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ORIGINAL RESEARCH

Sex-Specific Differences in the Clinical Profile Among Patients with Tracheobronchial Tuberculosis: A Hospital-Based Cross-Sectional Study in Shenzhen, China

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Purpose: Tracheobronchial tuberculosis (TBTB) has been proposed to occur more commonly in female patients. However, to date, studies that systematically delineate differences between female and male patients with TB infection are lacking. We aimed to comprehensively assess the sex-specific differences in clinical manifestation, bronchoscopy performance, bacteriological examination, and imaging of TBTB in Shenzhen, China.

Methods: All patients with diagnosed TBTB from August 1, 2018 to July 31, 2021 at The Third People's Hospital of Shenzhen were enrolled in the present study. Demographic information, clinical manifestations, blood tests, chest computed tomography, and bronchoscopic findings were collected, and assessed their sex-specific differences.

Results: Of these 331 patients, 238 patients (71.9%) were female, and 93 patients (28.1%) were male, with an overall average age of 37.3 years. The average age of male patients with TBTB was more than 5 years older than that of female patients. The prevalence of lymph fistula and diabetes mellitus was significantly higher in male patients than female patients (8.6% vs 1.7%, $P = 0.005$; 17.2% vs 2.1%, $P < 0.001$). The positive proportion of sputum smear was higher in male patients (27.9%) than in female patients (16.7%, $P = 0.026$). Moreover, the mean monocyte-to-lymphocyte ratio, serum CRP, and IL-6 levels were significantly higher in male patients than in female patients ($P < 0.05$).

Conclusion: In summary, in patients with TBTB diagnosis, male sex was associated with a high prevalence of diabetes mellitus, lymph fistula, and smear-positive ratio, as well as high inflammation levels. The management of young female and male patients with diabetes mellitus and high inflammation levels should be strengthened. Furthermore, to reduce the burden of TBTB, we must pay attention to the risk of TBTB in past tuberculosis patients, especially male patients under 45 years old and female patients over 45 years old.

Keywords: sex difference, tracheobronchial tuberculosis, inflammation

Introduction

Pulmonary tuberculosis (TB), caused by *Mycobacterium tuberculosis* complex, is the ninth leading cause of death worldwide and remains a major global public health priority.[1] According to the World Health Organization, there are approximately 10.0 million people with TB disease, and 1.4 million deaths from TB occurred in 2019.[2] Tracheobronchial TB (TBTB) is

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a special type of TB infecting the tracheobronchial tree that could affect any part and any layer of the tracheobronchial wall.[3,4] TBTB is present in approximately 4.1–54.3% of patients with active TB.[5] Moreover, more than two-thirds of patients develop severe bronchial stenosis and stricture formation despite adequate medical treatment.[6–8] Refractory tracheobronchial stenosis may eventually lead to a decline in pulmonary function, respiratory failure, or death.[9]

In previous studies, TBTB was more common in female than male adult patients.[5,10–12] Moreover, a large-scale, multi-center, prospective investigation revealed the risk of TBTB in female patients is 1.53 higher than in male patients in southern China. In addition, another prospective study in a tertiary referral hospital in Korea found female sex is an important risk factor for both TBTB and severe bronchostenosis.[5] A possible explanation might be that the bronchial lumen size is smaller in female patients than in patients, and thus female patients would not actively expectorate to the same degree as male patients.[11–13] Furthermore, long-term exposure to sputum may make female patients more vulnerable to tubercle bacilli infection. Accordingly, different anatomy, living habits, and sociocultural and esthetic factors might lead to sex-specific differences in susceptibility to TBTB, including the clinical manifestations and prognosis. However, there is a paucity of studies systematically examining the differences between female patients and male patients with TB infection.

Therefore, this study aimed to comprehensively assess the sex-specific differences in the clinical manifestation, bronchoscopy performance, bacteriological examination, and imaging of TBTB in Shenzhen, China, from 2018 to 2021.

Methods

Study Population

All patients with diagnosed TBTB from August 1, 2018 to July 31, 2021 at The Third People's Hospital of Shenzhen were enrolled in the present study. The Third People's Hospital of Shenzhen is the largest specialized TB hospital in Shenzhen and undertakes the prevention, diagnosis, and treatment of TB infection in Shenzhen.

The following patients were excluded: (1) those younger than 18 years, (2) those with serious cardiopulmonary diseases, (3) those unable to tolerate bronchoscopy, and (4) bronchoscopy and pathological examination showed nontuberculous tracheobronchial lesions.

The present study was approved by the Ethics Committee of The Third People's Hospital of Shenzhen and conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from all patients.

Diagnostic Criteria for TBTB

The TBTB diagnosis and treatment guidelines in China were adopted;[14] TBTB was diagnosed based on visible tracheobronchial lesions under bronchoscopy and either (1) pathological diagnosis of TB; (2) positive acid-fast bacilli (AFB) in a sputum smear, brushing smear, or bronchial alveolar lavage fluid; (3) positive *M. tuberculosis* culture; or (4) typical TB pathologic changes on bronchoscopy biopsy. All patients in this study underwent bronchoscopy and pathological examination to ensure the accuracy of diagnosis.

Physical Examinations

All data were obtained from the hospital medical record system, including demographic information (including name, sex, date of birth, and educational level), individual medical history (including the presence of hypertension, diabetes mellitus, coronary artery disease, and previous TB), and lifestyle factors (including smoking and drinking). The levels of C-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) were tested in the central laboratory of the Third People's Hospital of Shenzhen. The criteria for TB drug resistance classification was referred to the World Health Organization Criteria in 2013.[15]

Imaging Analysis

All patients underwent chest computed tomography examination. The cavity, as defined by the Fleischner Society, is a gas-filled space, seen as a lucency or low-attenuation area, within a nodule, mass, or area of parenchymal consolidation.[16]

Bronchoscopic Examination

Bronchoscopy was performed in all patients. According to the Chinese guidelines for the classification of TBTB,[14] TBTB was classified into six subtypes: inflammatory infiltration, ulceration necrosis, granulation hyperplasia, cicatrices stricture, tracheobronchial malacia, and lymph fistula. Each bronchoscopic examination was reviewed and classified by two pulmonary specialists.

Definitions

Hypertension was defined as a history of hypertension or taking antihypertensive drugs. Diabetes was defined as a fasting blood glucose ≥7.0 mmol/L, taking medication for diabetes, or a self-reported history of diabetes. Smoking was defined as smoking ≥1 cigarette daily for more than 1 year. Drinking was defined as drinking >50 mL of alcohol at least once per week for more than 6 months. Moreover, the participants were categorized into three educational groups according to the length of formal education (0–11, 12–15, and ≥16 years). According to the age classification of the World Health Organization, this study defined the group of <45 years old as the youth group, and the patients over 45 years old as the middle-aged and elderly group.

Statistical Analysis

Continuous variables were summarized by means and standard deviations; Student's *t*-test was used to compare between-group differences. Categorical variables were summarized as numbers with frequencies, and the chi-squared test was performed to compare the differences between the two groups. All statistical analyses were performed using SPSS version 25.0 statistical software (SPSS Inc., Chicago, IL), and two-sided $P < 0.05$ was considered statistically significant.

Results

Demographic Characteristics of All Participants

A total of 331 patients diagnosed with TBTB were analyzed in this study. Of these 331 patients, 238 patients (71.9%) were female, and 93 (28.1%) were male, with an average overall age of 37.3 years. The mean age of the male patients was higher than that of the female patients (41.10 years vs 35.85 years $P= 0.005$). The prevalence of diabetes mellitus was 6.3% overall, 17.2% in male patients, and 2.1% in female patients ($P < 0.001$). Male patients had a higher prevalence of smoking and drinking compared to that of female patients (all $P < 0.05$) (Table 1).

Clinical Characteristics for Patients with TBTB Between Sex Groups

The frequency of lymph fistula was 3.6% overall and was significantly higher in male patients than in female patients (8.6% vs 1.7%; $P = 0.005$). The positive proportion of sputum smear was higher in male patients than in female patients (27.9% vs 16.7%, $P = 0.026$). Moreover, the mean monocyte-to-lymphocyte ratio and serum CRP level were significantly higher in men than in women ($P < 0.05$; Table 2).

Clinical Characteristics Between Sex Groups Among Patients with TBTB Younger Than 45 Years

Among all 234 patients aged <45 years old, male patients accounted for 22.6% (n = 53). Compared to female patients, male patients were more likely to have higher frequency of diabetes (5.7% vs 0; $P = 0.011$), smoking (17% vs 0.6%; $P < 0.001$), pulmonary TB history (26.4% vs 10.5%, $P = 0.003$), and lymph fistula (7.5% vs 1.1%; $P = 0.025$). Moreover, there was no statistical difference in inflammatory indicators between the sex groups (all $P > 0.05$; Table 3).

Table 1 Demographic Characteristics for All Patients with Tracheobronchial Tuberculosis

Category	Male	Female	Total	*P*
Total:	93 (28.1)	238 (71.9)	331 (100)	–
Age, means (SD)	41.10 (15.76)	35.85 (13.61)	37.3 (14.41)	0.005
Age groups, years				0.006
0~30	28 (30.1)	89 (37.4)	117 (35.3)	
30~44	25 (26.9)	92 (38.7)	117 (35.3)	
45~54	23 (24.7)	29 (12.2)	52 (15.7)	
≥ 55	17 (18.3)	28 (11.8)	45 (13.6)	
Education, n (%)				0.711
0~11 years	26 (32.5)	78 (37.7)	104 (36.2)	
12~15 years	31 (38.8)	73 (35.3)	104 (36.2)	
≥ 16 years	23 (28.7)	56 (27.1)	79 (27.5)	
Hypertension, n (%)	5 (5.4)	4 (1.7)	9 (2.7)	0.063
Diabetes, n (%)	16 (17.2)	5 (2.1)	21 (6.3)	< 0.001
Coronary artery disease, n (%)	1 (1.1)	2 (0.8)	3 (0.9)	0.842
Smoking, n (%)				< 0.001
No	71 (76.3)	237 (99.6)	308 (93.1)	
Yes	22 (23.7)	1 (0.4)	23 (6.9)	
Drinking, n (%)				< 0.001
No	86 (92.5)	236 (99.2)	322 (97.3)	
Yes	7 (7.5)	2 (0.8)	9 (2.7)	

Abbreviation: SD, standard deviation.

Clinical Characteristics Between Sex Groups Among Patients with TBTB 45 Years or Older

Among patients aged 45 years old and over, male patients were more likely than female patients to have a higher frequency of diabetes (32.5% vs 8.8; $P = 0.003$), smoking (32.5% vs 0; $P < 0.001$), and positive proportion of sputum smear (40.5% vs 16.7%, $P = 0.011$). But the frequency of expectoration (82.5% vs 57.5%; $P = 0.007$), and pulmonary TB history (22.8% vs 7.5%, $P = 0.046$) was higher in female patients than in male patients. Moreover, the mean monocyte-to-lymphocyte ratio, serum CRP, and IL6 levels were significantly higher in male patients than in female patients (all $P < 0.05$; Table 4).

Discussion

In this study, the epidemiology and clinical manifestations of TBTB in different genders were analyzed by the combined method of bronchoscopy and pathology. In the present study, TBTB occurred mainly in young female patients. Male TBTB patients were more complicated with diabetes and lymphatic fistula, and the positive ratio of sputum smear, CRP, and IL-6 were significantly higher than those of female patients. Notably, the prevalence of prior TB history was significantly higher in men than in women patients younger than 45 years; however, women were significantly higher than men in patients 45 years and older.

The size of the bronchial lumen of women is smaller than that of men, and sputum retention may make the bronchial lumen more susceptible to infection by Mycobacterium tuberculosis.[11,17] Therefore, TBTB is more common in women.[5] Previous studies have showed that female younger than 50 years old is an independent risk factor for TBTB.[18] In addition, studies have shown that smoking may be a protective factor for TBTB, making it difficult for Mycobacterium tuberculosis to invade the trachea and bronchi.[19] Since the smoking rate of men is significantly higher than that of women, this may be the reason why the prevalence of TBTB in men is lower than that in women in this study. The results of this study found that male tuberculosis patients younger than 45 years old and female tuberculosis patients older than

Table 2 Clinical Characteristics for Patients with Tracheobronchial Tuberculosis Between Sex Groups

Category	Male	Female	Total	*P*
Clinical manifestation:				
Cough, n (%)	88 (95.7)	232 (97.5)	320 (97.0)	0.385
Expectoration, n (%)	63 (67.7)	181 (76.1)	244 (73.7)	0.123
Haemoptysis, n (%)	4 (4.3)	11 (4.6)	15 (4.5)	0.900
Fever, n (%)	15 (16.1)	31 (13.0)	46 (13.9)	0.463
Extrapulmonary TB, n (%)	11 (11.8)	28 (11.8)	39 (11.8)	0.987
History of tuberculosis, n (%)	17 (18.3)	32 (13.4)	49 (14.8)	0.266
Drug-resistant, n (%)				0.846
No	84 (90.3)	218 (92.0)	302 (91.5)	
Monoresistant tuberculosis	4 (4.3)	6 (2.5)	10 (3.0)	
Polydrug-resistant tuberculosis	5 (5.4)	13 (5.5)	18 (5.5)	
CT Cavity, n (%)	14 (15.1)	30 (12.6)	44 (13.3)	0.555
Location, n (%)				
Trachea	10 (25.0)	12 (21.1)	22 (22.7)	0.648
Main bronchi	11 (27.5)	19 (33.3)	30 (30.9)	0.541
Lobar bronchi	30 (75.0)	47 (82.5)	77 (79.4)	0.372
Bronchoscopic subtypes				
Inflammatory infiltration	16 (17.2)	42 (17.6)	58 (17.5)	0.924
Ulceration necrosis	50 (53.8)	147 (61.8)	197 (59.5)	0.183
Granulation hyperplasia	20 (21.5)	36 (15.1)	56 (16.9)	0.164
Cicatrices stricture	25 (26.9)	74 (31.1)	99 (29.9)	0.452
Tracheobronchial malacia	2 (2.2)	5 (2.1)	7 (2.1)	0.977
Lymph fistula	8 (8.6)	4 (1.7)	12 (3.6)	0.005
Sputum AFB				
Smear positive	24 (27.9)	37 (16.7)	61 (19.8)	0.026
Culture positive	5 (8.9)	17 (10.6)	22 (10.1)	0.728
TB-DNA positive	41 (44.1)	98 (41.2)	139 (42.0)	0.630
Bronchoalveolar lavage fluid AFB				
Smear positive	28 (32.3)	61 (27.5)	89 (28.8)	0.411
Culture positive	8 (14.5)	27 (16.8)	35 (16.2)	0.699
TB-DNA positive	71 (76.3)	169 (71.0)	240 (72.5)	0.328
Laboratory examination				
Monocyte-to-lymphocyte ratio	0.56 (0.31)	0.44 (0.24)	0.47 (0.27)	< 0.001
PCT	0.30 (0.10)	0.30 (0.08)	0.30 (0.09)	0.473
CRP	35.05 (47.68)	23.29 (33.47)	26.67 (38.40)	0.033
IL-6	211.83 (26.44)	14.80 (21.72)	16.66 (23.14)	0.214

Abbreviations: TB, tuberculosis; CT, computerized tomography; AFB, acid-fast bacilli; DNA, deoxyribonucleic acid; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6.

45 years old are more prone to relapse from TBTB. This study supplements the results of previous studies. We must pay attention to the risk of TBTB in past tuberculosis patients, especially male patients under 45 years old and female patients over 45 years old.

Moreover, diabetes is the main risk factor for the development of active and latent tuberculosis.[20,21] People with diabetes are approximately three times more likely to develop tuberculosis than non-diabetics.[22] An Iranian study showed that the majority of DM-TB patients are over 50 years old, and women account for more than half. The prevalence of DM-TB in women is significantly higher than that in men.[23] However, in contrast to the results of this study, the

Table 3 Demographic and Clinical Characteristics Between Sex Groups Among Patients with Tracheobronchial Tuberculosis Younger Than 45 Years Old

Category	Male	Female	Total	*P*
Education, n (%)				0.547
0~11 years	9 (19.6)	42 (26.9)	51 (25.2)	
12~15 years	18 (39.1)	60 (38.5)	78 (38.6)	
≥ 16 years	19 (41.3)	54 (34.6)	73 (36.1)	
Hypertension, n (%)	1 (1.9)	0 (0)	1 (0.4)	0.226
Diabetes, n (%)	3 (5.7)	0 (0)	3 (1.3)	0.011
Coronary artery disease, n (%)	0 (0)	0 (0)	0 (0)	–
Smoking, n (%)				< 0.001
No	44 (83.0)	180 (99.4)	224 (95.7)	
Yes	9 (17.0)	1 (0.6)	10 (4.3)	
Drinking, n (%)				0.129
No	51 (96.2)	180 (99.4)	231 (98.7)	
Yes	2 (3.8)	1 (0.6)	3 (1.3)	
Clinical manifestation:				
Expectoration, n (%)	40 (75.5)	134 (74.0)	174 (74.4)	0.833
Haemoptysis, n (%)	2 (3.8)	9 (5.0)	11 (4.7)	0.717
Fever, n (%)	9 (17.0)	29 (16.0)	38 (16.2)	0.868
Extrapulmonary TB, n (%)	4 (7.5)	18 (9.9)	22 (9.4)	0.599
History of tuberculosis, n (%)	14 (26.4)	19 (10.5)	33 (14.1)	0.003
Drug-resistant, n (%)				0.956
No	49 (92.5)	165 (91.7)	214 (91.8)	
Monoresistant tuberculosis	1 (1.9)	5 (2.8)	6 (2.5)	
Polydrug-resistant tuberculosis	3 (5.7)	10 (5.6)	13 (5.6)	
Cavity, n (%)	6 (11.3)	22 (12.2)	28 (12.0)	0.869
Location, n (%)				
Trachea	12 (22.6)	51 (28.2)	63 (26.9)	0.424
Main bronchi	28 (52.8)	93 (51.4)	121 (51.7)	0.853
Lobar bronchi	35 (66.0)	130 (71.8)	165 (70.5)	0.417
Bronchoscopic subtypes				
Inflammatory infiltration	8 (15.1)	31 (17.1)	39 (16.7)	0.727
Ulceration necrosis	28 (52.8)	114 (63.0)	142 (60.7)	0.183
Granulation hyperplasia	10 (18.9)	28 (15.5)	38 (16.2)	0.555
Cicatrices stricture	16 (30.2)	56 (30.9)	72 (30.8)	0.917
Tracheobronchial malacia	0 (0)	3 (1.7)	3 (1.3)	0.346
Lymph fistula	4 (7.5)	2 (1.1)	6 (2.6)	0.025
Sputum AFB				
Smear positive	9 (18.4)	28 (16.7)	37 (17.1)	0.781
Culture positive	1 (3.5)	14 (11.3)	15 (9.8)	0.201
TB-DNA positive	20 (37.7)	71 (39.2)	91 (38.9)	0.845
Bronchoalveolar lavage fluid AFB				
Smear positive	11 (21.6)	43 (25.6)	54 (24.7)	0.559
Culture positive	4 (14.3)	20 (16.1)	24 (15.8)	0.809
TB-DNA positive	42 (79.2)	130 (71.8)	172 (73.5)	0.282
Laboratory examination				
Monocyte-to-lymphocyte ratio	0.51 (0.30)	0.43 (0.22)	0.45 (0.24)	0.064
PCT	0.29 (0.09)	0.31 (0.09)	0.30 (0.09)	0.447
CRP	24.35 (30.12)	22.66 (33.31)	23.05 (32.54)	0.741
IL6	9.15 (8.62)	16.11 (24.21)	14.63 (21.97)	0.727

Abbreviations: TB, tuberculosis; CT, computerized tomography; AFB, acid-fast bacilli; DNA, deoxyribonucleic acid; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6.

Table 4 Demographic and Clinical Characteristics Between Sex Groups Among Patients with Tracheobronchial Tuberculosis Older Than 45 Years Old

Category	Male	Female	Total	*P*
Education, n (%)				0.120
0~11 years	17 (50.0)	36 (70.6)	53 (62.4)	
12~15 years	13 (38.2)	13 (25.5)	26 (30.6)	
≥ 16 years	4 (11.8)	2 (3.9)	6 (7.1)	
Hypertension, n (%)	4 (10.0)	4 (7.0)	8 (8.2)	0.714
Diabetes, n (%)	13 (32.5)	5 (8.8)	18 (18.6)	0.003
Coronary artery disease, n (%)	1 (2.5)	2 (3.5)	3 (3.1)	0.778
Smoking, n (%)				< 0.001
No	27 (67.5)	57 (100)	84 (86.6)	
Yes	13 (32.5)	0 (0)	13 (13.4)	
Drinking, n (%)				0.079
No	35 (87.5)	56 (98.2)	91 (93.8)	
Yes	5 (12.5)	1 (1.8)	6 (6.2)	
Clinical manifestation:				
Cough, n (%)	36 (92.3)	57 (100)	93 (96.9)	0.064
Expectoration, n (%)	23 (57.5)	47 (82.5)	70 (72.2)	0.007
Haemoptysis, n (%)	2 (5.0)	2 (3.5)	4 (4.1)	1.000
Fever, n (%)	6 (15.0)	2 (3.5)	8 (8.2)	0.062
Extrapulmonary TB, n (%)	7 (17.5)	10 (17.5)	17 (17.5)	0.996
History of tuberculosis, n (%)	3 (7.5)	13 (22.8)	16 (16.5)	0.046
Drug-resistant, n (%)				0.376
No	35 (87.5)	53 (94.6)	88 (91.7)	
Monoresistant tuberculosis	3 (7.5)	1 (1.8)	4 (4.2)	
Polydrug-resistant tuberculosis	2 (5.0)	2 (3.6)	4 (4.2)	
Cavity, n (%)	8 (20.0)	8 (14.0)	16 (16.5)	0.436
Location, n (%)				
Trachea	10 (25.0)	12 (21.1)	22 (22.7)	0.648
Main bronchi	11 (27.5)	19 (33.3)	30 (30.9)	0.541
Lobar bronchi	30 (75.0)	47 (82.5)	77 (79.4)	0.372
Bronchoscopic subtypes				
Inflammatory infiltration	8 (20.0)	11 (19.3)	19 (19.6)	0.932
Ulceration necrosis	22 (55.0)	33 (57.9)	55 (56.7)	0.777
Granulation hyperplasia	10 (25.0)	8 (14.0)	18 (18.6)	0.171
Cicatrices stricture	9 (22.5)	18 (31.6)	27 (27.8)	0.326
Tracheobronchial malacia	2 (5.0)	2 (3.5)	4 (4.1)	0.716
Lymph fistula	4 (10.0)	2 (3.5)	6 (6.2)	0.191
Sputum AFB				
Smear positive	15 (40.5)	9 (16.7)	24 (26.4)	0.011
Culture positive	4 (14.8)	3 (8.1)	7 (10.9)	0.396
TB-DNA positive	21 (52.5)	27 (47.4)	48 (49.5)	0.619
Bronchoalveolar lavage fluid AFB				
Smear positive	17 (47.2)	18 (33.3)	35 (38.9)	0.185
Culture positive	4 (14.8)	7 (18.9)	11 (17.2)	0.667
TB-DNA positive	29 (72.5)	39 (68.4)	68 (70.1)	0.666
Laboratory examination				
Monocyte-to-lymphocyte ratio	0.61 (0.32)	0.45 (0.31)	0.52 (0.32)	0.013
PCT	0.30 (0.11)	0.30 (0.09)	0.30 (0.10)	0.910
CRP	49.58 (61.86)	25.39 (34.23)	35.65 (49.11)	0.032
IL6	38.75 (32.70)	10.74 (10.37)	21.58 (25.47)	0.013

Abbreviations: TB, tuberculosis; CT, computerized tomography; AFB, acid-fast bacilli; DNA, deoxyribonucleic acid; PCT, procalcitonin; CRP, C- reactive protein; IL-6, interleukin-6.

prevalence of DM-TB in men is higher. This study is a single-center study, and the subjects are all hospitalized patients, which is different from the previous population, so there may be differences in the results of the study.

TBTB is difficult to diagnose because of the nonspecific clinical manifestations, chest radiographs, and low incidence of positive acid-fast bacilli staining. In addition, the clinical diagnosis of TBTB mainly relies on bronchoscopic examination,[8] and it is classified into six types based on bronchoscopic findings, including inflammatory infiltration (type I), ulceration necrosis (type II), granulation hyperplasia (type III), cicatrices stricture (type IV), tracheobronchial malacia (type V), and lymph fistula (type VI).[24] Lymph fistula type is a very rare type among the Chinese population.[25] A retrospective study in Wuhan demonstrated that the incidence of VI type was higher in young adults and in male patients, where the prevalence of lymph fistula was significantly higher in male patients than in female patients.[26] Consistent with previous studies, in the present study, the prevalence of lymph fistula in male patients was 5-fold greater than that in female patients.

M. tuberculosis usually invades the respiratory tract via aerosol delivery and interacts with alveolar macrophages, dendritic cells, neutrophils, type II pneumocytes, and epithelial cells in the microenvironment, resulting in the release of a wide array of cytokines, chemokines, and other molecules by different immune cells.[27] A large cross-sectional study demonstrated that serum CRP levels in patients with active TB disease are substantially increased.[28] Moreover, CRP level is associated with severe lung tissue damage.[29] The CRP +1444C/T polymorphism is associated with increased TB risk among men, while no such connection was found in women.[30] Moreover, IL-6 plays a crucial role in the pathogenesis of TB infection, mediating numerous chronic inflammatory and immune processes. The link between IL-6 polymorphisms and TB risk has been investigated.[31] Serum IL-6 level increased significantly in patients with active TB and was correlated with TB-related inflammation.[32,33] In addition, IL-6 is a useful inflammatory marker for unfavorable TB outcomes.[34,35] In this study, the serum CRP level and IL-6 levels in male patients were significantly higher than that in female patients. This may indicate that males have stronger immune responses than females when they are infected with Mycobacterium tuberculosis.

The current data further suggest that the sex-specific immune response might be due to sex hormones. Both estrogens and androgens affect the immune response.[36] Female patients exhibit a higher degree of immunocompetence than do male patients, as indicated by a higher incidence of autoimmune disease. Male sex is associated with high inflammation levels and a less effective immune response; this may be caused by androgens, which can suppress immune reactivity and inflammation reactions, thus resulting in a greater number of infections and more severe infections in male patients.[36,37]

Moreover, the rate of TB history was higher in male patients than in female patients with TBTB aged less than 45 years. The prevalence of lymph fistula and pulmonary TB history was significantly higher in male patients than in female patients with TBTB aged more than 45 years. This conclusion is difficult to explain based on existing knowledge, and it is hoped that further research will be conducted into this phenomenon.

There are certain limitations to this study. First, the investigation was performed at a single site in southern China, so its representation and generalizability are limited. Second, some potential risk factors, including symptom duration and severity of TBTB, were not assessed. Third, the subjects in this study were all diagnosed TBTB patients and did not expand to tuberculosis. Fourth, the information related to radiological findings in this study is limited. Further expanded study is needed. Finally, this was a cross-sectional study, so causal relationships could not be determined.

Perspectives and Significance

It is crucial to monitor the bronchoscopy to reduce the incidence of TBTB for men aged <45 years and women aged ≥45 years.

Conclusion

In summary, in patients diagnosed with TBTB, male sex was associated with a high prevalence of diabetes mellitus, lymph fistula, and smear-positive ratio and high inflammation levels. Although TBTB is more common in female patients, the high inflammation levels in male patients demand attention. To reduce the burden of TBTB, management of young women, men with diabetes mellitus, and high inflammation levels should be strengthened. We must pay attention

to the risk of TBTB in past tuberculosis patients, especially male patients under 45 years old and female patients over 45 years old.

Ethics approval and informed consent

The present study was approved by the Ethics Committee of The Third People's Hospital of Shenzhen and conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from all patients.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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