Systematic Review and Meta-Analysis

Medicine®

OPEN

# Diagnostic significance of long non-coding RNAs expression in tuberculosis patients

## A systematic review and meta-analysis

Xiaoling Zhong, MM[a], Qin Guo, MD[a], Jing Zhao, MM[b], Yinyue Li, MM[a], Xue Li, MM[a], Min Ren, MM[a], Min Shu, MM[a,*]

**Abstract**

**Objectives:** It is crucial to identify effective diagnostic biosignatures of tuberculosis (TB) to optimize its treatment. Herein, we conducted a systematic review to elucidate the diagnostic efficacy of long noncoding RNA (lncRNAs) as TB biomarkers.

**Methods:** We searched Medline, Web of Science, Embase, Cochrane Library, CNKI, Wanfang, VIP, and China Biology Medicine disc databases up to February 18, 2020. These studies focusing on lncRNAs as diagnosis markers of TB were collected. STATA 12.0 and Meta-disc1.4 software were used to analyze the data extracted from eligible studies.

**Results:** We included 8 articles with 1058 TB patients, and 1896 healthy controls in our study. The values of pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.63, 0.86, 4.48, 0.43, and 10.31, respectively. Additionally, we plotted the summary receiver operating characteristic curve to evaluate the diagnostic accuracy, and the area under the curve was 0.80.

**Conclusion:** The present study is the first meta-analysis to assess the diagnostic accuracy of lncRNAs in TB patients. We found that lncRNAs might constitute potential biomarkers for the diagnosis of TB patients. More population-based high-quality research should be conducted to validate the efficacy lncRNAs in TB patients.

**Abbreviations:** AUC = area under the curve, CI = confidence interval, CNKI = China national knowledge infrastructure, DOR = diagnostic odds ratio, LncRNA = long non-coding RNA, NLR = negative likelihood ratio, PLR = positive likelihood ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2, ROC = receiver-operating characteristic curves, TB = tuberculosis.

**Keywords:** LncRNA, meta-analysis, systematic review, tuberculosis

## 1. Introduction

Tuberculosis (TB) remains one of the most significant public health threats.[1] In 2017, there were 10 million newly diagnosed TB cases and approximately 1.6 million TB-associated deaths globally.[2–4] China ranks top 20 worldwide regarding the TB burden and had the second largest number of new cases.[5] Considering such a huge burden of TB, the development of tools for early detection of TB is significant. Eearly diagnosis and appropriate treatment can improve prognosis.[4] The conventional diagnostic criterion including microscopysputum smear microscopy and traditional *Mycobacterium tuberculosis* cultures, are too insensitive and time-consuming.[6] Greater efforts were supposed to develop new tools to detect TB fast and reduce morbidity and mortality.[7]

Long noncoding RNA (lncRNAs) are nonprotein coding RNAs with >200 nucleotides in length.[8] Previous studies demonstrated that lncRNAs play a crucial role in a wide range of cell biological activities, including cell proliferation, differentiation, pre-transcription, and post-transcription,.[9–12] It had been proved that lncRNAS were also involved in different types of infectious diseases.[13] Notably, they have effects on the development and progression of tuberculosis infection and may serve as promising diagnostic biomarkers.[14–16] Some studies indicated that lncRNAs are abnormally expressed in TB and latent tuberculosis infection patients.[13,15–17]

*Editor: Mihnea-Alexandru Găman.*

*Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

*The authors report no conflicts of interest statement.*

*All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are publicly available.*

*[a] Department of Infectious Pediatrics, West China Second Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China, [b] Emergency Department, Lanzhou University Second Hospital, Lanzhou 730030, China.*

*[*] Correspondence: Min Shu, Department of Infectious Pediatrics, West China Second Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Chendu 610041, China (e-mail: shirlie1995@163.com).*



*How to cite this article: Zhong X, Guo Q, Zhao J, Li Y, Li X, Ren M, Shu M. Diagnostic significance of long non-coding RNAs expression in tuberculosis patients: a systematic review and meta-analysis. Medicine 2022;101:7(e28879).*

*Received: 29 July 2020 / Received in final form: 25 December 2020 / Accepted: 28 January 2021*

*http://dx.doi.org/10.1097/MD.0000000000028879*

Some studies have revealed that lncRNAs exerct efficiency as novel diagnostic biomarkers with high sensitivity and specificity in diagnosing tuberculosis.[16,22–23] They have demonstrated the high sensitivity and specificity of lncRNAs in diagnosing tuberculosis.[16,23] However, the diagnosis efficiency of different lncRNAs for TB is controversial. Some studies revealed that the diagnostic efficacy of lncRNAs as TB biosignature is low.[24,25] Based on these inconsistent findings and the small sample in these individual studies, we conducted a meta-analysis to comprehensively explore the diagnostic value of lncRNAs in TB and provide relatively reliable research evidence. Best to our knowledge, this is the first meta-analysis about lncRNAs and tuberculosis diagnosis. We intend to demonstrate the potential of lncRNAs as markers for tuberculosis diagnosis in our study.

## 2. Methods

### 2.1. Data source and search strategy

We conducted a literature search in Medline (via PubMed), Web of Science, and Embase (via Ovid SP, from1982), Cochrane Library, CNKI, Wanfang, VIP, and China Biology Medicine disc databases up to February 18, 2020. We used the following terms to search in these databases: "Long non-coding RNA" or "long noncoding RNA" or lncRNA and TB or tuberculosis. We conducted our searches via combining text words and medical subject headings words, without language restriction. Additionally, we searched through the references of the retrieved studies to identify other potentially eligible studies. We have registered this meta-analysis in International Platform of Registered Systematic Review and Meta-analysis Protocols. The ethical review is not applicable for this study.

### 2.2. Inclusion criteria and exclusion criteria

All eligible studies in this meta-analysis satisfied the following criteria: (human research subjects; evaluating the diagnostic value of abnormally expressed lncRNAs in TB; providing sufficient data to tabulate $2 \times 2$ table for diagnostic meta-analysis. We utilized the following exclusion criteria: duplicate studies; not control study; letters, conferences, reviews, or meta-analysis.

### 2.3. Data extraction and study quality assessment

The values of true-positives, false-positives, true-negatives, and false-negatives were accessed from the included studies. We used the GetData Graph Digitizer 2.24 software to compute the sensitivity and specificity in some articles which only provided receiver-operating characteristic curves. This systematic review and meta-analysis was performed as the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[18] We conducted a quality assessment by adapting the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist.[19] The QUADAS-2 checklist consists of 4 critical domains including patient selection, index test, reference standard, flow, and timing. Two reviewers independently extracted data from included studies and assessed methodological quality. Any disagreements were resolved through consensus.

### 2.4. Statistical analysis

Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) were used to evaluate the overall diagnostic performance of the lncRNAs. Heterogeneity between studies was assessed using the Cochran $Q$ test, the Higgins $I^2$.[20] Moreover, the threshold effect that causes heterogeneity among studies was quantified using Spearman correlation coefficient, which must be $\geq 0.6$.[21]

The random-effects model was used to analyze the results when heterogeneity was caused by the non-threshold effect ($I_2 > 50\%$, $P < .05$). In contrast, the fixed-effects model was utilized when heterogeneity was absent in the eligible studies ($I_2 < 50\%$, $P > .05$). Subgroup analysis and sensitivity analysis was used to explore the potential sources of heterogeneity. The publication bias was assessed using the Deek funnel-plot. A $P$ value of $<.05$ indicated statistical significance. Meta-disc1.4 and Stata 12.0 software (version 12, College Station, TX) were used to analyze the data in this meta-analysis. We utilized the Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK) software in generating QUADAS-2 graphs.

## 3. Results

### 3.1. Selection of eligible studies

As shown in Figure 1 282 articles were initially retrieved from the electronic databases. Of these, 119 articles were removed as duplications. After screening the titles and abstracts, we identified 39 articles. Subsequently, we excluded 31 articles due to insufficient data to access sensitivity and specificity after full-text screening. No additional studies were found from the screening of the references of the eligible articles. Finally, 8 articles containing 23 studies were included in this meta-analysis.[16,22–28] The flow diagram of the selection of the relevant studies is shown in Figure 1.

### 3.2. Study characteristics and quality assessments

We included 23 studies involving 1 058 patients with TB, and 1896 controls focusing on the diagnostic performance of lncRNAs in TB patients (Table 1 and Table 2). These studies were conducted between 2016 and 2019 in China. The results indicated that 12 lncRNAs were upregulated, whereas 8 lncRNAs were downregulated. Three studies focused on the diagnostic performance of multiple lncRNAs in TB patients. Notably, lncRNA MALAT1 was investigated in at least 3 studies. The characteristics of the included studies are shown in Table 1. The QUADAS-2 assessment indicated that a significant number of the studies (>80%) had a moderate to high risk of bias, and all had concerns regarding applicability. The results are shown in Figure 2A and Figure 2B.

### 3.3. Diagnostic performance

Overall, 23 studies focused on the value of lncRNAs as TB diagnostic markers. We reported significant heterogeneity (Fig. 3 and Fig. 4). Therefore, we carefully chose the random-effects model to calculate the pooled effect. The indexes were as follows: sensitivity, 0.63 (95% confidence interval [CI] 0.52–0.72), specificity, 0.86 (95% CI 0.77–0.96); the pooled PLR, 4.48 (95% CI 2.87–6.99), NLR, 0.43 (95% CI 0.35–0.54), and DOR, 10.31 (95% CI 6.49–16.38).

The forest plots of the sensitivity and specificity of lncRNAs for TB diagnosis are shown in Figure 3. Additionally, the summary receiver-operating characteristic curve was used to evaluate

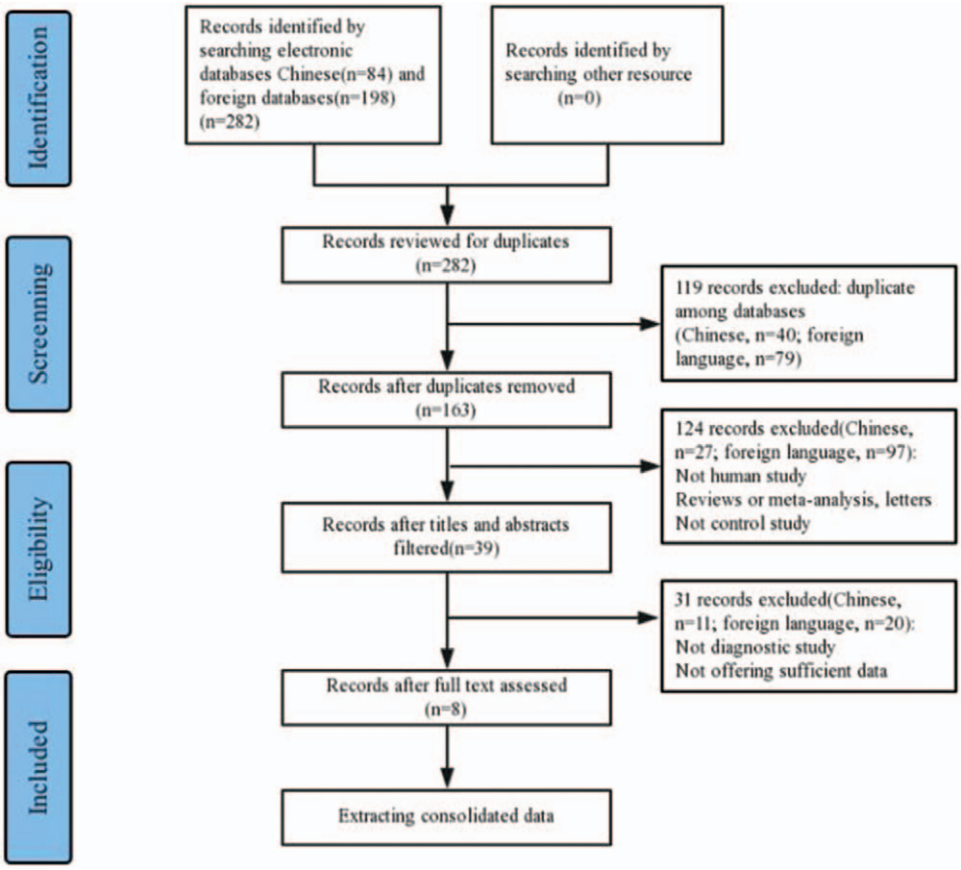


**Figure 1.** A flow diagram demonstrating the study selection process.

**Table 1**

**The primary characteristics of the 23 included studies in this review.**

| | | | | Active TB | | Healthy control | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study ID** | **Area** | **Study type** | **Specimen** | **Age** | **n** | **Age** | **n** | **LncRNA** | **Method** | **Expression** |
| Fake, 2019[22] | China | Case–control | PBMC | 39 (18–79) | 31 | 54 (29–83) | 32 | MALAT1 | qPCR | Downregulation |
| Luo et al, 2017[23] | China | Case–control | Serum | 36.7 ± 10.5 | 56 | 38.2 ± 11.6 | 40 | MALAT1 | RT-qPCR | Upregulation |
| Song et al, 2018[24] (training set) | China | Nomogram model | Whole blood | Unclear | 445 | Unclear | 826 | lnc-PA | RT-qPCR | Downregulation |
| Song et al, 2018[24] (validation set) | China | Nomogram model | Whole blood | Unclear | 353 | Unclear | 824 | lnc-PA | RT-qPCR | Downregulation |
| Zhao et al, 2017[25] | China | Case–control | Whole blood | Unclear | 20 | Unclear | 20 | TCONS-l2–00002132 | RT-qPCR | Downregulation |
| Zhao et al, 2017[25] | China | Case–control | Whole blood | Unclear | 20 | Unclear | 20 | TCONS-l2-0000048 | RT-qPCR | Upregulation |
| Luo, 2018[26] | China | Case–control | PBMC | 41.1 ± 17.5 | 35 | 43.7 ± 18.3 | 35 | lnc-FAM110B-10 | RT-qPCR | Upregulation |
| Luo, 2018[26] | China | Case–control | PBMC | 41.1 ± 17.5 | 35 | 43.7 ± 18.3 | 35 | lnc-GUCY2C-1 | RT-qPCR | Upregulation |
| Luo, 2018[26] | China | Case–control | PBMC | 41.1 ± 17.5 | 35 | 43.7 ± 18.3 | 35 | lnc-NEAT1 | RT-qPCR | Downregulation |
| Luo, 2018[26] | China | Case–control | PBMC | 41.1 ± 17.5 | 35 | 43.7 ± 18.3 | 35 | lnc-MALAT1 | RT-qPCR | Downregulation |
| Luo, 2018[26] | China | Case–control | PBMC | 41.1 ± 17.5 | 35 | 43.7 ± 18.3 | 35 | combine | RT-qPCR | Unclear |
| Hu, 2019[27] | China | Case–control | Plasma | 32 (26-54) | 35 | 44.5 (37–50) | 35 | lncrna NR-110750 | RT-qPCR | Upregulation |
| Hu, 2019[27] | China | Case–control | Plasma | 32 (26–54) | 35 | 44.5 (37–50) | 35 | lncrna uc.212 | RT-qPCR | Upregulation |
| Hu, 2019[27] | China | Case–control | Plasma | 32 (26–54) | 35 | 44.5 (37–50) | 35 | lncrna NR-131237 | RT-qPCR | Upregulation |
| Hu, 2019[27] | China | Case–control | Plasma | 32 (26–54) | 35 | 44.5 (37–50) | 35 | combine | RT-qPCR | Unclear |
| Yang et al, 2016[16] | China | Case–control | PBMC | 26 (19–35) | 31 | 23 (19–32) | 32 | ENST00000360485 | RT-qPCR | Downregulation |
| Yang et al, 2016[16] | China | Case–control | PBMC | 26 (19–35) | 31 | 23 (19–32) | 32 | MIR3945HG V1 | RT-qPCR | Upregulation |
| Yang et al, 2016[16] | China | Case–control | PBMC | 26 (19–35) | 31 | 23 (19–32) | 32 | MIR3945HG V2 | RT-qPCR | Upregulation |
| Chen et al, 2017[28] | China | Case–control | Plasma | 41.35 ± 17.27 | 52 | 38.92 ± 10.6 | 52 | NR-038221 | qPCR | Upregulation |
| Chen et al, 2017[28] | China | Case–control | Plasma | 41.35 ± 17.27 | 52 | 38.92 ± 10.6 | 52 | NR-003142 | qPCR | Upregulation |
| Chen et al, 2017[28] | China | Case–control | Plasma | 41.35 ± 17.27 | 52 | 38.92 ± 10.6 | 52 | ENST00000570366 | qPCR | Upregulation |
| Chen et al, 2017[28] | China | Case–control | Plasma | 41.35 ± 17.27 | 52 | 38.92 ± 10.6 | 52 | ENST00000422l83 | qPCR | Downregulation |
| Chen et al, 2017[28] | China | Case–control | Plasma | 41.35 ± 17.27 | 52 | 38.92 ± 10.6 | 52 | Combine | qPCR | Unclear |

**Table 2**

**Main characteristics of the included studies.**

| TB/HC | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study ID** | **AUC** | **95%CI** | **Sensitivity** | **95%CI** | **Specificity** | **95%CI** | **TP** | **FP** | **FN** | **TN** |
| Fake, 2019[22] | 0.679 | Unclear | 0.9631 | Unclear | 0.4235 | Unclear | 30 | 18 | 1 | 14 |
| Luo, 2017[23] | 0.821 | 0.735–0.907 | 0.732 | Unclear | 0.85 | Unclear | 41 | 6 | 15 | 34 |
| Song et al, 2018[24] (training set) | 0.619 | Unclear | 0.5791 | Unclear | 0.625 | Unclear | 258 | 310 | 187 | 516 |
| Song et al, 2018[24] (validation set) | 0.626 | Unclear | 0.8263 | Unclear | 0.3988 | Unclear | 292 | 495 | 61 | 329 |
| Zhao et al, 2017[17] | 0.4 | Unclear | 0.75 | Unclear | 0.30 | Unclear | 15 | 14 | 5 | 6 |
| Zhao et al, 2017[17] | 0.762 | Unclear | 0.55 | Unclear | 0.95 | Unclear | 11 | 1 | 9 | 19 |
| Luo, 2018[26] | 0.7151 | 0.5947–0.8355 | 0.6286 | Unclear | 0.8 | Unclear | 22 | 7 | 13 | 28 |
| Luo, 2018[26] | 0.7162 | 0.5883–0.8441 | 0.5313 | Unclear | 0.871 | Unclear | 19 | 5 | 16 | 30 |
| Luo, 2018[26] | 0.7341 | 0.6006–0.8675 | 0.6897 | Unclear | 0.7692 | Unclear | 24 | 8 | 11 | 27 |
| Luo, 2018[26] | 0.6774 | 0.5434–0.8114 | 0.4242 | Unclear | 0.9677 | Unclear | 15 | 1 | 20 | 34 |
| Luo, 2018[26] | 0.8703 | 0.7745–0.9662 | 0.7586 | Unclear | 0.92 | Unclear | 27 | 3 | 8 | 32 |
| Hu, 2019[27] | 0.553 | Unclear | 0.167 | Unclear | 1 | Unclear | 6 | 0 | 29 | 35 |
| Hu, 2019[27] | 0.51 | Unclear | 0.486 | Unclear | 0.735 | Unclear | 17 | 9 | 18 | 26 |
| Hu, 2019[27] | 0.54 | Unclear | 0.296 | Unclear | 1 | Unclear | 10 | 0 | 25 | 35 |
| Hu, 2019[27] | 0.694 | Unclear | 0.2273 | Unclear | 1 | Unclear | 8 | 0 | 27 | 35 |
| Yang et al, 2016[16] | 0.7984 | 0.687–0.909 | 0.8387 | 0.6627–0.9455 | 0.7188 | 0.5325–0.8625 | 26 | 9 | 5 | 23 |
| Yang et al, 2016[16] | 0.925 | 0.863–0.987 | 0.9 | 0.7347–0.9789 | 0.8125 | 0.6356–0.9279 | 28 | 6 | 3 | 26 |
| Yang et al2016[16] | 0.956 | 0.9lo-1.002 | 0.8966 | 0.7265—0.9781 | 0.9063 | 0.7498—0.9802 | 28 | 3 | 3 | 29 |
| Chen et al, 2017[28] | 0.677 | 0.528—0.826 | 0.5199 | Unclear | 0.8347 | Unclear | 27 | 9 | 25 | 43 |
| Chen et al, 2017[28] | 0.657 | 0.503—0.81 1 | 0.4388 | Unclear | 0.9024 | Unclear | 23 | 5 | 29 | 47 |
| Chen et al, 2017[28] | 0.672 | 0 515—0 829 | 0.4794 | Unclear | 0.9024 | Unclear | 25 | 5 | 27 | 47 |
| Chen et al, 2017[28] | 0.738 | 0.592—0.884 | 0.5608 | Unclear | 0.9377 | Unclear | 29 | 3 | 23 | 49 |
| Chen et al 2017[28] | 0.845 | 0.742—0 949 | 0.792 | Unclear | 0.75 | Unclear | 41 | 13 | 11 | 39 |

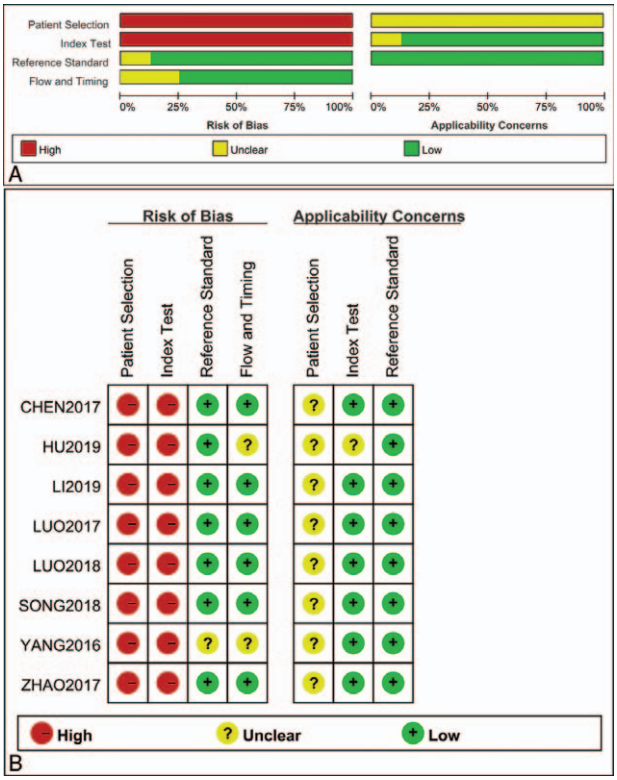


**Figure 2.** (A) Risk of bias and applicability concerns graph: reviews the judgements of the author about each domain presented as percentages across included studies. (B) Risk of bias and applicability concerns summary: reviews judgements of the author about each domain for each included study.

diagnostic accuracy (Fig. 5). AUC was 0.80 (95% CI 0.77–0.84), indicating a good diagnostic accuracy of the lncRNAs in diagnosing TB. We performed sensitivity, subgroup, and publication bias analysis to elucidate the potential sources of heterogeneity between the included studies.

### 3.4. Heterogeneity

***3.4.1. Threshold effect.*** Although we used strict inclusion and exclusion criteria to retrieve eligible studies, heterogeneity still existed because of the potential confounding factors. The threshold effect is a crucial reason for heterogeneity in meta-analysis in a diagnostic accuracy test. In the present meta-analysis, the calculated Spearman correlation coefficient value was 0.645 ($P = .001$), which was >0.6. This reveals the existence of some extent threshold effect in the accuracy estimate of lncRNAs.

***3.4.2. Sensitivity analysis, and publication bias.*** The sensitivity analysis was performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and reestimate the pooled odds ratio estimate of the remaining studies. None of the exclusions altered the magnitude of the pooled effect about lncRNAs expression and TB patients, which further confirmed the validity of the results (Fig. 6). We performed Deek test to assess the publication bias. The results indicated that publication bias exists in our study (Fig. 7).

***3.4.3. Subgroup analysis.*** We performed a subgroup analysis across several different variables to further investigate the sources of heterogeneity in the meta-analysis. We performed the subgroup analysis based on single or multiple lncRNAs and

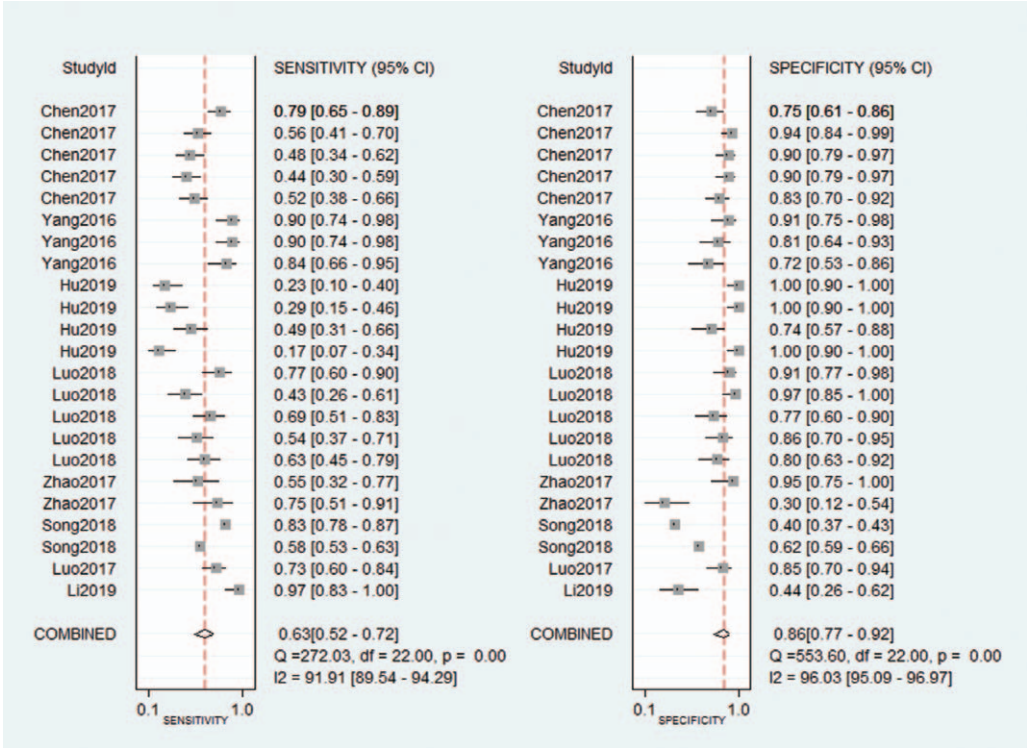


**Figure 3.** Pooled sensitivity and specificity of the studies on overall lncRNAs used in the diagnosis of TB patients among 23 studies included in the meta-analysis.

specimen types. Heterogeneity still existed in our subgroups ($P < .05$). We found that multiple lncRNAs have a higher accuracy compared with single lncRNAs, with sensitivity of 0.623 (95% CI 0.531–0.709) versus 0.643 (95% CI 0.618–0.668), specificity of 0.869 (95% CI 0.796–0.923) versus 0.605 (95%CI 0.584–0.625), and DOR of 16.093 (95% CI 7.650–33.851) versus

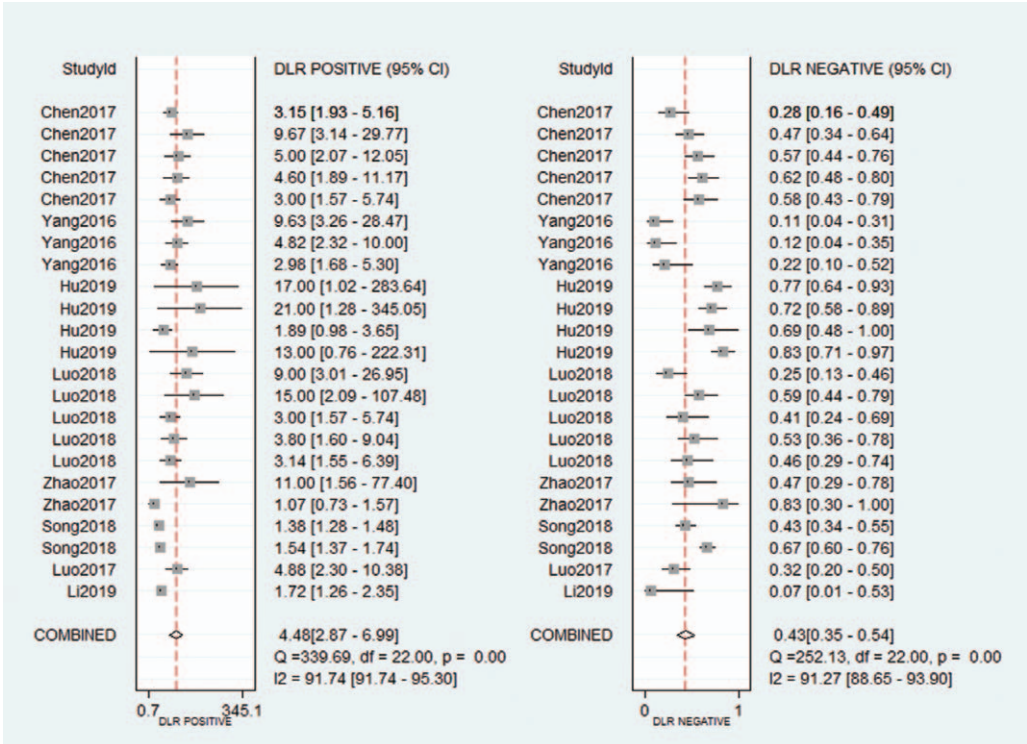


**Figure 4.** Pooled PLR and NLR of the studies on overall lncRNAs used in the diagnosis of TB patients among 23 studies included in the meta-analysis.

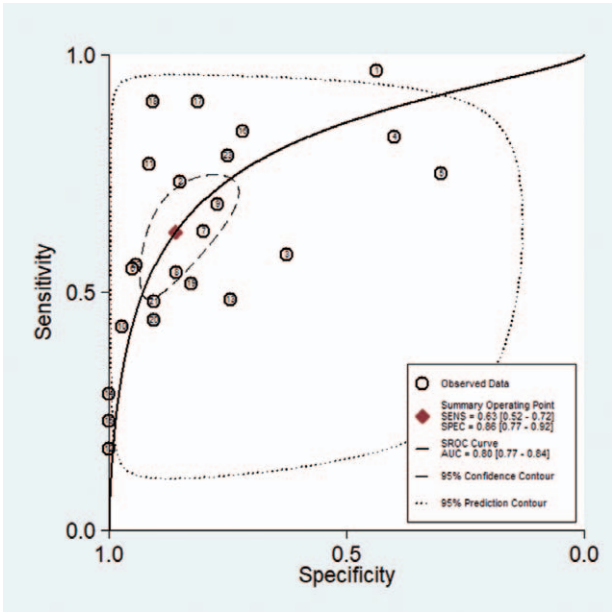


**Figure 5.** Summary receiver operator characteristic curves (SROC) of lncRNAs for the diagnosis of TB in the overall population.

8.226 (95% CI 5.271–12.837). This indicates the existence of an effective lncRNA fingerprint, including NR-038221, NR-003142, ENST00000570366, ENSTO0000422l83, or FAM110B-10, GUCY2C-1, NEAT1, MALAT1 and NR-110750, uc.212, NR-131237 for combined diagnosis of TB (Table 3). We found that there are 3 combinations in total and the comprehensive diagnostic efficacy of FAM110B-10, GUCY2C-1, NEAT1, MALAT1 is the best.

Compared with other sample types, lncRNAs in serum had a higher overall diagnostic accuracy, with a sensitivity of 0.732 (95% CI 0.597–0.842), a specificity of 0.850 (95% CI 0.702–0.943), PLR of 4.881 (95% CI 2.295–10.380), NLR of 0.315 (95% CI 0.200–0.495), DOR of 15.489 (95% CI 7.370–32.549). However, there was only one study using serum samples in this meta-analysis.[23] We additionally found that peripheral blood mononuclear cell has relatively high sensitivity and specificity. Subgroup analysis by detection methods revealed no significant difference in the diagnosis of TB. Because of limited literature data, we did not perform subgroup analysis regarding population and age. The detailed results in each subgroup are shown in Table 3.

## 4. Discussion

Recent studies revealed the critical roles of lncRNAs in modulating the initiation and progression of TB.[29] The diagnosis of tuberculosis remains a significant challenge in a clinical setup. The presently diagnosis methods have reduced sensitivity and specificity.[6] Within a relatively short period, a lot of researches showed that lncRNAs are abnormally expressed in TB patients.[15,17] LncRNAs are possible TB diagnostic biomarkers and potential targets for individualized therapy.[17,30] To the best of our knowledge, this is the first systematic review and meta-analysis exploring the diagnostic accuracy of lncRNAs for TB patients.

In this meta-analysis, we searched multiple databases and included 23 eligible studies about the diagnostic value of

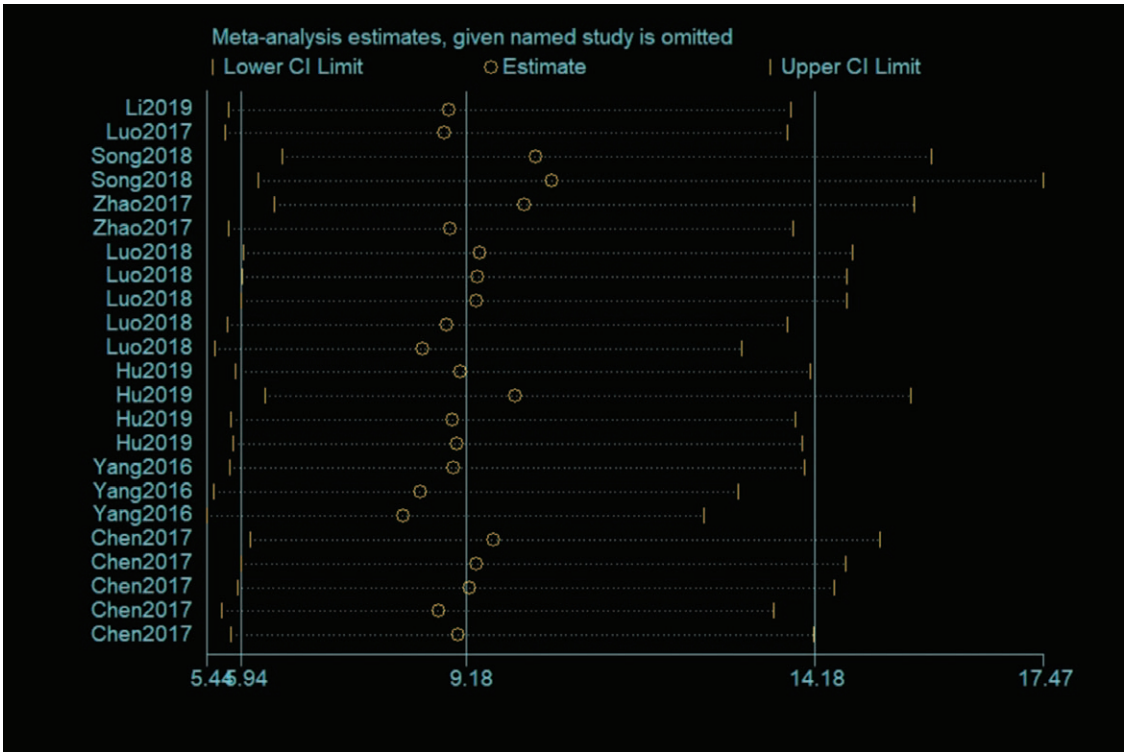


**Figure 6.** Sensitivity analysis of the results of the meta-analysis.

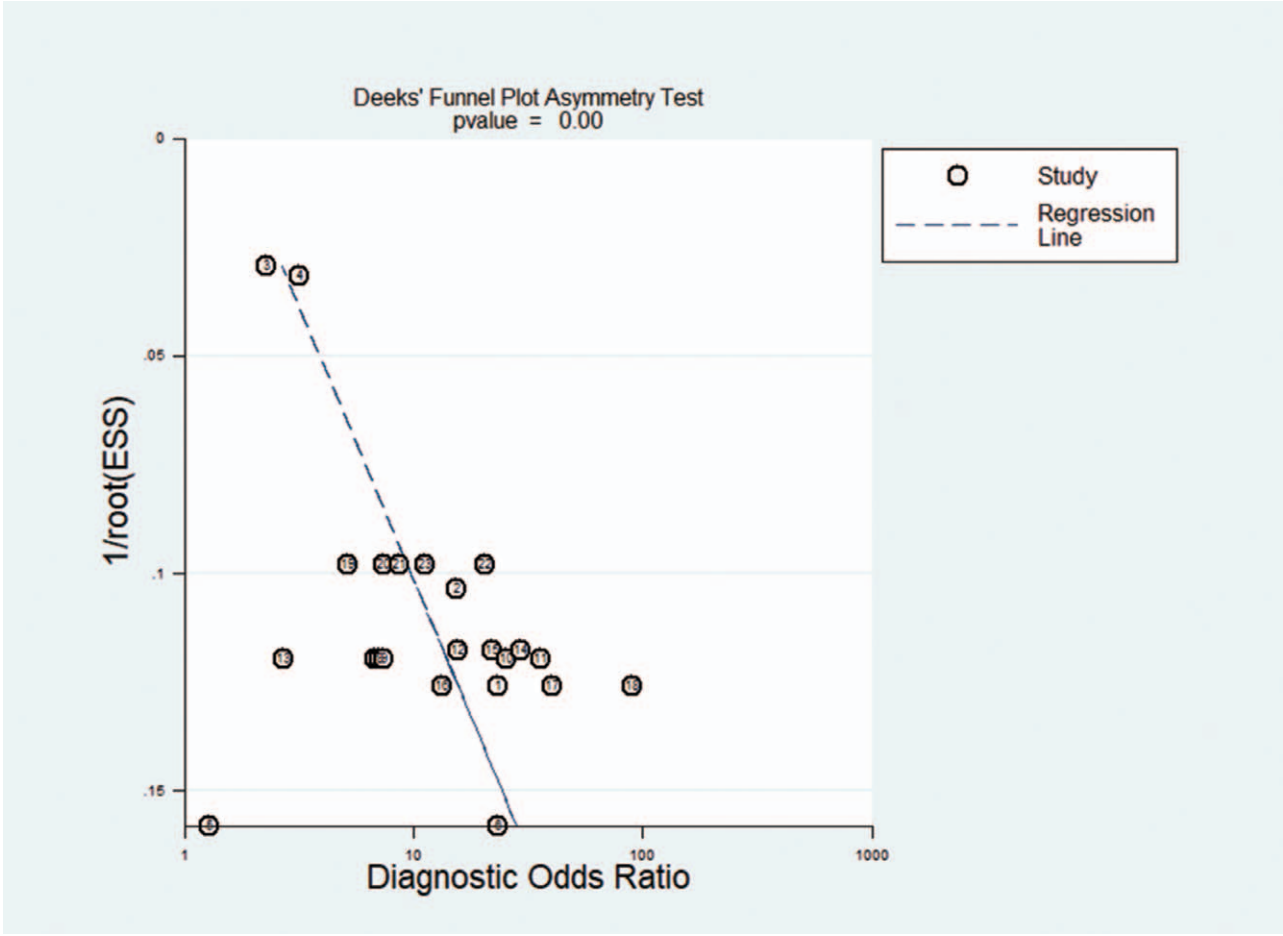


**Figure 7.** Deeks' funnel plot evaluating the potential publication bias of the included studies.

lncRNAs for TB. We identified 12 upregulated and 8 downregulated in TB patients. The pooled effect sizes for diagnosis revealed that the lncRNAs signature had a low sensitivity of 0.63 (95% CI 0.52–0.72) and high specificity of 0.86 (95% CI 0.77–0.96). The AUC was 0.80 (95% CI 0.77–0.84) for differentiating TB from healthy controls. The pooled PLR was 4.48, indicating that the likelihood of TB diagnosis increases by 4.48-fold with positive lncRNAs testing. Moreover, the NLR was 0.43, implying that the probability of diagnosis of TB increases by 57% with an lncRNAs negative test. In addition, the pooled DOR was 10.31. It indicated a powerful diagnosis capacity of lncRNAs for TB. All these results suggested that lncRNAs might serve as diagnostic markers for TB patients.

This meta-analysis has some limitations. Firstly, all the included studies are Chinese. Therefore, generalizing our findings to the general global population is a challenge. Secondly, the methodology quality of the included research in the meta-analysis was assessed by QUADAS-2, and the risk of bias varied from moderate to high, which could influence the stability of the pooled results. Thirdly, most of included studies used a small sample size. Fifteen studies (15/23) had a study population of 100 participants or less. Fourthly, the study may exist a threshold

**Table 3**

**Subgroup analyses for the selected studies.**

| Subgroup analysis | Sensitivity (95% CI) | Specificity (95% CI) | LR+ (95% CI) | LR− (95% CI) | DOR (95% CI) |
|---|---|---|---|---|---|
| LncRNA profiling | | | | | |
| Single lncRNA | 0.643 (0.618–0.668) | 0.605 (0.584–0.625) | 2.912 (2.246–3.776) | 0.513 (0.436–0.603) | 8.226 (5.271–12.837) |
| Multiple lncRNAs | 0.623 (0.531–0.709) | 0.869 (0.796–0.923) | 5.466 (2.007–14.886) | 0.387 (0.120–1.241) | 16.093 (7.650–33.851) |
| Specimen | | | | | |
| Serum | 0.732 (0.597–0.842) | 0.850 (0.702–0.943) | 4.881 (2.295–10.380) | 0.315 (0.200–0.495) | 15.489 (7.370–32.549) |
| Plasma | 0.465 (0.415–0.515) | 0.890 (0.855–0.919) | 3.893 (2.597–5.835) | 0.621 (0.517–0.747) | 7.851 (4.983–12.369) |
| PBMC | 0.732 (0.678–0.782) | 0.802 (0.753–0.845) | 3.969 (2.436–6.467) | 0.311 (0.205–0.473) | 16.164 (8.853–29.513) |
| Whole blood | 0.650 (0.483–0.794) | 0.625 (0.458–0.773) | 3.065 (0.145–64.907) | 0.531 (0.335–0.841) | 4.822 (0.272–85.568) |

CI = confidence intervals, LR+ = positive likelihood ratio, LR− = negative likelihood ratio, DOR = diagnostic odds ratio.

effect. The cutoff values of lncRNAs lacked uniform standard because of the different methods and criteria used in various studies. Threshold effect may result in some heterogeneity and affect the results of this meta-analysis. Therefore, further high-quality original studies are expected to validate our findings.

## 5. Conclusions

All in all, the present study is the first meta-analysis on the diagnostic accuracy of lncRNAs for TB patients. We identified some aberrantly expressed lncRNAs in patients, particularly multiple lncRNAs in serum and peripheral blood mononuclear cells. Those lncRNAs might serve as potential biomarkers for diagnosis of TB patients. However, further more high-quality original studies should be conducted to validate these findings.

## Author contributions

Xiaoling Zhong designed the study, made the review, and wrote the manuscript. Qin Guo , Jing Zhao , Yinyue Li, Xue Li and Min Ren made the literature search, made table and extracted data. Min Shu and Qin Guo reviewed the manuscript. All authors readand approved the final manuscript.

**Data curation:** Jing Zhao.
**Methodology:** Yinyue Li, Xue Li.
**Project administration:** Xiaoling Zhong.
**Software:** Min Ren.
**Writing – original draft:** Xiaoling Zhong.
**Writing – review & editing:** QinGuo, Min Shu.

## References


[1] Altez-Fernandez C, Ortiz V, Mirzazadeh M, Zegarra L, Seas C, Ugarte-Gil C. Diagnostic accuracy of nucleic acid amplifification tests (NAATs) in urine for genitourinary tuberculosis: a systematic review and meta-analysis. BMC Infect Dis 2017;17:390.

[2] Evans TG, Schrager L, Thole J. Status of vaccine research and development of vaccines for tuberculosis. Vaccine 2016;34:2911–4.

[3] Zumla A, George A, Sharma V. The WHO 2014 global tuberculosis report–further to go. Lancet Global Health 2015;3:e10–2.

[4] World Health Organization. Global tuberculosis report 2018. 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf.

[5] Wu Q, Zhong H, Bai H, et al. Clinical relevance of the lnc-HNF1B-3:1 genetic polymorphisms in Western Chinese tuberculosis patients. J Clin Lab Anal 2020;34:e23076.

[6] Modi M, Sharma K, Sharma M, et al. Multitargeted loop-mediated isothermal amplifification for rapid diagnosis of tuberculous meningitis. Int J Tuberc Lung Dis 2016;20:625–30.

[7] Lynn S. Zijenah. The World Health Organization recommended TB diagnostic tools. Tuberclosis 2018;71–90.

[8] Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. Mol Cell 2011;43:904–14.

[9] Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell 2009;136:629–41.

[10] Jin G, Sun J, Isaacs SD, et al. Human polymorphisms at long non-coding RNAs (lncRNAs) and association with prostate cancer risk. Carcinogenesis 2011;32:1655–9.

[11] Wapinski O, Chang HY. Long noncoding RNAs and human disease. Trends Cell Biol 2011;21:354–61.

[12] Yang L, Froberg JE, Lee JT. Long noncoding RNAs: fresh perspectives into the RNA world. Trends Biochem Sci 2014;39:35–43.

[13] Uchida S, Dimmeler S. Long noncoding RNAs in cardiovascular diseases. Circ Res 2015;116:737–50.

[14] Pawar K, Hanisch C, Palma Vera SE, Einspanier R, Sharbati S. Down regulated lncRNA MEG3 eliminates mycobacteria in macrophages via autophagy. Sci Rep 2016;6:1–13.

[15] Wang Y, Zhong H, Xie X, Chen CY, et al. Long noncoding RNA derived from CD244 signaling epigenetically controls CD8þ T-cell immune responses in tuberculosis infection. Proc Natl Acad Sci USA 2015; 112:3883–92.

[16] Yang X, Yang J, Wang J, et al. Microarray analysis of long noncoding RNA and mRNA expression profiles in human macrophages infected with Mycobacterium tuberculosis. Sci Rep 2016;6:1–12.

[17] Zhao Z, Zhang M, Ying J, et al. Signifificance of genetic polymorphisms in long non-coding RNA AC079767.4 in tuberculosis susceptibility and clinical phenotype in Western Chinese Han population. Sci Rep 2017; 7:1–11.

[18] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA GroupPreferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

[19] Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.

[20] Dinnes J, Deeks J, Kirby J, Roderick P. A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy. Heal Technol Assess 2005;9:1–113.

[21] Devillé WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2002;2:9.

[22] Fake L, Jie L, Delu G, et al. The value of long non-coding RNA MALAT1 in differential diagnosis of tuberculosis. Immunol J 2019;35:885–90.

[23] Qing L, Fangyi Y, Yiping P, et al. Clinical value of serum long non-coding RNA metastasis-associated lung adenocarcinoma transcript in the diagnosis of pulmonary tuberculosis. Chin J Infect Dis 2017;35:684–7.

[24] Jiajia S, Mengge B, Tangyuheng L, et al. Expression and diagnostic value of long non-coding RNA lnc-PAPSS2-2 in peripheral blood of active pulmonary tuberculosis patients. West China Med J 2018;33:953–7.

[25] Jili Z, Wei L, Shuaili C, et al. Differences in expression of lncRNA in peripheral blood from patients with tuberculosis. J Path Biol 2017; 12:328–34.

[26] Luo Jie . Diagnostic value of cytokines and long non-coding RNAs in different infection status of mycobacterium tuberculosis [D]. Army Medical University 2018.

[27] Hu , Yuting . Screening and identification of potenial biomarkers for multidrug-resistant tuberculosis and its traditional Chinese medicine syndromes[D]. South China University of Technology 2019.

[28] Chen Z-L, Wei L-L, Shi L-Y, et al. Screening and identifcation of lncRNAs as potential biomarkers for pulmonary tuberculosis. Sci Rep 2017;7:1–10.

[29] Fu Y, Gao K, Tao E. Aberrantly expressed long non-coding RNAs in CD8þ T cells response to active tuberculosis. J Cell Biochem 2017; 118:4275–84.

[30] Yi Z, Li J, Gao K. Identifcation of differentially expressed long non-coding RNAs in CD4+ T cells response to latent tuberculosis infection. J Infect 2014;69:558–68.