World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i44.8133

World J Gastroenterol 2013 November 28; 19(44): 8133-8140
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

Effectiveness of interferon-gamma release assays for differentiating intestinal tuberculosis from Crohn's disease: A meta-analysis

Wen Chen, Jun-Hua Fan, Wei Luo, Peng Peng, Si-Biao Su

Wen Chen, Department of Educational Administration, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China
Jun-Hua Fan, Wei Luo, Peng Peng, Si-Biao Su, Department of Gastroenterology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China
Author contributions: Su SB designed the study, searched the databases, extracted the data, analyzed the results, and wrote the manuscript; Chen W helped design the study, searched the databases, and wrote and revised the manuscript; Fan JH formulated the research question, and helped with database searches and analysis; Luo W and Peng P helped design the data abstraction form and served as second reviewers in extracting the data; all authors have read and approved the final manuscript.
Correspondence to: Dr. Si-Biao Su, Department of Gastroenterology, The First Affiliated Hospital of Guangxi Medical University, No. 22, Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. susibiao@gmail.com
Telephone: +86-771-5356501 Fax: +86-771-5356585
Received: August 5, 2013 Revised: September 15, 2013
Accepted: October 17, 2013
Published online: November 28, 2013

Abstract

AIM: To investigate the clinical usefulness of interferon-gamma release assays (IGRAs) in the differential diagnosis of intestinal tuberculosis (ITB) from Crohn's disease (CD) by meta-analysis.

METHODS: A systematic search of English language studies was performed. We searched the following databases: Medline, Embase, Web of Science and the Cochrane Library. The Standards for Reporting Diagnostic Accuracy initiative and Quality Assessment for Studies of Diagnostic Accuracy tool were used to assess the methodological quality of the studies. Sensitivity, specificity, and other measures of the accuracy of IGRAs in the differential diagnosis of ITB from CD were pooled and analyzed using random-effects models. Receiver operating characteristic curves were applied to summarize overall test performance. Two reviewers independently judged study eligibility while screening the citations.

RESULTS: Five studies met the inclusion criteria. The average inter-rater agreement between the two reviewers for items in the quality checklist was 0.95. Analysis of IGRAs for the differential diagnosis of ITB from CD produced summary estimates as follows: sensitivity, 0.74 (95%CI: 0.68-0.80); specificity, 0.87 (95%CI: 0.82-0.90); positive likelihood ratio, 5.98 (95%CI: 3.79-9.43); negative likelihood ratio, 0.28 (95%CI: 0.18-0.43); and diagnostic odds ratio, 26.21 (95%CI: 14.15-48.57). The area under the curve was 0.92. The evaluation of publication bias was not significant (P = 0.235).

CONCLUSION: Although IGRAs are not sensitive enough, they provide good specificity for the accurate diagnosis of ITB, which may be helpful in the differential diagnosis of ITB from CD.

Key words: Intestinal tuberculosis; Crohn's disease; Interferon-gamma; Meta-analysis

Core tip: The misdiagnosis rate between Crohn's disease (CD) and intestinal tuberculosis (ITB) is 50%-70%. Interferon-gamma release assays (IGRAs) have been used mainly to identify latent tuberculosis infection in patients in several areas and countries. However, the clinical usefulness of IGRAs in the differential diagnosis of ITB from CD is unknown. This is the first study to investigate the clinical usefulness of IGRAs in the differential diagnosis of ITB from CD by meta-analysis. IGRAs provided good specificity for ITB,

and should be helpful in the differential diagnosis of ITB from CD.

Chen W, Fan JH, Luo W, Peng P, Su SB. Effectiveness of interferon-gamma release assays for differentiating intestinal tuberculosis from Crohn's disease: A meta-analysis. *World J Gastroenterol* 2013; 19(44): 8133-8140 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i44/8133.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i44.8133

INTRODUCTION

Tuberculosis (TB) is a major worldwide cause of morbidity and mortality[1,2]. The geography of TB is changing and expanding due to immigration, human immune deficiency virus, immune suppressants, and the development of multidrug-resistant strains of TB[1-5], especially in privileged areas of the world. Intestinal tuberculosis (ITB) is an important extra-pulmonary TB that primarily affects the ileum and colon, causing gastrointestinal symptoms such as diarrhea or abdominal pain. Along with the increased incidence of TB, the incidence of ITB has also increased. Recently, with the emergence of Crohn's disease (CD) in Asian countries[3,6,7], differentiating between ITB and CD is more important than ever. Unfortunately, it is difficult to differentiate ITB from CD due to similar symptoms, and pathologic, radiologic, and endoscopic findings[4,8].

ITB and CD are both chronic granulomatous inflammatory disorders of the intestine[9,10], but have a different pathophysiology, clinical course, and treatment options. ITB could be completely cured if diagnosed early and treated appropriately. CD is not curable and recurs easily. Although several endoscopic and histologic parameters to differentiate these two diseases have been suggested[11,12], a large number of ITB cases are diagnosed by assessing the outcomes of empirical anti-tuberculosis therapy. Moreover, in South Korea, 42%-45% of patients with CD received empirical anti-tuberculosis therapy before they were finally diagnosed with CD[13,14].

A delayed diagnosis of ITB and CD may result in a delay in initiating effective therapy, resulting in a negative economic impact and increased morbidity and mortality. Furthermore, the use of steroids, immune suppressants and biological agents after a presumptive diagnosis of CD, can result in severe and sometimes fatal complications such as systemic dissemination of TB. In recent years, T-cell based interferon-gamma (IFN-γ) release assays (IGRAs) have increasingly been used to replace the traditional tuberculin skin test (TST) as a diagnostic tool for TB. IGRAs have been shown to have superior sensitivity and specificity[15,16]. There are two commercially available methods for IGRAs: the QuantiFERON-TB Gold In-Tube (QFT-G-IT) method and the T-SPOT-TB method. QFT-G-IT uses an enzyme-linked immunosorbent assay to measure antigen-specific production of IFN-γ by circulating T-cells in whole blood being challenged with *Mycobacterium tuberculosis* (MTB)-specific antigens. T-SPOT-TB test is a blood IFN-γ assay measuring the number of activated T-cells by identifying IFN-γ release when stimulated by MTB-specific antigens, including early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). However, whether IGRAs contribute to the differential diagnosis of ITB from CD remains controversial. In the present study, we systematically analyzed and assessed the clinical utility of IGRAs in distinguishing ITB from CD *via* meta-analysis techniques.

MATERIALS AND METHODS

Search strategy and study selection

We searched the following databases: Medline (1980-2013), Embase (1980-2013), Web of Science (1990-2013) and the Cochrane Library. An updated search was carried out in March 2013. The following search terms were used: "intestinal tuberculosis", "Crohn's disease", "interferon-gamma/IFN-γ", "sensitivity", "specificity" and "accuracy". We contacted experts in the specialty and searched the reference lists of primary and review articles. Although no language restrictions were imposed initially, our resources only permitted the review of articles published in the English language for the full text review and final analysis. Conference abstracts and letters were excluded due to unavailable data.

A study was included if it provided both sensitivity (true-positive rate) and specificity (false-positive rate) of IGRAs for the differential diagnosis of ITB from CD, or provided IGRAs values in a dot-plot form which allowed the results to be extracted for individual study subjects. Patients of any age diagnosed with ITB underwent smear or culture of MTB and/or histologic observation of ileum and/or colon tissue, as well as clinical diagnosis, such as response to anti-TB therapy. All patients were diagnosed with CD according to the Japanese diagnostic criteria[17] or the World Health Organization diagnostic criteria[18] based on clinical, endoscopic, radiological and pathological features. In addition, we selected studies which included at least 10 ITB/CD specimens eligible for inclusion in order to reduce selection bias due to a small number of participants. Two reviewers (Chen W and Fan JH) independently judged study eligibility while screening the citations. Disagreements were resolved by consensus.

Data extraction and quality assessment

Two reviewers (Chen W and Fan JH) checked and extracted data independently. The reviewers were blinded to publication details, and disagreements were resolved by consensus. Data retrieved from the reports included participant characteristics, assay methods, sensitivity and specificity data, cutoff values, year of publication, and methodological quality. The value of IGRAs provided in dot plots were measured by placing scalar grids over

Table 1 Summary of the included studies

Study	Country/Area	Patients (*n*)	Assay method	Cutoff	Test results				Quality score	
					TP	FP	FN	TN	STARD	QUADAS
Lee *et al*[28]	South Korea	60	T-SPOT-TB	-	12	8	0	40	16	11
Lei *et al*[29]	China	191	T-SPOT-TB	-	36	5	6	62	18	13
Kim *et al*[30]	South Korea	128	QFT-G-IT	0.35 IU/mL	43	6	21	58	17	12
Li *et al*[31]	China	84	T-SPOT-TB	-	16	16	3	49	17	12
Kim *et al*[32]	South Korea	147	QFT-G-IT	0.35 IU/mL	50	7	25	65	18	13

T-SPOT-TB: An enzyme-linked immunosorbent spot assay; QFT-G-IT: Quanti-FERON-TB Gold In-Tube; TP: True-positive; FP: False-positive; FN: False-negative; TN: True-negative; STARD: Standards for reporting diagnostic accuracy; QUADAS: Quality assessment for studies of diagnostic accuracy.

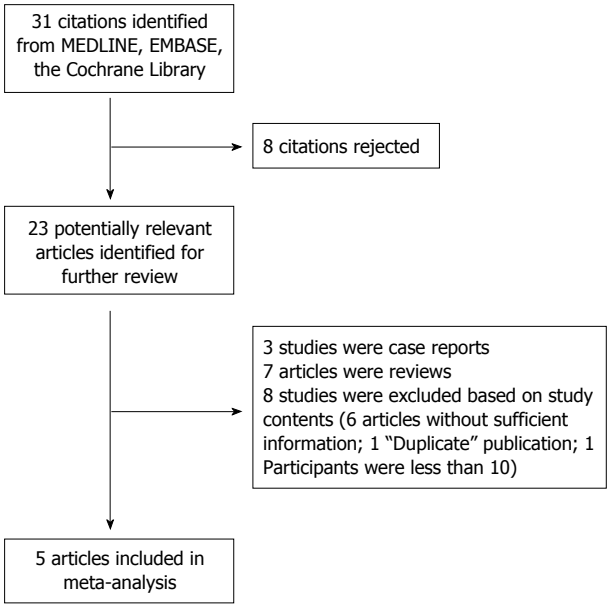

Figure 1 Flowchart of study selection.

the plots, and analyzed using a receiver operating characteristic (ROC) curve for each study (SPSS; Chicago, IL, United States). A summary of each study, including the numbers of true-positive, false-positive, false-negative and true-negative results, is shown in Table 1.

We assessed the methodological quality of studies using guidelines established by the standards for reporting diagnostic accuracy (STARD)[19] initiative and the quality assessment for studies of diagnostic accuracy (QUADAS) tool[20]. In addition, the following study design characteristics were retrieved: (1) cross-sectional design (*vs* case-control design); (2) consecutive or random sampling of patients; (3) blind (single or double) interpretation of determination and reference standard results; and (4) prospective data collection. If primary studies did not show data that met the above criteria, we requested the data from the authors. The "unknown" items were treated as "no" if we did not receive a response from the authors.

Statistical analysis

We used standard methods recommended for meta-analyses of diagnostic test evaluations[21]. Analyses were performed using two professional statistical software programs (STATA, version 11; Stata Corporation, College Station, TX, United States and Meta-DiSc for Windows; XI Cochrane Colloquium; Barcelona, Spain). The following measures of test accuracy were analyzed for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR).

The analysis was based on a summary ROC (SROC) curve[21]. Sensitivity and specificity as a single test threshold identified for each study were used to plot an SROC curve[22]. A random-effects model was adopted to calculate the average sensitivity, specificity, and other measures across studies[23,24].

The term heterogeneity refers to the degree of variability in results across studies, which was used in relation to meta-analyses. We detected statistically significant heterogeneity with the χ^2 test. To assess the effects of STARD and QUADAS scores on the diagnostic ability of IGRAs, we included them as covariates in the univariate meta-regression analysis (inverse variance weighted). We also analyzed the effects of other covariates on DOR, such as cross-sectional design, consecutive or random sampling of patients, single or double interpretation of determination, reference standard results, and prospective data collection. The relative DOR (RDOR) was calculated according to standard methods to analyze the change in diagnostic precision in the study per unit increase in the covariate[25,26]. Since publication bias is of concern for meta-analyses of diagnostic studies, we tested for the potential presence of this bias with funnel plots and the Egger test[27].

RESULTS

Selection and summary of studies

Five out of 31 publications reporting IFN-γ for the differential diagnosis of ITB from CD were considered to be eligible for inclusion in the analysis[28-32]. Of these 31 publications, 8 citations were rejected, 3 studies were case reports, 7 papers were reviews, and 8 studies were excluded based on study contents (Figure 1). A total of 5 studies including 616 patients were available for analysis, and the clinical characteristics of these studies, along with STARD and QUADAS scores, are outlined in Table 1.

Table 2 Characteristics of the included studies

Ref.	ITB/CD patients (*n*)	Reference standard	Cross-sectional design	Consecutive or random	Blinded design	Prospective
Lee *et al*[28]	12/44	Bac/His or Clin	Unknown	Yes	Unknown	Yes
Lei *et al*[29]	88/103	Bac/His	Unknown	Yes	No	Yes
Kim *et al*[30]	64/64	Bac/His	No	Yes	No	Yes
Li *et al*[31]	19/65	Bac/His or Clin	Yes	Yes	No	Yes
Kim *et al*[32]	75/72	Bac/His or Clin	No	Yes	No	Yes

ITB: Intestinal tuberculosis; CD: Crohn's disease; Bac: Bacteriology; His: Histology; Clin: Clinical course.

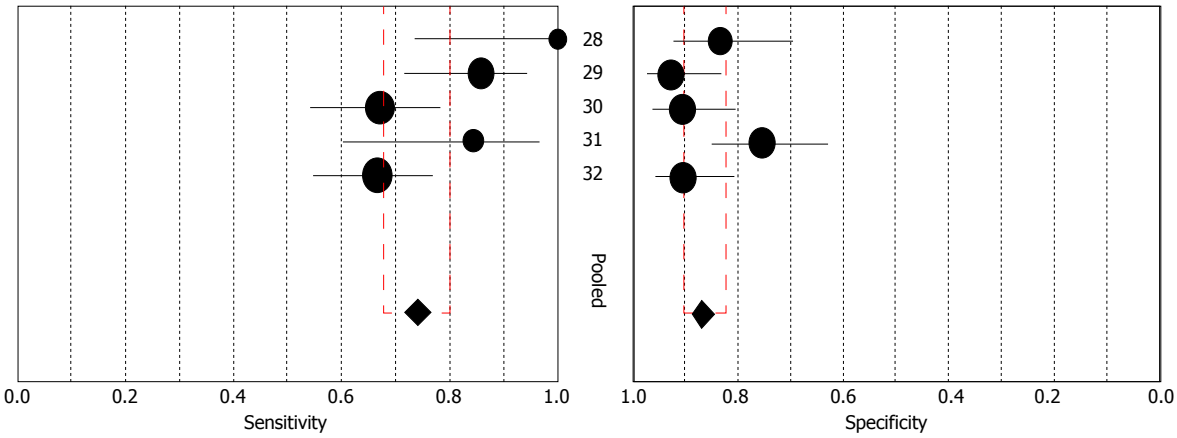

Figure 2 Forest plot of estimates of sensitivity and specificity for interferon-gamma release assays in the differential diagnosis of intestinal tuberculosis from Crohn's disease. Forest plot shows sensitivity and specificity of interferon-gamma release assays for intestinal tuberculosis diagnosis. The point estimates of sensitivity and specificity from each study are shown as solid circles. Error bars indicated 95%CI. Numbers indicate the studies included in the meta-analysis, as cited in the reference list. Pooled estimates for interferon-gamma release assays were as follows: sensitivity, 0.74 (95%CI: 0.68-0.80) and specificity, 0.87 (95%CI: 0.82-0.90).

Quality of reporting and study characteristics

The average inter-rater agreement between the two reviewers for items in the quality checklist was 0.95. All studies were collected from consecutive patients. The average sample size was 112 (range, 60-191) in the included studies. All studies reported that the study design was prospective (Table 2). None of the studies reported blinded interpretation of the IGRAs independent of the reference standard.

Diagnostic accuracy

The sensitivity and specificity of IGRAs in the 5 studies for the differential diagnosis of ITB from CD are shown in the forest plot (Figure 2). Sensitivity of IGRAs for ITB diagnosis ranged from 0.54 to 1.00 (mean, 0.74; 95%CI: 0.68-0.80), while specificity ranged from 0.63 to 0.98 (mean, 0.87; 95%CI: 0.82-0.90). We also noted that PLR was 5.98 (95%CI: 3.79-9.43), NLR was 0.28 (95%CI: 0.18-0.43) and DOR was 26.21 (95%CI: 14.15-48.57). The Chi-square values of sensitivity, specificity, PLR, NLR and DOR were 15.22 (P = 0.0043), 10.55 (P = 0.0322), 9.28 (P = 0.0544), 9.74 (P = 0.0504) and 4.99 (P = 0.2882), respectively, indicating heterogeneity for sensitivity and specificity between studies.

Two methods of IGRAs were used in the included studies in this meta-analysis. One was the T-SPOT-TB test, in which mononuclear cells from blood are used and the number of IFN-γ producing cells responding to antigens such as the ESAT-6 and CFP-10 is reported. The other method of IGRAs was Quanti-FERON-TB Gold In-Tube (QFT-G-IT), which measures T-cell INF-γ production (expressed as pg/mL or IU/mL) in blood in response to a cocktail of ESAT-6, CFP-10 and TB 7.7. The P value following a comparison of overall diagnostic values from T-SPOT-TB and QFT-G-IT was 0.3073. It could not be concluded that the overall accuracy of T-SPOT-TB for the differential diagnosis of ITB from CD was superior or inferior to that of QFT-G-IT.

The SROC plot is different from the traditional ROC plot that explores the effect of varying thresholds on sensitivity and specificity in a single study. In a SROC plot, any of the data points represent a separate study. The SROC curve presents a global summary of test performance and shows the tradeoff between sensitivity and specificity. A graph of the SROC curve for IGRA determination showing true-positive rates and false-positive rates from individual studies is shown in Figure 3. As a global measure of test efficacy we used the Q-value, the intersection point of the SROC curve with a diagonal line from the left upper corner to the right lower corner of the ROC space, which corresponds to the highest common value of sensitivity and specificity for the test. This point represents an overall measure of the discriminatory power of a test. Our data showed that the SROC curve was positioned near the upper left corner and that the maximum joint sensitivity and specificity was 0.87.

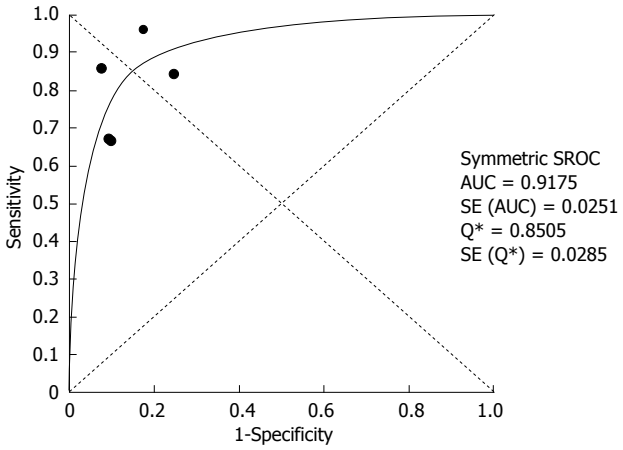

Figure 3 Summary receiver operating characteristic curves for interferon-gamma release assays. Solid circles represent each study included in the meta-analysis. The size of each study is indicated by the size of the solid circle. Summary receiver operating characteristic (SROC) curves summarize the overall diagnostic accuracy.

The area under the curve (AUC) was 0.92. These data indicated that the overall accuracy of IGRAs was not as high as expected.

Multiple regression analysis

By using the STARD guidelines[19], a quality score for each study was compiled on the basis of title and introduction, methods, results and discussion (Table 1). Quality scoring was also carried out using QUADAS[20], in which a score of 1 indicated a fulfilled criterion, 0 if an unclear criterion, and -1 if the criterion was not achieved. These scores were used in the meta-regression analysis to assess the effect of study quality on the RDOR of IGRAs in the differential diagnosis of ITB from CD. All studies were of high quality (STARD score, $\geqslant$ 13; QUADAS score, $\geqslant$ 10) in this review. The differences in the studies with or without blinding, cross-sectional, consecutive/random and prospective designs did not reach statistical significance (P = 0.218), indicating that the study design did not substantially affect the diagnostic accuracy.

Publication bias

Although the Egger test is widely used to evaluate publication bias, it is not useful if less than 10 studies are included. Based on this meta-analysis, which included five articles, we would consider that there was potential for publication bias.

DISCUSSION

The misdiagnosis rate between CD and ITB is 50%-70%[4,5,33,34]. It is important to differentiate between ITB and CD in order to provide effective and prompt therapies due to the increasing incidence of CD and widespread drug-resistant TB[8]. In recent years, methods including TST, MTB culture and acid fast bacilli staining have been used for the detection of TB infection. However, the low sensitivity and specificity and complicated processing of samples has limited the use of these methods[35,36]. New techniques, such as CT enteroclysis, capsule endoscopy, single and double balloon enteroscopy, polymerase chain reaction (PCR) and immunological assays for MTB, have also been used in clinical practice. PCR was associated with high sensitivity, but low specificity[37,38]. Endoscopic and histopathological examinations are also conducted to differentiate between the two disorders[39], but specific and precise criteria are lacking. The T-SPOT-TB test, an IGRA, has mainly been used to identify latent tuberculosis infection in patients in several areas and countries including the United States, Europe and Japan. However, the clinical usefulness of IGRAs for the differential diagnosis of ITB from CD is unknown.

In recent studies, the most popular biomarkers proposed for the diagnosis of TB-related disease were adenosine deaminase and INF-γ[40,41]. The levels of both biomarkers were significantly higher in tuberculous peritonitis than in non-tuberculous peritonitis patients. Both showed relatively high sensitivity and specificity in diagnosing tuberculous peritonitis[42-47]. However, for distinguishing ITB from CD, the present meta-analysis has shown that the mean sensitivity of IRGAs was 0.74, while the mean specificity was 0.87. The maximum joint sensitivity and specificity was 0.85, while the AUC was 0.92, indicating that overall accuracy was relatively high, but not as high as expected.

The DOR is a single indicator of test accuracy that combines the sensitivity and specificity data into a single number[48]. The DOR of a test is the ratio of the odds of positive test results in the patient with disease relative to the odds of positive test results in the patient without disease. The value of DOR ranges from 0 to infinity, and higher values indicate better discriminatory test performance (higher accuracy). A DOR of 1.0 indicates that a test did not discriminate between patients with and those without disease. In the present meta-analysis, the mean DOR was 26.21, indicating that IGRAs may be helpful in the differential diagnosis of ITB from CD.

Since the SROC curve and the DOR are not easy to interpret and use in clinical practice[49], the likelihood ratios are considered to be more clinically meaningful[49]. We also determined both PLR and NLR as measures of diagnostic accuracy. Likelihood ratios of > 10 or < 0.1 generate large and often conclusive shifts from pretest to posttest probability (indicating high accuracy). A PLR value of 5.98 suggests that patients with ITB have an approximately six-fold higher chance of being IFN-γ assay-positive compared with CD patients. This six-fold high probability would be considered not high enough to begin or to continue anti-TB treatment in ITB patients, especially in the absence of any malignant evidence (for clinical purposes). On the other hand, NLR was found to be 0.28 in the present meta-analysis. If the IFN-γ assay result was negative, the probability that this patient has ITB is approximately 28%, which is not low enough to rule out ITB from CD. These data suggest that a negative IFN-γ assay result should not be used alone as a justification to deny or to discontinue anti-TB therapy. The

choice of therapeutic strategy should be based on the results of culture of MTB, morphological observation of capsule endoscopy or single/double balloon enteroscopy, and/or histologic observation of peritoneal tissue, as well as other clinical data, such as response to anti-TB therapy.

The PPV is the proportion of patients with positive test results who are correctly diagnosed, while the NPV is the proportion of patients with negative test results who are correctly diagnosed. The pooled results showed that the PPV for IGRAs was 0.74, suggesting that 26% of positive results would actually be false positives. On the other hand, the NPV for IGRAs was 0.87, indicating a false negative rate of 13%. The relatively high NPV suggests that IGRAs would be acceptable for clinical purposes.

An exploration of the reasons for heterogeneity rather than computation of a single summary measure is an important goal of meta-analysis[50]. In our meta-analysis, both STARD and QUADAS scores were used in the meta-regression analysis to assess the effect of study quality on RDOR. All the studies were of high quality (STARD score of $\geqslant$ 13 or QUADAS score of $\geqslant$ 10). We found that there was no statistical heterogeneity for sensitivity, specificity, PLR, NLR, and DOR among the studies, which indicated that the differences in the studies with or without blinding, cross-sectional, consecutive/random and prospective designs did not reach statistical significance, and the study design did not substantially affect diagnostic accuracy.

Our meta-analysis has several limitations. Firstly, the exclusion of conference abstracts, letters to the editors, and non-English-language studies might have led to publication bias. Secondly, misclassification bias may have occurred. ITB is not always diagnosed by either histologic or microbiological examination. Some patients were diagnosed with ITB based on the clinical course. This issue regarding accuracy of diagnosis could cause nonrandom misclassification, leading to biased results. Thirdly, all the articles were from Asia, and this may also have led to publication bias. Finally, the number of studies that met the inclusion criteria was not large enough. Multi-center and large blinded randomized controlled trials using IGRAs for ITB diagnosis should be performed.

In conclusion, evidence from the present meta-analysis showed that although IGRAs are not sensitive enough, they did show good specificity for the diagnosis of ITB, which may be helpful in the differential diagnosis of ITB from CD. IFN-γ may be a clinical diagnostic marker for the differential diagnosis of ITB from CD. Currently, the literature focusing on the use of IGRAs in ITB is limited; thus, further large multicenter studies are necessary to substantiate the diagnostic accuracy of IGRAs in patients with ITB or CD.

ACKNOWLEDGMENTS

We are grateful to Dr. Li YH for her professional translation of foreign language articles.

COMMENTS

Background

The differential diagnosis of intestinal tuberculosis (ITB) from Crohn's disease (CD) is challenging. The misdiagnosis rate between CD and ITB is 50%-70%. T-cell based interferon-gamma release assays (IGRAs) have increasingly been used as a diagnostic tool in the differential diagnosis of ITB from CD. However, whether IGRAs contribute to accurate ITB diagnosis remains controversial.

Research frontiers

IGRAs have mainly been used to identify latent tuberculosis infection in patients in several areas and countries including the United States, Europe and Japan. However, the clinical usefulness of IGRAs for the differential diagnosis of ITB from CD is unknown.

Innovations and breakthroughs

This is the first time that the clinical usefulness of IGRAs for the differential diagnosis of ITB from CD has been investigated by meta-analysis.

Applications

IGRAs provided good specificity for ITB, and should be helpful in the differential diagnosis of ITB from CD. Interferon-gamma may be a clinical diagnostic marker for the differential diagnosis of ITB from CD.

Terminology

IGRAs: T-cell based interferon-gamma release assays have increasingly been used to replace the traditional tuberculin skin test as a diagnostic tool for tuberculosis. IGRAs have been shown to have superior sensitivity and specificity. ITB: Intestinal tuberculosis is an important extra-pulmonary tuberculosis that primarily affects the ileum and colon, causing gastrointestinal symptoms such as diarrhea or abdominal pain. Standards for reporting diagnostic accuracy and quality assessment for studies of diagnostic accuracy scores: these scores are used in the meta-regression analysis to assess the effect of study quality on relative diagnostic odds ratio.

Peer review

This study is an interesting meta-analysis comment. It provides a new evidence of IGRAs helping differential diagnosis ITB from CD.

REFERENCES

1 **Dye C**, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999; **282**: 677-686 [PMID: 10517722]

2 **Dye C**. Global epidemiology of tuberculosis. *Lancet* 2006; **367**: 938-940 [PMID: 16546542 DOI: 10.1016/S0140-6736(06)68384-0]

3 **Corbett EL**, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**: 1009-1021 [PMID: 12742798 DOI: 10.1001/archinte.163.9.1009]

4 **Epstein D**, Watermeyer G, Kirsch R. Review article: the diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. *Aliment Pharmacol Ther* 2007; **25**: 1373-1388 [PMID: 17539977 DOI: 10.1111/j.1365-2036.2007.03332.x]

5 **Almadi MA**, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *Am J Gastroenterol* 2009; **104**: 1003-1012 [PMID: 19240705 DOI: 10.1038/ajg.2008.162]

6 **Thia KT**, Loftus EV, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008; **103**: 3167-3182 [PMID: 19086963 DOI: 10.1111/j.1572-0241.2008.02158.x]

7 **Logan I**, Bowlus CL. The geoepidemiology of autoimmune intestinal diseases. *Autoimmun Rev* 2010; **9**: A372-A378 [PMID: 19903540 DOI: 10.1016/j.autrev.2009.11.008]

8 **Jayanthi V**, Robinson RJ, Malathi S, Rani B, Balambal R, Chari S, Taghuram K, Madanagopalan N, Mayberry JF. Does Crohn's disease need differentiation from tuberculosis? *J*

Gastroenterol Hepatol 1996; **11**: 183-186 [PMID: 8672766]
9 **Pulimood AB**, Ramakrishna BS, Kurian G, Peter S, Patra S, Mathan VI, Mathan MM. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. *Gut* 1999; **45**: 537-541 [PMID: 10486361]
10 **Kirsch R**, Pentecost M, Hall Pde M, Epstein DP, Watermeyer G, Friederich PW. Role of colonoscopic biopsy in distinguishing between Crohn's disease and intestinal tuberculosis. *J Clin Pathol* 2006; **59**: 840-844 [PMID: 16873564 DOI: 10.1136/jcp.2005.032383]
11 **Lee YJ**, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI, Chang SJ, Yu CS. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. *Endoscopy* 2006; **38**: 592-597 [PMID: 16673312 DOI: 10.1055/s-2006-924996]
12 **Pulimood AB**, Peter S, Ramakrishna B, Chacko A, Jeyamani R, Jeyaseelan L, Kurian G. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. *J Gastroenterol Hepatol* 2005; **20**: 688-696 [PMID: 15853980 DOI: 10.1111/j.1440-1746.2005.03814.x]
13 **Kim HD**, Kim CG, Kim JW, Kim SG, Kim BG, Kim JS, Jung HC, Song IS. [Clinical features and therapeutic responses of perianal lesions in Crohn's disease]. *Korean J Gastroenterol* 2003; **42**: 128-133 [PMID: 14532717]
14 **Park JB**, Yang SK, Myung SJ, Byeon JS, Lee YJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI. [Clinical characteristics at diagnosis and course of Korean patients with Crohn's disease]. *Korean J Gastroenterol* 2004; **43**: 8-17 [PMID: 14745246]
15 **Kang YA**, Lee HW, Hwang SS, Um SW, Han SK, Shim YS, Yim JJ. Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. *Chest* 2007; **132**: 959-965 [PMID: 17505029 DOI: 10.1378/chest.06-2805]
16 **Lalvani A**. Diagnosing tuberculosis infection in the 21st century: new tools to tackle an old enemy. *Chest* 2007; **131**: 1898-1906 [PMID: 17565023 DOI: 10.1378/chest.06-2471]
17 **Yao T**, Matsui T, Hiwatashi N. Crohn's disease in Japan: diagnostic criteria and epidemiology. *Dis Colon Rectum* 2000; **43**: S85-S93 [PMID: 11052483]
18 **Bernstein CN**, Fried M, Krabshuis JH, Cohen H, Eliakim R, Fedail S, Gearry R, Goh KL, Hamid S, Khan AG, LeMair AW, Malfertheiner Q, Rey JF, Sood A, Steinwurz F, Thomsen OO, Thomson A, Watermeyer G. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis* 2010; **16**: 112-124 [PMID: 19653289 DOI: 10.1002/ibd.21048]
19 **Bossuyt PM**, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. The Standards for Reporting of Diagnostic Accuracy Group. *Croat Med J* 2003; **44**: 635-638 [PMID: 14515428]
20 **Whiting P**, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; **3**: 25 [PMID: 14606960 DOI: 10.1186/1471-2288-3-25]
21 **Devillé WL**, Buntinx F, Bouter LM, Montori VM, de Vet HC, van der Windt DA, Bezemer PD. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Med Res Methodol* 2002; **2**: 9 [PMID: 12097142]
22 **Lau J**, Ioannidis JP, Balk EM, Milch C, Terrin N, Chew PW, Salem D. Diagnosing acute cardiac ischemia in the emergency department: a systematic review of the accuracy and clinical effect of current technologies. *Ann Emerg Med* 2001; **37**: 453-460 [PMID: 11326181 DOI: 10.1067/mem.2001.114903]
23 **Irwig L**, Tosteson AN, Gatsonis C, Lau J, Colditz G, Chalmers TC, Mosteller F. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med* 1994; **120**: 667-676 [PMID: 8135452]
24 **Vamvakas EC**. Meta-analyses of studies of the diagnostic accuracy of laboratory tests: a review of the concepts and methods. *Arch Pathol Lab Med* 1998; **122**: 675-686 [PMID: 9701328]
25 **Suzuki S**, Moro-oka T, Choudhry NK. The conditional relative odds ratio provided less biased results for comparing diagnostic test accuracy in meta-analyses. *J Clin Epidemiol* 2004; **57**: 461-469 [PMID: 15196616 DOI: 10.1016/j.jclinepi.2003.09.017]
26 **Westwood ME**, Whiting PF, Kleijnen J. How does study quality affect the results of a diagnostic meta-analysis? *BMC Med Res Methodol* 2005; **5**: 20 [PMID: 15943861 DOI: 10.1186/1471-2288-5-20]
27 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563]
28 **Lee JN**, Ryu DY, Park SH, You HS, Lee BE, Kim DU, Kim TO, Heo J, Kim GH, Song GA, Kim S, Park do Y. [The usefulness of in vitro interferon-gamma assay for differential diagnosis between intestinal tuberculosis and Crohns disease]. *Korean J Gastroenterol* 2010; **55**: 376-383 [PMID: 20571305 DOI: 10.4166/kjg.2010.55.6.376]
29 **Lei Y**, Yi FM, Zhao J, Luckheeram RV, Huang S, Chen M, Huang MF, Li J, Zhou R, Yang GF, Xia B. Utility of in vitro interferon-γ release assay in differential diagnosis between intestinal tuberculosis and Crohn's disease. *J Dig Dis* 2013; **14**: 68-75 [PMID: 23176201 DOI: 10.1111/1751-2980.12017]
30 **Kim BJ**, Choi YS, Jang BI, Park YS, Kim WH, Kim YS, Jung SA, Han DS, Kim JS, Choi JH, Choi CH, Jeen YT, Cheon JH, Ye BD, Yang SK, Kim YH. Prospective evaluation of the clinical utility of interferon-γ assay in the differential diagnosis of intestinal tuberculosis and Crohn's disease. *Inflamm Bowel Dis* 2011; **17**: 1308-1313 [PMID: 21053248 DOI: 10.1002/ibd.21490]
31 **Li Y**, Zhang LF, Liu XQ, Wang L, Wang X, Wang J, Qian JM. The role of in vitro interferonγ-release assay in differentiating intestinal tuberculosis from Crohn's disease in China. *J Crohns Colitis* 2012; **6**: 317-323 [PMID: 22405168 DOI: 10.1016/j.crohns.2011.09.002]
32 **Kim YS**, Kim YH, Kim WH, Kim JS, Park YS, Yang SK, Ye BD, Jang BI, Jung SA, Jeen YT, Cheon JH, Choi YS, Choi JH, Kim BJ, Choi CH, Han DS. Diagnostic utility of anti-Saccharomyces cerevisiae antibody (ASCA) and Interferon-γ assay in the differential diagnosis of Crohn's disease and intestinal tuberculosis. *Clin Chim Acta* 2011; **412**: 1527-1532 [PMID: 21575618 DOI: 10.1016/j.cca.2011.04.029]
33 **Liu TH**, Pan GZ, Chen MZ. Crohn's disease. Clinicopathologic manifestations and differential diagnosis from enterocolonic tuberculosis. *Chin Med J (Engl)* 1981; **94**: 431-440 [PMID: 6796347]
34 **Singh V**, Kumar P, Kamal J, Prakash V, Vaiphei K, Singh K. Clinicocolonoscopic profile of colonic tuberculosis. *Am J Gastroenterol* 1996; **91**: 565-568 [PMID: 8633510]
35 **Hazbón MH**. Recent advances in molecular methods for early diagnosis of tuberculosis and drug-resistant tuberculosis. *Biomedica* 2004; **24** Supp 1: 149-162 [PMID: 15495583]
36 **Shah S**, Thomas V, Mathan M, Chacko A, Chandy G, Ramakrishna BS, Rolston DD. Colonoscopic study of 50 patients with colonic tuberculosis. *Gut* 1992; **33**: 347-351 [PMID: 1568653]
37 **Pulimood AB**, Peter S, Rook GW, Donoghue HD. In situ PCR for Mycobacterium tuberculosis in endoscopic mucosal biopsy specimens of intestinal tuberculosis and Crohn disease. *Am J Clin Pathol* 2008; **129**: 846-851 [PMID: 18479999 DOI: 10.1309/DKKECWQWMG4J23E3]
38 **Balamurugan R**, Venkataraman S, John KR, Ramakrishna BS. PCR amplification of the IS6110 insertion element of Mycobacterium tuberculosis in fecal samples from patients with intestinal tuberculosis. *J Clin Microbiol* 2006; **44**: 1884-1886

[PMID: 16672431 DOI: 10.1128/JCM.44.5.1884-1886.2006]
39 **Makharia GK**, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, Deo V, Aggarwal A, Tiwari RP, Sreenivas V, Gupta SD. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am J Gastroenterol* 2010; **105**: 642-651 [PMID: 20087333 DOI: 10.1038/ajg.2009.585]
40 **Liang QL**, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. *Respir Med* 2008; **102**: 744-754 [PMID: 18222681 DOI: 10.1016/j.rmed.2007.12.007]
41 **Zhou Q**, Chen YQ, Qin SM, Tao XN, Xin JB, Shi HZ. Diagnostic accuracy of T-cell interferon-γ release assays in tuberculous pleurisy: a meta-analysis. *Respirology* 2011; **16**: 473-480 [PMID: 21299686 DOI: 10.1111/j.1440-1843.2011.01941.x]
42 **Sathar MA**, Simjee AE, Coovadia YM, Soni PN, Moola SA, Insam B, Makumbi F. Ascitic fluid gamma interferon concentrations and adenosine deaminase activity in tuberculous peritonitis. *Gut* 1995; **36**: 419-421 [PMID: 7698702]
43 **Ariga H**, Kawabe Y, Nagai H, Kurashima A, Masuda K, Matsui H, Tamura A, Nagayama N, Akagawa S, Machida K, Hebisawa A, Nakajima Y, Yotsumoto H, Mori T. Diagnosis of active tuberculous serositis by antigen-specific interferon-gamma response of cavity fluid cells. *Clin Infect Dis* 2007; **45**: 1559-1567 [PMID: 18190316 DOI: 10.1086/523591]
44 **Sharma SK**, Tahir M, Mohan A, Smith-Rohrberg D, Mishra HK, Pandey RM. Diagnostic accuracy of ascitic fluid IFN-gamma and adenosine deaminase assays in the diagnosis of tuberculous ascites. *J Interferon Cytokine Res* 2006; **26**: 484-488 [PMID: 16800787 DOI: 10.1089/jir.2006.26.484]
45 **Liao CH**, Chou CH, Lai CC, Huang YT, Tan CK, Hsu HL, Hsueh PR. Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. *J Infect* 2009; **59**: 402-408 [PMID: 19819258 DOI: 10.1016/j.jinf.2009.10.001]
46 **Ribera E**, Martínez Vásquez JM, Ocaña I, Ruiz I, Jimínez JG, Encabo G, Segura RM, Pascual C. Diagnostic value of ascites gamma interferon levels in tuberculous peritonitis. Comparison with adenosine deaminase activity. *Tubercle* 1991; **72**: 193-197 [PMID: 1771679]
47 **Saleh MA**, Hammad E, Ramadan MM, Abd El-Rahman A, Enein AF. Use of adenosine deaminase measurements and QuantiFERON in the rapid diagnosis of tuberculous peritonitis. *J Med Microbiol* 2012; **61**: 514-519 [PMID: 22174374 DOI: 10.1099/jmm.0.035121-0]
48 **Glas AS**, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; **56**: 1129-1135 [PMID: 14615004]
49 **Deeks JJ**. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001; **323**: 157-162 [PMID: 11463691]
50 **Petitti DB**. Approaches to heterogeneity in meta-analysis. *Stat Med* 2001; **20**: 3625-3633 [PMID: 11746342]

P- Reviewers: Campo SMA, Moss AC, Perakath B
S- Editor: Gou SX **L- Editor**: Cant MR **E- Editor**: Zhang DN

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327