Monokine induced by gamma interferon for detecting pulmonary tuberculosis

A diagnostic meta-analysis

Yang Li, MD*, Dengqi He, MD, Yinfu Che, MD, Xinchen Zhao, MD

Abstract

Backgrounds: Pulmonary tuberculosis (PTB) is one of the oldest-known and most formidable disease. The standard microbiology culture is time-wasting. Monokine induced by gamma interferon (MIG) has been reported as a new biomarker to auxiliarily detect PTB. In our study, we used meta-analysis to assess the diagnostic value of MIG for PTB.

Methods: PubMed, Embase, Web of Science, and Cochrane Library were searched for relative records up to April 2, 2020. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, area under the curve, and summary receiver operating characteristic curve were estimated.

Results: Eight studies including 1487 participants were included. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of MIG for detecting PTB were 84%, 84%, 5.19, and 0.19, respectively. The diagnostic odds ratio and area under the curve were 27.88 and 0.90, respectively, indicating a good diagnostic ability of MIG. Meta-regression analysis showed that human immunodeficiency virus status might be a source of heterogeneity (P= .02).

Conclusions: Our results showed that MIG had a good diagnostic value for PTB.

Abbreviations: 95% CI = 95% confidence interval, AUC = area under the curve, DOR = diagnostic odds ratio, HIV = human immunodeficiency virus, MIG = monokine induced by gamma interferon, NLR = negative likelihood ratio, PLR = positive likelihood ratio, PTB = pulmonary tuberculosis.

Keywords: detection, meta-analysis, monokine induced by gamma interferon, pulmonary tuberculosis

1. Introduction

Tuberculosis (TB) is one of the oldest and most formidable diseases in humans, with approximately 10,000,000 newly confirmed cases and 1,500,000 deaths in 2018.[1,2] Pulmonary TB (PTB), accounting for 3-quarters of TB cases, contributes substantially to TB mortality, especially in developing countries and in individuals with human immunodeficiency virus (HIV) coinfection.[3,4] The accurate and rapid detection of PTB is critical for eradicating TB globally by 2035.[5]

Currently, microbiological culture and sputum smear microscopy are utilized for the routine diagnosis of PTB.[6] However, these approaches have various drawbacks, including the time delay for positive culture and poor sensitivity (20%–60%) of microscopy.[7,8] The Xpert MTB/RIF assay is recommended by the World Health Organization for the diagnosis of PTB.[9] However, this method is costly and limited in smear-negative sputum, especially in HIV-coinfected cases.[10] Therefore, additional methods are needed for accurate and practical PTB detection.

Monokine induced by gamma interferon (MIG) is a C-X-C motif chemokine receptor 3 ligand. After TB infection, MIG induces immune effector functions in the host by binding to the C-X-C motif chemokine receptor 3 receptor of monocytes and macrophages.[11] It is highly expressed in patients with pulmonary and extrapulmonary TB.[3] The high MIG level is reversed by anti-TB treatment.[12] Several studies have reported that MIG might be an auxiliary biomarker for PTB detection.[13–20] To address the gap in knowledge regarding the MIG in PTB, we evaluated its diagnostic value. In particular, we performed a meta-analysis to synthesize data related to the detection value of MIG for PTB.

2. Materials and methods

2.1. Data sources and search strategy

This study was conducted based on the preferred reporting items for systematic reviews and meta-analyses.[21] Four reference
databases (ie, PubMed, Embase, Web of Science, and Cochrane Library) were searched for relevant articles published up to April 2, 2020. The search terms were “chemokine CXCL9,” “monokine induced by IFN-γ,” “small inducible cytokine B9,” “tuberculosis,” “active tuberculosis,” and “pulmonary tuberculosis.” The search was limited to studies published in English. A detailed search strategy (MeSH and title/abstracts) was used in PubMed: (((“Chemokine CXCL9”[Mesh]) OR (((chemokine CXCL9 [Title/Abstract]) OR monokine induced by IFN-γ [Title/Abstract]) OR monokine induced by interferon gamma [Title/Abstract]) OR Small Inducible Cytokine B9 [Title/Abstract]) OR SCYB9 [Title/Abstract]) OR MIG [Title/Abstract]) OR CXCL9 [Title/Abstract]) AND (“Tuberculosis” [Mesh]) OR (((tuberculosis [Title/Abstract]) OR TB [Title/Abstract]) OR active tuberculosis [Title/Abstract]). The reference lists of identified articles were manually screened for eligible studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria of studies reporting MIG for detection of PTB were as follows:

1. studies assessing blood samples of participants with PTB,
2. studies using MIG as an index test,
3. studies involving positive microbiological culture as the gold standard, and
4. studies presenting the sensitivity and specificity of MIG as the primary outcome.

Figure 1. Flow chart of the process of included articles.
A study was included twice when both stimulated and unstimulated MIG were reported. Additionally, 2 researchers independently conducted study selection. The exclusion criteria were animal experiments, reviews, non-English publications, guidelines, conference abstracts, mechanistic studies, and case reports.

### 2.3. Data extraction and quality assessment

The data extracted included the author, year, country, where the research was conducted, study type, samples from patients with TB and non-TB controls, reference standard, cut-off of index test (MIG), HIV status, type of non-TB control, technology for MIG detection, antigen for MIG (stimulated or unstimulated), was also used to evaluate the risk of bias and applicability of included studies, as implemented in RevMan 5.3.\[22\] Quality Assessment of Diagnostic Accuracy Studies-2 tool was utilized to evaluate heterogeneity, where values of $I^2 < 50\%$ and $P > .1$ indicated low heterogeneity and values of $I^2 > 50\%$ and $P < .1$ indicated high heterogeneity.\[23,24\] An $I^2$ value of 0% indicated no inconsistency. A Galbraith plot analysis was used to identify outlier studies.

A bivariate random effects model was used to determine the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and AUC to evaluate the diagnostic performance of MIG for PTB.\[25\] An AUC value exceeding 0.9 indicated that MIG had an excellent diagnostic ability for PTB. A summary receiver operating characteristic curve was also generated to determine the diagnostic accuracy of MIG.\[26\]

In addition, a meta-regression analysis was applied to explore possible sources of heterogeneity. A subgroup analysis, including HIV status (HIV-coinfected or not), type of non-TB control (healthy controls or other respiratory diseases), technology for MIG detection (Luminex multiplex immunoassay or not), and antigen for MIG (stimulated or unstimulated), was also performed. Deeks' funnel plot was used to judge whether publication bias existed ($P < .05$) or not ($P > .05$).\[27\]

### Table 1

**Characteristics of included studies.**

| Author          | Year | Country/where the research was conducted | TB incidence (/100,000) | Study type | Samples (N) | Index test | Cut-off (MIG) |
|-----------------|------|------------------------------------------|-------------------------|------------|-------------|-------------|---------------|
| Manngo PM\[11\] | 2019 | South Africa 781 (543–1060)              | Cohort                  | 35 69      | Positive culture, Xpert MTB/RIF | MIG   | 940.3 pg/mL  |
| La Manna MP\[12\]| 2018 | Italy 6.1 (5.3–7.1)                      | Cohort                  | 27 20      | Positive culture, Xpert MTB/RIF | MIG   | 6.456 relative fluorescence intensity |
| Jacobs R\[13\]  | 2016 | South Africa 781 (543–1060)              | Cohort                  | 22 33      | Positive culture | MIG   | 1700 pg/mL   |
| Chung W\[15\]   | 2015 | Republic of Korea 77 (71–82)             | Cohort                  | 28 29      | Positive culture | MIG   | 9.16         |
| Chung W\[17\]   | 2014 | Republic of Korea 77 (71–82)             | Cohort                  | 165 256    | Positive culture | MIG   | 11.14 pg/mL  |
| Wang X\[18\]    | 2012 | China 64 (55–74)                         | Cross sectional         | 178 156    | Positive culture, positive sputum smears | MIG   | 368.5 pg/mL  |

MIG = monokine induced by gamma interferon, PTB = pulmonary tuberculosis, TB = tuberculosis.

### Table 2

**Baseline data of included studies.**

| Author          | Year | HIV status | Type of non-TB controls | Technology (MIG) | Antigen (MIG) | Sensitivity (%) | Specificity (%) | AUC | TP  | FP  | FN  | TN  |
|-----------------|------|------------|-------------------------|------------------|---------------|----------------|----------------|-----|-----|-----|-----|-----|
| Manngo PM\[11\]| 2019 | 9 (8.65%)  | Other respiratory diseases | Multiplex immunoassay | Unstimulated | 70             | 57             | 0.73 | 25  | 30  | 10  | 39  |
| La Manna MP\[12\]| 2018 | None       | Other respiratory diseases | Multiplex immunoassay | Stimulated    | 94.44          | 90             | 0.8944 | 25  | 2   | 2   | 18  |
| Jacobs R\[13\]  | 2016 | 14 (25.5%) | Other respiratory diseases | Multiplex immunoassay | Unstimulated | 68             | 88             | 0.81  | 15  | 4   | 7   | 29  |
| Kim S\[14\]    | 2015 | None       | Healthy controls         | RT-PCR           | Stimulated    | 85.71          | 86.21          | -         | 24  | 4   | 25  |
| Chung W\[15\]  | 2015 | None       | Other respiratory diseases | ELISA            | Unstimulated | 81.1           | 88.5           | 0.89  | 163 | 6   | 38  | 46  |
| Chung W\[17\]  | 2014 | None       | Healthy controls         | ELISA            | Unstimulated | 89.3           | 89.1           | 0.935 | 147 | 28  | 18  | 228 |
| Wang X\[18\]   | 2012 | None       | Other respiratory diseases | ELISA            | Stimulated    | 88.6           | 87.9           | 0.941 | 140 | 7   | 18  | 51  |

AUC = area under curve, ELISA = enzyme-linked immunosorbent assay, FN = false negative, FP = false positive, HIV = human immunodeficiency virus, RT-PCR = reverse transcription-polymerase chain reaction, TB = tuberculosis, TN = true negative, TP = true positive.
3. Results

3.1. Research findings

Overall, 462 literature records were identified (Fig. 1). Initially, we removed 197 duplications. We excluded 243 records by screening titles and abstracts: 64 were focused on other diseases; 90 were focused on other cytokines (vitamin D, interleukin-4, and interleukin-8); 21 were reviews, case reports, or guidelines; 45 were animal experiments, including studies of cattle, mice, macaques, and African buffaloes, 14 were not eligible based on primary outcomes, and 9 were other unrelated topics. Ultimately, 22 full studies were assessed for inclusion, and 8 studies were included in the meta-analysis. 

3.2. Characteristics and quality appraisal of the included studies

The baseline characteristics of the 8 studies are shown in Table 1. From 2012 to 2019, 1487 participants, including 814 patients with PTB and 673 non-TB controls, were included. The TB incidence ranged from 6.1 to 781 per 100,000 residents. Seven studies had cohort designs, and 1 study used a cross-sectional design. All studies used positive culture as the reference standard. Xpert MTB/RIF and positive sputum smears were also used in 3 studies. The index test was MIG. The cut-off MIG ranged from 111.4 to 2183 pg/mL. Rates of HIV coinfection in 2 studies were 8.65% and 25.5%. Five studies selected individuals with other respiratory diseases as non-TB controls, and 3 studies included healthy controls. With respect to detection technology (MIG), 3 studies used a multiplex immunoassay, 3 studies used enzyme-linked immunosorbent assay, 1 study used reverse transcription-polymerase chain reaction, and 1 study used microbead-based assays. Half of the studies detected stimulated MIG, while the remaining studies focused on unstimulated MIG. The sensitivity, specificity, AUC, true positive, false positive, false negative, and true negative of MIG for PTB are listed in Table 2.

The quality of eligible studies is summarized in Figure 2. Patient selection bias was unclear for 1 study because the time of participant enrolment was unknown. Half of the studies had...
unclear bias in index tests because we could not determine whether the MIG detection was blinded.[13,14,20] Three studies had unclear bias in the reference standard because other methods (Xpert MTB/RIF and positive sputum smears) were additionally used.[13,14,20] Flow and timing bias were unclear for 3 studies because data for a few participants were lost without explanation.[13,14,19] Applicability concerns were generally low.

3.3. Galbraith plot and pooled analysis

In the meta-analysis, no threshold effect was detected ($P = 1.00$). Heterogeneity was low ($I^2 = 0\%$, $P = .234$). In addition, based on the Galbraith plot, there were no outlier studies (Fig. 3).

A total of 1487 participants were evaluated. Sensitivity ranged from 68% to 94.44% (pooled sensitivity: 0.84, 95% confidence interval [CI]: 0.80–0.88). The specificity ranged from 57% to 90% (pooled specificity: 0.84, 95% CI: 0.76–0.89). The pooled PLR and NLR were 5.19 (95% CI: 3.37–97) and 0.19 (95% CI: 0.13–0.26), respectively. The pooled DOR and AUC were 27.88 (95% CI: 13.43–57.89) and 0.90 (95% CI: 0.88–0.93), respectively, indicating that MIG had a good diagnostic value for PTB. The summary receiver operating characteristic curves are shown in Figure 4.

3.4. Meta-regression and subgroup analyses

In a meta-regression analysis, HIV status was a potential source of heterogeneity ($P = .02$). The type of non-TB control, technology, and antigen for MIG were not sources of heterogeneity ($P = .36$, .23, and .17, respectively).

Concerning HIV status, 23/159 (14.47%) participants were co-infected with HIV, and 1328 participants were not co-infected with HIV. The sensitivity and specificity for participants with PTB/HIV co-infection were much lower than those for patients with PTB alone (0.70 vs 0.86 and 0.70 vs 0.87, respectively). The overall performance was slightly higher for studies using healthy controls than for studies using patients with other respiratory diseases (sensitivity: 0.87 and 0.82; specificity: 0.86 and 0.83). With respect to the MIG detection technology, the sensitivity and specificity of the luminex multiplex immunoassay/microbead-based assay were lower than those of enzyme-linked immunosorbent assay/reverse transcription-polymerase chain reaction (0.82 vs 0.86, 0.77 vs 0.88, respectively). With respect to the antigen for MIG, the diagnostic performance was slightly higher for stimulated MIG than unstimulated MIG (sensitivity: 0.88 and 0.81; specificity: 0.86 and 0.81).

3.5. Publication bias

Deeks’ funnel plot indicated no striking publication bias ($P = .49$) (Fig. 5).

4. Discussion

PTB remains a leading cause of death worldwide, especially for patients with HIV-infection.[28] The accurate discrimination of PTB is a key element of the World Health Organization “End TB Strategy.”[29] Conventional methods for PTB detection are limited by the need for sputum samples, time, expense, and BCG-vaccination status. In recent years, researchers have explored some new biomarkers (eg, interferon gamma-induced protein 10 and C-reactive protein) for auxiliary discrimination of PTB. Several studies have shown that MIG is a promising marker for PTB.[13–20] However, the overall diagnostic accuracy of MIG is unclear.

We firstly performed a meta-analysis to estimate the overall diagnostic performance of MIG for PTB. MIG has a moderate...
sputum samples are paucibacillary and unreliable. Further, 0.87). PTB is differ-as a potential source of heterogeneity (publication bias should not be ignored; owing to limited reliability of marker combinations including MIG. Third, with other biomarkers; however, we did not address the excluded. Furthermore, MIG is usually evaluated in combination with other biomarkers; however, we did not address the reliability of marker combinations including MIG. Third, publication bias should not be ignored; owing to limited linguistic abilities, only English studies were included.

5. Conclusion
This meta-analysis showed that MIG has good diagnostic value for PTB. Further multi-center, large, and prospective studies are required to support this finding.

Author contributions
Conceptualization: Yang Li. Data curation: Yang Li, Dengqi He. Formal analysis: Yang Li, Dengqi He, Yinfu Che, Xinchen Zhao. Funding acquisition: Yang Li. Investigation: Yang Li, Dengqi He, Yinfu Che, Xinchen Zhao. Methodology: Yang Li, Dengqi He, Yinfu Che. Software: Yang Li, Dengqi He, Yinfu Che, Xinchen Zhao. Writing – original draft: Yang Li. Writing – review & editing: Yang Li.

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