Latent Tuberculosis Infection Among Individuals with Pulmonary Fibrosis in Rural China: A Screening Study

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Research

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Abstract

Background: Individuals with pulmonary fibrotic radiological lesions, indicating prior tuberculosis (TB), have been suggested to be at high likelihood of developing active disease from latent TB infection (LTBI). The burden of LTBI among this specific population has been rarely studied in China.

Methods: We conducted a population-based screening study to investigate the prevalence of fibrotic radiological lesions and their TB infection rate among rural residents in China. Chest radiography examination was performed for all eligible participants, and Interferon Gamma Release Assay (IGRA) testing was conducted for those with a history of anti-TB treatment and those with radiographic abnormalities suggestive of prior TB. Risk factors associated with the present of fibrosis and IGRA positivity were analyzed.

Results: A total of 45,901 rural residents participated in the study, 2,231 of them reported a history of anti-TB treatment. The prevalence of pulmonary fibrosis was 34.16% (762/2,231) and 2.81% (1,230/43,670) among the participants with and without anti-TB treatment. The present of fibrosis was found to be more frequent among individuals with a history of relapse of TB (50.35%, 72/143) or previous smear positive TB (44.23%,157/355). Among participants with fibrotic radiological lesions, IGRA positivity was 50.39% (384/762) and 25.44% (313/1,230) for those with and without anti-TB treatment records, respectively. Males, younger age and a previous smear positive TB were associated with higher IGRA positivity among individuals with anti-TB treatment record.

Conclusions: Individuals with fibrotic radiological lesions and their remarkably high burden of TB infection should be attached more attention for TB control in China.

Background

Close to a quarter of the global population was latently infected with *Mycobacterium tuberculosis*, millions of active tuberculosis (TB) cases might develop with a lifetime risk of 5%-10% [1–2]. Treatment of latent tuberculosis infection (LTBI) among populations at high-risk of developing active disease is now a globally critical component of the End TB Strategy. Several target populations have been recommended by the World Health Organization (WHO), such as people living with HIV and household close contacts [3–4]. Apart from this, the latest consolidated guidelines on TB also stressed a previous history of TB should not be a contraindication for preventive treatment in case of exposure, following the exclusion of reactivated disease [5]. A Meta-analysis showed chest radiography abnormalities suggestive of previous infection with TB were significantly associated with the status of LTBI [6]. Such radiographic lesions were also associated with an increased risk of TB reactivation [7]. Our previous population-based prospective study observed as well that only 7.7% (567/7,388) of the Interferon Gamma Release Assay (IGRA) positives reported a history of prior TB but they contributed to 45.3% (53/117) of TB occurrence during 5-year follow-up [8]. In American and Canada, individuals with chest radiography abnormalities suggestive of inactive healed TB, such as those with fibrotic radiological lesions, were suggested to be at increased risk of disease progression (6–19 times) and has been recommended as targets for LTBI testing and treatment [9–12]. However, we know little about the burden of this specific population and their TB infection status in China. In this context, aiming to evaluate the feasibility and lay foundation for further intervention, we conducted a population-based screening study to investigate the prevalence of fibrotic radiological lesions among rural residents and to estimate their current TB infection status.

Methods

Study design and populations

This is a recruitment phrase of a randomized controlled trial (ChiCTR-1800018224) aiming to explore short-course LTBI treatment regimens for individuals with prior TB history in rural communities of Zhongmu County, China. The current screening study aimed to recruit eligible participants and investigate their prevalence of fibrotic radiological lesions using chest radiography examination and further to identify their infection status by IGRA testing. According to sample size for next phrase clinical trial, a total of 46,000 participants needed to be screened firstly. Our study population consisted of two parts: one group was individuals with history of anti-TB treatment, either from official record of anti-TB treatment who has been registered in the Tuberculosis Information Management System (TBIMS) and had completed the treatment two years before the investigation or self-reported history of TB during investigation. Another group was local rural residents without a history of anti-TB treatment. They were recruited for purpose of acquiring the prevalence of fibrotic radiological lesions in general population and including those eligible for further clinical trial. For the enrollment for screening, the inclusion criteria were: aged ≥ 18 years old; with household registration or residence permit in Zhongmu County; with ability to complete the investigations and tests; willing to provide signed informed consent. Exclusion criteria were with current active TB; pregnant or expectant women. The ethics committees of the Institute of Pathogen Biology and the Chinese Academy of Medical Sciences approved the study protocol (IPB-2018-1).

Procedures

For individuals with a history of anti-TB treatment, we re-checked their recorded information by door-to-door survey. A standard questionnaire, chest radiography examination and IGRA testing were performed. While for individuals without history of anti-TB treatment, all eligible participants were firstly investigated by questionnaire and examined by chest radiography examination, and then IGRA were tested only for those with report of inactive TB radiographic lesions. First, a standard questionnaire mainly containing information on birthday, gender, history of prior TB and current suspected symptoms of active TB was administered. In addition, prior diagnostic and treatment information was also collected for individuals with history of anti-TB treatment. Then, panel of radiologist with experienced clinical practice, interpreted each participant’s radiographs using standard criteria for reading results, adapted from People's Republic of China Health Industry Standard (Classification of tuberculosis (WS196—2017)). Abnormal radiography results consistence with inactive TB lesions were defined as no active TB-related clinical symptoms and signs, radiological findings meeting one or more of the following manifestations (fibrotic scarring, calcification, nodule, and pleural thickening). Finally, QuantiFERON-TB Gold In-Tube (QFT-GIT; Qiagen, Hilden, Germany) was used to detect TB infection according to manufacturer's recommendation with a cutoff value of 0.35 IU/mL.

Statistical analysis

The data were analyzed with SAS 9.4 and GraphPad Prism 8. For individuals with a history of anti-TB treatment, their diagnostic and treatment information came from previous records and for parts of participants with missing information, the corresponding variables were treated with null value during analysis. The participants were classified into two groups according to their history of anti-TB treatment. Age was categorized into four categories (18–49 years, 50–59 years, 60–69 years, and ≥ 70 years). Diagnostic time was categorized into three categories (within past 5 years, within past 5–10 years, within past > 10 years). The Pearson's χ^2 test was used to compare the different distribution of the categorical variables. Cochran–Armitage (chi-square) tests were used to test the linear trend of TB infection rate along with age. Variables with $p < 0.05$ in the univariate analysis were included into the unconditional multiple logistic regression analyses and the associations was assessed with odds ratio (OR) and 95% confidence interval (CI). Tests for linear trend by entering the median value of each category of age as a continuous variable in the models. Mann Whitney tests were used to compare the median level of quantitative QFT-GIT results between subgroups. $P < 0.05$ was considered reaching statistical significance.

Results

Major characteristics of the study population

Major characteristics of the study population and their chest radiography results were showed in Table 1. For the study population with history of anti-TB treatment, 2,231 participants were finally included. Nearly 65% (64.95%, 1,449/2,231) of them were males and the median age was 62 years. Seventy percent (1587/2231) of the participants with history of anti-TB treatment had hint of prior TB lesions and fibrotic radiological lesions were reported for 34.16% participants (762/2,231). For individuals without history of anti-TB treatment, a total of 43,670 subjects participated in the screening under informed consent. Sixty percent (26,498/43,670) of them were females and the median age was 59 years. The prevalence of fibrotic radiological lesions was 2.81% (1,230/43,670). Clinically suspected TB cases were transferred to the local CDC for diagnosis and 32 of them were finally confirmed.

Table 1
Major characteristics of the study participants

Variables	Study participants	
	With a history of anti-TB treatment n (%)	Without a history of anti-TB treatment n (%)
Total	2231 (100)	43670 (100)
Gender		
Male	1449 (64.95)	17172 (39.32)
Female	782 (35.05)	26498 (60.68)
Age		
Median (Q25-Q75)	62 (52–71)	59 (51–66)
18–49 years	456 (20.44)	8081 (18.50)
50–59 years	465 (20.84)	14476 (33.15)
60–69 years	656 (29.40)	15212 (34.83)
≥ 70 years	654 (29.31)	5901 (13.51)
Chest radiographic reading		
Normal	553 (24.79)	40451 (92.63)
With suspected active TB lesions	81 (3.63)	119 (0.27)
With fibrotic radiological lesions	762 (34.16)	1230 (2.81)
With other lesions suggestive of prior TB*	825 (36.98)	1758 (4.03)
With other pulmonary diseases	10 (0.45)	112 (0.26)

Abbreviation: Q25, 25% quartile; Q75, 75% quartile; TB, tuberculosis.

*Chest radiographic lesions suggestive of prior TB (i.e. calcification, nodule, pleural incrassation) were classified according to the national guideline and identified by an expert panel.

Association Analysis With The Present Of Fibrotic Radiological Lesions

Association analysis with the present of fibrotic radiological lesions among study participants were shown in Table 2. In the univariate analysis, males were more likely to have fibrotic radiological lesions than females for both groups with and without anti-TB treatment record. In addition, a positive liner relation was observed between the prevalence of fibrotic radiological lesions and increasing age (p for trend < 0.001). After adjusting for the covariables, the liner trend between age and the proportion of fibrotic scarring were still present for study participants with a history of anti-TB treatment. Furthermore, individuals with a smear positive results at first diagnosis and with a history of relapse were also more likely to have fibrotic scarring with OR of 1.58 (95% CI: 1.22–2.06) and 1.70 (95% CI: 1.18–2.44), respectively. For study participants without a history of anti-TB treatment, males were found to have 1.66 times higher risk of showing fibrotic radiological lesions then females.

Table 2
The present of fibrotic radiological lesions among study participants

Variables	Study participants with a history of anti-TB treatment			Study participants without a history of anti-TB treatment		
	Fibrotic radiological lesions n/N# (%)	**p for χ2 test**	**Adjusted OR (95% CI)***	**Fibrotic radiological lesions n/N# (%)**	**p for χ2 test**	**Adjusted OR (95%CI)***
Gender						
Female	234/782 (29.92)	**0.002**	Ref.	573/26498 (2.16)	**< 0.001**	Ref.
Male	528/1449 (36.44)		1.20 (0.93–1.56)	657/17172 (3.83)		**1.66 (1.42–1.94)**
Age						
18–49 years	112/456 (24.56)	**< 0.001**	Ref.	128/8081 (1.58)	**< 0.001**	Ref.
50–59 years	137/465 (29.46)		**1.24 (0.85–1.79)**	289/14476 (2.00)		0.89 (0.68–1.17)
60–69 years	236/656 (35.98)		**1.36 (0.96–1.93)**	506/15212 (3.33)		0.88 (0.68–1.14)
≥ 70 years	277/654 (42.35)		**1.81 (1.29–2.54)**	307/5901 (5.20)		1.10 (0.84–1.44)
p for trend		**< 0.001**	**< 0.001**		**< 0.001**	0.350
Diagnostic time						
Within past 5 years	116/290 (40.00)	0.095				
Within past 5–10 years	189/523 (36.14)					
Within past > 10 years	185/567 (32.63)					
Smear positive at diagnosis						
No	321/973 (32.99)	**< 0.001**	Ref.			

Abbreviation: CI, confidence interval; OR, odds ratio; TB, tuberculosis. #The sum of the sample sizes might not equal the total because of missing data. *Variables with p < 0.05 in the univariate analysis were all entered into the unconditional multiple logistic regression analyses

Variables	Study participants with a history of anti-TB treatment			Study participants without a history of anti-TB treatment		
	Fibrotic radiological lesions n/N# (%)	p for χ2 test	Adjusted OR (95% CI)*	Fibrotic radiological lesions n/N# (%)	p for χ2 test	Adjusted OR (95%CI)*
Yes	157/355 (44.23)		**1.58 (1.22–2.06)**			
With relapse of TB						
No	425/1251 (33.97)	**< 0.001**	Ref.			
Yes	72/143 (50.35)		**1.70 (1.18–2.44)**			
Abbreviation: CI, confidence interval; OR, odds ratio; TB, tuberculosis. #The sum of the sample sizes might not equal the total because of missing data. *Variables with p < 0.05 in the univariate analysis were all entered into the unconditional multiple logistic regression analyses						

Association analysis with respect to QFT-GIT positivity among study participants with fibrotic radiological lesions

Among the study participants with fibrotic radiological lesions, QFT-GIT positivity was 50.39% (384/762) and 25.44% (313/1,230) for those with and without a history of anti-TB treatment, respectively. After excluding 6 subjects with indeterminant results, association analysis with respect to QFT-GIT positivity was shown in Table 3. Males were observed with higher prevalence of QFT-GIT positivity as compared to females. The risk was still existed after adjusted for the co-variables for both subgroups with adjusted OR of 1.97 (95% CI: 1.28–3.02) and 1.53 (95% CI: 1.17-2.00). For study participants with a history of anti-TB treatment, a higher risk of QFT-GIT positivity was found for those with smear positive results as comparted with those with smear negative results with adjusted OR of 2.23 (95%CI: 1.48–3.35). In addition, a reverse dose-response relation was found between increasing age and QFT-GIT positivity with *p* for trend < 0.001. The relation was still existed in multivariable analysis. In order to limit the influence of missing data on the results, further stratification analyses were conducted among study participants with complete data according to the diagnostic times and smear result at first diagnosis (Additional Table 1). The reverse trends between age QFT-GIT positivity in subgroup analysis was not changed.

Table 3
The frequency of QFT-GIT positivity among study participants with fibrotic radiological lesions

Variables	Study participants with a history of anti-TB treatment			Study participants without a history of anti-TB treatment		
	QFT-GIT positivity n/N# (%)	p for χ^2 test	Adjusted OR (95% CI)*	QFT-GIT positivity n/N# (%)	p for χ^2 test	Adjusted OR (95%CI)*
Total	384/762 (50.39)			313/1230 (25.44)		
Gender						
Female	99/233 (42.49)	**0.003**	Ref.	122/570 (21.40)	**0.002**	Ref.
Male	285/526 (54.18)		**1.97 (1.28–3.02)**	191/657 (29.07)		**1.53 (1.17-2.00)**
Age						
18–49 years	75/112 (66.96)	**< 0.001**	Ref.	42/128 (32.03)	**< 0.001**	Ref.
50–59 years	75/137 (54.74)		**0.46 (0.24–0.87)**	63/289 (21.80)		**0.58 (0.37–0.93)**
60–69 years	105/235 (44.68)		**0.33 (0.18–0.60)**	105/503 (20.87)		**0.54 (0.35–0.83)**
≥ 70 years	129/275 (46.91)		**0.30 (0.17–0.54)**	104/307 (33.88)		1.06 (0.68–1.64)
p for trend		**< 0.001**	**< 0.001**		0.214	0.277
Diagnostic time of TB						
Within past 5 years	50/116 (43.10)	0.394				
Within past 5–10 years	93/187 (49.73)					
Within past > 10 years	94/185 (50.81)					
Smear positive at diagnosis						
No	133/319 (41.69)	**< 0.001**	Ref.			

Abbreviation: CI, confidence interval; OR, odds ratio; QFT-GIT, QuantiFERON-TB Gold In-Tube; TB, tuberculosis. # The sum of the sample sizes might not equal the total because of missing data. * Variables with p < 0.05 in the univariate analysis were all entered into the unconditional multiple logistic regression analyses.

Variables	Study participants with a history of anti-TB treatment			Study participants without a history of anti-TB treatment		
	QFT-GIT positivity n/N# (%)	p for χ^2 test	Adjusted OR (95% CI)*	QFT-GIT positivity n/N# (%)	p for χ^2 test	Adjusted OR (95%CI)*
Yes	98/156 (62.82)		**2.23 (1.48–3.35)**			
With relapse of TB						
No	209/424 (49.29)	0.661				
Yes	33/71 (46.48)					

Abbreviation: CI, confidence interval; OR, odds ratio; QFT-GIT, QuantiFERON-TB Gold In-Tube; TB, tuberculosis. # The sum of the sample sizes might not equal the total because of missing data. * Variables with p < 0.05 in the univariate analysis were all entered into the unconditional multiple logistic regression analyses.

The distribution of quantitative results among QFT-GIT positives between individuals with and without a history of anti-TB treatment classified by age were showed in Fig. 1. No statistically significant difference was observed for median level of primary QFT-GIT results between the two groups apart from 60–69 years group ($p = 0.039$).

Discussion

As far as we knew, this is the first large-scale investigation to evaluate the prevalence of LTBI among individuals with fibrotic radiological lesions by means of screening in rural China. Around one thirds (34.16%, 762/2,231) of registered prior TB cases showed hint of fibrotic radiological lesions, while it was about 3% (2.81%, 1,230/4,3670) in the general population without a history of anti-TB treatment. Among participants with such radiographic abnormalities, QFT-GIT positivity was 50.39% (384/762) and 25.44% (313/1,230) for those with and without anti-TB treatment history, respectively.

The prevalence of QFT-GIT positivity in the general rural adults from the same study site was observed to be 19.0% (801/4,223) [13], which was remarkably lower than in individuals with fibrotic scarring particular and a record of anti-TB treatment. It was difficult to clarify whether such higher QFT-GIT positivity was caused by the persistent adaptive immune response to last un-cleared TB infection or newly acquired immune response to reinfection as exogenous reinfection is still common in China [14]. However, such re-exposure could not fully explain the difference between individuals with and without record of anti-tuberculosis treatment. It was most likely caused by differences in exposure gradient and host protective immunity. Those self-cured individuals might experience lower-level exposure or had stronger immune response to clear the infection, but those developed active disease and acquired anti-TB treatment might be incapable of clearing the infection.

It is well known that individuals with fibrotic lesions consistent with inactive TB were high-priority candidates for LTBI testing and treatment [9–10, 15]. It was noted that in most guidelines such targets were restricted to be self-cured or not regularly treated, which meant those accepted standard treatment was not suggested to be considered for LTBI management [9]. However, such evidences coming from regions with lower risk of reinfection might not be consistent in regions where new infection was common. Therefore, LTBI management guidelines should be developed according to local epidemiological characteristics of active TB and LTBI. Generally, persons at high risk for developing TB disease fall into two broad categories: recent infections or persons with clinical conditions or other factors associated with an increased risk of progression from LTBI to TB disease. In high-burden countries, individuals with fibrotic radiological lesions should be attached importance for LTBI testing and treatment as they face dual risks of MTB exposure and active disease progression. Thus, a previous a history of anti-TB treatment should not be a contraindication for preventive treatment in case of exposure occurred. Longitudinal studies are needed to identify whether fibrotic radiological lesion was associated with significantly increased risk of developing active TB among those with anti-TB treatment history.

Our previous findings suggested that increasing age was associated with increased risk of LTBI in rural China, as older persons might have more social contact with active TB patients at old age as well. Furthermore, the attenuation of immunity among the elderly might predict lower infection clearance capability and higher risk of persistent infection as compared to young people [13, 16]. However, to our surprise, for individuals with treatment record, a negative relation between increasing age and QFT-GIT positivity was found. Classified analysis by previous active TB diagnostic time and the smear results didn't change the trend. The attenuated test sensitivity among elderly might be one potential underlying explanation. The ability of IGRA to identify TB infection was suggested to be decreased with age because of the waned immune response of lymphocytes to TB-specific antigens. Consistently, several previous studies have observed declined sensitivity of IGRAs along with age among patients with active TB [17–18]. Our previous prospective study also identified incident cases during follow-up among middle aged and elderly subgroups with negative QFT-GIT results [8]. Of course, the influence of reinfection could not be completely excluded. For those relatively young subjects, the more social activity means more risks of re-exposure. In any case, it is noteworthy that the sensitivity of LTBI testing needs to be improved in the elderly.

When interpreting the results, several limitations of our study should be kept in mind. First, the size and location of the studied fibrotic scarring were not documented in the current study which might be associated with the risks of LTBI and active disease [19]. Second, although fibrosis has been regarded as typical patterns of old healed TB, the interpretation could be inaccurate in some cases as radiographic lesions suggestive of TB may also be present in conditions such as histoplasmosis, pneumoconiosis and hypersensitivity pneumonitis [20]. Third, detailed information on clinical characteristics of the participants and other potential factors associated with TB infection, such as TB contact history and socioeconomic information, were not completely collected, it limited stratified analysis to explore the relations between fibrotic radiological lesions and LTBI status. Forth, information bias can't be avoided for individuals with self-reported history of TB as official TBIMS built until 2005.

Conclusions

In summary, this population-based larger-scale screening study got a better understanding of the burden of fibrotic radiological lesions in the populations with and without previously treated TB in rural China. The remarkably high prevalence of LTBI among this specific population should be attached more attention, further prospective studies are needed to assess their risks of developing active disease with respect to the history of anti-TB treatment. It will provide very important clues for identify the subgroups with fibrotic radiological lesions as target population for LTBI testing and preventive treatment.

Abbreviations

Confidence interval, CI; Interferon-γ release assay, IGRA; Latent TB infection, LTBI; Odds ratio, OR; QuantiFERON-TB Gold In-Tube, QFT-GIT; Tuberculosis, TB; World Health Organization, WHO.

Declarations

Ethics approval and consent to participate: All participants included in the study signed the informed consent and the ethics committees of the Institute of Pathogen Biology and the Chinese Academy of Medical Sciences approved the study protocol (IPB-2018-1).

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Consent for publication: Not applicable

Contributors: LG and QJ designed the study. LG, JL, SP, HX, HZ, XC, ZL organized the implement of the study. HX, HZ, BF, XC, LG, FS, and DW did epidemiological investigation and intervention management. BF, XC, YD, ZQ and JY did QFT-GIT test. XG and ZZ interpreted radiographs. HX and LG did data management and data analysis. LG and HX wrote the report. All authors contributed to review and revision and have seen and approved the final version of manuscript.

Conflict of interest: All co-authors declare that we have no conflicts of interest.

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References

1. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016;13(10):e1002152.
2. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974;99:131–8.
3. Latent tuberculosis infection. updated and consolidated guidelines for programmatic management. Geneva: World Health Organization 2018. Available at: http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/. Accessed Aug 2018.
4. Post-2015 global TB strategy and targets (A67/62). Geneva: World Health Organization 2014. Available at: https://www.who.int/tb/post2015_ TBstrategy.pdf?ua = 1. Accessed 10 July 2019.
5. WHO consolidated guidelines on tuberculosis. Module 1: Prevention Tuberculosis preventive treatment. Geneva: World Health Organization 2020. Available at: https://www.who.int/publications-detail/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment. Accessed 24 March 2020.
6. Uzorka JW, Wallinga J, Kroft L-JM, Ottenhoff THM, Arend SM. Radiological Signs of Latent Tuberculosis on Chest Radiography: A Systematic Review and Meta-Analysis. Open Forum Infect Dis. 2019;6(7):ofz313.
7. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med. 2004;350:2060–7.
8. Xin H, Zhang H, Yang S, Liu J, Lu W, Bai L, et al. 5-year follow-up of active tuberculosis development from latent infection in rural China. Clin Infect Dis. 2020;70:947–50.
9. Menzies D, Alvarez GG, Khan K. Canadian Tuberculosis Standard, 7th edition. Chapter 6: Treatment of Latent Tuberculosis Infection.
10. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Centers for Disease Control and Prevention. 2013. Available at: https://www.cdc.gov/tb/publications/ltbi/. Accessed Aug 2018.
11. Nolan CM, Elarth AM. Tuberculosis in a cohort of Southeast Asian refugees: a five-year surveillance study. Am Rev Resp Dis. 1988;137:805–9.
12. Grzybowski S, Fishaut H, Rowe J, Brown A. Tuberculosis among patients with various radiologic abnormalities, followed by the chest clinic service. Am Rev Resp Dis. 1971;104:605–8.
13. Gao L, Lu W, Bai L, Wang X, Xu J, Catanzaro A, et al. Latent tuberculosis infection in rural China: baseline results of a population-based, multicenter, prospective cohort study. Lancet Infect Dis. 2015;15:310–19.
14. Shen X, Yang C, Wu J, Lin S, Gao X, Wu Z, et al. Recurrent tuberculosis in an urban area in China: Relapse or exogenous reinfection? Tuberculosis (Edinb). 2017;103:97–104.
15. Linas BP, Wong AY, Freedberg KA, Horsburgh CR Jr. Priorities for screening and treatment of latent tuberculosis infection in the United States. Am J Respir Crit Care Med. 2011;184(5):590–601.

16. Gao L, Bai L, Liu J, Lu W, Wang X, Li X, et al. Annual risk of tuberculosis infection in rural China: a population-based prospective study. Eur Respir J. 2016;48:168–78.
17. Bae W, Park KU, Song EY, Kim SJ, Lee YJ, Park JS, et al. Comparison of the Sensitivity of QuantiFERON-TB Gold In-Tube and T-SPOT.TB According to Patient Age. PLoS One. 2016;11(6):e0156917.
18. Pan L, Jia H, Liu F, Sun H, Gao M, Du F, et al. Risk factors for false-negative T-SPOT.TB assay results in patients with pulmonary and extra-pulmonary TB. J Infect. 2015;70(4):367–80.
19. International Union Against Tuberculosis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. Bull World Health Organ. 1982;60:555–64.
20. Jeong YJ, Yoon S, Koo HK, Lim HJ, Lee JS, Lee SM, et al. Positive tuberculin skin test or interferon-gamma release assay in patients with radiographic lesion suggesting old healed tuberculosis. J Korean Med Sci. 2012;27(7):761–66.

Figures

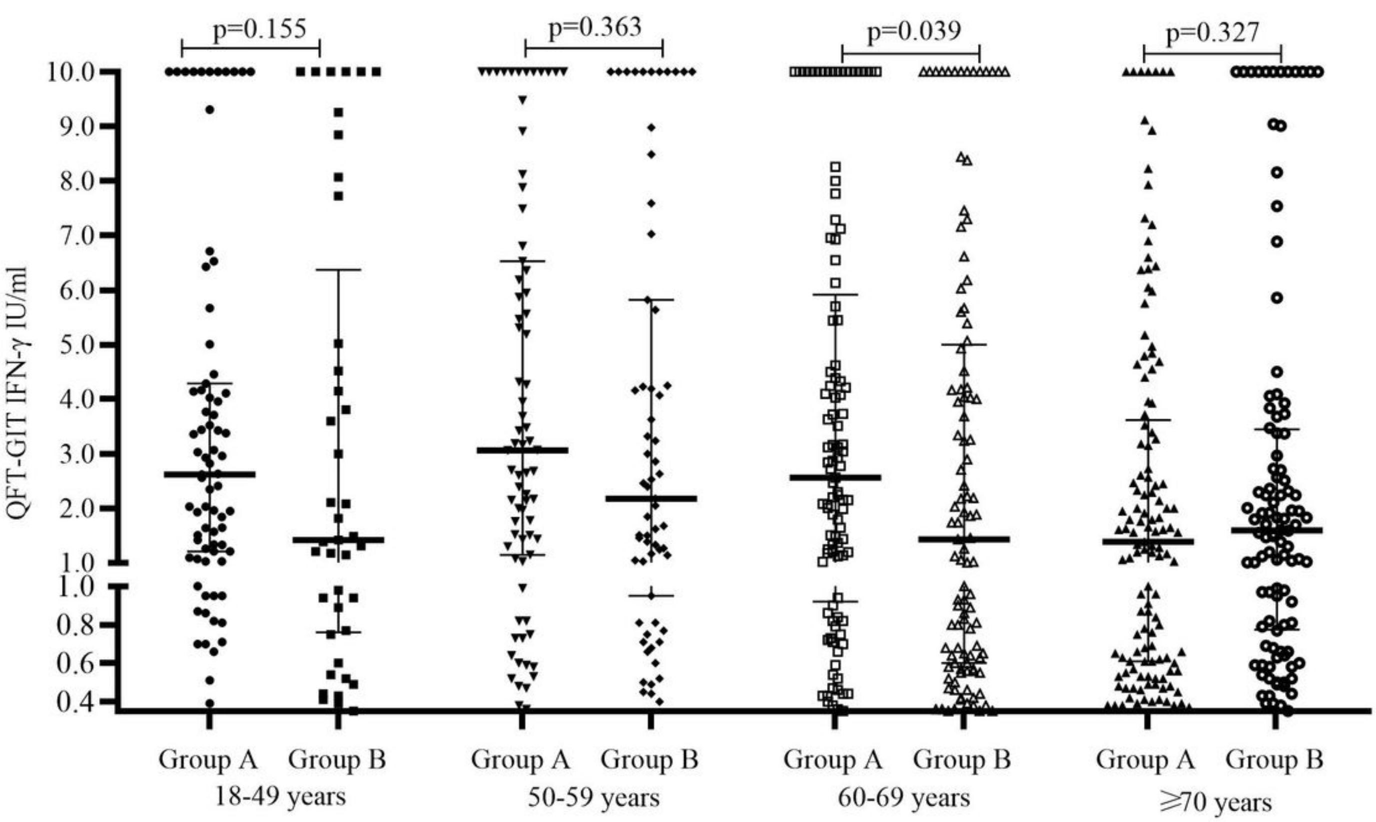

Figure 1

Distribution of quantitative results among QFT-GIT+ participants between individuals with and without a history of anti-TB treatment classified by age QFT-GIT quantitative results were compared between subjects with and without a history of anti-TB treatment with respect to age. No statistically significant difference was observed for median level of primary QFT-GIT results between the two groups apart from 60-69 years group ($p=0.039$). Group A represents individuals with history of anti-TB treatment, Group B represents individuals without history of anti-TB treatment. The dark line represents median level and the two light lines represents 25% quartile and 75% quartile. Mann Whitney tests were used to compare the median level of quantitative QFT-GIT results among different subgroups. $p<0.05$ was considered reaching statistical significance.

Supplementary Files

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