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Meta-Analysis

The Effects of Diabetes Mellitus Comorbidities on the Risk of Treatment Failure in Tuberculosis Patients: A Meta-Analysis

Sri Iswahyuni, Ani Nur Fauziah, Indarto, Joko Tri Atmojo, Aris Widiyanto

School of Health Sciences Mamba'ul Ulum Surakarta, Central Java

ABSTRACT

Background: Tuberculosis or TB is a disease caused by the Mycobacterium tuberculosis complex. There are several comorbidities that experience severity and death when infected with tuberculosis or TB, namely hypertension, diabetes mellitus, cardiovascular disease, chronic kidney disease, cerebrovascular disease, and other diseases. This study aims to estimate the magnitude of the risk of treatment failure in Tuberculosis patients with Diabetes Mellitus comorbidity, with a meta-analysis of primary studies conducted by previous authors.
Subjects and Method: This was a systematic review and meta-analysis with the following PICO, population: tuberculosis patients. Intervention: chronic comorbid diabetes mellitus. Comparison: without comorbid diabetes mellitus. Outcome: treatment failure. The articles used in this study were obtained from three databases, namely Google Scholar, PubMed, and Science Direct. Keywords to search for articles "Tuberculosis" OR "TBC" AND "Diabetes Mellitus" OR "DM" AND "Treatment failure". The included article is a full-text English cohort study design from 2007 to 2021 and reports the adjusted odds ratio (aOR) in multivariate analysis. The selection of articles is done using PRISMA flow diagrams. Articles were analyzed using the Review Manager 5.3 application.
Results: A total of 7 cohort studies involving TB patients undergoing treatment from America, Europe, Africa and Asia were selected for systematic review and meta-analysis. The data collected showed that tuberculosis patients undergoing treatment with comorbid diabetes mellitus had a 1.57 time the risk of treatment failure compared to patients without comorbid diabetes mellitus (aOR= 1.57; 95% CI= 1.08 to 2.30; p= 0.002).
Conclusion: Comorbidity Diabetes mellitus increases the risk of experiencing treatment failure in tuberculosis patients.

Keywords: diabetes mellitus, tuberculosis, mortality.

Correspondence:
Sri Iswahyuni. School of Health Sciences Mamba'ul Ulum Surakarta. Jl. Ringroad Utara, Mojosongo, Jebres, Surakarta, Central Java, Indonesia. Email: iswahyunisri@yahoo.co.id. Mobile: +62 815-6720-715.

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BACKGROUND

Tuberculosis is defined as a disease caused by the bacterium Mycobacterium tuberculosis. There are more than 8 million new cases of tuberculosis each year and around 1.3 million deaths in 2018. Tuberculosis is a public health problem worldwide (WHO, 2018). Tuberculosis is an infectious disease which is the main cause of disease. Tuberculosis is caused by Bacillus Mycobacterium Tuberculosis, which spreads when people with TB expel bacteria into the air through coughing,

for example. Tuberculosis usually affects the lungs but can also affect other sites. About a quarter of the world's population is infected with tuberculosis and thus is at risk of developing tuberculosis (WHO, 2019). According to the World Health Organization (WHO) in the Global Tuberculosis Report 2019 that globally in 2018 an estimated 10.0 million (range 9.0-11.1 million) 2 people fell ill with TB in 2018, a number that has been relatively stable in recent years. TB disease affects people of both sexes in all age groups but the highest burden is in men (age ≥15 years), who accounted for 57% of all TB cases in 2018.

In the global community, TB cases continue to increase in several countries, with several countries having the highest number of TB cases, including India which ranks first, followed by China, the Philippines, Pakistan and Indonesia. Tuberculosis cases are quite high in these countries. TB case. Tuberculosis is a droplet disease and often occurs in people who are not aware of environmental health. Indonesia is classified as a country with a high infection rate.

Effective treatments for tuberculosis are available, but today tuberculosis remains a major global health problem. In 1993, WHO declared tuberculosis as a global health crisis because it is a major global health problem that kills millions of people each year and recommended the DOTS strategy as a strategy to combat TB. Tuberculosis is considered a global public health problem, although control efforts have been made through the DOTS strategy since 1995 (WHO, 2014).

The influence of diabetes mellitus (DM) on the development and poor outcome of tuberculosis (TB) has been recognized for more than a century. While diabetes was ranked 7th among the leading causes of death in 2015, TB has been recognized as the leading cause of death from infectious diseases (WHO 2017). With the global increase in obesity and type 2 diabetes, the combination of diabetes and tuberculosis (TB-DM) has posed a public health threat and a challenge for TB control programs around the world (Al- Rifai, 2017). In the United States (US), the prevalence of diabetes has consistently increased from 0.93% in 1958 to 7.40% in 2015 with an estimated 30.3 million people of all ages (9.4% of the US population) living with diabetes (CDC, 2017). This trend of increasing diabetes morbidity in the US is particularly concerning in US states (such as Texas) where the prevalence of TB and DM is higher than the national average. Given that comorbid TB-DM patients may have a mortality rate 2-5 times higher than non-diabetic TB patients (Faurholt, 2013), more effective management strategies including the development of TB mortality prediction models are urgently needed (Qian et al., 2018).

TB treatment failure has causal factors such as non-adherence in taking the drug, besides that there are also comorbidities that hinder the performance of these drugs such as Diabetes Mellitus and other diseases. The success rate of treatment in global tuberculosis patients is 56%. The low failure of treatment in tuberculosis patients is also one of the causes of death in tuberculosis patients (Widiyanto, 2017; WHO, 2019; Diniati 2021).

This study aims to estimate the magnitude of the risk of treatment failure in tuberculosis patients with comorbid diabetes mellitus, with a meta-analysis of primary studies conducted by previous authors.

SUBJECTS AND METHOD

1. Study Design

This research was obtained from several databases, namely Google Scholar, Pubmed, and ScienceDirect between 2007 and 2021.

The selection of articles was carried out using the PRISMA flow diagram. The keywords to search for articles are as follows "Tuberclosis" OR "TBC" AND "Diabetes Mellitus" OR "DM" AND "Treatment Failure".

2. Steps of Meta-Analysis

Meta analysis was carried out in 5 steps as follows:

1) Formulate research questions in PICO format (Population, Intervention, Comparison, Outcome).
2) Look for primary study articles from various electronic and non-electronic databases such as PubMed, ScienceDirect, Google Scholar, Scopus.
3) Perform screening to determine inclusion and exclusion criteria and carry out a critical assessment
4) Extract primary study data and synthesize effect estimates using the RevMan 5.3 application.
5) Interpret the results and draw conclusions.

3. Inclusion Criteria

The inclusion criteria in this research article were: full-text articles using a cohort study design, the study subjects were tuberculosis patients, the study outcome was treatment failure, multivariate analysis with adjusted odds ratio (aOR) to measure the estimated effect.

4. Exclusion Criteria

The exclusion criteria in this research article were: articles published in languages other than English, statistical results reported in the form of bivariate analysis, articles before 2020.

5. Operational Definition of Variables

Article search was carried out by considering the eligibility criteria determined using the PICO model. Population: Patients with Tuberculosis. Intervention: Comorbid Diabetes Mellitus. Comparison: Without comorbid Diabetes Mellitus. Outcome: treatment failure.

Comorbid diabetes mellitus is defined as a condition which is a metabolic disease with characteristics of blood glucose levels above normal caused by insulin deficiency by the pancreas and decreased insulin effecttiveness, with the categorization of comorbid diabetes mellitus or without comorbid diabetes mellitus, with the categorization of comorbid diabetes mellitus. or without comorbid diabetes mellitus. The instruments used were health records/medical records and staff data collection records related to the diagnosis of Diabetes Mellitus. The measurement scale is categorical.

Treatment failure of tuberculosis patients is defined as the status of treatment failure of patients diagnosed with tuberculosis, with the categorization of treatment as successful or failed. The instrument used was a medical certificate document with a diagnosis of Tuberculosis. The measurement scale is categorical.

6. Study Instruments

The research is guided by the PRISMA flow diagram and quality assessment using the Critical Appraisal Skills Program (CASP, 2018).

7. Data Analysis

The collected articles are then processed using the Review Manager (RevMan 5.3). Data processing is done by calculating the aOR. Forest plots and funnel plots are used to determine the size of the relationship and the heterogeneity of the data.

RESULTS

The process of searching for articles is carried out through several journal databases which include Google Scholar, PubMed, and ScienceDirect. The review process for related articles can be seen in the PRISMA flow diagram in figure 1. Research related to the risk of treatment failure in tuberculosis patients with comorbid diabetes mellitus consisted of 7 articles from the initial

search process yielding 1.500 articles, after the deletion process of published articles obtained 1.000 articles with 47 in -among them met the requirements for further full text review. As many as 7 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis.

It can be seen in Figure 2 that research articles come from the Asian continent (Taiwan, China, Korea, Iran and Malaysia). Table 1, researchers conducted an assessment of the quality of the study. Table 2 shows that 7 articles from cohort studies as evidence of the linkage of the effect of comorbid diabetes mellitus on the rate of treatment failure in TB patients.

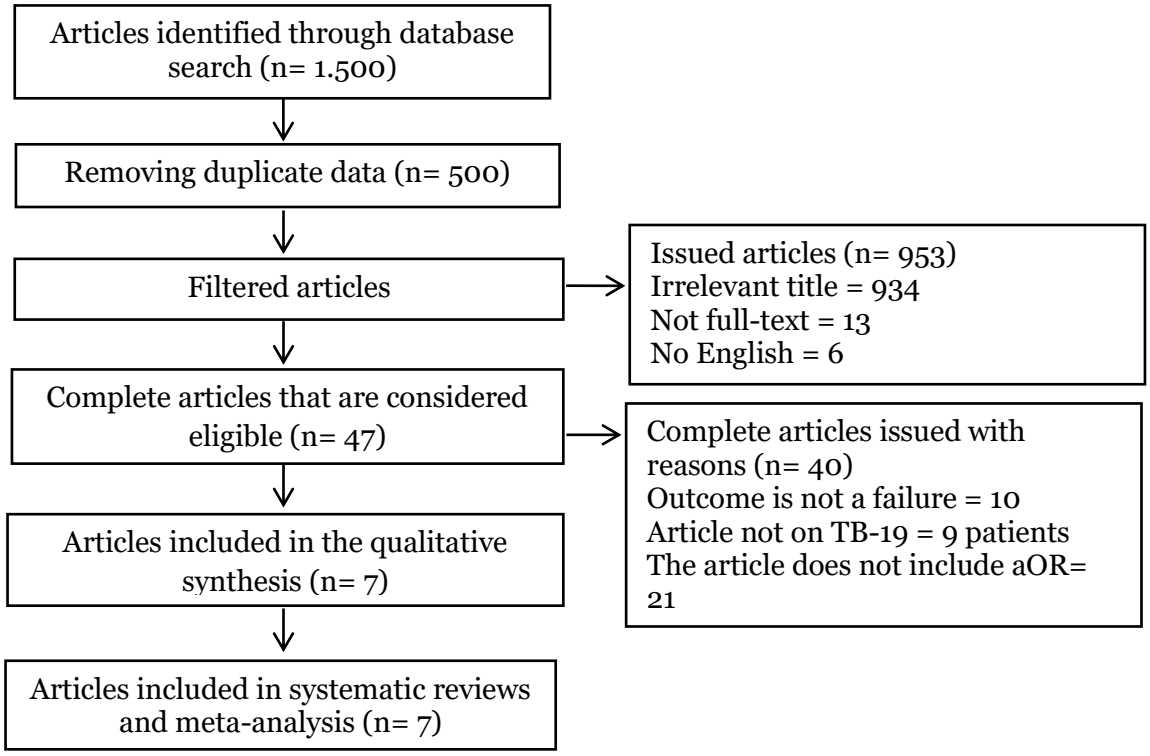

Figure 1. Results of Prisma Flow Diagrams

Figure 2. Resarch Distribution Map

Table 1. Critical Appraisal Checklist using CASP

Primary Study	Criteria												
	1	2	3	4	5	6	7	8	9	10	11	12	Total
Shabrawy et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	24
Atif et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	24
Yan et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	24
Corona et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	2	24
Evangelista et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Tok et al. (2020)	2	2	2	2	2	2	2	2	2	1	2	2	23
Pradipta et al. (2019)	2	2	0	2	2	2	2	2	2	2	2	2	22

Description of the question criteria:

1 = Does the research address a clearly focused problem?
2 = Was the group recruited in an acceptable way?
3 = Is chronic kidney disease exposure measured accurately to minimize bias?
4 = Were the results (death status) measured accurately to minimize bias?
5 = Did the author identify all the important confounding factors? Have the authors accounted for confounding factors in the design and/or analysis?
6 = Was subject follow-up sufficiently complete? Is the follow up of the subject long enough?
7 = Are the results of this study reported in the aOR?
8 = How precise are the results?
9 = Can the results be trusted?
10 = Can the results be applied to local residents?
11 = Are the results of this study consistent with other available evidence?
12 = What are the implications of this research for practice?

Answer score description:

0 = No
1 = Can't tell
2 = Yes

Tabel 2. Summary of primary cohort study with PICO (N=130,584)

Author (Year)	Country	Study Design	Sample		P	I	C	O
			TBC	DM				
Shabrawy et al. (2017)	Taiwan	Cohort	80	400	TB patients with positive culture undergoing treatment	Comorbidity of DM	No comorbid DM	Treatment Failure
Atif et al. (2018)	China	Cohort	147	690	TB patients undergoing treatment	Comorbidity of DM	No comorbid DM	Treatment Failure
Yan et al. (2017)	Korea	Cohort	130	785	TB patients undergoing treatment over 65 years	Comorbidity of DM	No comorbid DM	Treatment Failure
Corona et al. (2013)	Korea	Cohort	180	374	TB patients undergoing treatment between 20 - 50 years and over	Comorbidity of DM	No comorbid DM	Treatment Failure
Evangelista et al. (2020)	Iran	Cohort	2800	4000	TB patients undergoing treatment	Comorbidity of DM	No comorbid DM	Treatment Failure
Tok et al. (2020)	Malaysia	Cohort	17,551	97,505	TB patients undergoing treatment	Comorbidity of DM	No comorbid DM	Treatment Failure
Pradipta et al. (2019)	Malaysia	Cohort	268	5674	TB patients undergoing treatment	DM comorbidity	No comorbid DM	Treatment Failure

After assessing the quality of the study, a total of 7 articles were obtained with a cohort study design that will be used as a source of meta-analysis of the effects of Diabetes Mellitus comorbidities on the risk of treatment failure in Tuberculosis patients. The source of the article comes from 1 continent, namely Asia. The articles were then extracted and summarized according to the PICO study.

Tabel 3. Adjusted Odds Ratio the effects of diabetes mellitus comorbidities on the risk of treatment failure in tuberculosis patients

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Shabrawy et al. (2017))	1.52	0.42	5.55
Atif et al. (2018)	1.28	0.66	2.47
Yan et al. (2017)	2.12	1.57	3.48
Corona et al. (2013)	2.93	1.18	7.23
Evangelista et al. (2020)	2.11	0.96	4.56
Tok et al. (2020)	1.08	1.04	1.13
Pradipta et al. (2019)	1.10	0.46	2.65

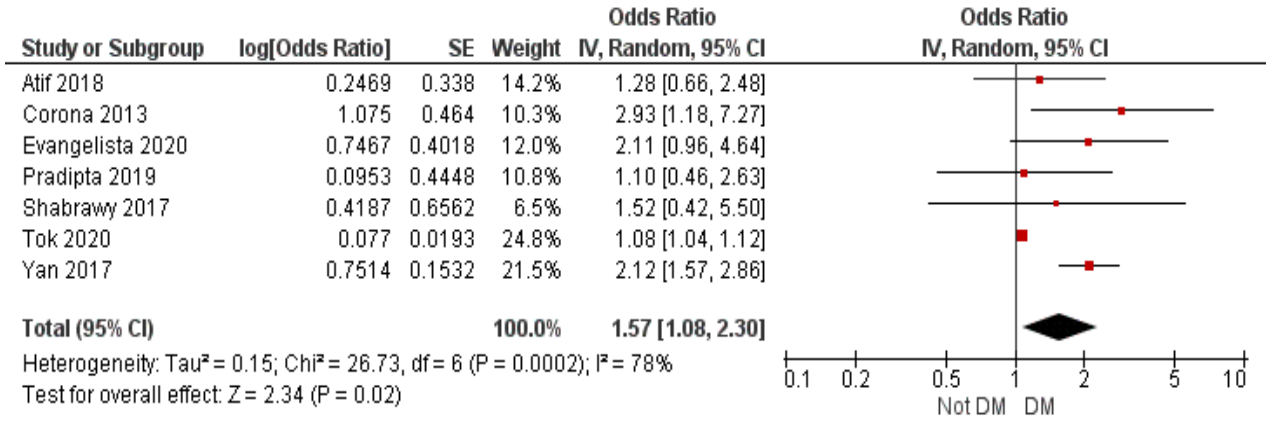

Figure 3. Forest plot of the risk of treatment failure in tuberculosis patients with comorbid diabetes mellitus

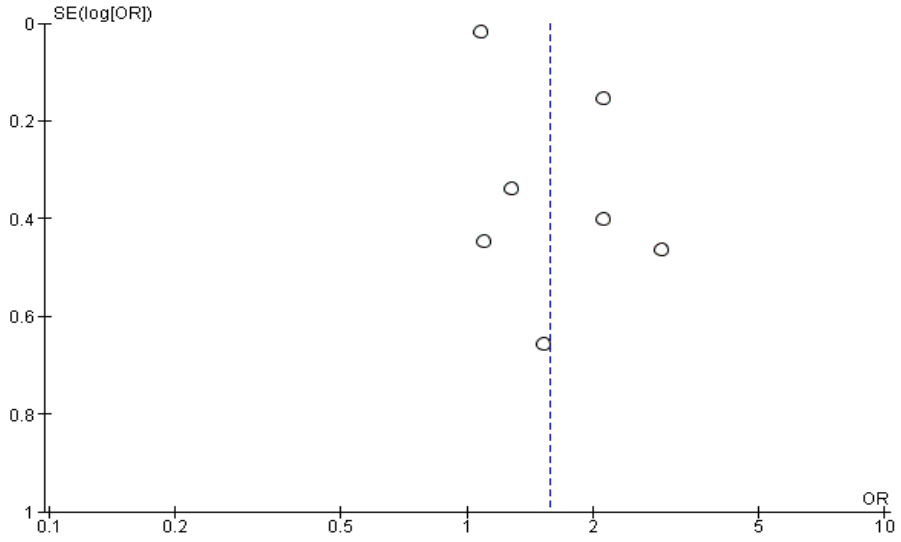

Figure 4. Funnel plot of the risk of treatment failure in tuberculosis patients with comorbid diabetes mellitus

The results of the Forest plot in figure 3 show that there is an effect of comorbid diabetes mellitus on the risk of treatment failure in tuberculosis patients. Tuberculosis patients with comorbid diabetes mellitus have a risk of having a treatment failure rate of 1.57 times compared to those without comorbid diabetes mellitus and the effect is statistically significant (aOR = 1.57 ; 95% CI; 1.08 to 2.30; p= 0.002).

Funnel plot figure 4. shows the distribution of effect estimates of the various primary studies included in the meta-analysis. In this study the funnel plots show a symmetrical distribution of effects, so no publication bias was shown in the individual primary studies.

DISCUSSION

This systematic study and meta-analysis of research raised the risk of treatment failure in tuberculosis patients with comorbid diabetes mellitus. This study discusses the comorbidity of diabetes mellitus which is considered important because it is one of the risk factors that can exacerbate to the point of causing death in tuberculosis patients undergoing treatment.

Shabrawy et al. (2009) revealed that the effect of death on TB patients was significantly more common in the PTB-DM group than the PTB group (OR = 1.52; 95% CI = 0.42 to 5.55). Other findings from a retrospective cohort study of China Province which included 1,313 tuberculosis patients and 157 (11.9%) individuals with comorbid diabetes mellitus, also revealed an increased risk of mortality in TB patients undergoing treatment with comorbid diabetes mellitus (aOR= 1.53; 95% CI = 1.01 to 2.62) (Yan et al., 2017).

A study conducted in Korea also stated that of 2,481 patients who received TB treatment at eight hospitals from January 2009 to December 2010 there were treatment failures including death and cases occurred in 148 patients (6.0%). In multivariate analysis, age, sex, diabetes mellitus, lifestyle (smoking and alcohol consumption), BMI, hypertension and education level were significant risk factors for death during TB treatment. Therefore, these factors are the basic prognostic factors in the death of TB patients undergoing treatment (Kwon et al., 2014).

Tuberculosis patients treated concurrently with diabetes show pathological changes, including thickening of the alveolar epithelial walls and the basement membrane of the pulmonary capillaries. This process is a secondary consequence of microangiopathy complications, which are similar to those seen in retinopathy and nephropathy. Autonomic neuropathic disorders may include central hypoventilation and sleep apnea. In addition, there may also be a decrease in lung recoil elasticity, a decrease in carbon monoxide diffusion, and an increase in endogenous carbon dioxide production (Rohman, 2018).

Apart from pathological TB with diabetes mellitus, TB treatment in patients suffering from DM, while undergoing TB treatment must be diligent in controlling their blood sugar levels. This is because the use of rifampicin as an anti-tuberculosis drug (OAT) will reduce the effectiveness of oral anti-diabetic drugs (sulfonyl urea) so that the dose of oral anti-diabetic drugs needs to be increased. Meanwhile, isoniazid is an inhibitor of the P450 enzyme, so it can reduce the effects of rifampin.

The diagnosis in tuberculosis patients accompanied by diabetes mellitus is the discovery of the Mycobacterium tuberculosis complex identified from clinical specimens (tissue, body fluids, throat swabs, etc.) and culture. In countries with limited laboratory capacity in identifying M. tuberculosis, pulmonary TB cases can be enforced if one or

more smear-positive sputum is found. Another definition also states that a patient who, after carrying out a supporting examination for TB, is diagnosed with TB by a doctor or health worker and is treated with complete guidelines and duration of treatment (Indonesian Lung Doctors Association 2009)

Immune system dysfunction causes activation of latent tuberculosis as a risk factor for DM. It is said that DM can manifest itself in more severe clinical forms (Restrepo 2007, 2008). Both innate and adaptive cellular responses are impaired in DM patients, although the cellular response is the most important response in limiting TB infection (Restrepo, 2008). In general, there was no difference in the number of lymphocytes, macrophages, and monocytes from previous studies. However, research by Aweis (2010) showed a decrease in the number of lymphocytes in TB patients with DM. DM The levels of TNF and IFN cytokines are increased in patients with tuberculosis and DM. Both cytokines are important for activating macrophages and limiting infection. This indicates that the cellular immune response is reduced and requires greater stimulation to optimize the immune response (Resrepo, 2008).

Several studies have shown that TB patients with DM have higher sputum samples, longer smear conversion, and are more likely to have resistance to anti-TB drugs. This shows that TB sufferers with DM are very likely to be in a more severe condition and have a higher risk of experiencing TB (Restrepo, 2007). In a study in Saudi Arabia cited by Alisjahbana (2007), the positive sputum sample rate was higher in DM patients at initial diagnosis than non-DM TB patients. The same was observed in a study in Texas and America with an OR of 1.8. However, an Indonesian study cited in Alisjahbana's research came to a different conclusion. At the initial diagnosis, 29.8% of DM patients gave positive sputum samples, while 38.9% of DM patients did not. One of the important conclusions from Alisjahbana's study (2007) was that after 6 months of TB treatment, positive culture results were 7.65 times higher in DM patients than patients without DM. This study also shows an increased risk of +++ OR 1.71. in TB patients with DM Meta-analysis by Baker et al. showed mixed results in sputum culture results after 2-3 months of TB treatment in TB and DM patients. However, this study showed an increased risk of sputum culture conversion time in TB patients with DM (Baker, 2011).

DM sufferers are more difficult to treat. Diabetics who receive TB treatment are more likely to fail and die during treatment than patients without DM. The link between TB and DM requires intervention in both diseases. To improve the detection and prevention of diabetes or TB-related complications, diabetics should be screened for TB and TB patients should be screened for diabetes (IDF, 2012). TB patients with concomitant DM have a higher risk of treatment failure during treatment and an increased risk of recurrence after treatment, which can also increase the risk of infection. (Dooley et al., 2009). Baker et al., 2011 concluded that diabetes simultaneously increases the risk of recurrence, treatment failure and death in TB patients. The limitations of this research are language bias because it uses only English articles, publication bias seen in the funnel plot results, and search bias because it only uses three databases.

AUTHOR CONTRIBUTION

All authors contributed to this study

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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