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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 an 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

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Department of Stomatology, Lanzhou University First Affiliated Hospital, Lanzhou University, Lanzhou, China.

* Correspondence: Yang Li, Department of Stomatology, Lanzhou University First Hospital, Lanzhou University, Lanzhou, Gansu 730000, China (e-mail: yang18894032228@163.com).

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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]) OR ATB[Title/Abstract]) OR pulmonary tuberculosis [Title/Abstract]) OR PTB[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.

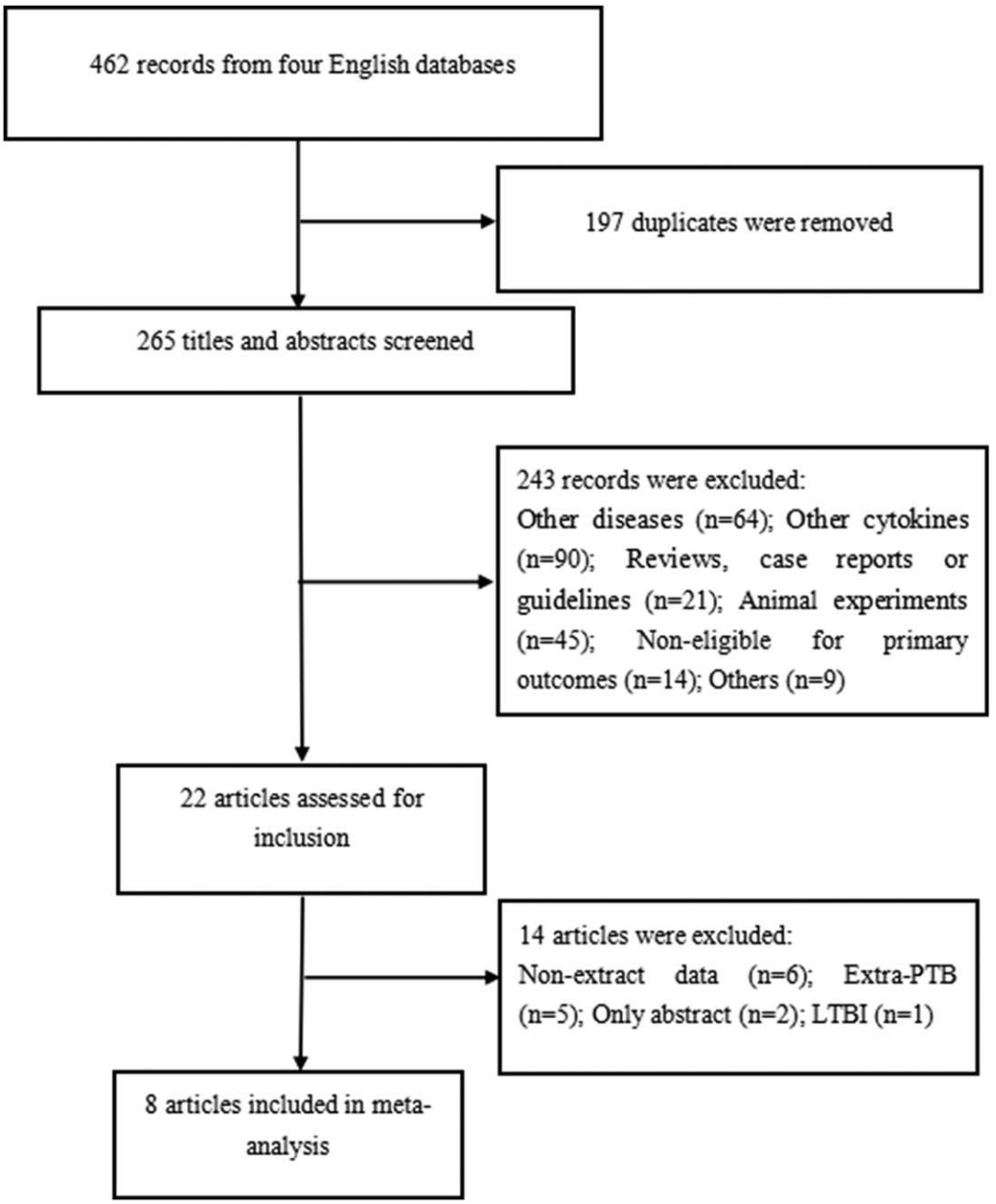

Figure 1. Flow chart of the process of included articles.

Table 1

Characteristics of included studies.

Author	Year	Country/where the research was conducted	TB incidence (/100,000)	Study type	Samples (N)		Reference standard	Index test	Cut-off (MIG)
					PTB patients	non-TB controls			
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
Kim S[14]	2015	Republic of Korea	77 (71–82)	Cohort	28	29	Positive culture	MIG	9.18
Chung W[15]	2015	Republic of Korea	77 (71–82)	Cohort	201	52	Positive culture	MIG	155.1 pg/mL
Lee K[16]	2015	Republic of Korea	77 (71–82)	Cohort	165	256	Positive culture	MIG	111.4 pg/mL
Chung WY[17]	2014	Republic of Korea	77 (71–82)	Cohort	158	58	Positive culture	MIG	2183 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.

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, TB incidence (per 100,000 individuals), study type, samples from patients with PTB 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, sensitivity (%), specificity (%), area under the curve (AUC), and the true positive, false positive, false negative, and true negative rates. Two researchers independently extracted data from the included articles, and disagreements were resolved by discussion and consensus. Previous publications were included without the requirement for ethical reviews.

The Quality Assessment of Diagnostic Accuracy Studies-2 tool was 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 was composed of patient selection, index test, reference standard, and flow and timing.

2.4. Statistical and meta-analyses

Stata 14.0 was used to evaluate the primary data. The Spearman correlation coefficient was used to investigate the threshold effect. I^2 was utilized to evaluate heterogeneity, where values of $I^2 < 50\%$ and $P > .1$ indicated low heterogeneity and values of $I^2 > 50\%$ and $P < .1$ indicates 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 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	4	25
Chung W[15]	2015	None	Other respiratory diseases	ELISA	Unstimulated	81.1	88.5	0.89	163	6	38	46
Lee K[16]	2015	None	Healthy controls	ELISA	Unstimulated	89.3	89.1	0.935	147	28	18	228
Chung WY[17]	2014	None	Other respiratory diseases	ELISA	Stimulated	88.6	87.9	0.941	140	7	18	51
Wang X[18]	2012	None	Healthy controls	Microbead-based assay	Stimulated	85.4	80.8	0.896	152	30	26	126

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.

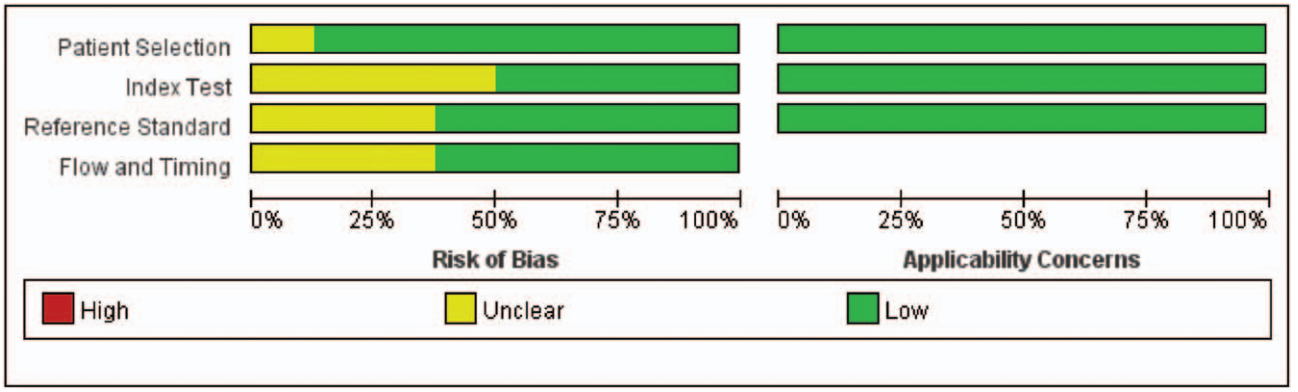

Figure 2. Quality of included studies.

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.[13–20]

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.[20] All studies used positive culture as the reference standard. Xpert MTB/RIF and positive sputum smears were also used in 3 studies.[13,14,20] 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%.[13,15] Five studies selected individuals with other respiratory diseases as non-TB controls,[13–15,17,19] and 3 studies included healthy controls.[16,18,20] With respect to detection technology (MIG), 3 studies used a multiplex immunoassay,[13–15] 3 studies used enzyme-linked immunosorbent assay,[17–19] 1 study used reverse transcription-polymerase chain reaction,[16] and 1 study used microbead-based assays.[20] Half of the studies detected stimulated MIG,[14,16,19,20] while the remaining studies focused on unstimulated MIG.[13,15,17,18] 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.[20] Half of the studies had

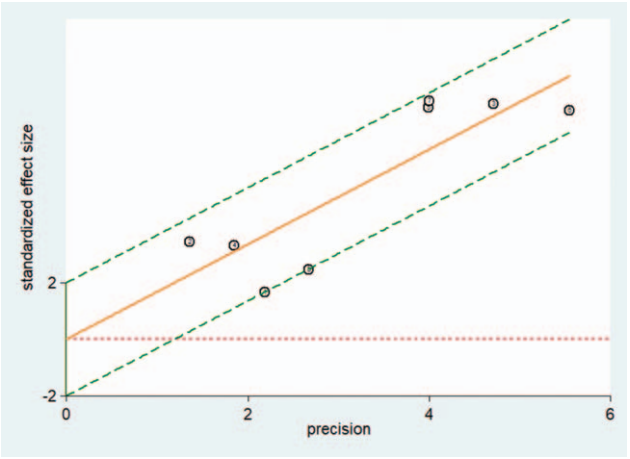

Figure 3. The Galbraith plot of MIG to detect PTB. MIG = monokine induced by gamma interferon, PTB = pulmonary tuberculosis.

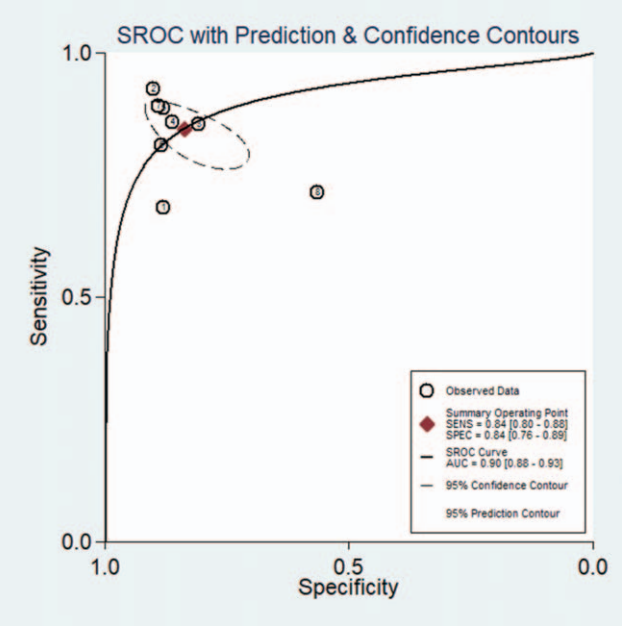

Figure 4. The SROC curve for assessment of MIG to detect PTB. AUC = area under curve, MIG = monokine induced by gamma interferon, PTB = pulmonary tuberculosis, SROC = summary receiver operating characteristic.

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: 3.37.7–97) 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-coinfection.[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

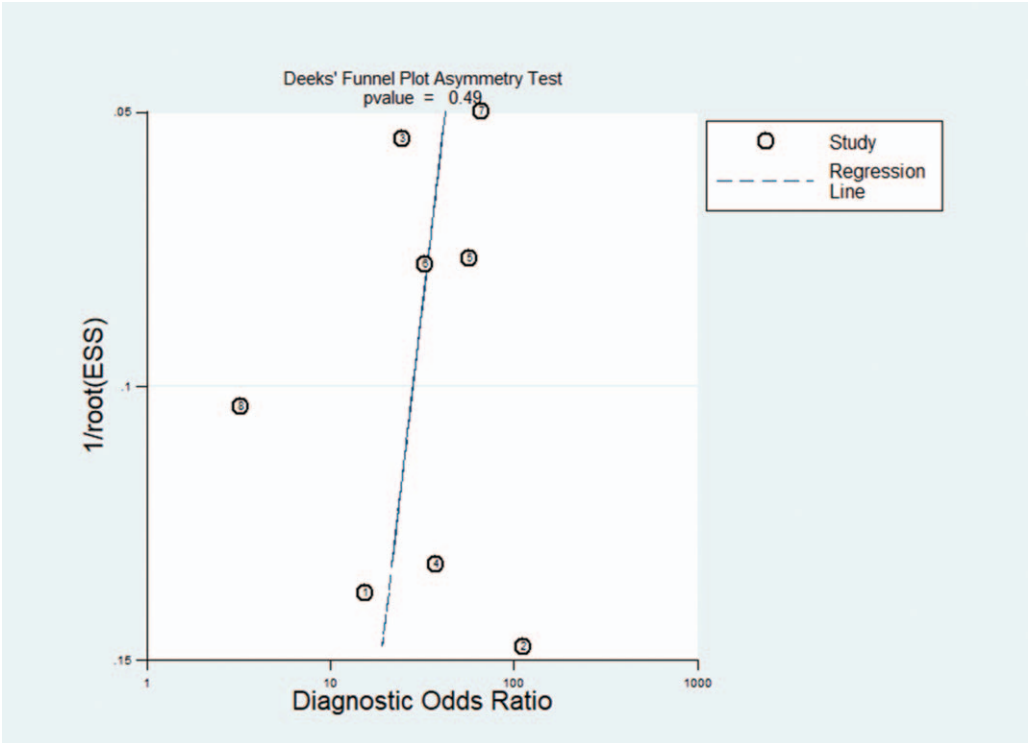

Figure 5. The Deek funnel plot.

possibility of missed diagnoses (16%, sensitivity: 84%) and misdiagnoses (16%, specificity: 84%). The DOR and AUC were 27.88 and 0.90, respectively, indicating a good overall performance for PTB detection. A PLR of 5.19 and NLR of 0.19 further suggested that MIG had a good diagnostic value. Although the cut-off for MIG varied substantially (from 111.4 to 2183 pg/mL), the heterogeneity was relatively low ($I^2 = 0\%$, $P = .234$) and no outlier studies were identified by the Galbraith plot, indicating the high stability and reliability of the results. No striking publication bias ($P = .49$) also improved the objectivity of the results. Besides, MIG is more rapid (requiring no more than 6 hours) than microbiological culture (4–6 weeks to obtain results). MIG also had a higher sensitivity (84%) than that of sputum smear microscopy (20%–60%).

In our meta-regression analysis, HIV-coinfection was identified as a potential source of heterogeneity ($P = .02$). The sensitivity and specificity for patients with PTB/HIV co-infection were much lower than those for patients with only TB (0.70 vs 0.86, 0.70 vs 0.87). PTB is difficult to diagnose in patients with HIV because sputum samples are paucibacillary and unreliable.[30,31] Furthermore, patients with PTB/HIV coinfection are often in critical condition and have a high rate of death, thereby requiring rapid laboratory confirmation.[32] Only 2 studies (158 participants) reported HIV coinfection; although we agree with the results, further studies of patients with PTB/HIV co-infection are needed.

The precise diagnostic value of MIG for PTB might be lower than that previously reported for several reasons. First, heterogeneity is a concern. HIV coinfection could increase heterogeneity. Second, some of the included studies were from the Republic of Korea, and 2 studies from the same group were conducted at the same hospital; 1 focused on stimulated MIG and enrolled patients from August 2012 to July 2014,[17] and the other concentrated with unstimulated MIG and enrolled patients from January 2010 to April 2012.[19] Selection bias cannot be 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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