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Original Article

Discrimination between active pulmonary tuberculosis and latent tuberculosis with pneumonia based on IP10 levels

Yongqiang Wang, Shijun Liu, Tonghui Zou, Jing Luo, Jiarong You

Department of Laboratory Medicine, The Second People's Hospital of Neijiang City, Neijiang 641001, Sichuan Province, China

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Abstract: The aim of this study was to determine the ability of interferon-gamma inducible protein 10 (IP10) stimulated by specific TB-Ag (early secretary antigen target 6 (ESAT-6), culture filtrate protein 10 (CEP-10)) to discriminate between active pulmonary tuberculosis and latent tuberculosis with pneumonia. A total of 89 hospitalized patients with suspected tuberculosis were recruited. Among them, 41 patients were diagnosed with active pulmonary tuberculosis whereas 48 were newly diagnosed with suspected tuberculosis (finally diagnosed as pneumonia) and were classified into: LTBI$^+$pneumonia group (latent tuberculosis with pneumonia, 21 Cases) and LTBI$^-$pneumonia group (non-latent tuberculosis pneumonia, 27 cases) based on results of IGRA test. The plasma levels of IP-10 were quantified using ELISA. The ability of IP10 to differentiate active tuberculosis from LTBI$^+$pneumonia was determined using ROC curves. Using 48 cases as controls, the sensitivity of IGRA in the diagnosis of active pulmonary tuberculosis was found to be 90.24% (37/41, 95% CI: 76.87-97.28), and the specificity was 56.25% (27/48, 95% CI: 41.18-70.52). The positive predictive value was 63.79% (37/58, 95% CI: 50.12-76.01), the negative predictive value was 87.10% (27/31, 95% CI: 70.17-96.37), and the total coincidence rate was 65.17% (58/89, 95% CI: 54.33-74.96). Before and after stimulation with tuberculosis-specific antigen, IP10 levels in the active pulmonary tuberculosis group were higher than in LTBI$^+$pneumonia and LTBI$^-$pneumonia group $P<0.001$. The area under the ROC curve of IP10 TB-Ag (AUC=0.8130, 95% CI: 0.6948-0.9313, $P=6.10\times10^{-5}$) was used to differentiate active pulmonary tuberculosis from LTBI$^+$pneumonia. Taking patients with LTBI$^+$pneumonia as control when IP10TB-Ag>203.4 was the cut-off, the sensitivity for diagnosing active tuberculosis was 85.37% with a specificity of 80.95%. These results indicate that IP10 stimulated by specific tuberculosis antigens can differentiate active pulmonary from latent tuberculosis with pneumonia.

Keywords: Tuberculosis, interferon-gamma release test, active pulmonary tuberculosis, latent tuberculosis, pneumonia, IP10

Introduction

Based on the data from the World Health Organization, at least a third of the global population is infected by *Mycobacterium tuberculosis* infection, and an estimated 1.5 million people die from tuberculosis and tuberculosis-related diseases annually. In 2016, 1.04 million newly confirmed cases of tuberculosis and 1.674 million deaths were reported globally [1, 2]. Interferon-gamma release test (IGRA) has been extensively applied in clinical practice for rapid detection of tuberculosis and is based on tuberculosis-specific antigens, including ESAT-6, CFP-10, and TB7.7 antigen synthetic peptide. QuantiFERON TB Gold or T-spot TB tests have higher specificity compared to the conventional TST test [3]. Nevertheless, in countries with high burden of TB including China, the positive rate of T-SPOT is nearly 43.6% in individuals without active TB, and the specificity of T-spot TB in the diagnosis of active TB is 56.37%. This indicates that the ability of IGRA to singly differentiate active TB from latent TB is limited [4]. Moreover, IGRA has limited diagnostic value in active TB in countries with high prevalence of high TB burden.

The clinical symptoms of early active pulmonary tuberculosis and non-tuberculosis pneumonia

are indistinguishable. This causes delays in diagnosis and treatment. Some patients with pneumonia have latent tuberculosis infection, rendering the clinical diagnosis more difficult due to the low positive rate of this infection [5]. Therefore, it is necessary to identify biomarkers that accurately differentiate active pulmonary tuberculosis from latent tuberculosis complicated with pneumonia.

Serum IP10 has been widely used to distinguish between active pulmonary tuberculosis and latent tuberculosis. Several studies have attempted to evaluate the value of IP10 in diagnosing active TB and discriminating between active TB and LTBI. A systematic study showed that the AUC under the ROC curve of IP10 when used to distinguish between LTBI and active TB was 0.8638, with a sensitivity of 72% and specificity of 83% [6]. Elsewhere, Estévez O *et al.* reported that serum IP10 was significantly higher in patients with active TB than in those with latent TB and healthy controls without TB specific antigen stimulation. Moreover, the combination of serum IP10 and BCA-1 (B lymphocyte attraction chemokine) detected active tuberculosis and LTBI with AUC of 0.83 [7]. These studies suggest that IP-10 can potentially distinguish between active tuberculosis and latent tuberculosis. Nonetheless, the majority of previous studies did not include patients with pneumonia as controls. Besides, given the different TB specific antigen stimulation, Quantiferon-TB Gold Plus and QFT-3Gtests can quantify plasma levels of different cytokines [8]. Herein, using a locally developed specific cell immunity reagent for chemiluminescence detection of *Mycobacterium tuberculosis,* we subdivided patients into active pulmonary tuberculosis, LTBI$^+$pneumonia, and LTBI$^-$pneumonia groups. We then assessed the ability of IP10 stimulated with specific TB Ag to distinguish between active pulmonary tuberculosis and latent tuberculosis with pneumonia.

Materials and methods

Study design and participants

Study participants were recruited from February 2018 to January 2020. Ethical approval for this study was obtained from the ethics committee of the Second People's Hospital of Neijiang, Sichuan, P.R. China (reference number: 20180109001). Procedures were performed following the ethical principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients. Pulmonary TB was diagnosed based on clinical symptoms, radiological information, and microbiological confirmation using culture or PCR tests on respiratory specimens. Pneumonia patients without clinical and radiological symptoms for TB were diagnosed with LTBI$^+$pneumonia based on a positive IGRA. Participants were excluded from the study if they were: below 16 years of age, pregnant, with a tumor disease, extrapulmonary tuberculosis, or had received anti-TB treatment. Patients with autoimmune diseases or any other active infection with in the previous month were also excluded.

IFN-γ determination by QFT-GIT based on chemiluminescence detection

The IFN-γ release assay was performed using the QFT-GIT assay kit (WantaiKerry, China) according to the manufacturer's instructions. About 5 ml of whole blood was drawn into 3 QFT-GIT tubes pre-coated with saline (N tube, control), *M.tuberculosis*-specific antigens (ESAT-6 and CFP-10, T tube), or mitogen (positive control tube containing mitogen, P tube) and incubated at 37°C for 22±2 h. After centrifugation at 3000-5000 rpm/min for 10 min, the supernatant was harvested for IFN-γ quantification by chemiluminescence detection (*Mycobacterium tuberculosis*-specific cell immune response detection kit, chemiluminescence method, WantaiKerry, China). IGRA results were determined based on IFN-γ levels (**Table 1**).

IP-10 detection

Serum samples were stimulated with *M.tuberculosis*-specific antigens and mitogen. The IP-10 levels in QFT-GIT supernatants were quantified using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturers' instructions (Anhui Anbixin Biotechnology Co., LTD., China).

Statistical analysis

Data were analyzed using IBM SPSS statistics for windows, version 22 (IBM Corp. N.Y. USA). Graph Pad Prism version 6.0 was used for statistical mapping. Measurement data with normal distributions are presented as mean ± standard deviation ($\bar{x}$±SD). Analysis of

Table 1. IGRA were determined based on IFN-γ levels

b	a-b (pg/mL)	c-b (pg/mL)	Results
≤5000	≥14 and ≥25% of b	Any value	Positive
	<14	≥20	Negative
	≥14 but <25% of b	≥20	
	<14	<20	Indeterminate
	≥14 but <25% of b	<20	
>5000	Any value	Any value	

Note: Value of T tube =a (pg/mL), Value of N tube =b (pg/mL), Value of P tube =c (pg/mL).

Table 2. Comparison of etiological detection and IGRA detection

Index	active pulmonary tuberculosis n=41	LTBI$^+$pne n=21	LTBI$^-$pne n=27	*P*
IFN-γ (P tube >5000) n (%)	35 (85.4%)	20 (95.2%)	23 (85.2%)	0.481
IFN-γ (N tube) median	8.82	4.78	6.91	0.058
IFN-γ (T tube) median	473.17	136.00	1.98	1.39×10^{-10}
TB culture Positive n (%)	11 (37.9%, 11/29)			
Sensitivity of Anti-TB n (%)	10 (90.9%, 10/11)			

variance was used for comparisons of multiple groups, while the *LSD* test was used for comparisons between two groups. Variables that were not normally distributed were compared across and within groups using the non-parametric *Mann-Whitney* test. A Chi-square test was performed for categorical data. Diagnostic performances for each index were compared by receiver operating characteristic (ROC) curve analysis to determine the area under the curve (AUC) and optimal cut-off levels.

Results

The diagnostic value of IGRA in differentiating between active pulmonary tuberculosis from pneumonia

A total of 89 hospitalized patients with suspected tuberculosis were enrolled in this study. Among them, 41 had active pulmonary tuberculosis as diagnosed based on The National Health Commission of the People's Republic of China using the WS288-2017 Diagnosis for pulmonary tuberculosis standard. A total of 48 of the recruited study participants were finally diagnosed with pneumonia and treated as study controls. From the 48 patients, 21 were classified as LTBI$^+$pneumonia group while 27 were assigned to the LTBI$^-$pneumonia group based on a positive or negative interferon release test. Median age and ranges for patients were: 53 years for the 16-79 age group, 64 years for the 25-83 age group, and 51 years for the 16-83 age group (χ^2=6.190, *P*=0.045). Male to female ratios in the groups were 36/5, 11/10, and 18/9, respectively, (χ^2=1.313, *P*=0.519).

Compared to the 48 cases as controls, the sensitivity of IGRA in the diagnosis of active pulmonary tuberculosis was 90.24% (37/41, 95% CI: 76.87-97.28); specificity was 56.25% (27/48, 95% CI: 41.18-70.52); the positive predictive value was 63.79% (37/58, 95% CI: 50.12-76.01); the negative predictive value was 87.10% (27/31, 95% CI: 70.17-96.37); while the total coincidence rate was 65.17% (58/89, 95% CI: 54.33-74.96) (**Table 2**).

IP-10 levels before and after ESAT-6/CFP-10 stimulation

Baseline levels of IP-10 (IP 10 N) were 286.9 (223.7-421.8), 163.7 (126.1-175.4) and 122.7 (105.3-173.9) pg/ml in the active tuberculosis, LTBI$^+$pneumonia, and LTBI$^-$pneumonia groups, respectively, (χ^2=27.691, $P=9.70\times10^{-7}$; active TB vs LTBI$^+$pne χ^2=12.166, $P=4.87\times10^{-4}$; active TB vs LTBI$^-$pne χ^2=22.568, $P=2.00\times10^{-6}$; LTBI$^+$pne vs LTBI$^-$pne χ^2=4.107, *P*=0.043). Median levels of IP-10 after ESAT-6/CFP-10 antigen stimulation (IP10 TB-Ag) were 441.3

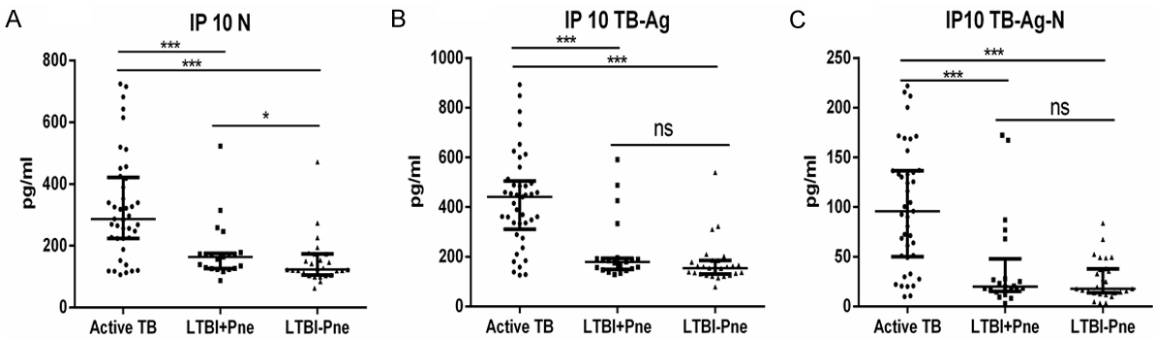

Figure 1. IP10 levels in active TB, LTBI$^+$pne, and LTBI$^-$pne. A. The baseline levels of IP10. B. Whole blood stimulated with *M.tuberculosis*-specific antigens (ESAT-6 and CFP-10, T tube) for 22±2 h at 37 °C. C. The baseline levels of IP10 were subtracted from the corresponding levels in *M.tuberculosis*-specific antigens. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, ns: no significant change.

(311.5-504.5), 179.8 (149.4-194.3), 154.6 (130.9-185.6) pg/ml in the active tuberculosis, LTBI$^+$pneumonia, and LTBI$^-$pneumonia groups, respectively, (χ^2=35.63, P=1.83×10^{-8}; active TB vs LTBI$^+$pne χ^2=16.07, P=6.10×10^{-5}; active TB vs LTBI$^-$pne χ^2=29.525, P=5.52×10^{-8}; LTBI$^+$pne vs LTBI$^-$pne χ^2=3.656, P=0.056). After subtraction of the baseline, the median IP-10 (IP 10 TB-Ag-N) for each group was 96.0 (50.1-136.8), 19.8 (15.3-48.0), 17.9 (13.8-38.0) pg/ml in the active tuberculosis, LTBI$^+$pneumonia, and LTBI$^-$pneumonia groups, respectively, (χ^2=31.27, P=1.62×10^{-7}; active TB vs LTBI$^+$pne χ^2=15.71, P=7.40×10^{-5}; active TB vs LTBI$^-$pne χ^2=26.28, P=2.95×10^{-7}; LTBI$^+$pne vs LTBI$^-$pne χ^2=0.239, P=0.625) (**Figure 1**). It was found that IP10 was elevated in the active TB group compared to that in both LTBI$^+$pne and LTBI$^-$pne groups before and after TB specific antigen stimulation. These findings imply that IP-10 might be a diagnostic marker for differentiating between active pulmonary TB and LTBI$^+$pneumonia.

The value of IP10 in distinguishing between ActiveTB and LTBI$^+$Pne

Figure 1 shows that there were no significant changes in IP10 TB-Ag and P10 TB-Ag-N between LTBI$^+$Pne and LTBI$^-$Pne. However, when LTBI$^+$pneumonia patients were used as the reference, ROC curves corresponding to IP10N, IP10TB-Ag, and IP10 TB-Ag-N revealed an AUC of 0.7724 (95% CI: 0.6485-0.8963, P=4.87×10^{-4}), 0.8130 (95% CI: 0.6948-0.9313, P=6.10×10^{-5}) and 0.8095 (95% CI: 0.6864-0.9326, P=7.40×10^{-5}), respectively to discriminate between active pulmonary TB and LTBI$^+$pneumonia (**Figure 2**). Therefore, IP10 TB-Ag exhibited a better diagnostic value after ESAT-6/CFP-10 stimulation. The cutoff for the median values of IP10 TB-Ag was 203.4 using the correct diagnosis index (Youden index). This identified 85.37% of the true active pulmonary TB (sensitivity) cases and 80.95% of the true LTBI$^+$pneumonia patients (specificity). The misdiagnosis rate was 19.05% (4/21), the positive predictive value was 89.74% (35/39) while the negative predictive value was 73.91% (17/23) (**Figure 2**). These findings suggest that IP10 TB-Ag can distinguish between active tuberculosis and LTBI$^+$pneumonia.

Discussion

In this study, we investigated the feasibility of IP10 levels to differentiate active pulmonary tuberculosis from latent tuberculosis complicated with pneumonia before and after induction of *M.tuberculosis*-specific antigens (ESAT-6 and CFP-10). The results showed that IP10 TB-Ag and IP10TB-Ag-N were similar between LTBI$^+$Pne and LTBI$^-$Pne patients. It was also found that IP10N and IP10 TB-Ag and IP10 TB-Ag-N could effectively differentiate active tuberculosis from latent tuberculosis complicated with pneumonia. Of note, Given that an AUC of 0.8 or greater is representative of good diagnostic performance, the diagnostic performance of IP10TB-Ag was higher.

Evidence from previous studies indicates that the IGRA test can diagnose active tuberculosis with high sensitivity and specificity [9]. Similar findings were observed in countries with high TB burden such as China [10, 11]. However,

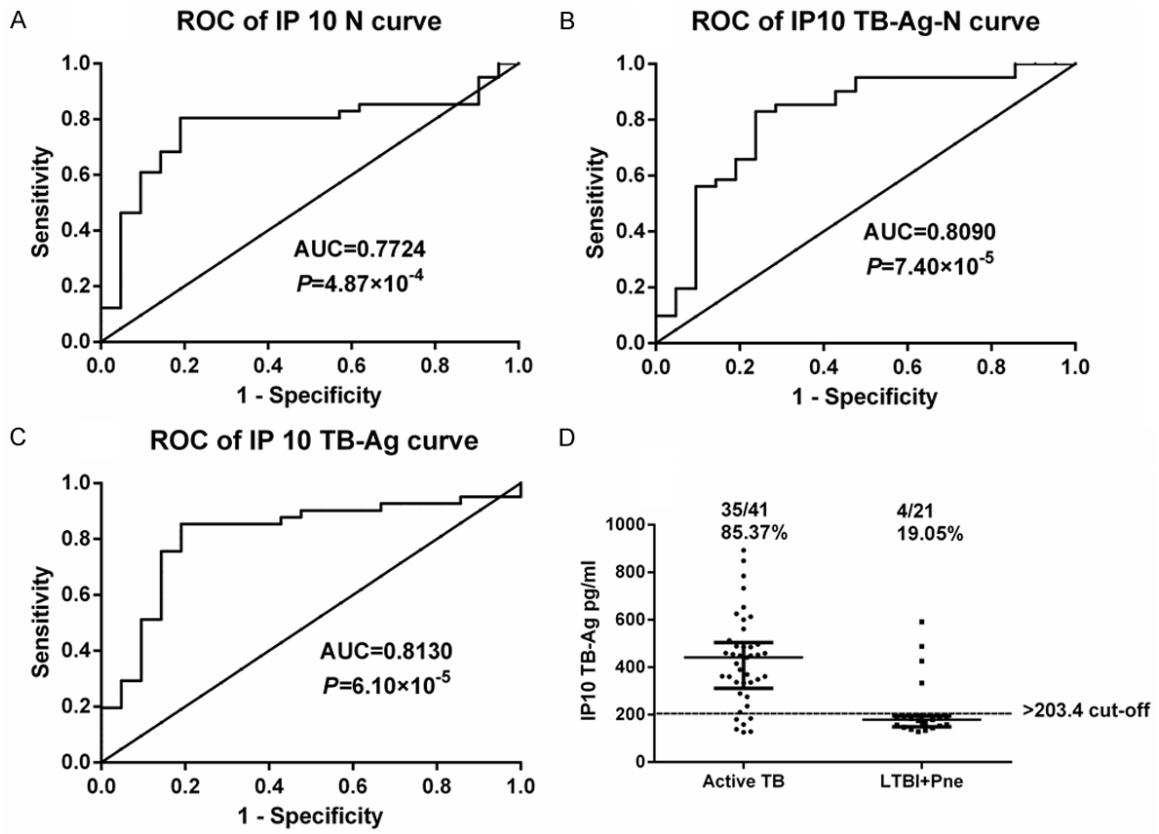

Figure 2. The ROC curve constructed to distinguish between active tuberculosis and LTBI$^+$pneumonia. A. The ROC curve of IP10 N. B. The ROC curve of IP10TB-Ag-N. C. The ROC curve of IP10TB-Ag. D. The cutoff value of IP10TB-Ag in distinguishing between active tuberculosis and LTBI$^+$pneumoniais 203.4, with positive cases shown on the graph. The AUCs and *P* values are also shown on the graphs.

these findings have been reported by studies in which healthy people were used as controls, which limit the clinical application relevance of such findings. Kang *et al.* [4] compared the performance of IGRA in diagnosing active tuberculosis and non-tuberculous respiratory diseases and discovered that the positive rate of IGRA for PTB patients with positive tuberculosis culture was higher than that for sputum negative tuberculosis culture. Nonetheless, the overall specificity of IGRA in diagnosing active tuberculosis was low. In our study, we compared the diagnostic performance of IGRA in active tuberculosis and non-tuberculous pneumonia (whether combined with latent tuberculosis or not). The results indicated that IGRA has a high sensitivity in diagnosing active tuberculosis, but a low specificity. These findings corroborated the findings reported by Kang *et al.* [4]. Combining previous reports with our findings, it can be deduced that IGRA has a higher sensitivity in distinguishing between active tuberculosis and non-tuberculous pneumonia; however, its specificity is relatively low.

Given that IGRA alone cannot distinguish between active tuberculosis and latent tuberculosis, there is a need for identification of more accurate serum markers [12]. A previous study reported that INF-γ and MMP-1 were markedly increased in patients with active pulmonary tuberculosis, whereas MMP-9 was significantly decreased in these patients. Moreover, the ROC curve failed to identify the best diagnostic point with high sensitivity and specificity in differentiating active tuberculosis from non-tuberculous pneumonia [5]. Some studies reported that IP10 was a promising biomarker for active TB diagnosis when using healthy people as controls. In comparison, when the latent tuberculosis group was used as the control, its diagnostic value for active TB was very low [13, 14], and although the IP10 level in active tuberculosis patients was higher than that of patients

with latent tuberculosis, the ROC curve failed to show the best diagnostic point with high sensitivity and specificity [15]. However, another study found no significant difference in IP10 level between patient with active tuberculosis and latent tuberculosis [16]. A possible reason for the differences in the results of various studied is the use of different TB antigens [8]. Collectively, these findings show that IP10 level has limited potential in distinguishing active tuberculosis from latent tuberculosis.

Regarding the ability of IP10 to differentiate active tuberculosis from non-tuberculous lung diseases, previous investigations revealed that there were differences in diagnostic sensitivity and specificity [17, 18]. Nevertheless, its specificity in differentiating active tuberculosis with HIV co-infection from other lung diseases was only 21% [18]. Therefore, the performance of IP10 in distinguishing between active tuberculosis and non-tuberculous pneumonia varies greatly. Here, the IGRA test was first used to classify patients into IGRA-negative and IGRA-positive groups. When $LTBI^{+}$pneumonia patients were considered as the reference group, results of this study demonstrated that the diagnostic value of IP10 TB-Ag was higher after ESAT-6/CFP-10 stimulation. Sensitivity rate was consistent with that reported in a previous systematic review, but the specificity rate was higher [18]. This is because of the potential biases in the systematic review. Moreover, the control group in our study was comprised of patients with latent tuberculosis with pneumonia, unlike in the systematic reviews where patients with latent tuberculosis were used as the control. However, there was no difference in IP10 TB-Ag between $LTBI^{+}$pneumonia and $LTBI^{-}$ pneumonia, similar to previous reports [19, 20].

Study limitation

This study has some limitations. First, the sample size was relatively small, and hence the 95% CI was broader. Secondly, the definition of latent TB required an IGRA positive test, which may lead to the exclusion of some cases with latent tuberculosis combined with pneumonia based on IGRAs false negatives. Thirdly, the control group was comprised of patients with latent tuberculosis complicated with pneumonia, implying that other cases of latent tuberculosis complicated with lung cancer and other diseases were not included.

Conclusions

In conclusion, this study shows that IGRA and IP10 levels after ESAT-6/CFP-10 stimulation can effectively differentiate active tuberculosis from latent tuberculosis complicated with pneumonia.

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Disclosure of conflict of interest

None.

Address correspondence to: Yongqiang Wang, Department of Laboratory Medicine, The Second People's Hospital of Neijiang City, Neijiang 641001, Sichuan Province, China. Tel: +86-13219580956; Fax: +86-832-2383178; E-mail: 709578724@qq.com

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