



Efficacy of inducible protein 10 as a biomarker for the diagnosis of tuberculosis

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SUMMARY

Objective: This study evaluated inducible protein 10 (IP-10) as a diagnostic biomarker for specific tuberculosis (TB) infection and evaluated the ability of IP-10 to distinguish between active TB and latent TB infection (LTBI).

Methods: Forty-six patients with active pulmonary TB, 22 participants with LTBI, and 32 non-TB controls were enrolled separately. We measured IP-10 in serum and in supernatants from whole blood stimulated with TB-specific antigens.

Results: TB antigen-dependent IP-10 secretion was significantly increased in the active TB patients and LTBI subjects compared with controls, but did not differ significantly between the active TB patients and LTBI subjects. Serum IP-10 levels were higher in active TB than in LTBI (174.9 vs. 102.7 pg/ml, $p = 0.002$). The respective rates of positive responders of TB antigen-dependent IP-10 were 97.8%, 90.9%, and 12.5% in active TB, LTBI, and non-TB controls, respectively. For serum IP-10, 87.5%, 45.5%, and 9.5% of responders were positive in the respective groups.

Conclusions: The IP-10 response to TB antigen may constitute a specific biomarker for TB infection, but does not by itself distinguish between active TB and LTBI. Serum IP-10 may enhance the diagnostic performance when used in combination with another marker.

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1. Introduction

Despite the global effort to reduce the burden of tuberculosis (TB), TB is the highest infectious cause of mortality and morbidity worldwide, with 1.7 million deaths and 9.4 million incident cases in 2009 alone.¹ Efforts to reduce the TB burden are linked to the development of rapid diagnostic tests for infection with *Mycobacterium tuberculosis*. The interferon- γ (IFN- γ) release assay (IGRA), a recently developed immunodiagnostic test for TB, is available as the QuantiFERON-TB Gold In-Tube Assay (QFT-GIT; Cellestis, Australia) and the T-SPOT.TB test (Oxford Immunotec, UK). Compared with the tuberculin skin test (TST), the IGRA is less influenced by the bacille Calmette–Guérin (BCG) vaccine and environmental mycobacterial exposure.² However, its sensitivity is suboptimal in immunocompromised patients, and it is unable to discriminate between active TB and latent TB infection (LTBI).^{3,4} The sensitivity of the IGRA can be enhanced by using alternative or additional biomarkers. In this context, IFN- γ -inducible protein 10 (IP-10) has been extensively studied in both adults and children.^{5–9}

IP-10 is produced primarily by monocytes/macrophages and has a role in trafficking of Th1 lymphocytes to inflamed foci through an interaction with a CXC chemokine receptor.¹⁰ High levels of IP-10 were found in the pleural effusion and lung tuberculosis granuloma of TB patients.¹¹ Previous studies have reported that IP-10 expression following stimulation with *M. tuberculosis*-specific antigens is a promising biomarker with high sensitivity for the immunodiagnosis of TB infection.^{5,6} In contrast to IFN- γ , IP-10 expression in response to TB-specific antigen was not influenced by the ability to respond to mitogens or by the CD4 cell number in HIV-infected patients.^{12,13} However, there have been discordant results regarding whether IP-10 can distinguish between active TB and LTBI. Plasma levels of IP-10 were higher in active TB than in LTBI and showed a reduction at the end of *M. tuberculosis* treatment.¹⁴ In addition, baseline plasma IP-10 and CFP-10-stimulated IP-10 levels were significantly higher in active TB than in LTBI in patients with rheumatoid arthritis.¹⁵ Conversely, TB-specific antigen-stimulated IP-10 could not distinguish between active TB and LTBI in children diagnosed by IGRA.^{7,16}

This study evaluated IP-10 as a diagnostic biomarker for specific TB infection in comparison with the QFT-GIT in Korea, a country where the incidence of TB is intermediate (70–90/100 000 patients per year). The ability of IP-10 to distinguish between active TB and LTBI was also evaluated.

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2. Methods

2.1. Study population

Participants were recruited from November 2010 to March 2012 in Severance Hospital, a tertiary referral hospital in South Korea, after the protocol had been approved by the Ethics Review Committee. Eligible subjects consenting to the study were recruited into three groups: active TB, LTBI, and non-TB control groups. The active TB group consisted of patients with active pulmonary TB. The diagnosis was confirmed by culturing *M. tuberculosis* from respiratory specimens. Individuals with HIV infection, end-stage renal disease, or leukemia/lymphoma, and those who had received anti-TB therapy for more than 2 weeks or immunosuppressive therapy, including anti-cancer chemotherapy for malignant disease, within 3 months of enrollment, were excluded from the study. For the LTBI group, household contacts with a positive TST who had lived with a microbiologically confirmed active pulmonary TB patient for longer than 1 month, were recruited. The non-TB control group consisted of healthy adults with a negative TST, who were free of TB symptoms and did not have any contact with active pulmonary TB patients. Participants in the LTBI and non-TB control groups were excluded if they showed clinical symptoms or had abnormal chest X-rays. All study subjects gave informed consent to the use of the samples obtained.

2.2. Diagnostic tests

2.2.1. Tuberculin skin test

A TST was performed by intradermal injection of 2 tuberculin units of purified protein derivative (PPD, RT23; Statens Serum Institute, Copenhagen, Denmark) using the Mantoux method. The induration was measured 48–72 h later, using a cut-off of 10 mm for positivity in immunocompetent subjects.

2.2.2. QuantiFERON-TB Gold In-Tube (QFT-GIT) assay

The QFT-GIT assay was performed in accordance with the manufacturer's instructions. Briefly, 1 ml of whole blood was collected in each of three tubes pre-coated with saline (control), *M. tuberculosis*-specific antigen (ESAT-6, CFP-10, and TB7.7), or

mitogen, and incubated for 20 h at 37 °C. The plasma supernatant was collected after centrifugation and stored frozen at –20 °C until assayed. The concentration of IFN- γ was determined using a QFT ELISA. Results were calculated using QFT-GIT software provided by the manufacturer. To facilitate comparisons with IP-10 levels, IFN- γ results are presented in pg/ml. According to previous studies, one international unit (IU) of IFN- γ corresponds to 50 pg/ml.^{5,8,17}

2.2.3. IP-10 determination

The IP-10 level was measured in duplicate in supernatants collected from the plasma of QFT-GIT tubes and in sera from all participants, using a commercial ELISA in accordance with the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The upper limit of IP-10 for the assay was set at 20 000 pg/ml.

2.3. Data analysis

Data are expressed as number (percentage) or median and interquartile range (IQR), and non-parametric analyses were used because the majority of the data did not follow a normal distribution. Categorical variables were analyzed using Pearson's Chi-square test or Fisher's exact test. Continuous variables were analyzed using the Kruskal–Wallis test with the Bonferroni correction for multiple comparisons. The most appropriate cut-off values for serum IP-10 and antigen-stimulated IP-10 for the detection of active TB disease were established by receiver operating characteristic (ROC) curve analysis to maximize the sum of the sensitivity and specificity. TB antigen-dependent cytokine secretion was determined as the difference in cytokine levels between the control tube and the TB antigen-coated tube.⁷ A *p*-value of ≤ 0.05 was taken to indicate a significant difference. All data were analyzed using GraphPad Prism (GraphPad, San Diego, CA, USA) and SPSS (v. 18.0; SPSS, Chicago, IL, USA).

3. Results

3.1. Characteristics of the participants

The study examined 46 active pulmonary TB patients, 22 subjects with LTBI, and 32 non-TB controls. Table 1 presents the

Table 1
Demographic and clinical characteristics of the subjects enrolled in the study

Characteristic	Active TB group (<i>n</i> = 46)	LTBI group (<i>n</i> = 22)	Non-TB group (<i>n</i> = 32)
Age, years, median (range)	30 (22–74)	37.5 (22–53)	28 (22–57)
Gender, male/female	21/25	4/18	14/18
BMI, kg/m ² , median (IQR)	20.73 (18.9–23.2)	21.82 (19.6–23.9)	22.42 (20.2–24.5)
Presence of BCG scar, <i>n</i> (%)	25 (54.3)	20 (90.9)	24 (75)
Prior TB treatment, <i>n</i> (%)	5 (10.9)	1 (4.5)	0 (0)
Co-morbidity, <i>n</i> (%)			
Hypertension	2 (4.3)	0 (0)	1 (3.1)
Diabetes mellitus	3 (6.5)	0 (0)	1 (3.1)
Other ^a	5 (10.9)	2 (9.1)	1 (3.1)
Pulmonary TB diagnosis, <i>n</i> (%)			
AFB smear, positive	9 (19.6)		
AFB culture, positive	37 (80.4)		
Extent of lesion in pulmonary TB, <i>n</i> (%)			
One-third of lung field	21 (45.7%)		
One-half of lung field	20 (43.5%)		
More than half of lung field	5 (10.9%)		
Combined extrapulmonary lesion, <i>n</i> (%)	2 (4.3%)		
TST induration, mm, median (IQR)	18 (17–19.5)	16 (13–21.5)	0 (0–2.75)
TST negative, <i>n</i> (%)	0 (0)	0 (0)	32 (100)
TST positive, <i>n</i> (%)	5 (100) ^b	22 (100)	0 (0)

AFB, acid-fast bacillus; BCG, bacille Calmette–Guérin; BMI, body mass index; IQR, interquartile range; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.

^a Active TB group: Langerhans cell histiocytosis, thyroid cancer, non-small cell lung cancer, colon cancer. LTBI group: breast cancer, endometrial cancer.

^b Available for five patients.

Table 2

IFN- γ and IFN- γ IP-10 release after antigen stimulation, and serum IP-10 levels in active TB, latent TB, and non-TB control groups

Test	Active TB group (n=46)	LTBI group (n=22)	Non-TB group (n=32)	p-Value ^a
IFN- γ				
Nil	9 (3.0–15.3)	12.3 (4.1–36.1)	5 (3–11.3)	0.094
TB antigen	352 (171.1–500)	148.8 (96.9–500)	8.5 (2.6–19.5)	<0.001 ^b
IP-10				
Nil	1176 (664.8–2444)	2248 (750.2–12010)	491.0 (207.2–1588)	0.001 ^c
TB antigen	20000 (13 858–20 000)	20000 (17 076–20 000)	963.3 (479.2–2619)	<0.001 ^d
Serum IP-10	174.9 (123.8–368.4)	102.7 (72.9–144.5)	71.14 (60.1–111.8)	<0.001 ^e

IFN- γ , interferon gamma; IP-10, inducible protein 10; LTBI, latent tuberculosis infection; TB, tuberculosis.

Data are presented as the median concentration in pg/ml (interquartile range).

^a p-Value in the table is the result of a Kruskal–Wallis analysis comparing the groups all together.

^b p=0.10 for active TB vs. LTBI; p < 0.001 for active TB vs. non-TB; p < 0.001 for LTBI vs. non-TB.

^c p=0.133 for active TB vs. LTBI; p=0.033 for active TB vs. non-TB; p=0.004 for LTBI vs. non-TB.

^d p=1.0 for active TB vs. LTBI; p < 0.001 for active TB vs. non-TB; p < 0.001 for LTBI vs. non-TB.

^e p=0.002 for active TB vs. LTBI; p < 0.001 for active TB vs. non-TB; p=0.047 for LTBI vs. non-TB.

general characteristics and TST results for each group. The age and gender distributions among the three groups were not different. Nine patients (19.6%) in the active TB group were AFB smear-positive. TST results were available for five patients in the active TB group, and all five were positive.

3.2. Measurement of IP-10 and IFN- γ

Table 2 shows IP-10 and IFN- γ following antigen stimulation in the active TB, LTBI, and non-TB control groups. The median IFN- γ and IP-10 responses to TB antigen were significantly greater in the active TB and LTBI groups than in the non-TB group. Neither the IP-10 nor IFN- γ response to TB antigen differed significantly between the active TB and LTBI groups (IP-10: p = 1.0; IFN- γ : p = 0.10). The IP-10 response in the nil-tube was different among the three groups. The IP-10 responses to nil in the active TB and LTBI groups were significantly higher than in the non-TB control group.

As shown in Figure 1, TB-specific antigen-dependent IP-10 was significantly higher in the active TB and LTBI groups compared with the non-TB control group, while there was no difference between the active TB and LTBI groups for IFN- γ (IP-10: p = 0.182; IFN- γ : p = 0.072).

The serum IP-10 level differed significantly among the three groups. The serum IP-10 was significantly higher in active TB patients (median 174.9 pg/ml; IQR 123.8–368.4) than in LTBI

subjects (median 102.7 pg/ml; IQR 72.9–144.5; p < 0.05) and non-TB subjects (median 71.14 pg/ml; IQR 60.1–111.8; p < 0.001).

3.3. Diagnostic usefulness of serum IP-10 and antigen-dependent IP-10 (IP-10 TB-nil)

To evaluate the usefulness of IP-10 in the diagnosis of TB-specific infection, we performed a ROC analysis of serum IP-10 and the antigen-dependent IP-10 response, comparing the active TB and non-TB groups. We selected cut-off points to maximize the sum of the sensitivity and specificity. The cut-off points for best performance were 119.5 pg/ml for serum IP-10 (sensitivity 87.5%, 95% confidence interval (CI) 67.6–97.3; specificity 90.5%, 95% CI 69.6–98.8; area under the curve 0.93, 95% CI 0.86–1.00; p < 0.001) (Figure 2a) and 2811 pg/ml for TB antigen-dependent IP-10 (sensitivity 97.8%, 95% CI 88.5–99.9; specificity 87.5%, 95% CI 71.0–96.5; area under the curve 0.96, 95% CI 0.91–1.01; p < 0.001) (Figure 2b). The proportion of positive responders was compared among the active TB, LTBI, and non-TB control groups using the selected cut-offs for IP-10 and IFN- γ (Table 3). Based on serum IP-10, the proportions of positive responders were 87.5%, 45.5%, and 9.5% in the active TB, LTBI, and non-TB control groups, respectively. Based on TB antigen-stimulated IP-10, the proportions of positive responders were 97.8%, 90.9%, and 12.5% in the respective groups. These responses are comparable to the positive results of the

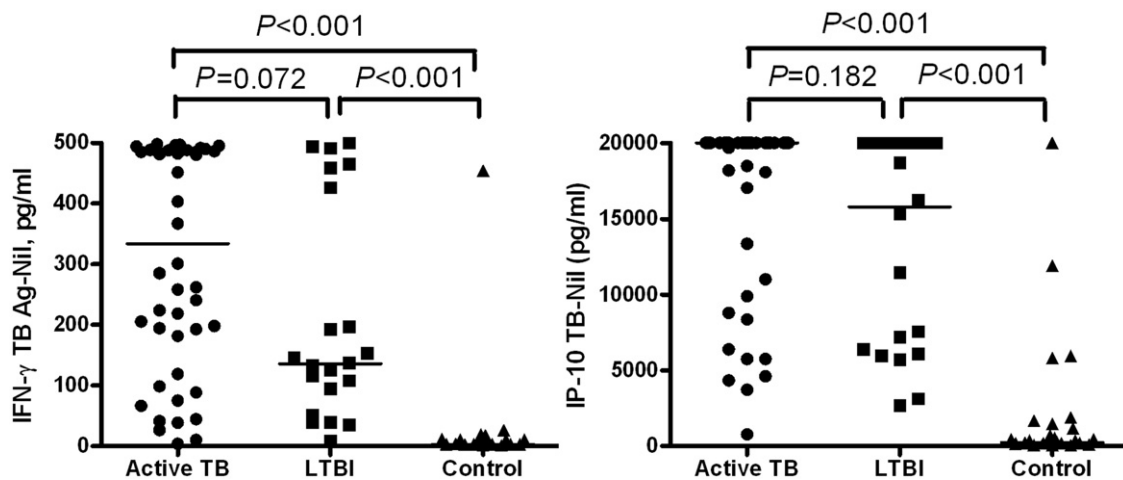


Figure 1. Distribution of IP-10 and IFN- γ responses to *Mycobacterium tuberculosis*-specific antigen in QFT-GIT assays, in active TB, LTBI, and non-TB groups. Horizontal lines indicate median values. ●, active TB; ■, LTBI; ▲, non-TB controls. TB Ag-nil: *M. tuberculosis* antigen-dependent response measured as the difference in cytokine levels between the nil tube and TB antigen-coated tube. IP-10, IFN- γ inducible protein 10; TB, tuberculosis; LTBI, latent TB infection; IFN- γ , interferon gamma; QFT-GIT, QuantiFERON[®]-TB Gold In-Tube assay.

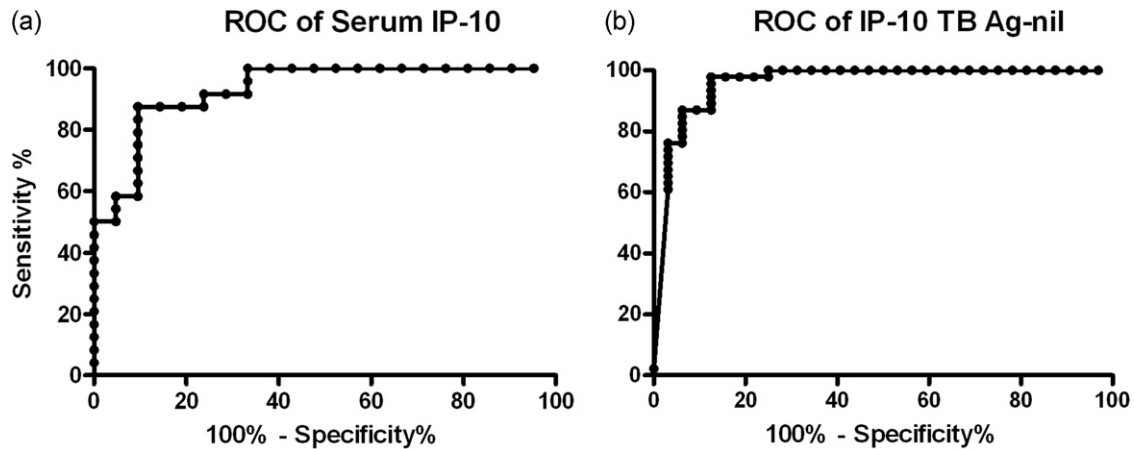


Figure 2. ROC curve showing the accuracy of IP-10 in the diagnosis of *Mycobacterium tuberculosis* infection. (a) Levels detected in serum and (b) *Mycobacterium tuberculosis*-specific levels after background correction. ROC curve analysis was performed using active TB patients and non-TB controls for comparison. (a) AUC 0.93 (95% CI 0.86–1.0), $p < 0.001$ for serum IP-10; (b) AUC 0.96 (95% CI 0.91–1.01), $p < 0.001$ for *Mycobacterium tuberculosis* antigen-dependent IP-10 release. ROC, receiver operating characteristics; IP-10, IFN- γ inducible protein 10; AUC, area under the curve; CI, confidence interval.

Table 3
Diagnostic usefulness of IFN- γ and IFN- γ IP-10 release after antigen stimulation, and serum IP-10

Test	Active TB group (n=46)	LTBI group (n=22)	Non-TB group (n=32)	p-Value
QTF-GIT, n (%)				<0.001
Positive	44 (95.7)	20 (90.9)	4 (12.5)	
Negative	2 (4.3)	2 (9.1)	28 (87.5)	
IP-10 release after TB antigen stimulation (2811 pg/ml), n (%)				<0.001
Positive	45 (97.8)	20 (90.9)	4 (12.5)	
Negative	1 (2.2)	2 (9.1)	28 (87.5)	
Serum IP-10 (119.5 pg/ml), n (%) ^a				<0.001
Positive	21 (87.5)	10 (45.5)	2 (9.5)	
Negative	3 (12.5)	12 (54.5)	19 (90.5)	

IFN- γ , interferon gamma; IP-10, inducible protein 10; LTBI, latent tuberculosis infection; QTF-GIT, QuantiFERON[®]-TB Gold In-Tube assay; TB, tuberculosis.

^a Serum IP-10 was measured in 24 active TB patients and in 21 of the non-TB group.

QTF-GIT in each group (95.7% in active TB, 90.9% in LTBI, and 12.5% in non-TB controls). In addition, there was very high agreement between the QTF-GIT and antigen-stimulated IP-10 test (91%, $\kappa = 0.79$, $p < 0.001$).

4. Discussion

This study demonstrates that IP-10 is a useful immunodiagnostic marker of *M. tuberculosis* infection in an area with an intermediate TB burden. We confirmed previous findings that IP-10 was secreted at high levels following *M. tuberculosis*-specific antigen stimulation after TB infection, in a similar manner to IFN- γ .^{7,15} However, the TB-specific IP-10 response could not differentiate the active TB group from the LTBI group.

The production of IP-10, a member of the CC chemokines, is increased in monocytes and polymorphonuclear granulocytes following *M. tuberculosis* infection.¹⁸ Increased IP-10 levels have also been identified in autoimmune disorders, including systemic lupus erythematosus,¹⁹ autoimmune hepatitis, primary biliary cirrhosis,²⁰ bronchial asthma,²¹ and atopic dermatitis.²²

Distinct from the assumption that IP-10 may reflect only inflammation and may be too non-specific to be used alone in diagnosing TB, Ruhwald et al. reported that the IP-10 response to *M. tuberculosis*-specific antigen could be used to diagnose TB infection.⁵ Similarly, the present study demonstrated that the area under the ROC curve for TB antigen-stimulated IP-10 (0.96, 95% CI 0.91–1.01; $p < 0.001$) was as high as that for IFN- γ (0.97, 95% CI 0.93–1.01; $p < 0.001$). The sensitivity was similar between IFN- γ

and TB antigen-stimulated IP-10 in active TB patients (Table 3), but TB antigen-stimulated IP-10 was not able to discriminate between active and latent TB infection. Our results agree with previous studies demonstrating that the IP-10 response to RD1 selected antigen did not differ significantly between active and latent TB infection.²³

Our results showed higher background IP-10 levels in whole blood from LTBI subjects compared with active TB and non-TB subjects. Whittaker et al.⁷ and Lighter et al.⁸ reported similar findings in children. This could be explained by the presence of a chronic inflammation state, evoking the recruitment of neutrophils, monocytes, and Th1 lymphocytes to control TB infection in LTBI subjects. Chen et al. showed that the levels of unstimulated IP-10 in the control tubes paralleled the occurrence of active TB and the clinical remission of TB after anti-tuberculosis treatment in rheumatoid arthritis patients.¹⁵ Whether high levels of unstimulated IP-10 in whole blood during LTBI can serve as an additional marker to predict the disease status of TB requires further evaluation.

It is worth noting the differences in serum IP-10 levels and in *M. tuberculosis*-antigen stimulated IP-10 levels among the three different TB groups. The serum values are the circulating cytokine levels at a given time-point, and the *M. tuberculosis*-stimulated levels reflect the potential for *M. tuberculosis* reactivity by circulating mononuclear cells. Thus, the higher level of serum IP-10 in the active TB group compared with the LTBI group represents the progressing inflammatory state of active TB patients. However, serum IP-10 can be elevated in a number of

inflammatory diseases,^{19–22} and thus because of its low specificity, the serum IP-10 level alone is insufficient for diagnosing active TB. In addition, the serum IP-10 positive response in the LTBI group in our study was 45.5%, which was lower than that of TB antigen-dependent IP-10 or QFT-GIT. Therefore, serum IP-10 might weakly reflect *M. tuberculosis*-specific infection as a single marker. According to the results, TB antigen-dependent IP-10 or QFT-GIT cannot differentiate active TB from LTBI and are not clinically useful for the diagnosis of TB disease in high TB burden settings due to the high prevalence of LTBI.

This study had some limitations. First, the sample size was too small to allow definitive conclusions and to establish cut-off points. Second, we used the TST to define LTBI. Since BCG vaccination is mandatory in our area, defining LTBI by TST might have compromised the specificity of selection of the LTBI group. However, we selected the participants in the LTBI group from those who had close contact with active pulmonary TB and 91% of them had positive QFT-GIT results. Third, we recruited a healthy group of LTBI and a non-TB control group and compared their IP-10 levels with those of the active TB group. Consequently, we were unable to estimate the clinical efficacy of IP-10 for the diagnosis of active TB in practice. A larger prospective study with active TB suspects would be required to validate the performance of IP-10 in the clinic. Furthermore, the active TB group included only culture-proven pulmonary TB patients without HIV infection. Although the serum IP-10 cut-off in this study (119.5 pg/ml) was similar to the value (132.8 pg/ml) in a previous study,²⁴ the cut-off for TB antigen-stimulated IP-10 release (2811 pg/ml) was higher than reported values of 300 pg/ml²⁵ and 673 pg/ml.²⁶ The discordance among these levels may be attributable to the different disease activities of patients or the effects of additional factors such as geographic location, ethnicity, and technical factors. Further studies in diverse well-defined patient populations are required to elucidate the diagnostic efficacy of IP-10 and to improve the diagnosis of TB by combining IP-10 and IFN- γ assay results.

In conclusion, although the IP-10 level does not appear to be superior to that of IFN- γ as a tool for TB diagnosis, the IP-10 response to TB antigen may represent a specific biomarker for TB infection, but does not by itself distinguish between active TB and LTBI. The serum IP-10 level may exhibit enhanced diagnostic performance when used in combination with another marker. Further studies in more diverse populations are required to validate the use of IP-10 as a diagnostic marker for TB.

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Conflict of interest: No conflict of interest to declare.

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