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Risk factors for rifampicin-susceptible and isoniazid-resistant tuberculosis in adult patients with type 2 diabetes mellitus in Nanjing

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Abstract

Objective Globally, Tuberculosis(TB) with type 2 diabetes mellitus (T2DM) is becoming increasingly serious, especially the emergence of rifampicin-susceptible and isoniazid-resistant tuberculosis (Hr-TB), which increases the difficulty of treatment and the burden of disease. Therefore, this single-center retrospective cohort study analyzed risk factors of Hr-TB in adult patients with T2DM and pulmonary tuberculosis (PTB) in Nanjing to guide clinical practice and improve the long-term prognosis of patients.

Methods The clinical data of 279 adult inpatients diagnosed with culture-positive PTB and T2DM in the Second Hospital of Nanjing from January 2019 and December 2021 were collected. According to the drug susceptibility testing (DST) results, 44 patients with Hr-TB were categorized as the Hr-TB group, while the remaining 235 patients with drug-susceptible tuberculosis (DS-TB) were classified as DS-TB group. Hierarchical logistic regression was employed for multivariate analysis to identify variables associated with Hr-TB in patients with T2DM.

Results There were no significant differences in age, sex, body mass index (BMI), smoking, drinking, ethnicity, education level, or comorbidities between the DS-TB and Hr-TB groups. Multivariate logistic regression analysis revealed that, history of previous tuberculosis treatment (*OR* = 2.348, *95%CI*: 1.025 ~ 5.379, *P* = 0.044), poor FPG control (*OR* = 2.402, *95%CI*: 1.208 ~ 4.776, *P* = 0.012), and serum iron levels ≥ 14.3μmol/l (*OR* = 2.808, *95%CI*: 1.334 ~ 5.910, *P* = 0.007) are independent risk factors for Hr-TB in adult patients with T2DM in Nanjing. Within the cohort, 241 patients were Newly treatment tuberculosis patients, and among them, poor FPG control (*OR* = 2.296, *95%CI*: 1.073 ~ 4.915, *P* = 0.032), and serum iron levels ≥ 14.3μmol/l (*OR* = 2.418, *95%CI*: 1.048 ~ 5.577, *P* = 0.038) were identified as risk factors for Hr-TB.

Conclusion Poor fasting glycemic control and serum iron levels ≥ 14.3μmol/L are independent risk factors for the development of Hr-TB in adults with T2DM and PTB, moreover, the contribution of these as risk factors were more pronounced in the newly treatment tuberculosis patients subgroup than patients with a history of previous

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tuberculosis treatment. History of previous tuberculosis treatment was also found to be a risk factor for Hr-TB in adults with T2DM.

Clinical trial number

Not applicable.

Keywords Tuberculosis, Type 2 diabetes mellitus, Isoniazid-resistant and rifampicin-susceptible tuberculosis, Isoniazid-resistant tuberculosis, Risk factor, Iron

Introduction

China is a country with a high burden of tuberculosis and drug-resistant tuberculosis, as well as a high incidence of diabetes, accounting for a quarter of the world's adult diabetes patients [1, 2]. One study has shown the risk of developing tuberculosis in diabetic patients was more than three times higher than that of the general population in eastern China [3]. Some studies [4, 5] have demonstrated that diabetes not only increases the prevalence of tuberculosis, but also increases the risk of multidrug-resistant tuberculosis (MDR-TB) morbidity and death. Increased susceptibility to tuberculosis infection and risk of drug resistance in DM patients are associated with factors such as high bacterial load, low effective concentrations of anti-tuberculosis drugs, host immune deficiency, and decreased levels of IFN-γ and IL-12 [6].

Global data showed that 7.1% of new TB cases and 7.9% of previously treated TB cases are rifampicin-susceptible and isoniazid-resistant tuberculosis (Hr-TB), Meanwhile, the overall prevalence of MDR-TB being 5.7% (2.3% among new cases and 13.9% among previously treated cases) [7]. The rate of isoniazid-related resistance in adults with active pulmonary tuberculosis (PTB) together with diabetes in Nanjing is increasing, especially in patients with Newly treatment tuberculosis [8]. Globally, TB with T2DM is becoming increasingly serious, especially the emergence of Hr-TB, which increases the difficulty of treatment and the burden of disease. The above conclusions all suggest that Hr-TB needs to receive more clinical attention.

Current research has confirmed that isoniazid resistance involves mutations in multiple genes, such as InhA (Rv1484), KatG (Rv1908c), AhpC (Rv2428), FabG1 (Rv1483), and FurA (Rv1909c), as well as mechanisms such as efflux pump upregulation and reduced drug serum concentration [9, 10]. Diabetes Mellitus has been identified as a risk factor for Hr-TB [11, 12]. In tuberculosis patients with hyperglycemia, delayed absorption and faster elimination of isoniazid lead to reduced plasma concentrations of isoniazid [13]. Glycosylated hemoglobin A1 (HbA1c) grading is an independent risk factor for isoniazid resistance and MDR in TB-T2DM patients [14]. However, whether other mechanisms such as nutrition, immunity, and iron metabolism are involved in this resistance is not yet fully disclosed. And iron metabolism plays a key role in the survival of Mycobacterium tuberculosis. So based on the researches above indicators, our study analyzed adult patients with culture-positive PTB and T2DM from January 2019 to December 2021 in The Second Hospital of Nanjing, and included serum iron and other factors to explored risk factors for Hr-TB in patients with T2DM. It is expected to achieve the purpose of guiding clinical diagnosis and treatment.

Methods

Study area and study design

This single-center, retrospective cohort study included patients with PTB with T2DM in the Nanjing district of China during the period from January 2019 to December 2021. As an infectious disease hospital in Nanjing, the second hospital of Nanjing is the only municipally designated medical institution for the diagnosis and treatment of tuberculosis and drug-resistant tuberculosis in Nanjing.

A total of 279 adult patients with PTB with T2DM who were positive for mycobacterial culture and had complete medical records were enrolled. According to the drug susceptibility test, the patients were divided into a Hr-TB group (44 cases) and a drug-susceptible tuberculosis (DS-TB) group (235 cases). This study was reviewed and approved by the Ethics Committee of the Second Hospital of Nanjing (2023-LY-kt02). All patients are exempt from informed consent.

Inclusion Criteria:

(1) Age ≥ 18 years.
(2) Availability of drug susceptibility test (DST) results [15, 16].
(3) Diagnosed with PTB by positive mycobacterial culture (Mycobacterium tuberculosis complex) [17].
(4) Diagnosed with type 2 Diabetes Mellitus (T2DM) [18].

Exclusion Criteria

(1) Rifampicin-resistant tuberculosis (RR-TB).
(2) Outpatients with incomplete clinical data.
(3) PTB with HIV and other infection.

Trained research clinicians gathered demographic and clinical data, which encompassed informations such as gender, age, smoking and drinking habits, race, body mass index (BMI), comorbidities (HIV status, hypertension), history of previous tuberculosis treatment, site of tuberculosis infection (pulmonary or extrapulmonary), imaging characteristics (unilateral or bilateral tuberculosis, presence of lung cavities), serum albumin (ALB) levels, monocyte counts, neutrophil counts, lymphocyte counts, serum iron levels (Iron Detection kit, Nanjing Aubrime Biotechnology Co., Ltd), fasting plasma glucose (FPG) levels, and HbA1C levels. The following calculations and standards were performed [5]:

Prognostic Nutritional Index (PNI) was calculated as PNI = serum albumin (ALB) (g/L) + 5 × total lymphocyte count (10^9/L).

Neutrophil-to-lymphocyte ratio (NLR) was determined as the ratio of neutrophils to lymphocytes.

Monocyte-to-lymphocyte ratio (MLR) was calculated as the ratio of monocytes to lymphocytes.

Poor FPG control was defined as a FPG level > 7 mmo/L (no complications) or > 10 mmo/L (with complications such as cardiovascular and cerebrovascular diseases, advanced age, and severe tuberculosis) [5].

Poor HbA1C control was defined as HbA1C ≥ 7% (no complications) or ≥ 8% (with complications such as cardiovascular and cerebrovascular diseases, advanced age, and severe tuberculosis) [5].

Quality control

Quality assessment and data extraction were performed by a minimum of two researchers who have professional training in this subject area. Generally, data was extracted twice for the same patient by two researchers, and if there any conflict between the two researchers, the original data should be checked before entering the correct data.

Statistical analysis

Statistical analysis was carried out using SPSS 26.0 for Microsoft Windows (SPSS Inc., http://www.spss.com.hk). Count data were expressed as frequency (percentage), and comparisons between two groups were conducted using a chi-square test or Fisher's exact test. Measurement data were represented as median and interquartile range [M (IQR)], with comparisons between the two groups using the Mann-Whitney U test. A significance level of $\alpha = 0.05$ was used, and $P < 0.05$ was considered statistically significant. The normal range for serum iron in this test is 14.3–35.6 μmol/l, divided into three groups: <14.3 μmol/l, 14.3–35.6 μmol/l, and > 35.6 μmol/l. Due to the small sample size in the serum iron > 35.6 μmol/l group, the serum iron 14.3–35.6 μmol/l group and the > 35.6 μmol/l group were combined.

A univariate logistic regression model was used to screen for factors related to Hr-TB in adult patients with T2DM. Variables with $P < 0.1$ were selected using a stepwise forward selection method to identify factors independently associated with Hr-TB. Subsequently, a multivariate logistic regression analysis was conducted to determine risk factors for Hr-TB in these patients. $P < 0.05$ was considered statistically significant.

There were some confounding factors. To explore the impact of diabetes as a single factor on outcomes, subgroup analyses were performed by history of previous tuberculosis treatment to control for these confounding factors.

Results

In total, 279 adult patients with PTB and T2DM were interviewed for the survey. It divided in two groups: Hr-TB and DS-TB. A total of 44 patients were included in the Hr-TB group, including 33 newly cases and 11 previously treatment cases, and 38 cases of male (38/44, 86.4%). There were 235 cases in the DS-TB group (including 208 newly cases and 27 previously treatment cases), and 197 cases (197/235, 83.8%) of males. There were no significant differences in age, gender, BMI [19], smoking history, alcohol consumption, ethnicity, place of residence, education level, hypertension, HIV status, or extrapulmonary tuberculosis between the DS-TB group and the Hr-TB group ($P > 0.05$). There was a statistically significant difference in the history of previous tuberculosis treatment between the two groups ($\chi^2 = 5.750$, $P = 0.016$; Table 1).

Univariate logistics regression analysis of risk factors for Hr-TB in adult PTB and T2DM

By univariate logistic regression analysis, it was determined that gender, age, BMI, HIV status, PTB combined with extra-pulmonary tuberculosis, smoking, alcohol consumption, ethnicity, lung cavity, bilateral pulmonary infiltration, PNI ≥ 40, MLR ≥ 0.5, NLR, FPG, HbA1C and poor control of HbA1C were not significantly associated with Hr-TB. However, history of previous tuberculosis treatment, poor fasting glycemic control, and serum iron levels ≥ 14.3 μmol/l showed a strong association with Hr-TB in adult with T2DM, with the following odds ratios: (OR = 2.568, 95%CI: 1.164 ~ 5.666, P = 0.020), (OR = 2.382, 95%CI: 1.231 ~ 4.612, P = 0.010), (OR = 1.057, 95%CI: 1.006 ~ 1.110, P = 0.028), and (OR = 2.599, 95% CI: 1.276 ~ 5.297, P = 0.009), respectively. Additionally, urban residence might be associated with an increased risk of acquiring Hr-TB in this study (OR = 3.431, 95%CI: 0.792 ~ 14.854, P = 0.099). So, we put it into the multivariate logistic regression equation (Table 2).

Table 1 Baseline characteristics of study participants

Characteristic	Hr-TB (*n* = 44)	DS-TB (*n* = 235)	Test χ2/Z	*P* value
Age, Median (IQR)	57.00 (46.25-64.00)	57.00 (47.00–67.00)	-0.726	0.468
Age group, n (%)			0.139	0.709
18–59	23 (52.3%)	130 (55.3%)		
>=60	21 (47.7%)	105 (44.7%)		
Male sex, n (%)	38 (86.4%)	197 (83.8%)	0.179	0.672
BMI (kg/m2), Median (IQR)	21.35 (20.35–24.10)	21.72 (19.53–24.09)	-0.522	0.602
BMI group, n (%)			1.262	0.532
< 18.5, n (%)	5 (11.4%)	43 (18.3%)		
18.5 - <25, n (%)	31 (70.5%)	154 (65.5%)		
≥ 25, n (%)	8 (18.2%)	38 (16.2%)		
Tuberculosis treatment, n (%)	11 (25.0%)	27 (11.5%)	5.750	0.016*
Ever-smoker, n (%)	16 (36.4%)	81 (34.5%)	0.059	0.809
Alcohol, n (%)	11 (25.0%)	44 (18.7%)	0.922	0.337
Race (Han), n (%)	43 (97.7%)	233 (99.1%)	0.704	0.401
Place of residence			2.243	0.134
Rural, n (%)	2 (4.5%)	33 (14.0%)		
Urban, n (%)	42 (95.5%)	202 (86.0%)		
Education			0.859	0.354
Primary or less, n (%)	7 (15.9%)	52 (22.1%)		
Senior school or Higher, n (%)	37 (84.1%)	183 (77.9%)		
Comorbidities				
HIV status, n (%)	0 (0.0%)	2 (0.9%)	-	1.000
Hypertension, n (%)	9 (20.5%)	77 (32.8%)	2.634	0.105
PTB and EPTB, n (%)	2 (4.5%)	25 (10.6%)	0.954	0.329

Abbreviations: BMI, body mass index; EPTB, extra-pulmonary tuberculosis; Data are median (IQR), n (%), or n/N (%). *$p < 0.05$

Multivariate logistic regression analyzes risk factors for Hr-TB in adult PTB and T2DM

Following the univariate logistic analysis, we incorporated history of previous tuberculosis treatment, poor FPG control [5], serum iron levels ≥ 14.3 μmol/l, and urban residence into the binary regression equation, which was established using the enter method. The results demonstrated the history of previous tuberculosis treatment (OR = 2.348, 95%CI: 1.025 ~ 5.379, P = 0.044), poor FPG control (OR = 2.402, 95%CI: 1.208 ~ 4.776, P = 0.012), and serum iron levels ≥ 14.3 μmol/l (OR = 2.808, 95%CI: 1.334 ~ 5.910, P = 0.007) are significant risk factors for adult Hr-TB with T2DM (Table 3).

Analysis of risk factor for Hr-TB in adult PTB and T2DM in different subgroup

In the subgroup analysis of Newly treatment tuberculosis patients, a multivariate analysis revealed compelling evidence that both poor FPG control (OR = 2.296, 95%CI: 1.073 ~ 4.915, P = 0.032), and serum iron levels ≥ 14.3 μmol/l (OR = 2.418, 95%CI: 1.048 ~ 5.577, P = 0.038) were significantly associated with an elevated risk of Hr-TB with T2DM (Table 4).

However, in the subgroup of patients with a history of previous tuberculosis treatment, there was insufficient evidence to suggest that poor FPG control and serum iron levels ≥ 14.3 μmol/l were associated with an increased risk of Hr-TB with T2DM (Table 4).

Discussion

As the core anti-tuberculosis drug, the resistance rate of isoniazid has increased significantly in recent years [7]. The 2019 Global Tuberculosis Report [20] noted that the global level of Hr-TB between 2002 and 2018 was 7.2% (95% CI: 6.2–8.2%) in Newly treatment tuberculosis patients and 11.6% (95% CI: 9.9–13.3%) in a history of previous tuberculosis treatment patients. Compared with susceptible tuberculosis, patients with Hr-TB have a lower success rate and are at risk of further increasing resistance to other drugs [21, 22]. The above facts should raise concerns on Hr-TB.

The concurrent studies of our group suggest [12] that T2DM (OR = 1.472, 95%CI: 1.037 ~ 2.088, P = 0.030) and history of previous tuberculosis treatment (OR = 2.913, 95%CI: 1.971 ~ 4.306, P = 0.000) are independent risk factors for Hr-TB in adults. Song W M reported [11] that diabetes was identified as a risk factor of total drug-resistant tuberculosis (DR-TB), Poly-resistant tuberculosis (PDR-TB), Streptomycin (SM) resistance and isoniazid + streptomycin resistance among newly diagnosed TB cases, consistent with our findings. The occurrence of these phenomena may involve HBA1C levels and hyperglycemia affecting the delayed absorption/faster

Table 2 Univariate logistic regression analysis of risk factor for Hr-TB in DM-PTB patients

Variable	Hr-TB (*n* = 44)	DS-TB (*n* = 235)	Unadjusted OR (95% CI)	*P* value
Male, n (%)	38 (86.4%)	197 (83.8%)	1.222 (0.483–3.091)	0.673
Age, Median (IQR)	57.00 (46.25-64.00)	57.00 (47.00–67.00)	0.990 (0.966–1.014)	0.412
Age group, n (%)				
18–59	23 (52.3%)	130 (55.3%)		
>=60	21 (47.7%)	105 (44.7%)	1.130 (0.593–2.155)	0.710
BMI (kg/m2), Median (IQR)	21.35 (20.35–24.10)	21.72 (19.53–24.09)	1.049 (0.955–1.153)	0.321
BMI group, n (%)				
< 18.5, n (%)	5 (11.4%)	43 (18.3%)	0.578 (0.212–1.575)	0.284
18.5 - <25, n (%)	31 (70.5%)	154 (65.5%)		0.539
≥ 25, n (%)	8 (18.2%)	38 (16.2%)	1.046 (0.445–2.458)	0.918
Hypertension, n (%)	9 (20.5%)	77 (32.8%)	0.528 (0.242–1.153)	0.109
Tuberculosis treatment, n (%)	11 (25.0%)	27 (11.5%)	2.568 (1.164–5.666)	0.020*
PTB and EPTB, n (%)	2 (4.5%)	25 (10.6%)	0.400 (0.091–1.753)	0.224
Ever-smoker, n (%)	16 (36.4%)	81 (34.5%)	1.086 (0.556–2.124)	0.809
Alcohol, n (%)	11 (25.0%)	44 (18.7%)	1.447 (0.679–3.085)	0.339
Urban, n (%)	42 (95.5%)	202 (86.0%)	3.431 (0.792–14.854)	0.099
Bilateral pulmonary infiltration, n (%)	36 (81.8%)	186 (79.1%)	1.185 (0.518–2.714)	0.687
Lung Cavity, n (%)	27 (61.4%)	150 (63.8%)	0.900 (0.464–1.746)	0.755
MLR, Median (IQR)	0.43 (0.31–0.71)	0.51 (0.33–0.72)	0.676 (0.254–1.802)	0.433
MLR ≥ 0.5, n (%)	18 (40.9%)	122 (51.9%)	0.641 (0.334–1.232)	0.182
NLR, Median (IQR)	4.11 (2.49–5.35)	4.07 (2.82–6.48)	0.969 (0.904–1.038)	0.371
PNI, Median (IQR)	45.33 (40.43–48.74)	42.40 (37.85-47.00)	1.025 (0.982–1.070)	0.263
PNI ≥ 40, n (%)	34 (77.3%)	152 (64.7%)	1.857 (0.873–3.947)	0.108
Fasting blood glucose, Median (IQR)	8.73 (5.55–10.59)	7.14 (5.61–9.67)	1.040 (0.966–1.120)	0.296
Poor fasting glycemic control, n (%)	27 (61.4%)	94 (40.0%)	2.382 (1.231–4.612)	0.010*
Glycated hemoglobin, Median (IQR)	9.20 (7.13–10.88)	9.20 (7.40–11.20)	0.949 (0.821–1.098)	0.481
Poor control of glycated hemoglobin, n (%)	33 (75.0%)	175 (74.5%)	1.029 (0.489–2.162)	0.941
Serum iron level, Median (IQR)	10.90 (6.60-15.18)	8.50 (4.80–12.50)	1.057 (1.006–1.110)	0.028*
Serum iron level ≥ 14.3umol/l, n (%)	15 (34.1%)	39 (16.6%)	2.599 (1.276–5.297)	0.009*

Abbreviations: BMI, body mass index; OR, odds ratio; EPTB, extra-pulmonary tuberculosis; PNI, prognostic nutritional index= [serum albumin (ALB) (g/L) + 5 × total lymphocyte count (109/L)]; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; FBG, fasting blood glucose; Data are median (IQR), n (%), or n/N (%). *$p < 0.05$

Table 3 Multivariate logistic regression analysis of risk factor for Hr-TB in DM-PTB patients

Variable	β	S.E.	Wald	adjusted OR(95% CI)	*P* value
Tuberculosis treatment(1)	0.854	0.423	4.072	2.348(1.025–5.379)	0.044*
Urban(1)	1.453	0.770	3.562	4.275(0.946–19.325)	0.059
Poor fasting glycemic control	0.876	0.351	6.246	2.402(1.208–4.776)	0.012*
Serum iron level ≥ 14.3umol/l	1.033	0.380	7.398	2.808(1.334–5.910)	0.007*

Variables with P < 0.1 were selected in the multivariate logistic regression equation using the stepwise forward selection method

elimination of isoniazid [13, 14]. It has also been reported that Diabetes Mellitus is associated with genotypic resistance to at least one anti-tuberculosis drug [23]. However, further research is needed on whether there are other causes of Hr-TB in adult patients with diabetes.

Based on this, we included nutrition, immunity, serum iron, and blood glucose control levels, and used binary logistic regression to explore the risk factors for Hr-TB in adult patients with T2DM. After excluding other interfering factors, it was uncovered that a history of anti-tuberculosis therapy, unsatisfactory FPG control, and serum iron levels ≥ 14.3 μmol/l were independent risk factors for Hr-TB with T2DM.

History of anti-TB therapy is a risk factor for MDR-TB [24], supporting history of anti-tuberculous therapy as an independent risk factor for the development of DR-TB.

The literature [14] confirmed that HbA1C is a risk factor for isoniazid resistance, but the results of this study suggest that the HbA1C in patients with T2DM cannot be considered as an independent risk factor for Hr-TB, whereas FPG control is an independent risk factor for Hr-TB in patients with T2DM. Different outcome causes may involve different ranges of isoniazid resistance definitions. Whereas some of the study subjects were isoniazid mono-resistant patients, this study was conducted in patients with Hr-TB and not in patients with RR-TB. In

Table 4 Univariate and multivariate logistic regression analysis of risk factor for Hr-TB in different stratification

Variable	Hr-TB (*n* = 44)	DS-TB (*n* = 235)	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Newly treatment, n (%)	33 (75.0%)	208 (88.5%)				
Male, n (%)	27 (81.8%)	173 (83.2%)	0.910 (0.350–2.369)	0.847		
Age, Median (IQR)	60.00 (46.50–64.00)	57.00 (47.00–67.00)	0.993 (0.966–1.020)	0.605		
Age group, n (%)						
18–59	15 (45.5%)	116 (55.8%)				
>=60	18 (54.5%)	92 (44.2%)	1.513 (0.723–3.164)	0.271		
BMI (kg/m2), Median (IQR)	21.26 (20.45–24.49)	21.74 (19.58–24.07)	1.052 (0.945–1.171)	0.351		
BMI group, n (%)						
< 18.5, n (%)	4 (12.1%)	37 (17.8%)	0.668 (0.217–2.060)	0.483		
18.5 - <25, n (%)	22 (66.7%)	136 (65.4%)		0.655		
≥ 25, n (%)	7 (21.2%)	35 (16.8%)	1.236 (0.489–3.128)	0.654		
Hypertension, n (%)	7 (21.2%)	67 (32.2%)	0.567 (0.234–1.371)	0.208		
PTB and EPTB, n (%)	2 (6.1%)	21 (10.1%)	0.575 (0.128–2.573)	0.469		
Ever-smoker, n (%)	12 (36.4%)	69 (33.2%)	1.151 (0.535–2.476)	0.719		
Alcohol, n (%)	10 (30.3%)	37 (17.8%)	2.009 (0.882–4.576)	0.097	2.027 (0.861–4.776)	0.106
Urban, n (%)	32 (97.0%)	180 (86.5%)	4.978 (0.654–37.893)	0.121		
Bilateral pulmonary infiltration, n (%)	27 (81.8%)	162 (77.9%)	1.278 (0.498–3.282)	0.611		
Lung Cavity, n (%)	19 (57.6%)	132 (63.5%)	0.781 (0.371–1.647)	0.517		
MLR, Median (IQR)	0.47 (0.33–0.75)	0.50 (0.32–0.72)	0.976 (0.367–2.599)	0.962		
MLR ≥ 0.5, n (%)	15 (45.5%)	106 (51.0%)	0.802 (0.384–1.676)	0.557		
NLR, Median (IQR)	4.29 (2.53–5.59)	4.06 (2.87–6.35)	0.972 (0.899–1.051)	0.474		
PNI, Median (IQR)	45.65 (39.55–49.48)	42.25 (37.74–46.84)	1.023 (0.974–1.075)	0.366		
PNI ≥ 40, n (%)	25 (75.8%)	132 (63.5%)	1.799 (0.733–4.187)	0.173		
Fasting blood glucose, Median (IQR)	8.62 (5.26–10.43)	6.82 (5.50–9.58)	1.063 (0.968–1.167)	0.203		
Poor fasting glycemic control, n (%)	19 (57.6%)	79 (38.0%)	2.216 (1.052–4.668)	0.036*	2.296 (1.073–4.915)	0.032*
Glycated hemoglobin, Median (IQR)	9.30 (7.15–10.90)	9.20 (7.33–11.18)	0.958 (0.809–1.133)	0.613		
Poor control of glycated hemoglobin, n (%)	25 (75.8%)	155 (74.5%)	1.069(0.454–2.513)	0.879		
Serum iron level, Median (IQR)	11.10 (6.15–15.15)	7.70 (4.80-12.15)	1.042 (0.983–1.104)	0.169		
Serum iron level ≥ 14.3umol/l, n (%)	11 (33.3%)	34 (16.3%)	2.559 (1.136–5.762)	0.023*	2.418 (1.048–5.577)	0.038*
Previously treatment	11 (25.0%)	27 (11.5%)				
Male, n (%)	11 (100.0%)	24 (88.9%)	740425839.5 (0.000-)	0.999		
Age, Median (IQR)	56.00 (46.00–64.00)	57.00 (48.00–67.00)	0.976 (0.920–1.034)	0.407		
Age group, n (%)						
18–59	8 (72.7%)	14 (51.9%)				
>=60	2 (27.3%)	13 (48.1%)	0.404 (0.088–1.859)	0.244		
BMI (kg/m2), Median (IQR)	21.43 (19.59–23.73)	21.60 (19.03–24.22)	1.060 (0.856–1.313)	0.591		
BMI group, n (%)						
< 18.5, n (%)	1 (9.1%)	6 (22.2%)	0.333 (0.035–3.205)	0.341		
18.5 - <25, n (%)	9 (81.8%)	18 (66.7%)		0.621		
≥ 25, n (%)	1 (9.1%)	3 (11.1%)	0.667 (0.060–7.352)	0.741		
Hypertension, n (%)	2 (18.2%)	10 (37.0%)	0.378 (0.068–2.109)	0.267		
PTB and EPTB, n (%)	0 (0.0%)	4 (14.8%)	0.000 (0.000-)	0.999		
Ever-smoker, n (%)	4 (36.4%)	12 (44.4%)	0.714 (0.169–3.027)	0.648		
Alcohol, n (%)	1 (9.1%)	7 (25.9%)	0.286 (0.031–2.653)	0.271		
Urban, n (%)	10 (90.9%)	22 (81.5%)	2.273 (0.234–22.074)	0.479		
Bilateral pulmonary infiltration, n (%)	9 (81.8%)	24 (88.9%)	0.563 (0.080–3.939)	0.562		
Lung Cavity, n (%)	8 (72.7%)	18 (66.7%)	1.333 (0.283–6.279)	0.716		
MLR, Median (IQR)	0.40 (0.22–0.54)	0.57 (0.34–0.70)	0.046 (0.001–1.684)	0.094		
MLR ≥ 0.5, n (%)	3 (27.3%)	16 (59.3%)	0.258 (0.056–1.194)	0.083		
NLR, Median (IQR)	3.04 (1.88–4.64)	4.40 (1.88–6.91)	0.969 (0.848–1.107)	0.642		

Table 4 (continued)

Variable	Hr-TB (*n* = 44)	DS-TB (*n* = 235)	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
PNI, Median (IQR)	45.00 (40.65–48.70)	43.75 (39.10–47.70)	1.024 (0.932–1.125)	0.620		
PNI ≥ 40, n (%)	9 (81.8%)	20 (74.1%)	1.575 (0.272–9.131)	0.612		
Fasting blood glucose, Median (IQR)	8.90 (6.70-10.68)	8.47 (6.89–11.02)	0.964 (0.825–1.126)	0.642		
Poor fasting glycemic control, n (%)	8 (72.7%)	15 (55.6%)	2.133 (0.463–9.839)	0.331		
Glycated hemoglobin, Median (IQR)	7.80 (6.70–10.80)	9.10 (7.80–11.40)	0.920 (0.688–1.231)	0.576		
Poor control of glycated hemoglobin, n (%)	8 (72.7%)	20 (74.1%)	0.933 (0.192–4.539)	0.932		
Serum iron level, Median (IQR)	10.70(9.20–19.40)	11.40 (7.40–13.70)	1.079 (0.966–1.205)	0.180		
Serum iron level ≥ 14.3umol/l, n (%)	4 (36.4%)	5 (18.5%)	2.514 (0.525–12.036)	0.248		

Note: BMI classification criteria: underweight (BMI < 18.5 kg/m2), normal weight (BMI 18.5 to < 25 kg/m2), overweight or obese (BMI ≥ 25 kg/m2)

the next step, we can expand the samples and continue to stratify based on HbA1C.

A serum iron level ≥ 14.3 μmol/l is an independent risk factor for adult Hr-TB patients with T2DM. Drug-resistant Mycobacterium tuberculosis strains have been reported to three times higher iron levels than drug-susceptible strains [25], consistent with the results of this research. The mechanism needs to be considered as follows: (1) According to previous reports [26–29], iron is required for the growth and reproduction of Mycobacterium tuberculosis in host macrophages, and plays a key role in the growth, pathogenicity, immune evasion, and host adaptation of Mycobacterium tuberculosis. (2) Mycobacterium tuberculosis has two iron uptake regulators, ferric uptake regulator (Fur) and iron-dependent repressor and activator (IdeR), among which the FurA gene, a homolog of Fur, is located upstream of KatG encoding catalase-peroxidase (a common resistance gene in isoniazid) [30]; Another IdeR protein regulates genes involved in iron acquisition and storage, such as genes encoding siderophore production and transport, siderophore, ferritin, and bacterial ferritin, as well as genes involved in the assembly of iron-sulfur clusters and genes encoding metabolic enzymes and iron cofactors [31]. (3) At the transcriptional level, actinomycetes-specific WhiB transcription factors and transcription initiation factor Sigma play a role in regulating drug resistance, with WhiB7 belonging to the actinomycetes-specific Fe-S-containing transcription factor family [32]. (4) There is a close relationship between siderophore secretion and drug efflux in Mycobacterium tuberculosis [33]. The efflux pump Rv1258c, which belongs to the major promoter superfamily (MFS), not only has the function of regulating drug resistance of Mycobacterium tuberculosis, but also the novel function of activating oxidative stress and regulating ESX-3-related iron metabolism in Mycobacterium tuberculosis [34]. (5) Increased dietary iron intake is strongly associated with prognosis during Mycobacterium tuberculosis infection [35]. The above evidence.

suggests a possible correlation between serum iron level and isoniazid resistance. However, further research is needed on the specific mechanisms between iron metabolism, Mycobacterium tuberculosis, and isoniazid resistance.

This study has certain limitations, such as potential biases (e.g., selection bias in single-center design) or unmeasured confounders (e.g., dietary iron intake or adherence to a history of previous tuberculosis treatment). We also did not further analyses of serum iron levels in patients with Hr-TB without T2DM, although iron is important for TB resistance. The next step we can choose genetic studies to explore how iron is involved in the comorbid group of Hr-TB. We can verify the risk factors and confounders with a prospective study and a proper sample size with a good power of study before venturing on genetic studies.

This study addresses T2DM and Hr-TB comorbidities, which affect public health, and elucidates relevant risk factors such as serum iron levels. Which allow us to raise awareness of Hr-TB in adult patients with T2DM, and improving glycemic control or monitoring serum iron levels to reduce Hr-TB risk. To achieve the goal of accurate diagnosis, early drug resistance screening, and reasonable treatment plans for patients with PTB and T2DM.

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Author contributions
Guo Jing, Zhang Xia, Feng Xuebing, and Lin Feishen designed the study. Pang Jialei and Cao Zhiyun collected data. Cai Min and Li Wenchao performed the statistical analyses and outcome assessments. Guo Jing prepared the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets generated and analyzed during the current study are not publicly available due to the fact that it contains personal information, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study has passed the ethics committee conformation of the Second Hospital of Nanjing (2023-LY-kt02). All experimental protocols were approved by an ethics committee of the Second Hospital of Nanjing. As this was a retrospective study, we could not access/provide informed consents from all the patients (whose data are used for research), hence the ethics committee of the Second Hospital of Nanjing waived the informed consent. Our research involving human participants, human material, or human data, have been performed in accordance with the Declaration of Helsinki. And all methods were carried out in accordance with relevant guidelines and regulations in the declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Magliano DJ, Boyko E, J D A. IDF DIABETES ATLAS[M]. Brussels: International Diabetes Federation; 2021.
2. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update[M]. Geneva: World Health Organization; 2022.
3. Liu Q, Lu P, Martinez L, et al. Undiagnosed diabetes mellitus and tuberculosis infection: A population-based, observational study from Eastern China[J]. Diabetes Metab Res Rev. 2020;36(3):e3227.
4. Nguyen CH, Pascopella L, Barry PM. Association between diabetes mellitus and mortality among patients with tuberculosis in California, 2010–2014[J]. Int J Tuberc Lung Dis. 2018;22(11):1269–76.
5. Antituberculosis. Expert consensus. On treatment and management of tuberculosis-diabetes mellitus[J]. J Chin Antituberculosis Association. 2021;43(1):12–22.
6. Rumende CM. Risk factors for Multidrug-resistant Tuberculosis[J]. Acta Med Indones. 2018;50(1):1–2.
7. WHO treatment guidelines for isoniazid-resistant tuberculosis. Supplement to the WHO treatment guidelines for drug-resistant tuberculosis[M]. Geneva: World Health Organization; 2018.
8. Guo J, Pang JL, Gao WW, et al. Phenotypic drug resistance spectrum analysis of adult patients with active pulmonary tuberculosis complicated with diabetes mellitus in Nanjing from 2019 to 2021[J]. Chin J Antituberculosis. 2024;46(01):62–9.
9. Goossens SN, Sampson SL, Van Rie A. Mechanisms of Drug-Induced tolerance in Mycobacterium tuberculosis[J]. Clin Microbiol Rev, 2020,34(1).
10. Walker TM, Miotto P, Koser CU, et al. The 2021 WHO catalogue of Mycobacterium tuberculosis complex mutations associated with drug resistance: A genotypic analysis[J]. Lancet Microbe. 2022;3(4):e265–73.
11. Song WM, Shao Y, Liu JY, et al. Primary drug resistance among tuberculosis patients with diabetes mellitus: a retrospective study among 7223 cases in China[J]. Infect Drug Resist. 2019;12:2397–407.
12. Guo J, Han Y, Zhang X, et al. Risk factors of adult isoniazid-resistant and rifampicin-susceptible tuberculosis in Nanjing, 2019–2021[J]. BMC Infect Dis. 2024;24(1):511.
13. Kumar AK, Chandrasekaran V, Kannan T, et al. Anti-tuberculosis drug concentrations in tuberculosis patients with and without diabetes mellitus[J]. Eur J Clin Pharmacol. 2017;73(1):65–70.
14. Lyu M, Wang D, Zhao J, et al. A novel risk factor for predicting anti-tuberculosis drug resistance in patients with tuberculosis complicated with type 2 diabetes mellitus[J]. Int J Infect Dis. 2020;97:69–77.
15. Chinese Anti-tuberculosis Association. Rules for laboratory examination of tuberculosis. Beijing: People's Medical Publishing House; 2015.
16. Zhao, Yanlin, et al. Standard operating procedures and quality assurance manual for isolation and culture of mycobacteria. People's Health Publishing House; 2013.
17. National health and family planning commission of the People's Republic of China. WS 288–2017 National Diagnosis for Pulmonary Tuberculosis. (2017-12-12). [2019-11-1].
18. LI Ch ZHOUJ. Interpretation of standards of medical care in Diabetes-2019[J]. Chin J Front Med Science(Electronic Version). 2019;11(01):66–74.
19. Physical status. The use and interpretation of anthropometry. Report of a WHO expert Committee[J]. Volume 854. World Health Organ Tech Rep Ser; 1995. pp. 1–452.
20. WHO guidelines on tuberculosis infection prevention. And control: 2019 update[M]. Geneva: World Health Organization; 2019.
21. Karo B, Kohlenberg A, Hollo V et al. Isoniazid (INH) mono-resistance and tuberculosis (TB) treatment success: analysis of European surveillance data, 2002 to 2014[J]. Euro Surveill. 2019;24(12).
22. Araujo-Pereira M, Arriaga MB, Carvalho A, et al. Isoniazid monoresistance and antituberculosis treatment outcome in persons with pulmonary tuberculosis in Brazil[J]. Open Forum Infect Dis. 2024;11(1):ofad691.
23. Ruesen C, Chaidir L, Ugarte-Gil C et al. Diabetes is associated with genotypically drug-resistant tuberculosis[J]. Eur Respir J, 2020,55(3).
24. Bagcchi S. WHO's global tuberculosis report 2022[J]. Lancet Microbe. 2023;4(1):e20.
25. Le J, Liu LR, Xie JP, et al. Comparison of the proteome of Mycobacterium tuberculosis Isoniazid susceptible strain with Isoniazid resistant strain[J]. Chin J Microbiol Immunol. 2004;24(04):258–62.
26. Abreu R, Giri P, Quinn F. Host-Pathogen interaction as a novel target for Host-Directed therapies in Tuberculosis[J]. Front Immunol. 2020;11:1553.
27. Li Y, Li Y, Liu Y, et al. Iron-related gene mutations driving global Mycobacterium tuberculosis transmission revealed by whole-genome sequencing[J]. BMC Genomics. 2024;25(1):249.
28. Arnold FM, Weber MS, Gonda I, et al. The ABC exporter IrtAB imports and reduces mycobacterial siderophores[J]. Nature. 2020;580(7803):413–7.
29. Pandey M, Talwar S, Bose S, et al. Iron homeostasis in Mycobacterium tuberculosis is essential for persistence[J]. Sci Rep. 2018;8(1):17359.
30. Pym AS, Domenech P, Honore N, et al. Regulation of catalase-peroxidase (KatG) expression, Isoniazid sensitivity and virulence by FurA of Mycobacterium tuberculosis[J]. Mol Microbiol. 2001;40(4):879–89.
31. Dussurget O, Smith I. Interdependence of mycobacterial iron regulation, oxidative-stress response and Isoniazid resistance[J]. Trends Microbiol. 1998;6(9):354–8.
32. Lilic M, Darst SA, Campbell EA. Structural basis of transcriptional activation by the Mycobacterium tuberculosis intrinsic antibiotic-resistance transcription factor WhiB7[J]. Mol Cell. 2021;81(14):2875–86.
33. Meikle V, Zhang L, Niederweis M. Intricate link between siderophore secretion and drug efflux in Mycobacterium tuberculosis[J]. Antimicrob Agents Chemother. 2023;67(10):e0162922.
34. Sun H, Sheng G, Xu Y, et al. Efflux pump Rv1258c activates novel functions of the oxidative stress and via the VII secretion system ESX-3-mediated iron metabolic pathway in Mycobacterium tuberculosis[J]. Microbes Infect. 2024;26(1–2):105239.
35. Boelaert JR, Vandecasteele SJ, Appelberg R, et al. The effect of the host's iron status on tuberculosis[J]. J Infect Dis. 2007;195(12):1745–53.

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