Performance of interferon-γ release assay in the diagnosis of tuberculous lymphadenitis: a meta-analysis

Qianqian Liu [1,2], Wenzhang Li [3], Yufeng Chen [1], Xinmiao Du [2], Chengdi Wang [2], Binmiao Liang [2], Yin Tang [4,5], Yulin Feng [2], Chuanmin Tao [6], Jian-Qing He [Corresp. 2]

[1] Department of Respiratory Diseases, Chengdu Municipal First People's Hospital, Chengdu, Sichuan, China

[2] Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

[3] Department of Cardiology, First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, China

[4] State Key Laboratory of Oral Disease, West China School & Hospital of Stomotology, Sichuan University, Chengdu, Sichuan, China

[5] Herman Ostrow School of Dentistry, University of Southern California, Los Angeles, California, USA

[6] Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Corresponding Author: Jian-Qing He
Email address: jianqhe@gmail.com

Background. The diagnostic values of interferon-gamma release assays (IGRA) in tuberculosis (TB) vary a lot with different site of infections, with especially higher sensitivities in chronic forms of TB, such as tuberculosis of lymph node. We conducted a meta-analysis to comprehensively evaluate the overall accuracy of diagnostic IGRA for tuberculous lymphadenitis.

Methods. Pubmed, Web of science, EMBASE, Wanfang and CNKI databases up to February 17, 2017 were searched to identify published studies. The study quality was evaluated using the QUADAS-2 checklist. The pooled estimates of diagnostic parameters were generated using a bivariate random-effects model and summary receiver operating characteristic (SROC) curves were used to summarize global performance.

Results. A total of ten qualified studies, performed in Korea or China, including 1084 patients, were enrolled in this meta-analysis. The pooled estimates of diagnostic accuracy were as follows: sensitivity, 0.89 (95%CI 0.85-0.92); specificity, 0.81 (95%CI 0.77-0.83); positive likelihood ratio (PLR), 4.25 (95%CI 2.79-6.47); negative likelihood ratio (NLR), 0.16 (95%CI 0.12-0.22); and area under the curve (AUC) was 0.93. According to subgroup analyses, studies conducted using QuantiFERON-TB, in Korean population and focusing on cervical lymphadenitis exhibited relative higher specificity while lower sensitivity. No evidence of publication bias was identified.

Conclusions. IGRA exhibits high diagnostic accuracy in tuberculous lymphadenitis. The diagnostic value of IGRA differed by different IGRA methods, ethnicity and lymphadenitis location. Our conclusion may be more applicable to population from TB prevalent areas.

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4   **Authors**

5   Qianqian Liu[1,2*], Wenzhang Li[3*], Yunfeng Chen[1], Xinmiao Du[2], Chengdi Wang[2], Binmiao

6   Liang[2], Yin Tang[4,5], Yulin Feng[2], Chuanmin Tao[6], Jian-Qing He[2†]

7   1. Department of Respiratory Diseases, Chengdu Municipal First People's Hospital, Chengdu,

8   Sichuan, China.

9   2. Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan

10   University, Chengdu, Sichuan, China.

11   3. Department of Cardiology, First Affiliated Hospital of Chengdu Medical College, Chengdu,

12   Sichuan, China.

13   4. State Key Laboratory of Oral Disease, West China School & Hospital of Stomotology,

14   Sichuan University, Chengdu, Sichuan, China.

15   5. Herman Ostrow School of Dentistry, University of Southern California, Los Angeles,

16   California, USA.

17   6. Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu,

18   Sichuan, China.

19   * These authors contributed equally.

20   † Corresponding author:

21   Dr. Jian-Qing He

22   Address: Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan

23   University, 37# Guo-xue-xiang, Chengdu 610041, Sichuan Province, China.

24   Tel: 01186-18980602293

25   Fax: 01186-85422571

26   E-mail: jianqhe@gmail.com

27   **Abstract**

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30   forms of TB, such as tuberculosis of lymph node. We conducted a meta-analysis to

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32   lymphadenitis.

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34   2017 were searched to identify published studies. The study quality was evaluated using the

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36   bivariate random-effects model and summary receiver operating characteristic (SROC) curves

37   were used to summarize global performance.

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39   were enrolled in this meta-analysis. The pooled estimates of diagnostic accuracy were as follows:

40   sensitivity, 0.89 (95%CI 0.85-0.92); specificity, 0.81 (95%CI 0.77-0.83); positive likelihood

41   ratio (PLR), 4.25 (95%CI 2.79-6.47); negative likelihood ratio (NLR), 0.16 (95%CI 0.12-0.22);

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43   using QuantiFERON-TB, in Korean population and focusing on cervical lymphadenitis exhibited

44   relative higher specificity while lower sensitivity. No evidence of publication bias was identified.

45   **Conclusions.** IGRA exhibits high diagnostic accuracy in tuberculous lymphadenitis. The

46   diagnostic value of IGRA differed by different IGRA methods, ethnicity and lymphadenitis

47   location. Our conclusion may be more applicable to population from TB prevalent areas.

Introduction

Despite the advances in effective chemotherapy regimens and slight decrease of incidence, tuberculosis (TB) still remains as a great challenge to public health. According to the most recent World Health Organization (WHO) report, TB has surpassed acquired immune deficiency syndrome (AIDS), becoming the leading cause of death from infectious disease, with an estimate of 9.6 million new cases and 1.5 million deaths every year (WHO. Global tuberculosis report 2015. Geneva). Moreover, the decline of extrapulmonary tuberculosis (EPTB) is regarded as suboptimal, and the proportion of EPTB among total TB cases has been increasing annually (Barry et al. 2012; Peto et al. 2009; Sandgren et al. 2013). Among all EPTB, tuberculous lymphadenitis, manifested as part of systemic processes or a unique lesion localized to lymph node, is the most common form in many areas, accounting for around 20–50% of total EPTB cases (Gonzalez et al. 2003; Ilgazli et al. 2004; Wiwatworapan & Anantasetagoon 2008). The characteristic local impaired presentation, such as spontaneous fistula to the skin, was noted in only 4-11% of tuberculous lymphadenitis cases, and those classic TB systemaic signs, such as prolonged fever, night sweats and anorexia et al. were also not frequent, compared with pulmonary TB. Thus the clinical physical findings of tuberculous lymphadenitis are usually indistinguishable from lymphadenitis caused by other etiologies, posing great diagnostic challenges to clinician, and giving it great potential for delayed treatment (Fontanilla et al. 2011; Handa et al. 2012; Yoon et al. 2004).

Up till now, several diagnostic choices are available for tuberculous lymphadenitis. Among

68 them, the radiographic findings are frequently inconclusive and are merely clues for

69 diagnosis(Brodie & Schluger 2005). Tuberculin skin test (TST) cannot distinguish

70 mycobacterium tuberculosis (MTB) infection from non-tuberculous mycobacteria (NTM)

71 infection, as well as Bacillus Calmette-Guerin (BCG) vaccine, thus limiting its diagnostic

72 application. Microbiologic and pathologic methods are usually the last procedures of choice,

73 however, they can only be performed through invasive operation. What's more, the

74 paucibacillary nature of the sample with non-uniform distributed bacilli often decreased the

75 sensitivity of microbiologic diagnostic tests (Brodie & Schluger 2005). Also, the highly variable

76 performance of rapid PCR assay and non-specificity of histological examination usually leave

77 the diagnosis of tuberculous lymphadenitis unsettled (Hirunwiwatkul et al. 2002; Manitchotpisit

78 et al. 1999).

79   Recent years an immune-based blood assay, interferon-γ (IFN-γ) release assay (IGRA), has

80 been introduced for the diagnosis of TB based on the detection of IFN-γ secreted by T cells

81 stimulated by two MTB–specific antigens, early secretory antigenic target (ESAT)-6 and culture

82 filtrate protein (CFP)-10. The advantage of IGRA over TST depends on its lack of cross-

83 reactivity with BCG vaccine strains and most NTM species (Berthet et al. 1998; Pai et al. 2014;

84 Pai et al. 2007). It is reported that the diagnostic value of the IGRA may differed by clinical

85 courses and site of infections, with especially higher sensitivities in chronic forms of TB, such as

86 lymph node TB (sensitivity 89%) than in acute forms of TB (i.e., TB meningitis, sensitivity 74%)

87 (Cho et al. 2011). The relative higher sensitivities among tuberculous lymphadenitis may be

88 explained by more efficient immune response allowing for the detection of IFN-γ production in

89 those patients (Pai et al. 2006). Over the past few years, a growing number of studies

90 investigating the diagnostic accuracy of IGRA for tuberculous lymphadenitis have come out with

91 inconsistent results, with sensitivity ranging from 0.81 to 0.95 and specificity ranging from 0.52

92 to 0.96 (Kim et al. 2013; Kim et al. 2016; Liao et al. 2009). The contradiction of previous studies

93 may be partly due to small sample size of individual studies which are lack of statistical power.

94 To get robust evidence guiding clinicians on the diagnostic accuracy of IGRA in the diagnosis of

95 tuberculous lymphadenitis, we conducted the present meta-analysis.

96 **Materials & Methods**

97 *Publication search*

98 Five databases were searched from their inception until February 17, 2017: Pubmed, Web of

99 science, EMBASE, Wanfang and CNKI databases. The search strategy included the following

100 terms: 'elispot' OR 'quantiferon*' OR 'interferon-gamma release assay' OR 'interferon-gamma

101 release assays' OR 'interferon-gamma releasing assay' OR 'interferon-gamma releasing assays'

102 OR 't cell assay' OR 't cell assays' OR 'IGRA*' OR 'T.SPOT*' OR 'TSPOT*' OR 'T-SPOT*' in

103 combination with 'lymphatic' OR 'lymph nodes' OR 'lymph node' OR 'lymphadenitis' in

104 combination with 'diagnos*' OR 'sensitivity'. Furthermore, a manual search for relevant studies

105 in reference list of identified articles was also conducted. No language restrictions were applied

106 in our study. Studies were included in this meta-analysis if they met the following criteria: (1)

107 IGRA was used to test for the diagnosis of tuberculous lymphadenitis; (2) diagnostic 2x2 tables

108   (the value of true positive, false positive, false negative, and true negative) were reported or

109   could be calculated from original articles; (3) bacteriological findings or clinical response to anti-

110   tuberculosis therapy were used as reference standard test. The following studies were excluded:

111   (1) review or meta-analysis; (2) studies available only as abstracts; (3) duplicate publication of

112   previous research.

113   *Data extraction*

114   Two reviewers (Qianqian Liu and Wenzhang Li) independently screened those identified articles

115   by titles and abstracts. Then the full texts were evaluated for eligibility based on pre-set inclusion

116   and exclusion criteria. Discrepancies were resolved by discussion. The following variables were

117   extracted from all included studies: first author, language, publication year, country, sample size,

118   IGRA methods, IGRA cut-off values, and diagnostic 2x2 table values. Indeterminate results may

119   occur in both IGRA tests and excluding these patients may lead our results to increased

120   sensitivity and specificity. Therefore, those patients with indeterminate results were regarded as

121   negative results in all analyses.

122   *Quality assessment*

123   The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to

124   assess the study quality focusing on the risk of bias and the applicability (Whiting et al. 2011).

125   Any discrepancies by two reviewers were resolved by consensus.

126   *Statistical analysis*

127 Heterogeneity was assessed by the Chi-squared test and I^2 test, setting P<0.10 as the threshold

128 for significance. The following accuracies with their 95% confidence interval (CI) were pooled

129 respectively: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio

130 (NLR), using bivariate random-effects model. Summary receiver operating characteristic (SROC)

131 curves were also generated. The Spearman rank correlation was conducted to test for potential

132 threshold effect, setting P<0.05 as threshold for significance. Presence of publication bias was

133 assessed by Deeks' funnel plot with P<0.10 for the slope coefficient suggested significant bias

134 (Deeks et al. 2005). All statistical tests were two-sided. Stata 12.0 (StataCorp, College Station,

135 TX, USA) and Meta-DiSc 1.4 were used for statistical analysis.

136 **Results**

137 *Study characteristics*

138 We initially identified 2875 relevant articles and a total of ten studies meeting inclusion criteria

139 were included in the final meta-analysis (Fig. 1) (Cho et al. 2011; Jia et al. 2016; Jia et al. 2014;

140 Kim et al. 2013; Kim et al. 2016; Kim et al. 2011; Liao et al. 2009; Lu et al. 2016; Shin et al.

141 2015; Song et al. 2009). The basic characteristics of each study are presented in Table 1. The ten

142 studies were conducted from 2009 to 2016, including 1084 patients distributed in China (4

143 studies) and Korea (6 studies) respectively. Two studies were published in Chinese language,

144 one in Korean language and the remaining were in English. The adopted IGRA methods were

145 QuantiFERON.TB Gold In Tube (QFT-GIT; Cellestis, Carnegie, VIC, Australia) in five studies

146 and T-SPOT.TB (Oxford Immunotech, Abingdon, UK) in the other five studies.

147 *Quality assessments of the eligible studies*

148 The quality assessments of the ten eligible studies are listed in Table 2. The risk bias of selection

149 domain was categorized as high in two studies, as they excluded patients with clinical diagnosed

150 tuberculous lymphadenitis, which may exaggerate diagnostic accuracy of index test. Only one

151 study had low risk bias of index test as it was interpreted without knowledge of the other test,

152 while the other studies did not report relevant information. As for the risk bias of references

153 standard test, two studies had low risk, one study had high risk and the others were scored

154 unknown. The risk bias of flow and timing domains and the concerns of applicability in all

155 domains were categorized as low.

156 *Diagnostic performance*

157 Chi-square values demonstrated no significant between-study heterogeneity among the following

158 diagnostic parameters: sensitivity, 5.38 (P=0.80) and NLR, 5.14 (P=0.82), while significant

159 heterogeneity was found for specificity (P<0.10) and PLR (P<0.10). The pooled estimates of

160 diagnostic accuracy were listed as follows (Fig. 2): sensitivity, 0.89 (95%CI 0.85-0.92);

161 specificity, 0.81 (95%CI 0.77-0.83); PLR, 4.25 (95%CI 2.79-6.47); NLR, 0.16 (95%CI 0.12-

162 0.22). Figure 3 shows the SROC curve and the area under the curve (AUC) was 0.93.

163 *Threshold effect and subgroup analyses*

164 If sensitivity and specificity were negatively correlated and ROC exhibited typical 'shoulder

165 arm-shaped' distribution, then threshold effect should be considered. Our statistical results

166 showed no significant threshold effect, with the spearman correlation coefficient to be 0.10

167 (P=0.78).

168   Subgroup analyses by IGRA methods, ethnicity and tuberculous lymphadenitis locations

169 were performed to identify potential sources of heterogeneity (Table 3). In general, the values of

170 AUC in all subgroup analyses were more than 0.9 without exception. When stratified by IGRA

171 methods, T-SPOT.TB had a relatively higher sensitivity and lower specificity than

172 QuantiFERON-TB. While when stratified by ethnicity, studies conducted in Chinese population

173 had a relatively higher sensitivity and lower specificity than those in Korean population. As

174 some studies included patients with lymphadenitis localizing to cervical areas while other studies

175 didn't restrict the location of lymph nodes, which may also lead to variability in diagnostic

176 accuracy. Our subsequent subgroup analysis showed that limiting lymph nodes to cervical areas

177 exhibited lower sensitivity and higher specificity compared with other studies.

178 *Publication bias*

179 Deeks' funnel plots was symmetric and the bias coefficient was not significant (*P*=0.54) (Fig. 4).

180 Our evaluation found no evidence of publication bias.

181 **Discussion**

182 The IGRA, an in vitro immunodiagnostic test, is being adopted increasingly for the detection of

183 MTB infection and has generated promising results as an alternative diagnostic tool for the LTBI

184 (Diel et al. 2011). However, the application of this newly emerging technique may not only be

185   exclusive to LTBI. Several recent studies have investigated the diagnostic value of IGRA upon

186   EPTB according to different sites of infection and uniformly reported a higher sensitivity of

187   IGRA in tuberculous lymphadenitis detection than in other form of EPTB (Cho et al. 2011; Song

188   et al. 2009). Thus we conducted the present meta-analysis to comprehensively evaluate the

189   overall diagnostic accuracy of IGRA upon tuberculous lymphadenitis.

190   The pooling results showed that the sensitivity and specificity of IGRA was 0.89 and 0.81

191   respectively, which means that 11% patients would have a missed diagnosis of tuberculous

192   lymphadenitis and 19% would be falsely diagnosed as tuberculous lymphadenitis if we use

193   IGRA as the only diagnostic method. The pooled PLR and NLR of IGRA was 4.25 and 0.16

194   respectively, which indicates that patients with tuberculous lymphadenitis have 4.25 times of

195   chance getting a positive result than those without tuberculous lymphadenitis and those with

196   tuberculous lymphadenitis have 0.16 times chance of getting negative result than those without

197   tuberculous lymphadenitis. AUC is a comprehensive index combining the sensitivity and

198   specificity. Generally, $AUC > 0.9$ is regarded to be highly accurate in diagnostic tests (Deeks

199   2001). Accordingly, our summarized result of AUC (0.93) indicated high diagnostic accuracy.

200   As meta-analysis is a pooling result of previous individual studies with larger statistical power,

201   our conclusion is more reliable than previous small sample sized individual studies.

202   The subgroup results showed T-SPOT.TB had a relatively higher sensitivity and lower

203   specificity than QuantiFERON-TB, which is in accordance with previous reports. Lee et al.

204   conducted a head-to-head comparison between the two assays in the diagnosis of MTB infection.

205   They reported higher sensitivity and inferior specificity of T-SPOT.TB over QuantiFERON-TB

206   (Lee et al. 2006). The same tendency in diagnosing active tuberculosis was found by another

207   study (Lai et al. 2011). It may be attributed to the fact that the QFT-GIT assay tends to be more

208   easily affected by immune status and peripheral lymphocyte counts or simply be related to the

209   pre-set cut-off values of the two commercial assays (Komiya et al. 2010; Lee et al. 2006).

210   Although we detected the same tendency with previous studies, our research focused on

211   tuberculous lymphadenitis, which is different from previous studies not focusing on this special

212   type of tuberculosis. When stratified by ethnicity, those studies conducted in Chinese population

213   had a relatively higher sensitivity and lower specificity than which in Korean population. Such

214   similar tendency may be partially explained by ethnic difference or by the fact that all studies

215   conducted in Chinese population of this meta-analysis were performed using T-SPOT.TB while

216   all but one study conducted in Korean population were performed using QuantiFERON-TB. Our

217   subgroup analysis also showed that studies with lymphadenitis localizing to cervical areas

218   exhibited lower sensitivity and higher specificity compared with studies which didn't restrict the

219   location of lymph nodes. Whether there is a biological basis or it is just a statistical coincidence

220   need to be further determined.

221   As for QUADAS-2 assessment, none of our included studies had low risk of bias in all

222   domains. In patient selection domain, eight studies scored unclear because they didn't clearly

223   state whether they enrolled sample of patients consecutively or randomly. What's more, in index

224   test and reference standard test domains, most studies did not report whether the index test or

225   reference standard test were interpreted without knowledge of the other test. It is important to

226   note that low quality original research may introduce heterogeneity in meta-analysis. Thus, it

227   needs to be stressed that the future diagnostic studies should be reported in detail according to

228   relevant diagnostic study guidelines.

229   After all, some limitations should be pointed out. First, as most of patients included in the

230   present study were immunocompetent, caution is advised when applying our conclusion to

231   immunocompromised patients. Second, despite our thorough literature searching without

232   language limitation, all studies of this meta-analysis were conducted either in Korea or in China,

233   both were TB high prevalence areas. As we know, the diagnostic parameters, such as sensitivity

234   and specificity, may be affected by the prevalence of the target disease. Thus, our conclusion

235   might be more appropriate when used in TB high-burden areas.

236   **Conclusion**

237   To sum up, IGRA exhibits high diagnostic accuracy in tuberculous lymphadenitis and may play

238   an increasing important role as a supplementary diagnostic tool with the advantage of

239   noninvasiveness and efficiency. The diagnostic value of IGRA differed by different IGRA

240   methods, ethnicity and lymphadenitis location. Our conclusion may be more applicable to

241   population from TB prevalent areas.

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Figure 1

Flow diagram of included studies.

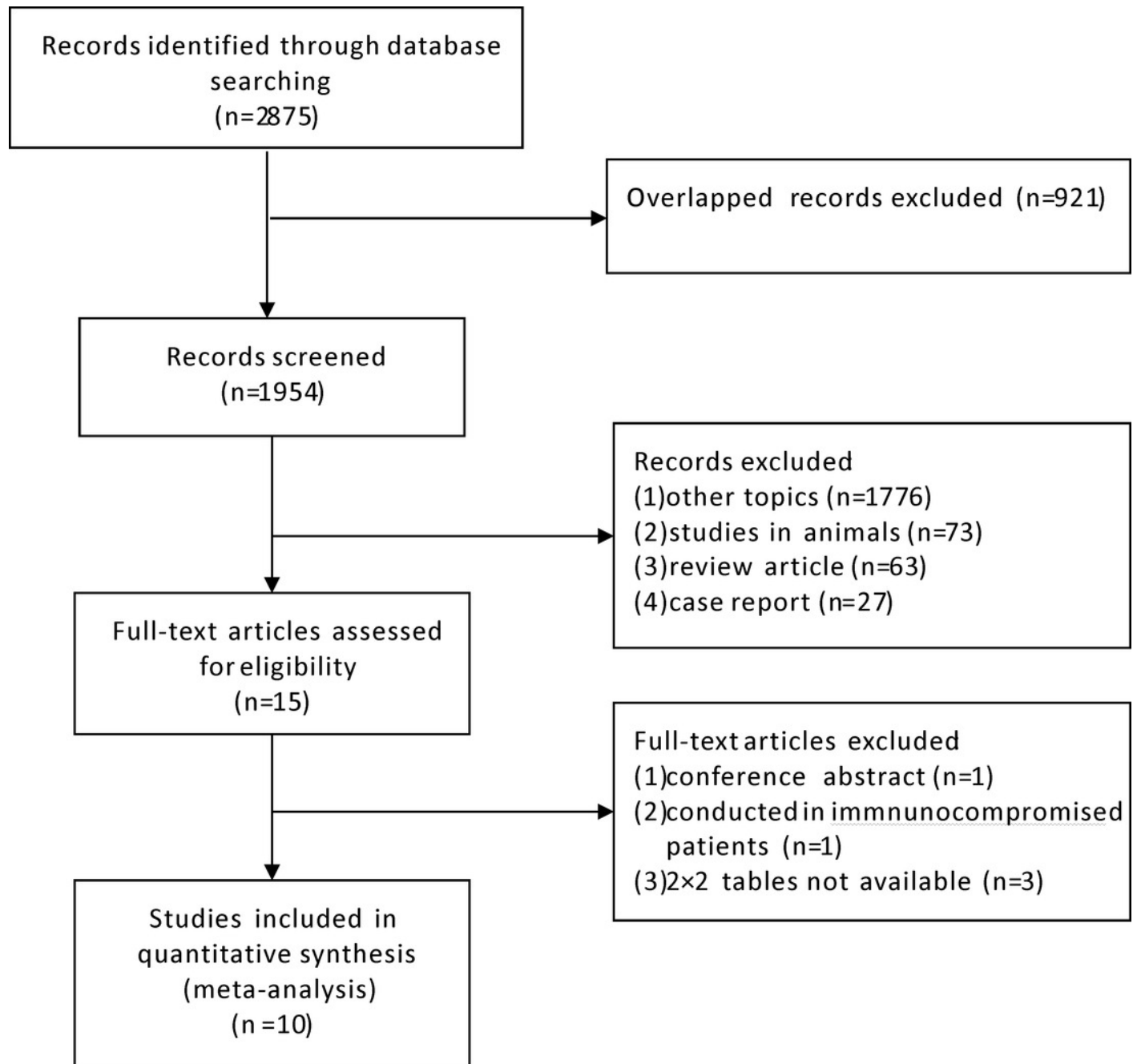



Figure 2

Forest plot evaluating the sensitivity and specificity of diagnostic performance of IGRA in tuberculous lymphadenitis.

CI, confidence interval. (A) Sensivitity; (B) Specificity.

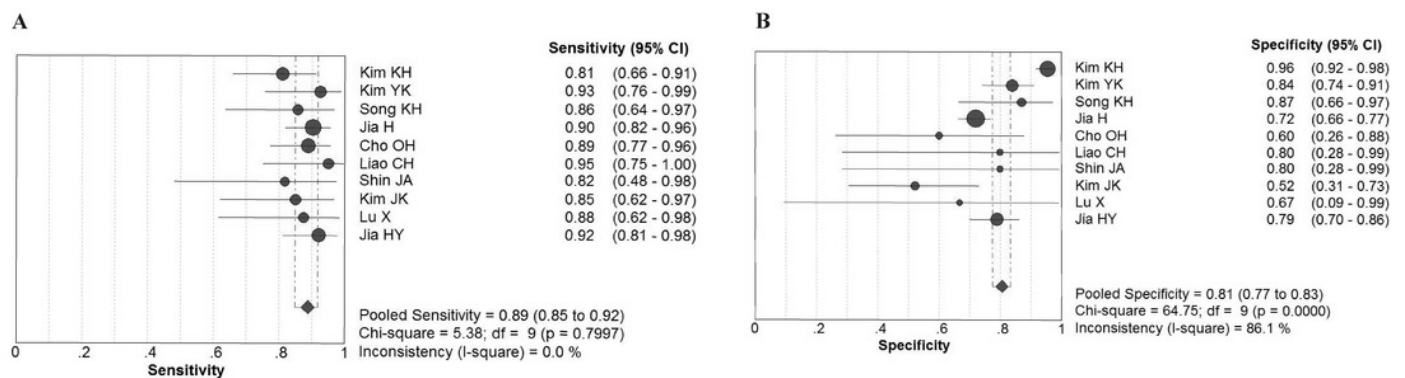



Figure 3

Summary receiver operator characteristics (SROC) of IGRA on summary estimates of sensitivity and specificity.

AUC, area under the curve; SE, standard error

Symmetric SROC
AUC = 0.9332
SE(AUC) = 0.0118
Q* = 0.8689
SE(Q*) = 0.0144

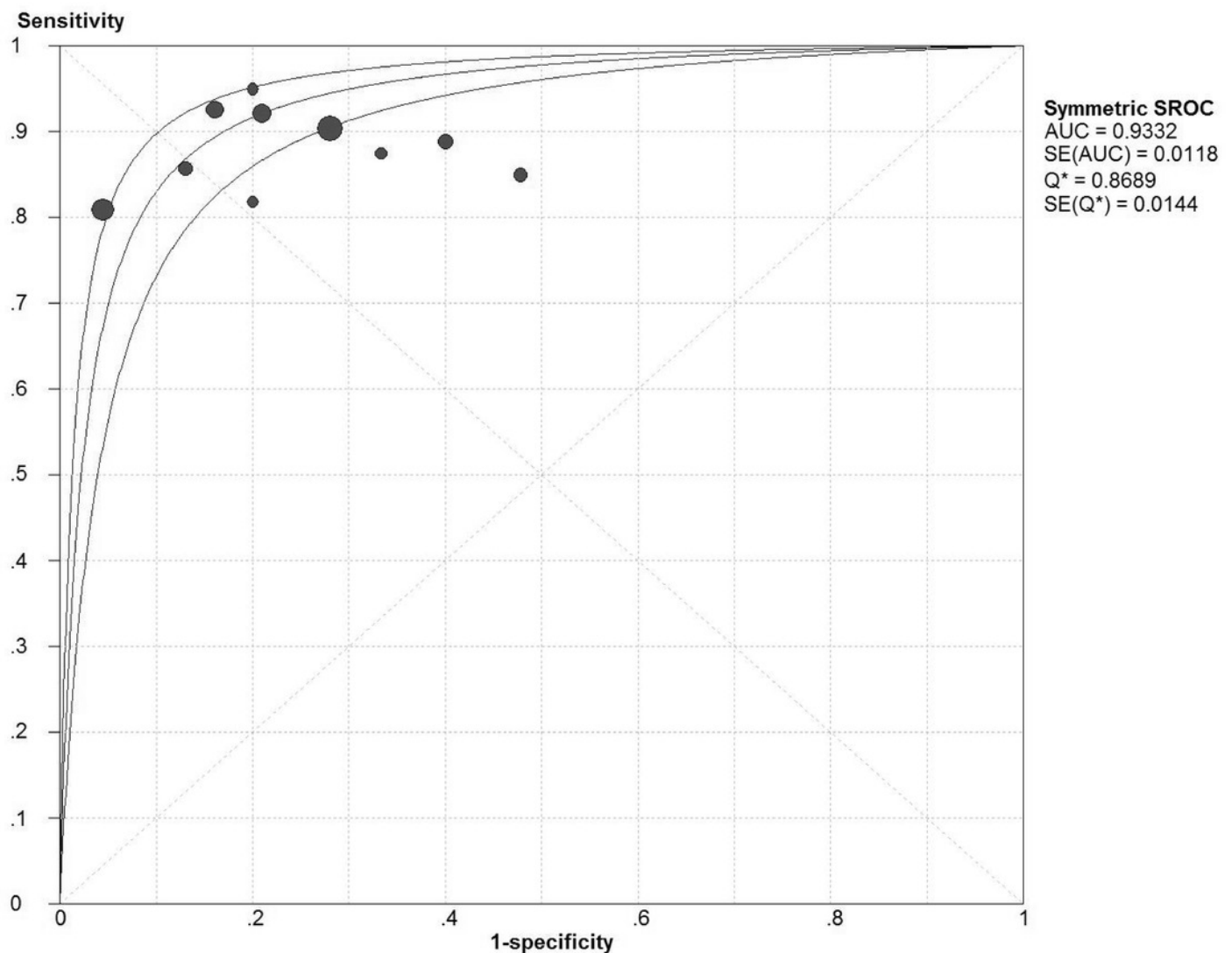
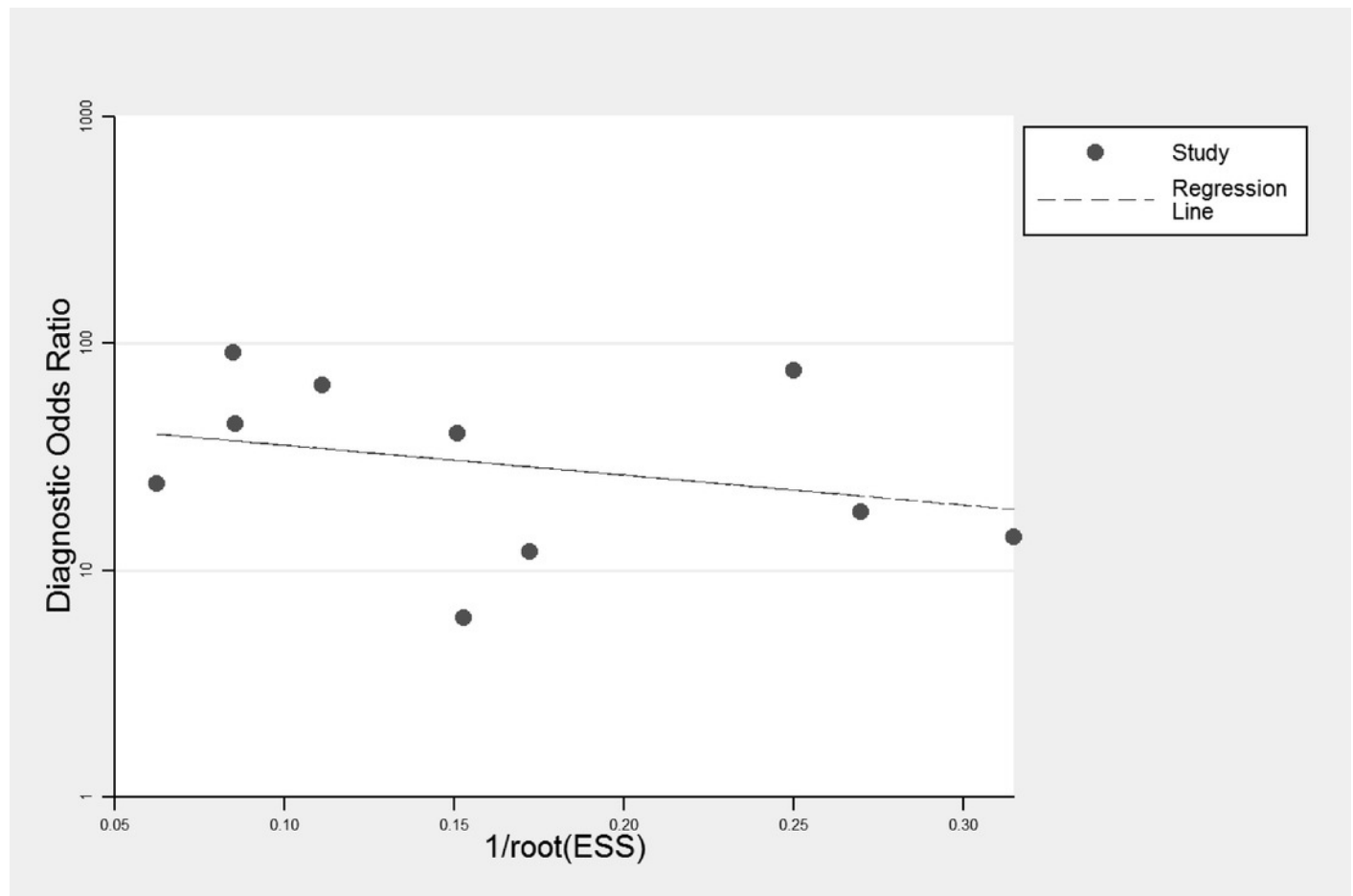



Figure 4

Deeks' funnel plots for publication bias.

Characteristics of studies included in meta-analysis.

IGRA, interferon-γ release assay; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

First author	Language	Year	Country	IGRA method	Sample size	TP	FP	FN	TN
Kim KH	English	2016	Korea	QuantiFERON-TB	244	34	9	8	193
Kim YK	English	2011	Korea	QuantiFERON-TB	108	25	13	2	68
Song KH	English	2009	Korea	QuantiFERON-TB	44	18	3	3	20
Jia H	English	2016	China	T-SPOT.TB	365	75	79	8	203
Cho OH	English	2011	Korea	T-SPOT.TB	64	48	4	6	6
Liao CH	English	2009	China	T-SPOT.TB	25	19	1	1	4
Shin JA	English	2015	Korea	QuantiFERON-TB	16	9	1	2	4
Kim JK	Korean	2013	Korea	QuantiFERON-TB	43	17	11	3	12
Lu X	Chinese	2016	China	T-SPOT.TB	19	14	1	2	2
Jia HY	Chinese	2014	China	T-SPOT.TB	156	47	22	4	83

Quality assessment of the eligible studies by QUADAS-2

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1	unkown	unknown	unknown	low	low	low	low
2	unkown	unknown	unknown	low	low	low	low
3	unkown	unknown	high	low	low	low	low
4	high	low	low	low	low	low	low
5	unkown	unknown	low	low	low	low	low
6	unknown	unknown	unknown	low	low	low	low
7	unknown	unknown	unknown	low	low	low	low
8	unknown	unknown	unknown	low	low	low	low
9	unknown	unknown	unknown	low	low	low	low
10	high	unknown	unknown	low	low	low	low

Subgroup analyses

PLR, positive likelihood ratio; NLR, negative likelihood ratio; AUC, area under the curve;TBL, Tuberculous lymphadenitis.

Subgroup	Studies	Sensitivity		Specificity		PLR		NLR		AUC
	(n)	Pooled value	P_{Heter}	Pooled value	P_{Heter}	Pooled value	P_{Heter}	Pooled value	P_{Heter}	Pooled value
T-SPOT.TB	5	0.91(0.86-0.94)	0.90	0.74(0.69-0.78)	0.54	3.37(2.85-4.00)	0.48	0.13(0.09-0.21)	0.78	0.98(0.03)
QuantiFERON-TB	5	0.85(0.78-0.91)	0.73	0.89(0.85-0.92)	<0.10	5.53(2.11-14.52)	<0.10	0.19(0.12-0.29)	0.72	0.92(0.02)
Korean	6	0.86(0.80-0.91)	0.77	0.88(0.84-0.91)	<0.10	4.71(2.08-10.67)	<0.10	0.19(0.13-0.28)	0.84	0.92(0.02)
Chinese	4	0.91(0.86-0.95)	0.85	0.74(0.69-0.78)	0.53	3.45(2.90-4.11)	0.50	0.12(0.07-0.20)	0.80	0.96(0.13)
Cervical TBL	3	0.83(0.73-0.90)	0.86	0.91(0.86-0.94)	<0.10	5.89(1.08-31.93)	<0.10	0.21(0.13-0.33)	0.77	0.91(0.03)
Not limit to Cervical TBL	7	0.90(0.86-0.94)	0.92	0.75(0.71-0.79)	0.29	3.72(2.97-4.66)	0.29	0.14(0.09-0.20)	0.82	0.95(0.04)