Diagnostic Accuracy of Interferon-Gamma Release Assays for Tuberculous Meningitis: A Systematic Review and Meta-Analysis

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Background: In this study, we evaluated and compared the accuracy of blood and cerebrospinal fluid (CSF) interferon release tests [interferon-gamma release assays (IGRAs)] in the diagnosis of tuberculous meningitis (TBM) by a meta-analysis of the relevant literature.

Methods: We searched for studies published before 2021 in Medline, Embase, the Cochrane database, and Chinese databases. All studies used the QuantiFERON-TB Gold In-Tube and/or T-SPOT.TB method. Blood and/or CSF tests that met the guidelines for the quality assessment of studies with diagnostic accuracy were included. We used the revised diagnostic accuracy study quality assessment to assess the quality of the included studies. Begg’s funnel plots were used to assess publication bias in the meta-analysis of the diagnostic studies, and statistical analyses were performed by using Stata (Version 12) software.

Results: A total of 12 blood and/or CSF IGRA studies were included in this meta-analysis, with 376 patients and 493 controls. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the summary receiver operating characteristic curve (SROC) of the blood IGRAs in the pooled data from 12 studies were 74% (95% CI: 0.65-0.82), 78% (95% CI: 0.68-0.86), 3.38 (95% CI 2.26-5.06), 0.33 (95% CI: 0.23-0.46), 10.25 (95% CI: 5.46-19.25), and 0.83 (95% CI: 0.79-0.86), respectively. For CSF IGRAs, these values for the pooled data from the 10 studies included were 79% (95% CI: 0.71-0.85), 95% (95% CI: 0.88-0.98), 16.30 (95% CI 6.5-40.83), 0.22 (95% CI: 0.16-0.31), 57.93 (95% CI: 22.56-148.78), and 0.91 (95% CI: 0.88-0.93), respectively.

Conclusion: CSF IGRAs exhibited a better diagnostic accuracy than blood IGRAs in diagnosing TBM.

Keywords: tuberculous meningitis, cerebrospinal fluid, meta-analysis, interferon-release assays, tuberculosis
INTRODUCTION

The World Health Organization (WHO) Global Tuberculosis Report 2020 estimates the number of people living with tuberculosis (TB) at around 10 million in 2019, which makes it the most common cause of death due to a single infectious agent (Chakaya et al., 2021). Tuberculous meningitis (TBM), the most serious form of extrapulmonary TB (Brancusi et al., 2012), is caused by Mycobacterium tuberculosis (M. tuberculosis, MTB) and is associated with significant morbidity and mortality, especially among children and people living with HIV (Ho et al., 2013). Early diagnosis and treatment of TBM is crucial for its prognosis (Garg, 2010). Unfortunately, early diagnosis of TBM is often difficult. Cerebrospinal fluid (CSF) smear, M. tuberculosis culture, and polymerase chain reaction are the gold standards for detecting M. tuberculosis in the CSF (Marais et al., 2010). However, the possibility of identifying acid-fast bacilli in CSF smears is very low, and the culture of M. tuberculosis in CSF is time consuming (Thwaites et al., 2004; Garg, 2019). Although polymerase chain reaction has a higher sensitivity in detecting M. tuberculosis DNA in CSF samples, it also has a higher false-positive rate (Donovan et al., 2020). In response to these challenges, a new technique for the rapid detection of M. tuberculosis has been developed.

In the past decade, the interferon-gamma release assay (IGRA) has become widely used as an immunodiagnostic method for M. tuberculosis infection (Bergot et al., 2018). It detects interferon (IFN)-gamma produced by T cells as a reaction to M. tuberculosis-specific antigens, such as early secretory antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10, which are thought to be present only in M. tuberculosis but not in M. bovis bacille Calmette–Guerin (BCG) vaccine and other mycobacteria (Pai et al., 2006). QuantiFERON-TB Gold In-Tube (QFT-G-IT) (Cellestis, Carnegie, VIC, Australia) and T-SPOT.TB (T-SPOT) (Oxford Immunotec, Abingdon, United Kingdom) are the two most widely used IGRA systems to date, using enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immunospot assay (ELISPOT) to detect IFN-gamma (Pai et al., 2006).

Blood IGRA are most commonly used. However, an alternative approach of IGRA is using effecter T cells from infected TB site specimens may be more likely to detect IFN against TB infection than using peripheral blood mononuclear cells (PBMCs). Recent studies have evaluated the use of CSF IGRA for the diagnosis of TBM; however, the sample sizes of these included studies were insufficient, and their accuracy was disputable. Therefore, this study aimed to perform a meta-analysis to systematically evaluate and compare the accuracy of blood and CSF IGRA in the diagnosis of TBM and to review relevant literature.

METHODS AND MATERIALS

Search Strategy

Relevant works of literature in English were retrieved using Web of Science, PubMed, EBSCO, Medline, Elsevier, and Cochrane Library, while those in Chinese were retrieved using Wanfang Data, China Biology Medicine discs, and China Knowledge Resource Integrated Database. The following keywords were used as search terms: “Tuberculosis meningitis”, “Mycobacterium tuberculosis”, “Tuberculosis”, “Interferon-gamma release assay”, “T cell-based assay”, “T-SPOT.TB”, “ELISPOT”, “IGRA”, “Quantiferon”, “ESAT-6”, “CFP-10”, “Cerebrospinal fluid”, “Sensitivity”, “Specificity”, and “Accuracy”. The study included all diagnostic studies published before 2021.

Study Selection

The inclusion criteria were as follows: (1) IGRA including T-SPOT (ELISPOT) and/or QFT-GIT were used for the diagnosis of TBM; (2) blood and/or CSF IGRA were performed and (3) research articles with original data were included. The exclusion criteria include the following: (1) duplicated studies, case reports, reviews, animal studies, and abstracts; (2) studies without any control group; (3) IGRA systems performed other than QFT-GIT and T-SPOT (ELISPOT); and (4) the fourfold table was not presented or could not be provided.

Data Extraction

Two reviewers independently extracted the data using standard data extraction forms (Table 1). The data extracted from these selected articles were as follows: study sites, the date of publication, author’s name, population studied, assay type, diagnostic method of TB, and cut-off of IGRA. Inconclusive results have been eliminated. Discrepancies were resolved by a third examiner.

Quality Assessment

The quality of the studies that aimed to calculate the accuracy of the analyses was assessed independently by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist, in which each assessment item was assigned the labels “yes”, “no”, or “unclear” (Whiting et al., 2011).

Statistical Analysis

The degree of heterogeneity of the selected studies was evaluated using the Q-test, and the size of the heterogeneity was quantified by computing for I². For each study, 2 × 2 tables representing true-positive, true-negative, false-positive, and false-negative values were identified. The sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the summary receiver operating characteristic (SROC) curve from the pooled data were calculated by meta-analysis and expressed in 95% confidence intervals (CIs). Begg’s funnel plot was used to assess publication bias in nine of the included studies. Fagan’s nomogram was used to calculate the post-test probability for each group. All data were analyzed using STATA version 12.0 software. Statistical significance was set at P < 0.05.

RESULTS

Characteristics of the Included Studies

A total of 832 published studies were screened using the process shown in Figure 1. Among these, 12 studies with 854 human
TABLE 1 | Characteristics of the included studies.

| Country           | Sample size (n/N) | Age (years) | Design          | QUADUS score | Blinding  | Type of IGRA          | Cut off                      |
|-------------------|------------------|-------------|-----------------|-------------|-----------|-----------------------|-----------------------------|
| Kim et al., 2008  | Korea            | 12/25       | 45.5 ± 16.5/39.3 ± 16.3‡ | Prospective | 13        | Yes                   | ELISPOT CSF/Blood ≥2        |
| Thomas et al., 2008 | India           | 11/9        | 328(69)/3616-64³ | Prospective | 14        | Yes                  | ELISPOT Manufacturers’ instructions (Blood-CSF) ≥6SFC(Blood); ≥6SFC (CSF) |
| Kim et al., 2010  | Korea            | 31/55       | 45.4 ± 14.8/44.0 ± 19.6³ | Prospective | 12        | Yes                   | ELISPOT CSF/Blood ≥6SFC (CSF) |
| Patel et al., 2010 | South Africa     | 38/48       | 33.5 ± 9.5/32.9 ± 9.7³ | Prospective | 11        | Unclear               | T-Spot.TB                   |
| Vidhate et al., 2011 | India           | 36/16       | 28.9 ± 11.8/34.5 ± 17.1³ | Unknown     | 13        | Unclear               | QFT-GIT >0.35 IU/ml (Blood) |
| Cho et al., 2011  | Korea            | 35/87       | 48.3 ± 16.1/48.1 ± 17.6³ | Prospective | 10        | Yes                   | T-Spot.TB                   |
| Park et al., 2012  | Korea            | 25/57       | ≥16³            | Prospective | 6         | Unclear               | ELISPOT CSF/Blood ≥6SFC (CSF) |
| Zhang et al., 2013 | China           | 30/30       | 17-74³         | Unknown     | 10        | Yes                   | ELISPOT CSF/Blood ≥6SFC (CSF) |
| Qin et al., 2015  | China            | 12/28       | 46 (24-59)/43(29-65)³ | Unknown     | 13        | Yes                   | QFT-GIT >0.35 IU/ml (Blood) |
| Caliman-Sturdza et al., 2015 | Romania | 63/62       | 0.7-17/2.1-17.2³ | Unknown     | 13        | Unclear               | QFT-GIT                     |
| Lu et al., 2016   | China            | 30/39       | 45 (18-79)/36(14-64)³ | Unknown     | 11        | Unclear               | QFT-G-IT/ELISPOT CSF/Blood ≥24SFC (CSF) |
| Pan et al., 2017  | China            | 53/37       | 31(18-79)/36(14-47)³ | Prospective | 12        | Yes                   | ELISPOT CSF/Blood ≥6SFC (CSF) |

IGRA, interferon-gamma release assay; CSF, cerebrospinal fluid; AFB, acid-fast bacilli; PCR, polymerase chain reaction; QFT-G-IT, QuantIFERON-TB Gold in-tube; ELISPOT, enzyme-linked immunospot; SFC, spot-forming cell.

‡Median (IQR).
¶Mean.
§Mean (range).
¶Mean (SD).
¶Median (IR).
FIGURE 1 | The study selection process flowchart.

TABLE 2 | Principal data characteristics of included studies.

| Year | Country | TBM patients | Diagnostic methods(N) | IGRA methods | Sample | Test result |
|------|---------|--------------|------------------------|--------------|--------|-------------|
|      |         |              |                        |              | TP     | FP          | FN          | TN          |
| Kim  | Korea   | 12           | Culture(4),PCR(3),AFB(1) | ELISPOT      | PB     | 10          | 9           | 1           | 15          |
|      |         |              |                        |              | CSF    | 3           | 3           | 1           | 9           |
| Thomas | India | 11           | Culture(1),PCR(1)       | ELISPOT      | PB     | 9           | 2           | 2           | 6           |
|      |         |              |                        |              | CSF    | 9           | 0           | 1           | 7           |
| Kim  | Korea   | 31           | Culture(7),PCR(4),AFB(4) | ELISPOT      | PB     | 22          | 9           | 20          | 30          |
|      |         |              |                        |              | CSF    | 13          | 1           | 5           | 25          |
| Patel | South Africa | 38       | Culture,PCR:(Unclear)  | T-Spot.TB    | PB     | 22          | 3           | 16          | 45          |
|      |         |              |                        |              | CSF    | 31          | 0           | 7           | 48          |
| Vidhate | India | 36           | Culture(1),PCR(13),AFB(2) | QFT-GIT      | PB     | 16          | 6           | 20          | 10          |
| Cho  | Korea   | 35           | Culture,PCR:(Unclear)  | T-Spot.TB    | PB     | 26          | 47          | 9           | 40          |
| Park | Korea   | 25           | unclear                 | T-Spot.TB    | PB     | 22          | 24          | 3           | 33          |
|      |         |              |                        |              | CSF    | 18          | 12          | 7           | 45          |
| Zhang | China  | 30           | Culture,PCR:(Unclear)  | T-Spot.TB    | PB     | 23          | 4           | 7           | 26          |
|      |         |              |                        |              | CSF    | 28          | 1           | 2           | 29          |
| Qin  | China   | 12           | Culture(2),PCR(1),AFB(1) | T-Spot.TB    | PB     | 10          | 2           | 5           | 23          |
|      |         |              |                        |              | CSF    | 11          | 1           | 2           | 26          |
| Caliman-Sturdza | Romania | 63       | Culture,AFB:(positive 25) | QFT-GIT      | PB     | 49          | 7           | 13          | 51          |
|      |         |              |                        |              | CSF    | 45          | 1           | 11          | 55          |
| Lu   | China   | 30           | Culture,AFB:(positive 6) | QFT-G-IT/ELISPOT | PB     | 21          | 5           | 7           | 34          |
|      |         |              |                        |              | CSF    | 25          | 6           | 5           | 33          |
| Pan  | China   | 53           | Culture(5),PCR(15),pathology(1) | ELISPOT      | PB     | 48          | 9           | 5           | 28          |
|      |         |              |                        |              | CSF    | 32          | 1           | 21          | 36          |

IGRA, interferon-gamma release assay; PB, peripheral blood; CSF, cerebrospinal fluid; AFB, acid-fast bacilli; PCR, polymerase chain reaction; QFT-G-IT, QuantiFERON-TB Gold in-tube; ELISPOT, enzyme-linked immunospot; TP, true positive; FP, false positive; FN, false negative; TN, true negative.
was 0.298, while QFT-GIT is 0.159 and 0.317, respectively. The area under the SROC curve of blood IGRA was 0.83 (95% CI: 0.79-0.86) (Figures 2A and 3A).

**Diagnostic Accuracy of Interferon-Gamma Release Assays in Cerebrospinal Fluid**

The Q-test and $I^2$ statistic results also showed high heterogeneity among the included studies that utilized CSF as the medium analyzed ($P=0.03$, $I^2>50$%). Therefore, a random-effects model was used for the meta-analysis. The sensitivity and specificity of CSF IGRAs obtained from pooled data were 79% (95% CI: 0.71-0.85) and 95% (95% CI: 0.88-0.98), respectively. In addition, the PLR, NLR, and DOR were 16.30 (95% CI: 6.50-40.83), 0.22 (95% CI: 0.16-0.31), and 57.93 (95% CI: 22.56-148.78), respectively. The false-positive rate of CSF detected by T-SPOT was 0.078 and the false-negative rate was 0.21, respectively. The AUC of the SROC curve was 0.91 (95% CI: 0.88-0.93) for CSF IGRAs (Figures 2B and 3B). Therefore, CSF IGRAs showed higher diagnostic sensitivity and specificity than blood IGRAs.

**Publication Bias Analysis**

The publication bias of the included studies was determined using Begg’s funnel plot. The Pr>|z| values of blood and CSF were 0.815 (Figure 4A) and 0.458 (Figure 4B), respectively, indicating that no publication bias was observed in blood or CSF IGRAs.

**Post-Test Probability of the Disease**

Fagan’s nomogram statistics showed that the positive post-test probabilities of TBM after either blood or CSF IGRAs were 46% and 80%, respectively (Figures 5A, B). A higher but limited probability of body fluids indicates that a positive IGRA result should not be used solely for the diagnosis of TBM, either from blood or from CSF. On the contrary, the negative post-test probabilities were 8% for blood and 5% for CSF IGRAs.
Figures 5A, B), which indicates that negative body fluid IGRA results would be more reliable in excluding suspected TBM.

**DISCUSSION**

Since early diagnosis and treatment of TBM save lives, tests must be performed to diagnose TBM quickly and accurately, especially in its early stages (Ho et al., 2013). Unfortunately, the diagnosis of TBM is often ambiguous because of nonspecific clinical manifestations and the low sensitivity of available diagnostic methods (Thwaites et al., 2013). The absolute and most widely used diagnostic tools for TBM are Ziehl-Neelsen staining and culture (Marais et al., 2010), but they are negative in the majority of TBM cases. Our results showed that the sensitivity for CSF culture and/or AFB was 16% in the TBM group. Increasing the volume of CSF (>6 ml) obtained and meticulous microscopy (for at least half an hour) further increases the chance of positive diagnosis (Heemskerk et al., 2018; Bahr et al., 2019). For this reason, we did not restrict diagnostic criteria to microbiological confirmation, which is usually not possible in a routine clinical setting. This may produce bias. The detection of *M. tuberculosis* DNA in CSF samples using nucleic acid amplification tests (NAATs) are a widely used diagnostic method (Marais et al., 2010). In recent years, some studies on NAATs (Modi et al., 2016; Jyothy et al., 2019; Kwizera et al., 2019; Pormohammad et al., 2019; Siddiqi et al., 2019; Poplin et al., 2020; Slane and Unakal, 2021) reported a potential to rule in or confirm diagnosis (specificity, 80%-100%), but low sensitivity (~40%-96%) precludes the use of these tests to rule out TBM. Up to now, adenosine deaminase (ADA) is still a hot spot in TB diagnosis. Numerous studies have been published regarding the usefulness in TBM. Performance varies according to the assay and cut-off used, the mean sensitivity and specificity of ADA assays were 60%-90% and 80%-90%, respectively (Pormohammad et al., 2017). ADA assays may be useful in
identifying TBM, but raised levels may also be seen in other central nervous system diseases such as purulent meningitis (Ekermans et al., 2017) (Table 3).

To address this, newer tests have emerged for the early diagnosis of TBM, such as IGRAs. The design and development of IGRAs were based on the fact that T lymphocytes release IFN-gamma in response to the stimulation of \textit{M. tuberculosis}-specific antigens such as ESAT-6 and CFP-10 (Andersen et al., 2000; Pai et al., 2007; Stevens et al., 2019). Moreover, blood-based tests have been widely evaluated and are considered promising tools for the rapid detection of \textit{M. tuberculosis} (Westermann and Pabst, 1992; Meier et al., 2005; Kawamura et al., 2012; Rangaka et al., 2012). In addition, the accuracy of CSF IGRAs has also been evaluated for the diagnosis of TBM (Kim et al., 2008; Thomas et al., 2008; Kim et al., 2010; Patel et al., 2010; Park et al., 2012; Zhang et al., 2013; Caliman-Sturdza et al., 2015; Qin et al., 2015; Lu et al., 2016; Pan et al., 2017). However, no studies comparing blood and CSF IGRAs have been performed yet. Therefore, we performed this meta-analysis to systematically evaluate and compare the diagnostic accuracy of blood and CSF IGRAs for diagnosing TBM. The obtained overall sensitivity, specificity, PLR, NLR, DOR, and the SROC AUC in blood samples were 74% (95% CI: 0.65-0.82), 78% (95% CI: 0.68-0.86), 3.38 (95% CI: 2.26-5.06), 0.33 (95% CI: 0.23-0.46), 10.25 (95% CI: 5.46-19.25), and 0.83 (95% CI: 0.79-0.86), respectively, and for CSF, these values were 79% (95% CI: 0.71-0.85), 95% (95% CI: 0.88-0.98), 16.30 (95% CI: 6.50-40.83), 0.22 (95% CI: 0.16-0.31), 57.93 (95% CI: 22.56-148.78), and 0.91 (95% CI: 0.88-0.93), respectively. The post-test probability of blood samples was 46%/8% and 80%/5% in CSF samples. These results suggest that the IGRAs carried out in CSF have better diagnostic sensitivity and specificity than IGRAs in blood for the diagnosis of TBM.

**FIGURE 4** | Funnel plot of the included studies. (A) Funnel plots of the included studies on blood (A) and CSF samples (B).
**TABLE 3** | Comparison of conventional and novel diagnostic tests for tuberculous meningitis performed on CSF specimens.

| Diagnostic test in CSF specimens | Sensitivity (%) | Specificity (%) | Comments | References |
|----------------------------------|-----------------|-----------------|----------|------------|
| Microbiological diagnosis        |                 |                 |          |            |
| Ziehl-Neelsen                    | 10-40           | 100             | Sensitivity substantially improved by meticulous microscopy of large volumes of CSF (>6 ml). | Bahr et al. (2019); Heemskerk et al. (2018) |
| Mycobacterial culture            |                 |                 |          |            |
| Nucleic acid amplification tests (NAATs) | 50-70           | 95-100          | Takes at least 2 weeks (and, in many cases, up to 6 weeks): clinicians cannot afford to wait for culture results before treating patients. | Bahr et al. (2019); Jyothy et al. (2019); Slane and Unakal (2021); Modi et al. (2016); Siddiqi et al. (2019); Kwizera et al. (2019); Poplin et al. (2020) |
| Xpert MTB/RIF                    | 50-70           | 95-100          | Good "rule in" test, but it does not appear to be adequate to rule out TBM. The requirements of trained laboratory staff and high costs. Requires further evaluation. | Jyothy et al. (2019); Slane and Unakal (2021) |
| LAMP                             | 88-96           | 80-100          |          |            |
| Amplicor TB PCR test             | –40             | 90-100          |          |            |
| MTD                              | 86              | 99              |          |            |
| Immune response-based diagnosis  |                 |                 |          |            |
| ADA                              | 60-90           | 80-90           | Variable results, cannot differentiate purulent meningitis from TBM. | Pormohammad et al. (2017); Ekermans et al. (2017) |
| CSF IGRA                         | 79% (95% CI: 0.71-0.85) | 95% (95% CI: 0.88-0.98) | CSF IGRA is better at distinguishing ATB and has a higher ability to predict the location of M. tuberculosis infection, especially in TBM cases. Very few studies, small subject numbers. Furthermore, cut-off and incubation cell numbers across the studies were inconsistent. | Present |

IGRA, interferon-gamma release assay; CSF, cerebrospinal fluid; LAMP, loop-mediated isothermal amplification; MTD, The Gen-probe amplified M. tuberculosis direct test; ADA, adenosine deaminase; ATB, active tuberculosis.
However, even if the sensitivity, specificity, and post-test probability were higher for CSF IGRA than for blood IGRA in this analysis, the diagnostic sensitivity of CSF IGRA alone was not high enough to support the diagnosis of TBM. Nevertheless, CSF IGRA have some advantages over blood IGRA. When peripheral blood IGRA are used alone, it becomes difficult to distinguish active tuberculosis (ATB) from latent tuberculosis infection in a clinical setting (Pai et al., 2004; Gao et al., 2017). In an ATB stimulation, antigen-specific T lymphocytes are recruited to the sites of infection and proliferate rapidly (Schwander et al., 1998; Hirsch et al., 2001). Because of this, CSF IGRA is better at distinguishing ATB and has a higher ability to predict the location of the M. tuberculosis infection, especially in TBM cases.

The current analysis had some limitations. First, among the ten included studies that utilized CSF IGRA, the sample size was fairly small. Second, the cut-off and incubation cell numbers across the studies were inconsistent. This is an important consideration because the cut-off values greatly influence the sensitivity and specificity. Finally, in some of the included studies, the diagnosis of TBM patients was not confirmed by microbiological methods (smear or culture).

CONCLUSION

The results of this meta-analysis showed that CSF IGRA had higher sensitivity and specificity in the diagnosis of TBM than peripheral blood IGRA. However, carefully designed higher-quality independent studies are required to reliably compare the diagnostic accuracies of blood and CSF IGRA.

AUTHOR CONTRIBUTIONS

AW, E-LL, and FH designed the study. The manuscript was written by AW, E-LL, and FH with the final approval. S-ML and Y-LZ did the data searches and study selection. W-FC and D-YY did the data synthesis and created the tables and figures. All authors contributed to the article and approved the submitted version.

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