Original Article

Association between IL-18, IFN-γ and TB susceptibility: a systematic review and meta-analysis

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Background: This study sought to evaluate the relationship between interleukin 18 (IL-18), interferon-gamma (IFN-γ), and susceptibility to tuberculosis (TB).

Methods: We searched multiple databases, such as PubMed, Embase, Cochrane and China National Knowledge Database, for full-text articles on IL-18, IFN-γ, and TB. Bias risk tool in Review Manager 5.2 was used to evaluate the seven kinds of bias. We used Review Manager 5.2 to evaluate the effects of the results in the selected articles, analyzed the heterogeneity of the included articles to make a forest map, and undertook a sensitivity analysis and publication bias analysis.

Results: Ultimately, 10 studies met the inclusion criteria, and were subjected to a data analysis. IL-18 was higher in the TB group than the health control (HC) group [mean difference (MD) =248.11, 95% confidence interval CI: 197.25, 298.98, P<0.0001; I^2=63%]. The meta-analysis also showed that IFN-γ was higher in the TB group than the HC group (MD =38.74, 95% CI: 14.84, 62.64, P=0.001; I^2=100%). Sensitivity analysis proved the robustness of this research and limited publication bias was observed in this study.

Discussion: This study showed that IL-18 and IF-γ had a relationship with TB and might be used to help diagnose TB, which might be helpful in the clinical diagnosis about TB.

Keywords: Interleukin 18 (IL-18); interferon-gamma (IFN-γ); tuberculosis (TB); meta-analysis

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Introduction

Although large-scale bacilli Calmette-Guerin vaccination was since 1921, tuberculosis (TB) is an infectious disease that has been a severe health problem for many years (1,2). In the past 10 years, the incidence of TB has continued to increase worldwide (1). According to the latest data of the World Health Organization, about 1.7 billion people are infected with mycobacterium TB (3,4). TB is an infection caused by mycobacterium TB and it plays an essential role in the cellular immune response. Thus, it is essential to understand the human immune response to TB, and its potential significance in immunological diagnosis and treatment (5).

The interaction between cytokines and their effects on the activities of the human immune system is an essential topic in many types of scientific research. In the cytokine interaction network, interleukin-18 (IL-18) is an important node. IL-18 belongs to the interleukin-1 family and is expressed by a series of immune cell types. IL-18 is involved in many reactions in the human body, from the maintenance of homeostasis to the development of autoimmune diseases in preventing TB (6,7). Recent studies have shown polymorphism in the regulatory sequence of the IL-18 gene, which is located in chromosome 11q22.2-22.3 and consists of 5 intron and 5 exons.

Interferon-gamma (IFN-γ) is a cytokine that is secreted by activated T cells and natural killer cells. It is a pleiotropic cytokine that is produced by a variety of hematopoietic and non-hematopoietic cells. It has a variety of immunomodulatory effects on a variety of cells (8,9). It is also a central cytokine that activates macrophages and mediates a non-specific, cell-mediated host defense. Ni reported that IFN-γ is increased in the lung and blood flow of patients with pulmonary TB (10). Furthermore, a recent Egypt research found that a significant risk to TB infection with SNP at the IL-18-137G/C with no LD with SNP at the IL-18-607 site. The homozygous AA genotype in INF-γ + 874 showed a significant higher risk to TB than the homozygous TT or heterozygous AT genotypes (11). There were researches reported that IL-18 promoter -137G/C polymorphism correlated with chronic hepatitis B, active Psoriasis and affected the expression of interleukins (4-6).

This study sought to evaluate the roles of IL-18 and IFN-γ in TB. In addition, we performed a meta-analysis to examine differences between TB patients and healthy control (HC) to analyzed association between IL-18, IFN-γ and TB. This research is an update comprehensive analysis for correlation between IL-18, IFN-γ and TB. This research has clinical meaning for diagnosis in TB. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2582).

Methods

Literature search strategy

We searched databases, including PubMed, EMBASE, Cochrane, and the China National Knowledge Database, for articles published from January 2000 to March 2020 on IL-18 and IFN-γ in patients with TB using the following search terms: (tuberculosis infection or tuberculosis) and (interleukin-18 or IL-18) and (interferon-γ or interferon-gamma). The language of publication did not limit the literature retrieval. To maximize the specificity and sensitivity of the retrieval, the author also referred to the reference lists of the articles to identify other relevant studies that were not retrieved in the database searches.

Study selection

Inclusion criteria and exclusion criteria

To be eligible for inclusion in the meta-analysis, the studies had to meet the following inclusion criteria: (I) adopt an observational design; (II) assess the levels of IL-18 and IFN-γ in HC and TB groups; (III) have been completed at different times; and (IV) have full-text that was available for download. Studies were excluded if they met any of the following exclusion criteria: (I) contained duplicate data; (II) the included sample was not a TB sample; and/or (III) the required study design was not adopted.

Data extraction and quality assessment

Two authors independently reviewed the manuscripts. To collect limited data from the included articles, the following data were extracted from each included study: the authors' names, patients' ages, the authors' country, the publication year, the sample size, and the research period.

Statistical analysis

In this study, we used Review Manager 5.2 software (Cochrane Collaboration, 2011) to assess the heterogeneity of indicators between the TB and HC groups. We used the Cochrane bias tool to assess the quality of the included studies. The following criteria were considered in the evaluation: (I) random sequence generation; (II) the blindness of participants and personnel; (III) allocation concealment; (IV) the blindness of the result evaluations; (V) selective reporting; (VI) incomplete data results; and (VII) other biases. The mean difference (MD) was calculated, and the indexes between TB and HC were compared. In this study, heterogeneity was evaluated by the index of inconsistency (I^2), and the statistical value of I^2 reflected the level of heterogeneity. If I^2>50%, the result was considered heterogeneous, and a random-effects model was use; otherwise, a fixed-effects model was used. In this study, a P value <0.05 was considered statistically significant. In addition, we used Review Manager 5.2 to create a funnel chart to analyze the bias of the study.

Results

Search process

A total of 112 articles were retrieved in our initial electronic searches. After careful reading, 38 papers met the preliminary criteria. After a further screening, 28 articles were excluded due to improper research types, insufficient

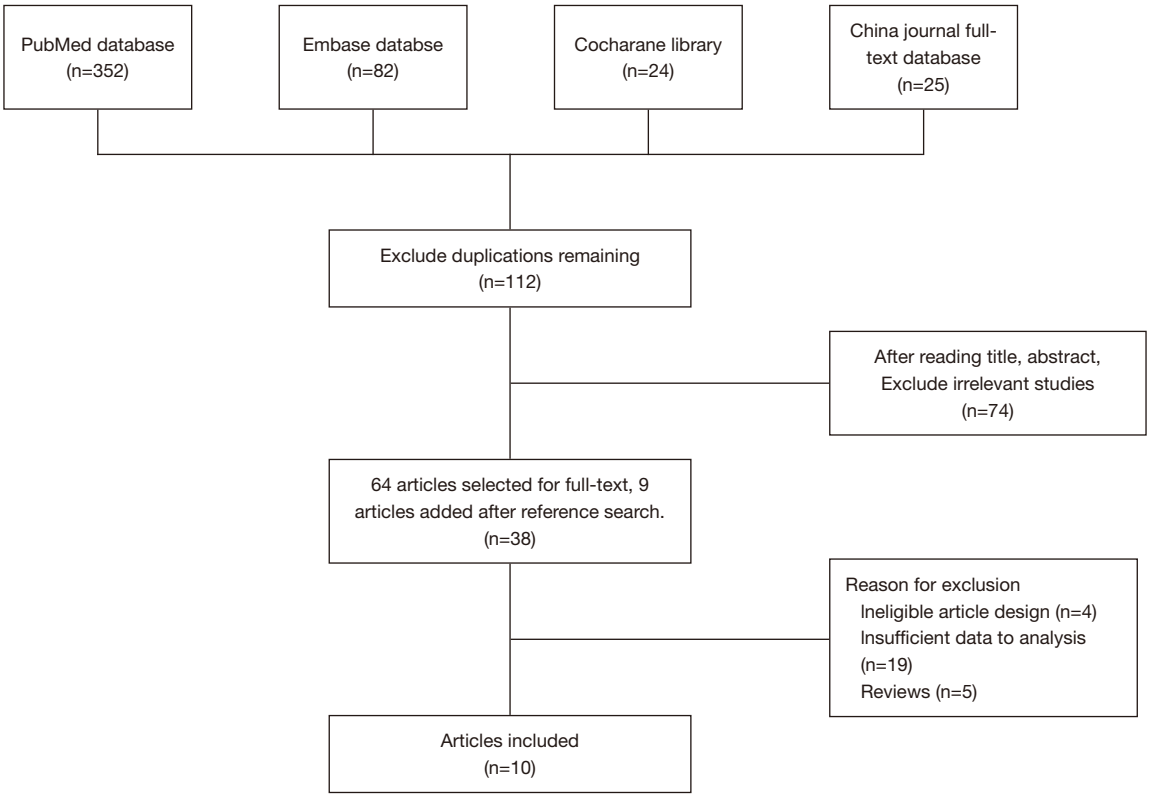

Figure 1 Flow diagram of study selection.

data, or improper article type. Ultimately, 10 articles were included in the analysis. *Figure 1* is a flowchart that shows the literature search process and reasons for exclusion.

Characteristics of included studies

Table 1 sets out the baseline characteristics of the included studies. All 10 included studies (12-21) were published from 2000 to 2020. The TB group comprised 431 patients, and the HC group comprised 414 healthy individuals. The sample sizes of the included studies ranged from 28 to 186.

Results of the quality assessment

We used the Cochrane bias risk assessment tool to assess the risk of patient selection problems in the 10 studies. According to the deviation summary chart, only 2 studies had problems of detection deviation and wear deviation, respectively. In general, the 10 included studies showed little risk of bias, and the quality of the literature was good (*Figures 2,3*).

Results of the meta-analysis

Meta-analysis of IL-18 levels in the TB and HC groups

As *Figure 4* shows, 8 of the included studies examined IL-18 levels in the TB and HC groups. The results showed that the IL-18 levels of patients in the TB group were higher than those of patients in the HC group (MD =248.11, 95% CI: 197.25, 298.98, overall P<0.0001; I^2=63%).

Meta-analysis of IFN-γ level in TB and HC

Seven included studies examined differences in IFN-γ levels between the TB and HC groups (see the forest plot in *Figure 5*). The results of the meta-analysis showed that IFN-γ levels were higher in patients in the TB group than those in the HC group (MD =38.74, 95% CI: 14.84, 62.64, P=0.001; I^2=100%).

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Language	Region	Age (years), mean ± SD	Groups	n	Years of onset
Inomata (12)	2005	English	Japan	39±14.1	Case	37	2000 to 2003
					Control	10	
Kathamuthu (13)	2017	English	India	35±20	Case	14	September 2013 to May 2015
					Control	14	
Lee (14)	2002	English	Korea	40±20.4	Case	18	September 1998 to March 2000
					Control	19	
El-Masry (15)	2007	English	Egypt	41.7±14.2	Case	50	January 2003 to May 2005
					Control	25	
Oliver (16)	2010	English	Australia	36±15.5	Case	15	January 2005 to December 2008
					Control	30	
Paidipally (17)	2018	English	India	40.2±17.2	Case	10	January 2013 to March 2015
					Control	30	
Wawrocki (18)	2019	English	Poland	44±20	Case	95	September 2012 to June 2017
					Control	91	
Wawrocki (19)	2019	English	Poland	43.2±18.3	Case	68	January 2011 to May 2016
					Control	124	
Yamada (20)	2000	English	Japan	44.2±15.2	Case	43	June 1998 to March 1999
					Control	25	
Yu (21)	2011	English	Taiwan	54.5±14.5	Case	81	June 2006 to May 2007
					Control	46	

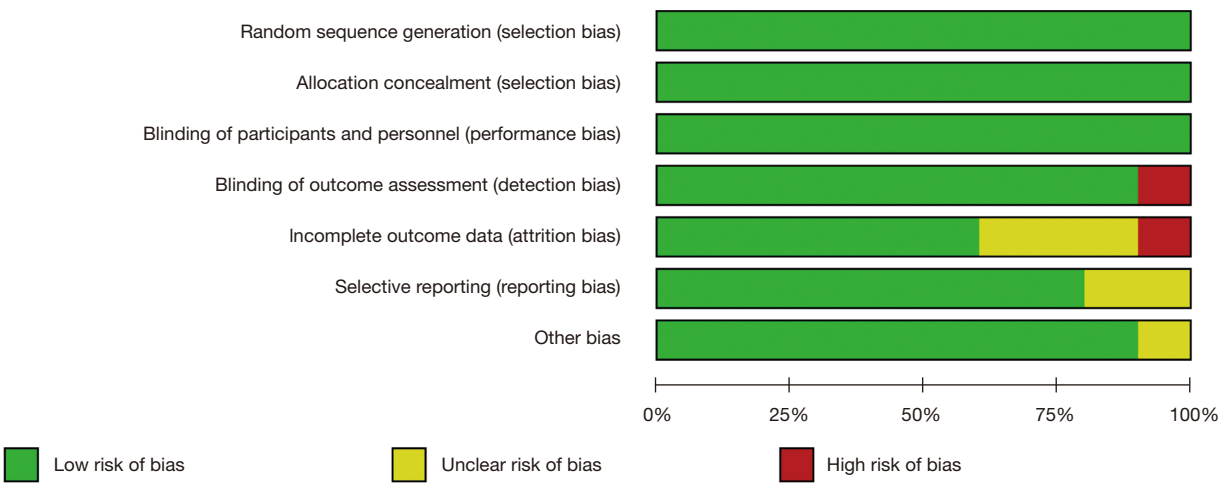

Figure 2 Assessment of the quality of the included studies: low risk of bias (green hexagons), unclear risk of bias (yellow hexagons), and high risk of bias (red hexagons).

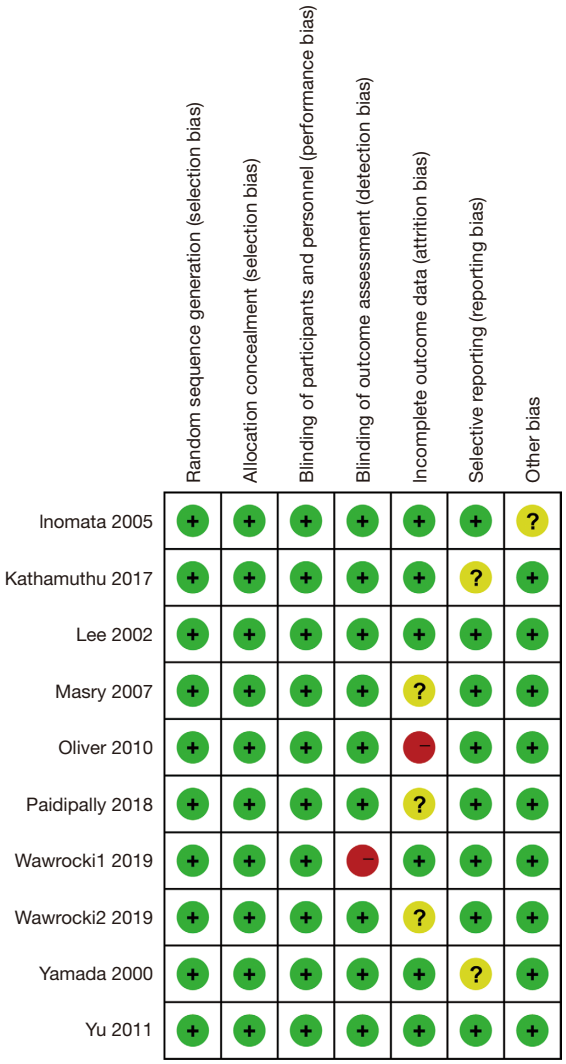

Figure 3 Quality assessment of the included studies.

Results of the sensitivity analysis and publication bias analysis

According to the results of the heterogeneity analysis, the heterogeneity of IL-18 was higher in patients in the TB group than in patients in the HC group (I^2=63%). As *Figure 6* shows, the heterogeneity of IL-18 may be attributed to one study in the included researches; thus, we eliminated each included article in turn to analyze the source of the heterogeneity. When the EI-Masry (2007) article was excluded, I^2 became 55%, which represented the most significant change among all the culling results; however, the change in I^2 was not very large. This change shows that the results of this article are reliable.

We produced a funnel chart showing comprehensive cognitive scoring. Eight studies are shown in the funnel chart. The symmetry of the funnel chart is good; thus, there was no publication bias in this meta-analysis (see *Figure* 7).

Discussion

The results showed that patients in the TB group had higher IL-18 levels than those in the HC group, which indicated that TB patients had high levels of IL-18. Similar to our findings, Kawakami and Taheri found that Single Nucleotide Polymorphism (SNP)-type mutations at –607c/an (rs1946518) and –137 γ/C (rs187238) in the IL-18 promoter region were particularly interesting, and speculated that the –607 position change from cytosine to adenine may harm the activation of camp and adenylate cyclase, while the evolution of –137 nucleosides (involving guanine to cytosine) may affect the activity of nuclear factor hum an histone transcription factor (H4TF-1), and the potential decrease of gene expression (22,23). Further, other studies have shown that compared to wild-type individuals, IL-18 knockout mice have lower IFN-γ secretion and are more likely to be infected with mycobacterium TB (24). Thus, the genetic variation in the IL-18 gene might affect the expression of cytokines, which in turn might affect the Type 1 T helper (Th1) response mediated by IFN-γ, which might induce human TB.

The results of the IFN-γ analysis showed that patients in the TB group had higher IFN-γ levels than those in the HC group, which suggests that IFN-γ could also be used to diagnose TB. Lee reported that the activation of cytokines (mainly IFN-γ) controls the granuloma structure of asymptomatic TB and the replication of mycobacterium TB (25). There were some limitations that TB was only diagnosed by the microscopic observation of sputum samples. An IFN-γ release test could be used to diagnose TB (26).

TB affect about 10 million people per year, and kills about 2 million people per year (1). Mycobacterium tuberculosis is transmitted through granuloma particles released by tuberculosis patients in the air. Tuberculous granuloma forms in the infected lung, surrounded by the border area of Mycobacterium infected lymphocytes with the aggregation of macrophages (27). These infections are usually latent; however, in at least 10% of cases, these infections can be transformed into the disease activity form (28). This problem is becoming increasingly severe because more and more people with immunodeficiencies

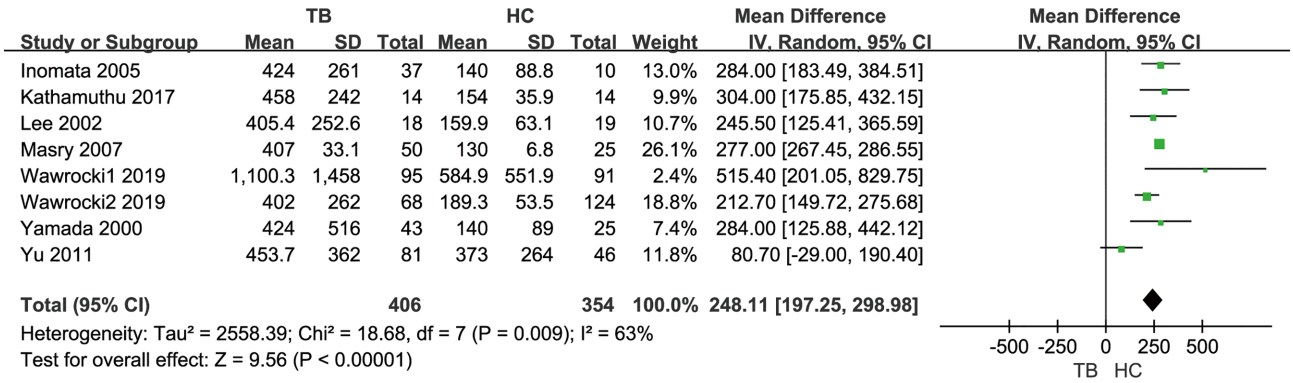

Figure 4 Forest plots of IL-18 levels in the TB and HC groups.

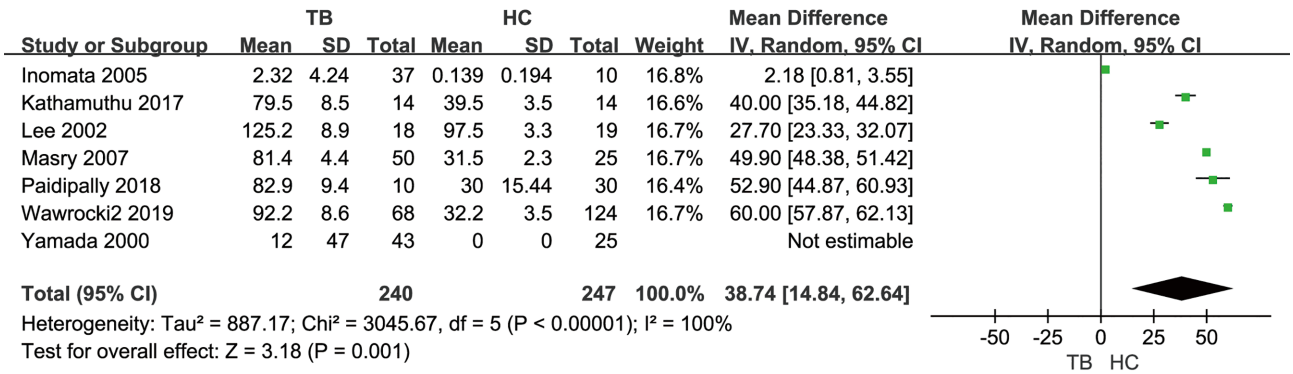

Figure 5 Forest plot of IFN-γ level in TB and HC. TB, tuberculosis; HC, health control.

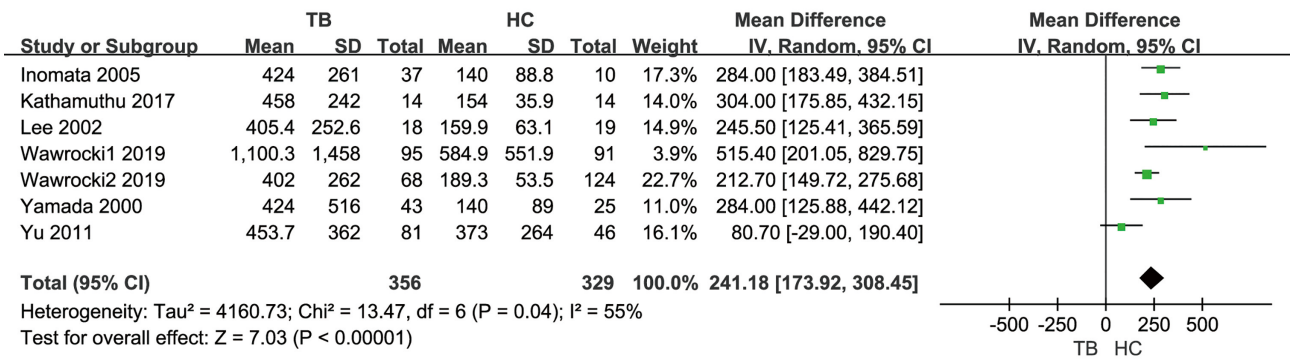

Figure 6 Sensitivity analysis forest plot of IL-18 levels in the TB and HC groups. TB, tuberculosis; HC, health control.

are taking immunosuppressants. In addition, older people are at a higher risk of reactivating potential mycobacterium TB infection due to their age (2).

For unpredictable reasons, 5–10% of latent TB infection (LTBI) subjects with reactivated bacilli develop caseous granuloma and clinical diseases, and spread toxic bacteria in their environments (1). The risk of progression from LTBI to active TB might be increased by certain factors, such

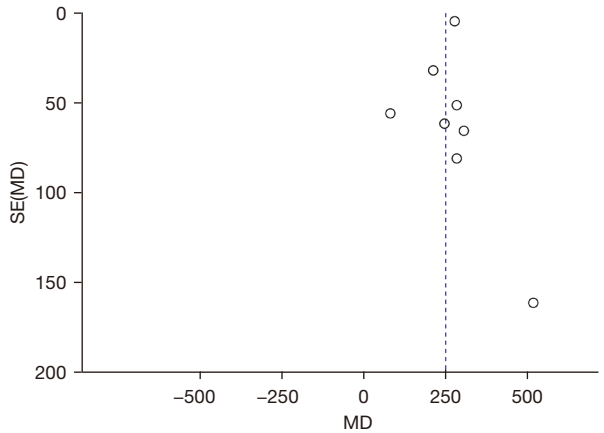

Figure 7 Funnel plot of publication bias.

as human immunodeficiency virus infection, chronic renal failure, diabetes, organ transplantation, or treatment with tumor necrosis factor-alpha receptor blockers (29). The key to effective TB control is identifying and treating those infected with mycobacterium TB and preventing those at increased risk of TB progression.

This study had some limitations. First, more cell factors evaluating other differences between TB and HC should have been included, and will be examined in the future. Second, comparisons (e.g., of age and area) were not made between the different subgroups, but they will be examined in future research.

In conclusion, this study showed that IL-18 and IFN-γ have a relationship with TB and could be used to help diagnose TB.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2582

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2582). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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