Comparison of different bacteriological testing strategies and factors for bacteriological confirmation among pulmonary TB patients: a retrospective study in Tianjin, China, 2017-2018

Guoqin Zhang (✉ zhanggq.cn@163.com)
Tianjin Center for Tuberculosis Control  https://orcid.org/0000-0001-7229-5248

Yuhua Zhang
Tianjin Center for Tuberculosis Control

Mingting Chen
Chinese Center for Disease Control and Prevention

Fan Zhang
Tianjin Center for Tuberculosis Control

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Abstract

Background

Bacteriological confirmation rate among notified pulmonary TB patients in China is among the lowest in the world. This study was to understand the yield of bacteriological confirmation using different testing strategies and patient-level factors associated with bacteriological confirmation among pulmonary TB patients in Tianjin, China between 2017 and 2018.

Methods

A retrospective study was conducted, enrolling pulmonary TB patients reported to National TB Information Management System (TIMS) in Tianjin during 2017–2018. Bacteriological confirmation was defined as a positive result by any of the followings: smear microscopy, culture, or nucleic acid amplification test. Individual characteristics were compared between patients with positive and negative bacteriological results using contingency tables and $\chi^2$ test. Multivariable logistic regression was applied to analyze factors associated with bacteriological confirmation, calculating adjusted odds ratios (aOR) and 95% confidence intervals (CI) ($\alpha = 0.05$).

Results

Of 6,364 reported patients, 4,181 (65.7%) were bacteriologically confirmed. Positivity proportion was 43.1% (2,746/6,364) for smear microscopy, 57.7% (3,380/5,853) for culture, 61.7% (1,608/2,605) for Xpert MTB/RIF and 73.4% (1,824/2,484) for combination of the three. Occupation as un-employed (aOR = 1.5, 95% CI: 1.0–2.2) and a farmer (aOR = 1.7, 95% CI: 1.1–2.8) compared with a student; diagnosis by inpatient hospitals compared with TB clinics (aOR = 3.4, 95% CI: 2.6–4.4); delay $\geq$ 2 weeks for TB care (aOR = 1.4, 95% CI: 1.1–1.8); cough (aOR = 2.2, 95% CI: 1.8–2.8); blood sputum (OR = 1.5, 95% CI: 1.0–2.2); cavitation on chest X-ray (OR = 3.3, 95% CI: 2.5–4.3); bilateral lung lobes affected (aOR = 1.7, 95% CI: 1.4–2.2) were factors associated with bacteriological confirmation.

Conclusions

Combination tests was an effective way to improve bacteriological confirmation among pulmonary TB patients. Being unemployed, farmers, delay for TB care, and more severe in TB condition were factors associated with bacteriological confirmation among the patients. We recommend combination of bacteriological tests and sputum collection intervention to improve bacteriological confirmation for pulmonary TB patients, especially who are in early stage of the disease or with conditions tend to be bacteriologically negative.
Background

Tuberculosis (TB) is caused by *Mycobacterium Tuberculosis (MTB)*. Despite a long history it remains a major threat to global health. In 2018, an estimation of 10.0 million people developed TB, and 1.5 million died from the disease.[1] Pulmonary TB is the most common type of TB, and the patients may produce droplet nuclei containing MTB through coughing, sneezing, spitting, speaking or singing, allowing it transmit from person to person. Testing for MTB in sputum samples is a direct way for pulmonary TB diagnosis, and patients with positive results are classified as bacteriologically confirmed patients.[2] Bacteriological confirmation helps TB diagnosis timely, determines contact investigation and allows further looking into susceptibility of drugs.[2–4] Fail to detect MTB among patients who actually bear significant bacilli can cause delay in TB diagnosis and treatment.[5–7]

MTB testing, from the long-used sputum smear microscopy and solid media culture, to liquid culture and the most novel tool Xpert MTB/RIF®, have improved rapidness or sensitivity.[8, 9] Despite the evolution of MTB tests, still a number of pulmonary TB patients are clinically diagnosed in the absence of bacteriological confirmation. In 2018, globally bacteriological confirmation among notified pulmonary TB was 55%.[1] In China this proportion was 37% in 2018, although improved from 32% in 2017, still among the lowest in the world.[1] With the second largest TB burden in the world, accounting for 9% in 2018,[1] China is facing a challenge of low bacteriological confirmation among pulmonary TB patients. Tianjin is one of the four municipalities in China, where sputum smear, culture and Xpert were gradually accessible to all pulmonary TB patients. This study was to better understand the role of sputum smear, culture and Xpert MTB/RIF in bacteriological confirmation, and patient-level factors associated with it, in order to inspire interventions to improve bacteriological confirmation for the whole country and also some other regions in the world.

Methods

Study design

A retrospective study using de-identified data from the National TB Information Management System (TBIMS) for Tianjin during 2017-2018.

Study population

Pulmonary TB was diagnosed according to the China national standard of “Diagnosis for pulmonary tuberculosis”, either based on a positive bacteriological test or determination by a panel of physicians in the absence of bacteriological evidence.[2, 6] Demographic and clinic information of patients were collected by physicians in medical records, and entered to TBIMS within 24 hours. Timeliness and quality of data reporting was supervised by Tianjin Center for TB Control. Data of pulmonary TB patients reported during 2017 to 2018 was exported from TBIMS in Excel forms, without variables containing identifiable information such as patients’ name, telephone number, address and personal ID number. Inclusion criteria: pulmonary TB patients notified in Tianjin during 2017-2018. Exclusion criteria: 1)
patients not recorded initial sputum smear result; 2) patients who were ruled out of pulmonary TB later on.

Bacteriological examinations

Presumable TB patients were required to collect three sputum specimens for smear microscopy, extra sputum specimens for mycobacterium culture and nucleic acid amplification assays. Sputum smear was performed using Ziehl-Neelsen staining, and culture was performed using either Mycobacterium Growth Indicator Tube (MGIT) 960 or Löwenstein-Jensen (LJ) medium according to WHO guidelines.[10] Xpert MTB/RIF (Cepheid, https://www.cepheid.com) was performed on sputum according to the manual instructions to improve the bacterium positivity as well as for Rifampin resistance detection.

Definition

A bacteriologically confirmed pulmonary TB patient is defined as a patient with any positive result shown by sputum smear microscopy, culture or a WHO-approved nucleic acid amplification test, such as Xpert MTB/RIF; a patient diagnosed in the absence of the above-mentioned evidence is defined as a clinically diagnosed pulmonary TB patient.

Data analysis

Separate positivity as well as the combined positivity for sputum smear, culture and Xpert MTB/RIF were calculated. We compared frequency distribution of characteristics between bacteriologically positive patients and negative patients using conventional 2-way contingency tables, tested statistical significance using c² test. A multivariable logistic regression was used to analyze factors associated with bacteriological confirmation among pulmonary TB patients, calculating odds ratios (ORs) and 95% confidence intervals (CIs) for all factors. All the analyses were carried out by using SAS 9.4 (SAS Institute, Cary, NC), α=0.05.

Ethic review

This study used de-identified data reported to TBIMS through routine patient care-linked surveillance. The protocol was reviewed by review board of Tianjin TB Center. Informed consent for the patients and ethical approval was not required for the study.

Results

Patient profile

During 2017 to 2018, a total of 6,415 pulmonary TB patients were reported to TBIMS (767 pure pleurisy not included) in Tianjin. Among them, 51 patients were later ruled out of TB, including 28 initially culture positive ones (diagnosed as Mycobacterium other then TB) and 23 initially culture negative ones (diagnosed as lung cancer, silicosis, pneumonia and so on). The remaining 6,364 patients were enrolled
as study subjects, including 3,159 reported in 2017 and 3,205 in 2018. Among them, 4,383 (68.9%) were male, 1,981 (31.1%) were female. The age ranged between 1 to 95 years (skewness=0.16, \( P<0.01 \)); age <15 years accounted for 30 (0.5%); the median age was 48 years (IQR: 28, 63). 5,626 (88.4%) were local registered residents, 738 (11.6%) were migrants. 5,356 (84.2%) were new patients, 1,008 (15.8%) were previously treated patients. 5,853 (92.0%) of the patients were tested culture on initial sputum, including 2,864 (90.7%) reported in 2017, 2,989 (93.3%) in 2018. A total of 2,605 (40.9%) patients were tested Xpert MTB/RIF on initial sputum, including 80 (2.5%) reported in 2017 and 2,525 (78.8%) in 2018.

Positivity yield by different strategies

A total of 4,181 (65.7%) patients were bacteriological confirmed, including 1,953 (61.8%) reported in 2017 and 2,228 (69.5%) in 2018, and the rest 2,183 (34.3%) were clinically diagnosed. When using as a single tool, positivity was 43.2% (2,746/6,364) for smear microscopy, 57.8% (3,380/5,851) for culture, and 61.7% (1,608/2,605) for Xpert. Overall, 2,484 (39.0%) of study subjects were initially tested simultaneously by smear, culture and Xpert, and 73.4% (1,824/2,484) were positive shown by any of the tests (shown in Table 1). The yields of positivity were statistically different in various combinations of the testing methods (\( P<0.01 \)). Regardless the testing methods, the add-on could always significantly achieve additional positivity. Adopting culture as an add-on testing to smear, an extra 19.9% positivity was achieved compared to smear alone; Xpert as an add-on test to smear, 24.7% extra positivity achieved. When combining the three, yield of positivity was 73.4%, the highest among all the strategies.

Comparison between bacteriologically positive and negative patients

Bacteriological testing results were significantly associated with several patient characteristics (\( P<0.01 \), shown in Table 2). The positivity rate of older aged (\( \geq 45 \)) was higher than that of younger aged (<45). As age increased, the positivity proportion went up from 63.6% among the <25 years to 83.3% among the \( \geq 65 \) years, the trend was statistically significant (\( P<0.01 \)). In terms of occupation, the un-employed, farmers and retirees had higher positivity rate (>70%) than that of students, service/manufacture workers and state employees (<70%). Regarding hospital type of TB diagnosis, the city-level TB designated hospital (with inpatient departments) was over presented among the positive group, while the other clinics were less presented. Besides, local registered residents other than migrants, delay to arrive in TB health care facilities \( \geq 2 \) weeks, previous treated other than new patients, symptoms with cough or with blood sputum, with cavitation on the chest X-ray, bilateral lobes of lung affected, and diabetes comorbidity were all significantly over presented among the positive patients than the negative ones. Gender, ethnicity and extra-pulmonary TB concomitance were not significantly associated with bacteriological confirmation (\( P>0.05 \)).

Factors associated with bacteriological positivity

In logistic regression, gender, age, ethnicity, residency, previous treatment, diabetes comorbidity and extra-pulmonary TB concomitance were not statistically associated with bacteriological confirmation (\( P>0.05 \), shown in table 3). The other characteristics were identified to significantly increase or decrease
bacteriological positivity. Compared with students, the un-employed and farmers had significant higher risk of being positive. Compared with patients diagnosed in the city-level TB clinic, patients in city level TB designated hospitals (with inpatient) were associated with bacteriological confirmation. Patients arrived in TB facilities $\geq 2$ weeks since onset of TB symptoms increased bacteriological positivity compared with those arrived more timely. Symptoms with cough, blood sputum, cavitation on chest X-ray and bilateral lobes of lung affected were all associated with increased bacteriological confirmation.

**Discussion**

In China, decline of bacteriological confirmation rate among pulmonary TB was not only reflected by the surveillance data, but also shown from the latest two decennial national TB surveys conducted in 2000 and 2010 respectively, in which the prevalence of active pulmonary TB remained almost the same (from 466/100,000 to 459/100,000), whereas the prevalence of bacteriologically positive pulmonary TB decreased (from 216/100,000 to 119/100,000), and even more sharply for the smear positive ones (from 169/100,000 to 66/100,000), meaning bacteriological confirmation rate shrunk from 46.4% to 25.9%, and smear-positivity rate from 36.3% to 14.4%.[11] Similar trend was also reported by some other regional data, that as smear-negative TB incidence remained, the incidence of smear-positive TB declined.[12] Globally bacteriological confirmation declined from 56% in 2017 to 55% in 2018.[1, 13] Given testing methods are on evolution, MTB testing strategy should be improved to keep in pace with the decline of bacteriological confirmation rate.

In our study, around 2/3 the notified pulmonary TB were bacteriologically confirmed, higher than the average level of the world, and even higher than the national level. This may be explained as follows. One was integration of sputum tests for pulmonary TB patients, which was shown by the fact that as coverage of culture (from 90.7% to 93.3%) and Xpert (from 2.5% to 78.8%) increased during the two years, the bacteriological confirmation rate improved significantly (from 61.8% to 69.5%). Xpert being used as the initial diagnostic test in all adult/children presumable patients has been recommended in WHO guidelines.[9] Either culture or Xpert had higher positivity yield than smear when using alone, so both culture and Xpert can be adopted as add-on tools to maximize bacteriological confirmation. The second points was the diagnostic procedure of pulmonary TB in the absence of bacteriological evidence, that a specific panel of physicians rather than a individual physician was required to make the diagnosis to minimize over-diagnosis.[6] As the results shown, less than 1% of notified patients were later ruled out of TB in the study. The third point was a regional feature in the city, that was over 80% of the patients were diagnosed in two city-level designated TB facilities, where the TB labs receive direct quality control by the national TB reference lab. In other word, the majority of patients received tests in labs with robust quality control. The high bacteriological confirmation in Tianjin has set an example to determine what level can be achieved in the whole country and other regions with the similar problem. Implementation of procedure for TB diagnosis in the absence of bacteriological evidence, good quality control for TB labs, and combination of sputum tests could be considered as measures to improve bacteriological confirmation of pulmonary TB patients.
However, the bacteriological confirmation rate in Tianjin was still lower than that of some regions. In the USA 78.1% of TB cases were confirmed via culture and an extra 2.9% were confirmed through positive nucleic acid amplification;[14] in New York 85% of the pulmonary TB patients were culture positive.[15] The gap may reflect different background of TB prevalence in countries/regions, and may also partly attribute to different profile of patient characteristics. Apart from factors relating to laboratory, patients with specific characteristics tend to have pauci-bacillary, such as HIV co-infection, children, and mild clinical manifestations.[16–18]

Generally, more severe and complex condition tend to cause bacteriological positivity. Cavitation on chest X-ray usually means enriched bacteria in the lesion and represents later stage of the disease, and cough can produce sputum containing MTB from the lesion to the air through droplets, increasing the possibility to detect MTB in sputum samples, which is in consistent with previous studies.[4, 15, 18, 19] Similarly, blood sputum and bilateral lung affected may also reflect extensive lesion, which were also found to increase bacteriological confirmation rate. Diabetes comorbidity were found to be associated with higher grading of sputum smear among TB patients in other studies.[7, 20, 21] However in this study, the effect of diabetes to bacteriological confirmation was marginal, probably because this condition had been represented by comprehensive severity and complexity of other factors. Patients with complex conditions such as more comorbidity and severity tend to be referred to and admitted by health care facilities with inpatient wards rather than TB clinic. And this selection bias might explain diagnosis in city level hospital with inpatient wards was related to higher bacteriological confirmation. Apart from clinic manifestation, delay to seek TB health care tend to cause bacteriological positivity in this study. In previous studies, treatment delay was found to be a risk factor associated with TB transmission from index patients to the contacts, although different cut-off points for categorizing treatment delay were used.[4, 22] Longer treatment delay meant longer period for the deterioration of the disease, and also made contacts longer time under exposure of transmission.

Regarding demographic factors, gender and age were found related to bacteriological results in some studies.[15, 18] In our study, although the older age were over presented in the bacteriologically confirmed group, after adjusting with clinical manifestation, age as well as gender were not statistically significant. Compared with state employees, unemployed and farmers usually had disadvantage in household income and living conditions, leading them vulnerable to TB.[23, 24] The vulnerability might lower their health seeking behavior or accessibility to health care, thus lead to later stage of the disease.

Limitation of the study: the study was based on surveillance data reported to TBIMS, and history of broad spectrum anti-bacterium medication before TB diagnosis was not routinely reported. For example, Levofloxacin is broadly used in general hospital, which may rapidly reduce the number of bacilli expelled. HIV was found to be associated with infectiousness of TB patients,[4] however in our dataset very low proportion of HIV comorbidity was reported to satisfy the statistics analysis. Despite the limitations, when China and some parts of the world facing challenge of low bacteriological confirmation among pulmonary TB patients, this study revealed a much higher proportion achieved regionally, which could be an example to the whole country and some other regions with similar problem.
Conclusions

Being unemployed, farmers, delay for TB care, and more severe in TB condition were factors associated with bacteriological confirmation among pulmonary TB patients. As TB control program being enhanced and active TB case finding being carried out to larger population, less patients may be diagnosed at later and severe stage of the disease, as a result bacteriological confirmation may decrease if testing strategy remain. Therefore, combination test was an effective way to improve bacteriological confirmation among pulmonary TB patients to keep in pace with decline of pulmonary TB incidence. Intervention on sputum collection such as induced sputum using nebulization can be considered as an option to improve bacteriological confirmation among presumable TB patients who tend to be bacteriologically negative. 

[25]

Abbreviations

TB
tuberculosis.
MTB
mycobacterium tuberculosis
TIMS
TB Information Management System

Tables

Table 1 Positivity yield by different bacteriological testing strategies among pulmonary TB patients in Tianjin China, 2017-2018

| Testing strategy (n)       | Negativity n (%) | Positivity n (%) |
|---------------------------|------------------|------------------|
| Smear (6,364)             | 3618 (56.9)      | 2746 (43.1)      |
| Culture (5,853)           | 2473 (42.3)      | 3380 (57.7)      |
| Xpert (2,605)             | 997 (38.3)       | 1608 (61.7)      |
| Smear+culture (5,853)     | 2162 (36.9)      | 3691 (63.1)      |
| Smear+Xpert (2,605)       | 838 (32.2)       | 1767 (67.8)      |
| Xpert+culture (2,484)     | 702 (28.3)       | 1782 (71.7)      |
| Smear+culture+Xpert (2,484)| 660 (26.6)     | 1824 (73.4)      |

Table 2 Comparison of characteristics between bacteriologically positive and negative patients who underwent all sputum smear, culture and Xpert in Tianjin, China, 2017-2018
| Characteristics (n) | Negativity (%) | Positivity (%) | Total | P by $\chi^2$ |
|---------------------|----------------|----------------|-------|--------------|
| **Gender (2,484)**  |                |                |       |              |
| Male                | 434 (65.8)     | 1,265 (69.4)   | 1,699 | 0.09         |
| Female              | 226 (34.2)     | 559 (30.6)     | 785   |              |
| **Age (2,484)**     |                |                |       |              |
| <25yr $^a$          | 162 (24.5)     | 283 (15.5)     | 445   | <0.01        |
| 25-44               | 241 (36.5)     | 513 (28.1)     | 754   |              |
| 45-64               | 173 (26.2)     | 608 (33.3)     | 781   |              |
| ≥65yr               | 84 (12.7)      | 420 (23.0)     | 504   |              |
| **Ethnic group (2,484)** |            |                |       |              |
| Han                 | 649 (98.3)     | 1,788 (98.0)   | 2,437 | 0.62         |
| Other               | 11 (1.7)       | 36 (2.0)       | 47    |              |
| **Migrant (2,484)** |                |                |       |              |
| No                  | 535 (81.1)     | 1,641 (90.0)   | 2,176 | <0.01        |
| Yes                 | 125 (18.9)     | 183 (10.0)     | 308   |              |
| **Occupation (2,484)** |            |                |       |              |
| Student             | 99 (15.0)      | 148 (8.1)      | 247   | <0.01        |
| Unemployed          | 107 (16.2)     | 512 (28.1)     | 619   |              |
| Farmer              | 68 (10.3)      | 218 (12.0)     | 286   |              |
| Service/manufacture worker $^b$ | 75 (11.4) | 126 (6.9) | 201 |
| State employee      | 179 (27.1)     | 355 (19.5)     | 534   |              |
| Retiree             | 90 (13.6)      | 314 (17.2)     | 404   |              |
| Not provided/unclear| 42 (6.4)       | 151 (8.3)      | 193   |              |
| **Hospital pattern of diagnosis (2,484)** | | | | |
| City-level TB       | 237 (35.9)     | 255 (14.0)     | 492   | <0.01        |
| Clinic                      | Number (Percentage) | Number (Percentage) | Number (Percentage) | p-Value |
|----------------------------|---------------------|---------------------|---------------------|---------|
| City-level TB hospital c   | 286 (43.3)          | 1,337 (73.3)        | 1,623               |         |
| District-level TB clinics  | 137 (20.8)          | 232 (12.7)          | 369                 |         |
| Delay for TB care (2,484)  |                     |                     |                     |         |
| <2 weeks                   | 413 (62.6)          | 809 (44.4)          | 1,222               | <0.01   |
| ≥2 weeks                   | 247 (37.4)          | 1,015 (55.6)        | 1,262               |         |
| Previously treated (2,484) |                     |                     |                     |         |
| No                         | 601 (91.1)          | 1,549 (84.9)        | 2,150               | <0.01   |
| Yes                        | 59 (8.9)            | 275 (15.1)          | 334                 |         |
| Symptoms with cough (2,463)|                     |                     |                     |         |
| No                         | 412 (62.5)          | 641 (35.5)          | 1,053               | <0.01   |
| Yes                        | 247 (37.5)          | 1,163 (64.5)        | 1,410               |         |
| Symptoms with blood sputum (2,463) |               |                     |                     |         |
| No                         | 618 (93.8)          | 1,598 (88.6)        | 2,216               | <0.01   |
| Yes                        | 41 (6.2)            | 206 (11.4)          | 247                 |         |
| Cavitation on chest X-ray (2,445) |                 |                     |                     |         |
| No                         | 574 (87.5)          | 1,099 (61.4)        | 1,673               | <0.01   |
| Yes                        | 82 (12.5)           | 690 (38.6)          | 772                 |         |
| Bilateral lung lobes affected (2,445) |               |                     |                     |         |
| No                         | 435 (66.3)          | 787 (44.0)          | 1,222               | <0.01   |
| Yes                        | 221 (33.7)          | 1,002 (56.0)        | 1,223               |         |
| Diabetes comorbidity (2,303)|                     |                     |                     |         |
| No                         | 560 (91.2)          | 1,412 (83.6)        | 1,972               | <0.01   |
| Yes                        |                     |                     |                     |         |
|                | Yes      | No        | Total |
|----------------|----------|-----------|-------|
| Extra-pulmonary TB concomitance (2,303) |          |           |       |
| Yes            | 54 (8.8) | 557 (90.7)| 611   |
|                | 277 (16.4)| 1,492 (88.3)| 1,769 |
|                | 331      | 2,049     | 2,380 |

Table 3 Factors associated with bacteriological positivity among pulmonary TB patients in Tianjin China, 2017-2018

a Totally 30 were age <15, among whom 20 were bacteriologically negative and 10 were bacteriologically positive; b Occupations in food industry, public transportation, public service attendants, and factory workers; c designated TB hospital with inpatients.
| Characteristic (n)                     | OR (95% CI) | aOR (95% CI) | P by type 3 test |
|--------------------------------------|-------------|--------------|-----------------|
| Gender (2,484)                       |             |              |                 |
| Male                                 | ref         | ref          | 0.85            |
| Female                               | 0.8 (0.7-1.0) | 1.0 (0.8-1.2) |                 |
| Age (2,484)                          |             |              |                 |
| <25yr                                | ref         | ref          | 0.19            |
| 25-44                                | 1.2 (1.0-1.6) | 1.1 (0.7-1.5) |                 |
| 45-64                                | 2.0 (1.6-2.6) | 1.2 (0.8-1.9) |                 |
| ≥65yr                                | 2.9 (2.1-3.9) | 1.6 (1.0-2.7) |                 |
| Ethnic group (2,484)                 |             |              |                 |
| Han                                  | ref         | ref          | 0.66            |
| Minority                             | 1.2 (0.6-2.3) | 1.2 (0.5-2.9) |                 |
| Migrant (2,484)                      |             |              |                 |
| No                                   | ref         | ref          | 0.37            |
| Yes                                  | 0.5 (0.4-0.6) | 1.2 (0.8-1.6) |                 |
| Occupation (2,484)                   |             |              |                 |
| Student                              | ref         | ref          | 0.02            |
| Unemployed                           | 3.2 (2.3-4.4) | 1.5 (1.0-2.2) |                 |
| Farmer                               | 2.1 (1.5-3.1) | 1.7 (1.1-2.8) |                 |
| Service/manufacture                  | 1.1 (0.8-1.6) | 1.2 (0.7-1.9) |                 |
| State employee                       | 1.3 (1.0-1.8) | 0.9 (0.6-1.4) |                 |
| Retiree                              | 2.3 (1.7-3.3) | 1.3 (0.8-1.9) |                 |
| Not provided/unclear                 | 2.4 (1.6-3.7) | 0.9 (0.5-1.5) |                 |
| Hospital pattern of diagnosis (2,484) |             |              |                 |
| City-level TB clinic                 | ref         | ref          | <0.01           |
| City-level TB hospital               | 4.3 (3.5-5.4) | 3.4 (2.6-4.4) |                 |
| District-level TB clinics            | 1.6 (1.2-2.1) | 0.8 (0.6-1.2) |                 |
### Delay for TB care (2,484)

| Delay | Ref | Ref | P-value |
|-------|-----|-----|---------|
| <2 weeks | ref | ref | 0.00 |
| ≥2 weeks | 2.1 (1.7-2.5) | 1.4 (1.1-1.8) | |

### Previously treated (2,484)

| Treatment | Ref | Ref | P-value |
|-----------|-----|-----|---------|
| No | ref | ref | 0.05 |
| Yes | 1.8 (1.3-2.4) | 1.4 (1.0-2.0) | |

### Symptoms with cough (2,463)

| Symptoms | Ref | Ref | P-value |
|----------|-----|-----|---------|
| No | ref | ref | <0.01 |
| Yes | 3.0 (2.5-3.6) | 2.2 (1.8-2.8) | |

### Symptoms with blood sputum (2,463)

| Symptoms | Ref | Ref | P-value |
|----------|-----|-----|---------|
| No | ref | ref | 0.04 |
| Yes | 1.9 (1.4-2.8) | 1.5 (1.0-2.2) | |

### Cavitation on chest X-ray (2,445)

| Cavitation | Ref | Ref | P-value |
|------------|-----|-----|---------|
| No | ref | ref | <0.01 |
| Yes | 4.4 (3.4-5.6) | 3.3 (2.5-4.3) | |

### Bilateral lung lobes affected (2,445)

| Bilateral | Ref | Ref | P-value |
|-----------|-----|-----|---------|
| No | ref | ref | <0.01 |
| Yes | 2.5 (2.1-3) | 1.7 (1.4-2.2) | |

### Diabetes comorbidity (2,303)

| Comorbidity | Ref | Ref | P-value |
|-------------|-----|-----|---------|
| No | ref | ref | 0.06 |
| Yes | 2.0 (1.5-2.8) | 1.4 (1.0-2.0) | |

### Extra-pulmonary TB concomitance (2,303)

| Concomitance | Ref | Ref | P-value |
|--------------|-----|-----|---------|
| No | ref | ref | 0.20 |
| Yes | 1.3 (0.9-1.8) | 1.3 (0.9-1.8) | |
a Occupations in food industry, public transportation, public service attendants, and factory workers; b designated TB hospital with inpatients.

**Declarations**

Ethics approval and consent to participate

The study protocol was reviewed by review board of Tianjin Center for TB Control. The study used retrospective and de-identified data reported to TBIMS through routine patient care-linked surveillance. The Informed consent for the patients and ethical approval was not required for the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the current study are exported from China National TB Information Management System (TBIMS), excluding identified information. The dataset are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GQ mainly designed the study, analyzed the data and wrote the manuscript. YH exported the data from National TBIMS, performed data cleaning. MT and F helped interpret the results. All authors were involved in manuscript revision and approved the final manuscript.

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Authors' information

GQ is an epidemiologist mainly in TB control, and currently a resident in China Field Epidemiology Training Program. YH is an epidemiologist mainly in TB control. MT is currently the deputy director of Center for TB Control and Prevention in China CDC. F is the director of Tianjin Center for TB Control.
References

1. WHO. Global Tuberculosis Report, 2019. Geneva: WHO; 2019.
2. WHO. Treatment of tuberculosis: guidelines (4th ed). 4th edition. Geneva: World Health Organization; 2010.
3. Report MW. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recomm Rep. 2005;54 RR-15:1–47.
4. Melsew YAA, Doan TNN, Gambhir M, Cheng ACC, McBryde E, Trauer JMM. Risk factors for infectiousness of patients with tuberculosis: a systematic review and meta-analysis. Epidemiol Infect. 2018;146:345–53. doi:10.1017/S0950268817003041.
5. Lisboa M, Fronteira I, Colove E, Nhamonga M, Martins M do RO. Time delay and associated mortality from negative smear to positive Xpert MTB/RIF test among TB/HIV patients: a retrospective study. BMC Infect Dis. 2019;19:1–10.
6. National Health Commission. Diagnosis of pulmonary tuberculosis. China; 2017.
7. Zhang ZX, Sng LH, Yong Y, Lin LM, Cheng TW, Seong NH, et al. Delays in diagnosis and treatment of pulmonary tuberculosis in AFB smear-negative patients with pneumonia. Int J Tuberc Lung Dis. 2017;21:544–9.
8. WHO. Laboratory diagnosis of tuberculosis by sputum microscopy. 2013.
   http://www.stoptb.org/wg/gli/assets/documents/TB MICROSCOPY HANDBOOK_FINAL.pdf.
9. WHO. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extra-pulmonary TB in adults and children. Policy update. Geneva; 2013.
10. WHO. TB diagnostics and laboratory strengthening, laboratory tool set.
    http://www.who.int/tb/laboratory/tool_set/en/index.html. Accessed 1 Jul 2015.
11. Yu W. The fifth national tuberculosis epidemiological survey in 2010. Chin J Antituberc. 2012;34:485–508.
12. Tao NN, Li YF, Wang SS, Liu YX, Liu JY, Song WM, et al. Epidemiological characteristics of pulmonary tuberculosis in Shandong, China, 2005-2017: A retrospective study. Medicine (Baltimore). 2019;98:e15778.
13. WHO. Global Tuberculosis report, 2018. Geneva; 2018.
    http://www.who.int/tb/publications/global_report/en/.
14. CDC. Reported Tuberculosis in the United States, 2017. Atlanta; 2018.
15. Nguyen M-VH, Levy NS, Ahuja SD, Trieu L, Proops DC, Achkar JM. Factors Associated With Sputum Culture-Negative vs Culture-Positive Diagnosis of Pulmonary Tuberculosis. JAMA Netw open. 2019;2:e187617. doi:10.1001/jamanetworkopen.2018.7617.
16. Méndez-Samperio P. Diagnosis of Tuberculosis in HIV Co-infected Individuals: Current Status, Challenges and Opportunities for the Future. Scand J Immunol. 2017;86:76–82.
17. WHO, Union. Childhood TB training toolkit. 2014.

18. Samb B, Sow PS, Kony S, Maynart-Badiane M, Diouf G, Cissokho S, et al. Risk factors for negative sputum acid-fast bacilli smears in pulmonary tuberculosis: Results from Dakar, Senegal, a city with low HIV seroprevalence. Int J Tuberc Lung Dis. 1999;3:330–6.

19. Nguyen MVH, Jenny-Avital ER, Burger S, Leibert EM, Achkar JM. Clinical and radiographic manifestations of sputum culture-negative pulmonary tuberculosis. PLoS One. 2015;10:1–9.

20. Fachri M, Hatta M, Abadi S, Santoso SS, Wikanningtyas TA, Syarifuddin A, et al. Comparison of acid fast bacilli (AFB) smear for Mycobacterium tuberculosis on adult pulmonary tuberculosis (TB) patients with type 2 diabetes mellitus (DM) and without type 2 DM. Respir Med Case Reports. 2018;23 February:158–62. doi:10.1016/j.rmcr.2018.02.008.

21. Wu Z, Guo J, Huang Y, Cai E, Zhang X, Pan Q, et al. Diabetes mellitus in patients with pulmonary tuberculosis in an aging population in Shanghai, China: Prevalence, clinical characteristics and outcomes. J Diabetes Complications. 2016;30:237–41. doi:10.1016/j.jdiacomp.2015.11.014.

22. Delayed tuberculosis diagnosis and tuberculosis transmission. INT J TUBERC LUNG DIS. 2006;10:24–30.

23. Gianella C, Pesantes MA, Ugarte-Gil C, Moore DAJ, Lema C. Vulnerable populations and the right to health: Lessons from the Peruvian Amazon around tuberculosis control. Int J Equity Health. 2019;18:1–13.

24. Shakoor S, Hasan R. Tuberculosis in vulnerable populations in Eastern Mediterranean Region—Implications for control. Int J Mycobacteriology. 2016;5:S15. doi:10.1016/j.ijmyco.2016.08.012.

25. Gopathi NR. A Comparative Study of Induced Sputum and Bronchial Washings in Diagnosing Sputum Smear Negative Pulmonary Tuberculosis. J Clin DIAGNOSTIC Res. 2016;10:7–10. doi:10.7860/JCDR/2016/18767.7474.

Figures
7,182 patients were diagnosed as having pulmonary TB and reported to NTBIMS (3,583 in 2017, 3,599 in 2018)

767 were only pleurisy, excluded in this study

6,415 were reported as having pulmonary TB, whether or not concomitant with extra-pulmonary TB

51 were latter rule out of TB after notification, were excluded

6,364 were enrolled as study subjects in this study

2,484 patients were tested by all sputum smear, mycobacterium culture and Xpert MTB/RIF®, were enrolled to compare characteristics between bacteriologically confirmed and clinically diagnosed patients
Figure 1

Recruitment of subjects in the study