, and IGRA+/-, we categorized the enrolled TB patients into six specific subgroups and further conducted the risk factors analysis.

A total of 351 TB patients were categorized as the subgroup cavitory+ based on the presence of cavities in their lungs. No significant risk factors of IGRA were observed ([Supplementary Table 2a](#)), and no significant association between IGRA and diabetes (OR, 1.42; 95% CI, 0.74–2.92; $p = 0.314$) was established. As shown in [Supplementary Table 2b](#), age (adjusted OR, 1.08; 95% CI, 1.05–1.11; $p < 0.001$), marital status (adjusted OR, 6.18; 95% CI, 2.03–26.86; $p = 0.004$), and HGB (adjusted OR, 1.02; 95% CI, 1.00–1.03; $p = 0.019$) were risk factors for diabetes. Similarly, there was no statistical significant difference between IGRA and diabetes (OR, 1.42; 95% CI, 0.74–2.92; $p = 0.314$) in the cavitory+ subgroup.

In the subgroup cavitory- ($n = 510$), age (adjusted OR, 0.97; 95% CI, 0.96–0.99; $p = 0.0008$), WBC (adjusted OR, 0.9; 95% CI, 0.84–0.97; $p = 0.0077$), and HGB (adjusted OR, 1.01; 95% CI, 1.0–1.02; $p = 0.0496$) were observed as significant risk factors of IGRA. There was no significant association between IGRA and diabetes (OR, 0.54; 95% CI, 0.27–1.11; $p = 0.0824$) in this subgroup ([Supplementary Table 3a](#)). The significant association between diabetes, age (adjusted OR, 1.10; 95% CI, 1.07–1.14; $p < 0.001$), and gender (adjusted OR, 0.38; 95% CI, 0.15–10.86; $p = 0.027$) were observed in cavitory- TB patients ([Supplementary Table 3b](#)).

In the subgroup diabetes+ ($n = 119$), there was no risk factors of IGRA were observed ([Supplementary Table 4a](#)). Several risk factors for cavitory, such as gender (adjusted OR, 0.54; 95% CI, 0.38–0.77; $p < 0.001$), recent alcohol use (adjusted OR, 2.26; 95% CI, 1.39–3.70; $p = 0.001$), work status (adjusted OR, 1.61; 95% CI, 1.14–2.26; $p = 0.006$), ethnicity (adjusted OR, 3.50; 95% CI, 1.46–9.00; $p = 0.006$), and WBC (adjusted OR, 1.12; 95% CI, 1.06–1.19; $p < 0.001$) were observed in this subgroup ([Supplementary Table 4b](#)). There was no significant association between IGRA and cavitory (adjusted OR, 2.1; 95% CI, 0.80–5.52; $p = 0.129$) in the diabetes+ subgroup.

In the subgroup diabetes- ($n = 742$), age (adjusted OR, 0.98; 95% CI, 0.96–0.99; $p = 0.001$) and HGB (adjusted OR, 1.01; 95% CI, 1.00–1.02; $p = 0.017$) were observed as significant risk factors of IGRA. There was no significant association between IGRA and diabetes (OR, 0.97; 95% CI, 0.67–1.41; $p = 0.878$) in this subgroup ([Supplementary Table 5a](#)). No risk factor was observed for the diabetes in these TB patients ([Supplementary Table 5b](#)).

In the subgroup IGRA+ ($n = 686$), work (adjusted OR, 0.60; 95% CI, 0.42–0.86; $p = 0.005$), ethnicity (adjusted OR, 4.12; 95% CI, 1.56–12.2; $p = 0.006$), smoking (adjusted OR, 1.65; 95% CI, 1.03–2.66; $p = 0.037$), drinking (adjusted OR, 1.85; 95% CI, 1.06–13.26; $p = 0.031$), WBC (adjusted OR, 1.14; 95% CI, 1.07–1.22; $p < 0.001$), and diabetes (adjusted OR, 3.07; 95% CI, 1.86–5.16; $p <$

TABLE 1 Univariate and multivariate logistic regression analyses of risk factors for pulmonary cavitation in TB patients (n = 861).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	Non-cavitary, N = 510 ¹	Cavitary, N = 351 ¹	Crude OR ²	95% CI ²	p-value	Adjusted OR ²	95% CI ²	p-value
Gender								
Male	285 (55.9%)	263 (74.9%)	Reference			Reference		
Female	225 (44.1%)	88 (25.1%)	0.42	0.31, 0.57	<0.001	0.65	0.46, 0.92	0.016
Age	35.70 (12.7)	38.10 (13.3)	1.01	1.00, 1.02	0.010			
Marital status								
Single	191 (37.5%)	120 (34.2%)	Reference			Reference		
Married	319 (62.5%)	231 (65.8%)	1.15	0.87, 1.53	0.30			
Work								
Unemployed	140 (27.5%)	130 (37.0%)	Reference			Reference		
Employed	370 (72.5%)	221 (63.0%)	0.64	0.48, 0.86	0.003	0.60	0.44, 0.82	0.001
Ethnicity								
Han	501 (98.2%)	334 (95.2%)	Reference			Reference		
Others	9 (1.8%)	17 (4.8%)	2.83	1.28, 6.72	0.013	3.00	1.29, 7.38	0.013
Smokers								
Never	400 (78.4%)	201 (57.3%)	Reference			Reference		
Current	87 (17.1%)	121 (34.5%)	2.77	2.01, 3.83	<0.001	1.58	1.05, 2.40	0.030
Former	23 (4.5%)	29 (8.3%)	2.51	1.42, 4.49	0.002	1.42	0.74, 2.73	0.30
Drinkers								
Never	462 (90.6%)	272 (77.5%)	Reference			Reference		
Current	41 (8.0%)	75 (21.4%)	3.11	2.07, 4.71	<0.001	1.79	1.10, 2.94	0.019
Former	7 (1.4%)	4 (1.1%)	0.97	0.25, 3.24	>0.90	0.39	0.10, 1.39	0.20
IGRA								
Negative	107 (21.0%)	68 (19.4%)	Reference			Reference		
Positive	403 (79.0%)	283 (80.6%)	1.10	0.79, 1.56	0.60			
Diabetes								
No	469 (92.0%)	273 (77.8%)	Reference			Reference		
Yes	41 (8.0%)	78 (22.2%)	3.27	2.19, 4.94	<0.001	2.54	1.66, 3.94	<0.001
WBC	7.2 (2.7)	8.4 (3.2)	1.14	1.09, 1.20	<0.001	1.10	1.05, 1.16	<0.001
GRA	5.1 (3.7)	6.1 (2.9)	1.11	1.06, 1.17	<0.001			
LYN	1.4 (0.6)	1.4 (0.6)	0.99	0.80, 1.23	>0.90			
MONO	0.7 (0.7)	0.7 (0.3)	1.05	0.83, 1.35	0.60			
HGB	123.4 (20.6)	122.2 (20.6)	1.00	0.99, 1.00	0.40			

¹n (%); Mean (SD); Reference used as control for comparison. ²OR = Odds Ratio, CI = Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences (p < 0.05) are bolded.

0.001) were observed as significant risk factors of cavitory (Table 4). As shown in Table 5, gender (adjusted OR, 0.41; 95% CI, 0.21–0.78; p = 0.009), age (adjusted OR, 1.08; 95% CI, 1.06–1.11; p < 0.001), marital status (adjusted OR, 3.76; 95% CI, 1.57–10.45; p = 0.005), and cavitory (adjusted OR, 3.07; 95% CI, 1.86–5.16; p < 0.001) were the risk factors for diabetes.

In the subgroup IGRA- (n = 175), gender was observed as the only significant risk factor of cavitory (adjusted OR, 0.51; 95% CI, 0.26–0.98; p = 0.046) (Table 6). And only the age (adjusted OR, 1.06; 95% CI, 1.01–1.10; p = 0.011) was observed as the risk factor of diabetes in this subgroup (Table 7).

TABLE 2 Univariate and multivariate logistic regression analyses of risk factors for type 2 diabetes in TB patients (n = 861).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	Diabetes, N = 119 ¹	Non-diabetes, N = 742 ¹	Crude OR ²	95% CI ²	p-value	Adjusted OR ²	95% CI ²	p-value
Gender								
Male	98 (82.4%)	450 (74.9%)	Reference			Reference		
Female	21 (17.6%)	292 (25.1%)	0.33	0.20, 0.53	<0.001	0.43	0.24, 0.72	0.002
Age	49.6 (9.2)	34.6 (12.3)	1.10	1.08, 1.12	<0.001	1.08	1.06, 1.10	<0.001
Marital status								
Single	7 (5.9%)	304 (41.0%)	Reference			Reference		
Married	112 (94.1%)	438 (59.0%)	11.10	5.48, 26.59	<0.001	3.87	1.75, 9.81	0.002
Work								
Unemployed	77 (64.7%)	514 (69.3%)	Reference					
Employed	42 (35.3%)	228 (30.7%)	1.23	0.81, 1.84	0.319			
Ethnicity								
Han	117(98.3%)	718 (96.8%)	Reference					
Others	2 (1.7%)	24 (3.2%)	0.51	0.08, 1.75	0.366			
Smokers								
Never	56 (47.1%)	545 (73.5%)	Reference					
Current	48(40.3%)	160 (21.6%)	2.92	1.91, 4.46	<0.001			
Former	15 (12.6%)	37 (5.0%)	3.94	1.99, 7.52	<0.001			
Drinkers								
Never	88 (73.9%)	646 (87.1%)	Reference					
Current	27 (22.7%)	89 (12.0%)	2.23	1.35, 3.58	0.001			
Former	4 (3.4%)	7 (0.9%)	4.19	1.08, 14.18	0.024			
IGRA								
Negative	25 (21.0%)	150 (20.2%)	Reference					
Positive	94 (79.0%)	592 (79.8%)	0.95	0.60, 1.56	0.842			
Cavitation								
Non-cavitary	78 (65.5%)	273 (36.8%)	Reference					
Cavitary	41 (34.5%)	469 (63.2%)	3.27	2.19, 4.94	<0.001			
WBC	8.6 (3.1)	7.5 (2.9)	1.11	1.05, 1.18	<0.001	1.10	1.02, 1.17	<0.001
GRA	6.3(3.0)	5.4 (3.5)	1.06	1.01, 1.12	0.031			
LYN	1.4 (0.6)	1.4 (0.6)	1.14	0.84, 1.52	0.389			
MONO	0.7 (0.3)	0.7 (0.6)	1.08	0.77, 1.39	0.554			
HGB	125.6 (19.7)	122.5 (20.7)	1.01	1.00, 1.02	0.125			

¹n (%); Mean (SD); Reference used as control for comparison. ²OR = Odds Ratio, CI = Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences (p < 0.05) are bolded.

4 Discussion

The univariate and multivariate logistic regression models have been established for data analysis in this project. As shown in Table 2, diabetes was significantly associated with pulmonary cavitation in the univariate analysis (OR, 3.27; 95% CI, 2.19–4.94; p < 0.001), and this association was not significant in

the multivariate regression analysis. Additionally, in Table 1, the significant association between cavitory and diabetes was identified in the TB group (adjusted OR, 2.54; 95% CI, 1.66–3.94; p < 0.001). An ROC curve was generated to assess the predictive value of the constructed model. The model exhibited intermediate accuracy with an area under the ROC curve (AUC) of 0.706, indicating the high accuracy of this model. In this smear

TABLE 3 Univariate and multivariate logistic regression analyses of risk factors for IGRA in TB patients (n = 861).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	IGRA (-), N = 175 ¹	IGRA (+), N = 686 ¹	Crude OR ²	95% CI ²	p-value	Adjusted OR ²	95% CI ²	p-value
Gender								
Male	110 (62.9%)	438 (63.8%)	Reference			Reference		
Female	65 (37.1%)	248 (36.2%)	0.96	0.68, 1.36	0.8			
Age	39.4 (13.8)	36.0 (12.7)	0.98	0.97, 0.99	0.002	0.98	0.97, 1.00	0.008
Marital status								
Single	53 (30.3%)	258 (37.6%)	Reference			Reference		
Married	122 (69.7%)	428 (62.4%)	0.72	0.50, 1.03	0.073			
Work								
Unemployed	53 (30.3%)	217 (31.6%)	Reference			Reference		
Employed	122 (69.7%)	469 (68.4%)	0.94	0.65, 1.34	0.70			
Ethnicity								
Han	170 (97.1%)	665 (96.9%)	Reference			Reference		
Others	5 (2.9%)	21 (3.1%)	1.07	0.43, 3.25	0.90			
Smokers								
Never	123 (70.3%)	478 (69.7%)	Reference			Reference		
Current	40 (22.9%)	168 (24.5%)	1.08	0.73, 1.62	0.70			
Former	12 (6.9%)	40 (5.8%)	0.86	0.45, 1.75	0.70			
Drinkers								
Never	151 (86.3%)	583 (85.0%)	Reference			Reference		
Current	20 (11.4%)	96 (14.0%)	1.24	0.76, 2.13	0.40			
Former	4 (2.3%)	7 (1.0%)	0.45	0.14, 1.75	0.20			
Diabetes								
No	150 (85.7%)	592 (86.3%)	Reference			Reference		
Yes	25 (14.3%)	94 (13.7%)	0.95	0.60, 1.56	0.80			
Cavitation								
Non-cavitary	107 (61.1%)	403 (58.7%)	Reference			Reference		
Cavitary	68 (38.9%)	283 (41.3%)	1.10	0.79, 1.56	0.60			
WBC	8.0 (3.2)	7.6 (2.9)	0.96	0.91, 1.01	0.10	0.92	0.86, 0.98	0.008
GRA	5.9 (3.1)	5.4 (3.5)	0.96	0.92, 1.01	0.095			
LYN	1.3 (0.7)	1.4 (0.6)	1.44	1.09, 1.93	0.013	1.25	0.92, 1.72	0.20
MONO	0.6 (0.3)	0.7 (0.7)	1.49	0.96, 2.60	0.14	1.91	1.07, 3.75	0.053
HGB	118.7 (21.9)	124.0 (20.1)	1.01	1.00, 1.02	0.003	1.01	1.00, 1.02	0.046

¹n (%); Mean (SD); Reference used as control for comparison. ²OR, Odds Ratio; CI, Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences (p < 0.05) are bolded.

or culture-positive, clinical, and 5-year population-based cross-sectional study, the investigation of the association between clinical characteristics and pulmonary cavitation among TB patients was conducted. We found consistent evidence for an increased risk of cavitary TB with diabetes. Additionally, the significant association between diabetes and cavitary has been narrowed to “IGRA positive” TB patients rather than “IGRA negative” TB patients.

Hyperglycemia significantly affected the presentation of radiographic manifestations and was associated with severe TB (26). The possible underlying mechanism was considered to be an impaired immune function in patients with diabetes. IFN- γ , TNF- α , IL-17, and IL-23 play crucial roles in the induction and maintenance of protective immune responses against TB (27). Accumulating evidence has shown that IFN- γ is responsible for driving cell-mediated immune responses through production by

TABLE 4 Univariate and multivariate logistic regression analyses of risk factors for pulmonary cavitation in TB patients who tested IGRA positive ($n = 686$).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	Non-cavitary, $N = 403^1$	Cavitary, $N = 283^1$	Crude OR ²	95% CI ²	p -value	Adjusted OR ²	95% CI ²	p -value
Gender								
Male	224 (55.6%)	214 (75.6%)	Reference			Reference		
Female	179 (44.4%)	69 (24.4%)	0.40	0.29, 0.56	<0.001	0.68	0.46, 1.02	0.064
Age	34.7 (12.1)	37.9 (13.3)	1.02	1.01, 1.03	0.001			
Marital								
Single	161 (40.0%)	97 (34.3%)	Reference			Reference		
Married	242 (60.0%)	186 (65.7%)	1.28	0.93, 1.75	0.13			
Work								
Unemployed	111 (27.5%)	106 (37.5%)	Reference			Reference		
Employed	292 (72.5%)	177 (62.5%)	0.63	0.46, 0.88	0.006	0.60	0.42, 0.86	0.005
Ethnicity								
Han	397 (98.5%)	268 (94.7%)	Reference			Reference		
Others	6 (1.5%)	15 (5.3%)	3.70	1.48, 10.5	0.007	4.12	1.56, 12.2	0.006
Smokers								
Never	319 (79.2%)	159 (56.2%)	Reference			Reference		
Current	68 (16.9%)	100 (35.3%)	2.95	2.06, 4.25	<0.001	1.65	1.03, 2.66	0.037
Former	16 (4.0%)	24 (8.5%)	3.01	1.57, 5.93	0.001	1.52	0.71, 3.28	0.30
Drinkers								
Never	367 (91.1%)	216 (76.3%)	Reference			Reference		
Current	32 (7.9%)	64 (22.6%)	3.40	2.17, 5.42	<0.001	1.85	1.06, 3.26	0.031
Former	4 (1.0%)	3 (1.1%)	1.27	0.25, 5.83	0.80	0.56	0.10, 2.78	0.50
Diabetes								
No	375 (93.1%)	217 (76.7%)	Reference			Reference		
Yes	28 (6.9%)	66 (23.3%)	4.07	2.57, 6.62	<0.001	3.07	1.86, 5.16	<0.001
WBC	7.0 (2.4)	8.4 (3.3)	1.19	1.13, 1.27	<0.001	1.14	1.07, 1.22	<0.001
GRA	4.9 (3.7)	6.1 (3.1)	1.15	1.08, 1.22	<0.001			
LYN	1.4 (0.6)	1.4 (0.6)	1.03	0.81, 1.32	0.80			
MONO	0.7 (0.8)	0.7 (0.3)	1.05	0.82, 1.36	0.70			
HGB	124.5 (20.1)	123.4 (20.1)	1.00	0.99, 1.00	0.50			

¹ n (%); Mean (SD); Reference used as control for comparison. ²OR, Odds Ratio; CI, Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences ($p < 0.05$) are bolded.

Th1 cells and has regulatory properties by acting as an inducer of Th2 responses. Using chronic M.tb infection in hyperglycemic mice, adaptive immunity was found to be delayed, as shown by reduced early production of IFN- γ in the lungs and by the presence of fewer M.tb antigen (ESAT-6)-responsive T cells (28). The animal data have been supported by two clinical studies from Tsukaguchi et al. (4, 29). Furthermore, using a model of *in vitro* granulomas generated by DM2 patients' peripheral blood mononuclear cells infected with M. bovis BCG, the authors observed that PBMCs from GSH-supplemented patients produced enhanced levels of

IFN- γ and controlled bacterial replication more efficiently than those from placebo-treated patients (30). In particular, the levels of IFN- γ were markedly reduced in samples from patients with poor glycemic control, which also failed to inhibit bacterial growth (31). Thus, the different immune responses involved in IFN- γ between TB with DM and without DM may be due not only to differences in the frequencies of innate and adaptive immune cells but also to uncontrolled hyperglycaemia.

Proinflammatory responses in the lungs can lead to tissue damage, disrupting normal tissue architecture and consequently

TABLE 5 Univariate and multivariate logistic regression analyses of risk factors for type 2 diabetes in TB patients who tested IGRA positive (n = 686).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	Diabetes, (N = 94) ¹	Non-diabetes, (N = 592) ¹	Crude OR ²	95% CI ²	p-value	Adjusted OR ²	95% CI ²	p-value
Gender								
Male	80 (85.1%)	358 (60.5%)	Reference			Reference		
Female	14(14.9%)	234 (39.5%)	0.27	0.14, 0.47	<0.001	0.41	0.21, 0.78	0.009
Age	49.5 (9.4)	33.8 (11.8)	1.10	1.08, 1.13	<0.001	1.08	1.06, 1.11	<0.001
Marital status								
Single	6 (6.4%)	252 (42.6%)	Reference			Reference		
Married	88 (93.6%)	340 (57.4%)	10.87	5.08, 28.25	<0.001	3.76	1.57, 10.45	0.005
Work								
Unemployed	58 (61.7%)	411 (69.4%)	Reference					
Employed	36 (38.3%)	181 (30.6%)	1.41	0.89, 2.20	0.136			
Ethnicity								
Han	92(97.9%)	573 (96.8%)	Reference					
Others	2 (2.1%)	19 (3.2%)	0.66	0.10, 2.31	0.574			
Smokers								
Never	43 (45.7%)	435 (73.5%)	Reference					
Current	39 (41.5%)	129 (21.8%)	3.06	1.90, 4.92	<0.001			
Former	12 (12.8%)	28 (4.7%)	4.34	2.00, 8.98	<0.001			
Drinkers								
Never	67 (71.3%)	516 (87.2%)	Reference					
Current	23 (24.5%)	73 (12.3%)	2.42	1.40, 4.09	0.001			
Former	4 (4.3%)	3 (0.5%)	10.27	2.22, 53.07	0.002			
Cavitation								
Non-cavitary	66 (70.2%)	217 (36.7%)	Reference			Reference		
Cavitary	28 (29.8%)	375 (63.3%)	4.07	2.57, 6.62	<0.001	3.07	1.86, 5.16	<0.001
WBC	8.5 (2.9)	7.5 (2.8)	1.11	1.03, 1.19	0.002	1.07	0.99, 1.16	0.102
GRA	6.0 (2.7)	5.3 (3.6)	1.04	0.99, 1.11	0.102			
LYN	1.5 (0.6)	1.4 (0.6)	1.27	0.90, 1.75	0.155			
MONO	0.8 (0.3)	0.7 (0.7)	1.09	0.77, 1.40	0.533			
HGB	127.3 (19.1)	123.5 (20.2)	1.01	1.00, 1.02	0.091			

¹n (%); Mean (SD); Reference used as control for comparison. ²OR, Odds Ratio; CI, Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences (p < 0.05) are bolded.

compromising efficient gaseous exchange. An earlier study showed that progressive caseation of pulmonary granulomas did not occur in IFN- γ knockout mice with virulent *Mycobacterium avium* infection (32). However, mice treated with recombinant adenovirus IFN- γ showed high IFN- γ expression and exhibited significantly lower bacilli loads and pneumonia infected with H37Rv or the MDR strain (33). Notably, the reduction in IFN- γ impairs the phagocytic activity of the macrophage, thus altering the intracellular bacterial persistence and providing a replication niche with clinical consequences as cavitation develops (34). Through a comparison experiment with IFN- γ knockout and WT mice,

Verma et al. showed that IFN- γ promoted the inflammatory cytokine storm response to cause lethal lung damages in a model of post-influenza methicillin-resistant *Staphylococcus aureus* pneumonia (35). Another study showed that administering IFN- γ after *P. aeruginosa* challenge resulted in a significant decrease in macroscopic lung pathology changes (36). Recent literature suggests that IFN- γ gene expression is positively correlated with skin lesion size in hamsters infected with *Leishmania braziliensis* (37). The data reported above indicate that the tissue damage from microbial infection, especially lung damage, is associated with IFN- γ .

TABLE 6 Univariate and multivariate logistic regression analyses of risk factors for pulmonary cavitation in TB patients who tested IGRA negative (*n* = 175).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	Non-cavitary, <i>N</i> = 107 ¹	Cavitary, <i>N</i> = 68 ¹	Crude OR ²	95% CI ²	<i>p</i> -value	Adjusted OR ²	95% CI ²	<i>p</i> -value
Gender								
Male	61 (57.0%)	49 (72.1%)	Reference			Reference		
Female	46 (43.0%)	19 (27.9%)	0.51	0.26, 0.98	0.046	0.51	0.26, 0.98	0.046
Age	39.7 (14.1)	38.9 (13.5)	1.00	0.97, 1.02	0.70			
Marital								
Single	30 (28.0%)	23 (33.8%)	Reference			Reference		
Married	77 (72.0%)	45 (66.2%)	0.76	0.40, 1.48	0.40			
Work								
Unemployed	29 (27.1%)	24 (35.3%)	Reference			Reference		
Employed	78 (72.9%)	44 (64.7%)	0.68	0.35, 1.32	0.30			
Ethnicity								
Han	104 (97.2%)	66 (97.1%)	Reference			Reference		
Others	3 (2.8%)	2 (2.9%)	1.05	0.14, 6.50	>0.90			
Smokers								
Never	81 (75.7%)	42 (61.8%)	Reference			Reference		
Current	19 (17.8%)	21 (30.9%)	2.13	1.03, 4.43	0.040			
Former	7 (6.5%)	5 (7.4%)	1.38	0.39, 4.58	0.60			
Drinkers								
Never	95 (88.8%)	56 (82.4%)	Reference			Reference		
Current	9 (8.4%)	11 (16.2%)	2.07	0.81, 5.44	0.13			
Former	3 (2.8%)	1 (1.5%)	0.57	0.03, 4.54	0.60			
Diabetes								
No	94 (87.9%)	56 (82.4%)	Reference			Reference		
Yes	13 (12.1%)	12 (17.6%)	1.55	0.65, 3.65	0.30			
WBC	7.9 (3.6)	8.2 (2.6)	1.02	0.93, 1.12	0.60			
GRA	5.8 (3.5)	6.1 (2.4)	1.04	0.94, 1.14	0.50			
LYN	1.3 (0.7)	1.2 (0.6)	0.83	0.52, 1.31	0.40			
MONO	0.6 (0.3)	0.6 (0.3)	1.04	0.40, 2.64	>0.90			
HGB	119.5 (22.0)	117.5 (21.9)	1.00	0.98, 1.01	0.60			

¹*n* (%); Mean (SD); Reference used as control for comparison. ²OR, Odds Ratio; CI, Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences (*p* < 0.05) are bolded.

Cell death is an essential attribute of tissue damage, including apoptosis, necroptosis, ferroptosis, and autophagy-dependent cell death. Lee et al. (38) reported that IFN-γ could attenuate necroptosis in collagen-induced arthritis mice by downregulating Th17 cell differentiation and inhibiting cellular FLICE-like inhibitory protein. *In vivo*, in mice bearing ovarian tumors, Wang et al. (39) reported that IFN-γ released from CD8+ T cells downregulated the expression of SLC3A2 and SLC7A11 and promoted tumor cell lipid peroxidation and ferroptosis. In addition, Orvedahl et al. (40) identified autophagy genes as central mediators of myeloid cell survival to IFN-γ mediated by

TNF signaling via receptor interacting protein kinase 1 (RIPK1)- and caspase 8-mediated cell death. Therefore, the IFN-γ activity involved in various forms of cell death suggests that IFN-γ may improve a complex phenotype, such as “tissue damage,” by modulating cell death. IGRA detects IFN-γ released by specific T cells, reflecting the TB lymphocyte function and the host immune state to TB. Patients with severe TB, such as military TB and tuberculous meningitis, have been proven to have lower CD4 T-cell counts and impaired T-cell function. In our study, we retrospectively included 861 microbiological PTB participants for analysis. And the association between type 2 diabetes and

TABLE 7 Univariate and multivariate logistic regression analyses of risk factors for type 2 diabetes in TB patients who tested IGRA negative (n = 175).

Characteristic	Statistics		Univariate analysis			Multivariable analysis		
	Diabetes, (N = 25) ¹	Non-diabetes, (N = 150) ¹	Crude OR ²	95% CI ²	p-value	Adjusted OR ²	95% CI ²	p-value
Gender								
Male	18 (72.0%)	92 (61.3%)	Reference					
Female	7 (28.0%)	58 (38.7%)	0.62	0.23, 1.51	0.310			
Age	50.2 (8.4)	37.6 (13.8)	1.08	1.04, 1.12	<0.001	1.06	1.01, 1.10	0.011
Marital								
Single	1 (4.0%)	52 (34.7%)	Reference			Reference		
Married	24 (96.0%)	98 (65.3%)	12.73	2.58, 230.83	<0.001	4.57	0.73, 90.01	0.173
Work								
Unemployed	19 (76.0%)	103 (68.7%)	Reference					
Employed	6 (24.0%)	47 (31.3%)	0.69	0.24, 1.76	0.462			
Ethnicity								
Han	25 (100.0%)	145 (96.7%)	Reference					
Others	0 (0%)	5 (3.3%)	_NA	_NA	_NA			
Smokers								
Never	13 (52.0%)	110 (73.3%)	Reference					
Current	9 (36.0%)	31 (20.7%)	2.46	0.94, 6.24	0.061			
Former	3 (12.0%)	9 (6.0%)	2.82	0.57, 10.92	0.154			
Drinkers								
Never	21 (84.0%)	130 (86.7%)	Reference					
Current	4 (16.0%)	16 (10.7%)	1.55	0.41, 4.72	0.471			
Former	0 (0%)	4 (2.7%)	_NA	_NA	_NA			
Cavitation								
Non-cavitory	12 (48.0%)	56 (37.3%)	Reference					
Cavitory	13 (52.0%)	94 (62.7%)	1.55	0.65, 3.65	0.313			
WBC	9.1 (3.7)	7.8 (3.1)	1.10	0.98, 1.24	0.085			
GRA	7.1 (3.7)	5.7 (2.9)	1.13	1.00, 1.28	0.039	1.12	0.98, 1.29	0.086
LYN	1.2 (0.6)	1.3 (0.7)	0.77	0.38, 1.47	0.451			
MONO	0.6 (0.3)	0.6 (0.3)	0.99	0.25, 3.49	0.985			
HGB	119.4 (20.9)	118.6 (22.2)	1.00	0.98, 1.02	0.862			

¹n (%); Mean (SD); Reference used as control for comparison; NA, not available. ²OR, Odds Ratio; CI, Confidence Interval. WBC, white blood cell; GRA, neutrophilic granulocyte; LYN, lymphocyte; MONO, monocyte; HGB, hemoglobin; ALB, albumin; and CRP, C-reactive protein. Significant differences (p < 0.05) are bolded.

pulmonary cavitation was found only in IGRA-positive TB patients. Our observation indicates that IFN-γ plays a crucial role in the development of cavitory with diabetes in TB patients.

The study had several limitations that should be considered. First, it was conducted in a specialized TB hospital with smear- or culture-positive confirmed TB patients, which resulted in a significantly lower number of negative IGRA patients (175) compared to positive IGRA patients (686). This retrospective study was based on the records of 5 years of clinical practice that were collected, indicating that further prospective cohort studies and follow-up studies are indispensable. Second, there were unexpected

pathological changes in the enrolled TB patients, including the onset of infection, progression stages, and relapse. Addressing the phenomena between the different stages of M.tb infection and IFN-γ-related immunological regulation requires further evaluation with diabetic and latent TB animal models. Nevertheless, the population in the present study was an unbiased group of smear or culture-confirmed TB patients. Therefore, we believe that our results are represents more real-world outcomes.

In conclusion, in this study we found that there was a significant association between pulmonary cavitation and type 2 diabetes among the IGRA positive TB patients. This observation strongly

suggests that different immunological mechanisms of pulmonary cavitory/DM would be employed in IGRA+ TB and IGRA- TB individuals. Further exploration of pulmonary cavitory/DM in IGRA+ and IGRA- TB patients would reveal more immunological characteristics of the tuberculosis disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Third People's Hospital of Shenzhen (IRB No.: 2021-014-02). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization and writing—review and editing: GZ, PZ, and GD. Formal analysis: PL and HL. Funding acquisition: GZ and GD. Investigation: MY and PZ. Methodology: XZ, PL, HL, and GZ. Writing—original draft: MY and PL. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2023.1245316/full#supplementary-material>

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