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Meta-Analysis

Effect of Diabetes Mellitus Comorbidity on Mortality Risk in Tuberculosis Patients who Received Tuberculosis Treatment: A Meta-Analysis

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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 death in Tuberculosis patients undergoing treatment with comorbid Diabetes Mellitus, 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: comorbidities of chronic diabetes mellitus. Comparison: without comorbid diabetes mellitus. Outcome: death. The articles used in this study were obtained from three databases, namely Google Scholar, Pubmed, and Science Direct. Keywords to search for articles "Tuberclosis" OR TBC AND "Diabetes Mellitus" OR DM AND Mortality OR Death The included full-text articles are in English with a cohort study design from 2007 to 2021 and report the adjusted Odds Ratio (aOR) in a multivariate analysis. Article selection is done by using PRISMA flow diagram. Articles were analyzed using the Review Manager 5.3 application.
Results: A total of 12 cohort studies involving tuberculosis patients undergoing treatment from America, Europe, Africa and Asia were selected for a systematic review and meta-analysis. The data collected showed tuberculosis patients undergoing treatment with comorbid Diabetes Mellitus had a 1.68 times risk of death compared to COVID-19 patients without comorbid chronic kidney disease (aOR = 1.68; 95% CI = 1.42 to 1.99; p<0.001).
Conclusion: Diabetes mellitus comorbidity increases the risk of death in tuberculosis patients undergoing treatment.

Keywords: Diabetes Melitus, Tuberculosis, mortality

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BACKGROUND

Tuberculosis or TB is a pentakit caused by the Myco-bacterium tuberculosis complex. With an estimated 10 million new TB cases each year and approximately 1.3 million deaths in 2018, Tuberculosis is a public health problem worldwide (WHO, 2018). Tuberculosis (TB) is an infectious disease with the main cause of poor health. TB disease is caused by Bacillus Mycobacterium Tuberculosis, which is spread when a person with TB expels bacteria into the air

for example by coughing. Tuberculosis usually affects the lungs but can also affect other places. About a quarter of the world's population has been infected by *M. tuberculosis* and is thus at risk of developing TB disease (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 to 11.1 million) 2 people fell ill with TB in 2018, the number 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.

The effect 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 challenge to TB control programs worldwide (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 worrying especially 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 development of TB mortality prediction models are urgently needed (Qian et al., 2018)

Based on this background, a comprehensive study is needed from various primary studies on the risk of death of Tuberculosis patients undergoing treatment with comorbid diabetes mellitus. This study aims to estimate the magnitude of the risk of death in tuberculosis patients undergoing treatment with comorbid diabetes mellitus, with a meta-analysis of primary studies conducted by previous authors.

SUBJECTS AND METHOD

1. Study Design

This research is a systematic review and meta analysis. The articles used in this study were obtained from several databases, namely Google Scholar, Pubmed, and Science Direct between 2007 and 2021. The selection of articles was carried out using PRISMA flow diagrams. Keywords to search for articles are as follows “Tuberculosis” OR TBC AND “Diabetes Mellitus” OR DM AND Mortality OR Death.

2. Inclusion Criteria

The inclusion criteria in this research article are: full-text articles using a cohort study design, the research subjects are Tuberculosis patients, the study outcome is death, multivariate analysis with adjusted Odds Ratio (aOR) to measure the estimated effect.

3. 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.

4. Operational Definition of Variables

The search for articles was carried out by considering the eligibility criteria determined using the PICO model. Population: Patients with Tuberculosis. Intervention: Comorbid Diabetes Mellitus. Comparison: No comorbid Diabetes Mellitus. Outcome: Death.

Comorbid diabetes mellitus is defined as a condition that is a metabolic disease with characteristics of blood glucose levels above normal caused by insulin deficiency by the pancreas and a decrease in insulin effectiveness, with the category of comorbid diabetes mellitus or without comorbid diabetes mellitus, with the category of comorbid diabetes mellitus or without comorbid diabetes mellitus. The instruments used are health records/medical records and officer data collection records related to the diagnosis of Diabetes Mellitus. The measurement scale is categorical.

Death in Tuberculosis patients was defined as the death status of patients diagnosed with Tuberculosis, categorized as dead or alive. The instrument used is a death certificate with a diagnosis of Tuberculosis. The measurement scale is categorical.

5. Study Instruments

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

6. Data Analysis

The data in the study were analyzed using the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to determine the size of the relationship and heterogeneity of the data. The fixed effect model is used for homogeneous data, while the random effect model is used for heterogeneous data across studies.

RESULTS

The article search process is carried out through several journal databases including Google Scholar, PubMed, and Science Direct. The review process for related articles can be seen in the PRISMA flow diagram in Figure 1. Research related to the risk of death of Tuberculosis patients undergoing treatment with comorbid diabetes mellitus consists of 12 articles from the initial search process giving results of 1,553 articles, after the deletion process of published articles obtained 1,041 articles with 47 of them met the requirements for further full text review. A total of 12 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis.

It can be seen in Figure 2 that the research articles come from four continents, namely America (Brazil), Europe (Netherland, Guetemala), Africa (Ethiopia) and Asia (Taiwan, China, Korea, Iran, and Malaysia). Table 1, the researchers conducted an assessment of the quality of the study. Table 2 shows that 12 articles from a cohort study provide evidence of the association of comorbid chronic kidney disease on the risk of death in COVID-19 patients.

The results of the Forest plot show that there is an effect of diabetes mellitus comorbidity on the risk of death in tuberculosis patients, tuberculosis patients with comorbid diabetes mellitus have a risk of dying 1.68 times compared to those without diabetes mellitus comorbidities and the effect is statistically significant (aOR = 1.68; 95% CI; 1.42 to 1.99; p<0.001).

The results of the funnel plots show that the distribution of the estimated effects of the various primary studies in this meta-analysis is not symmetrical to the right and to the left of the mean vertical line of the effect estimates. The effect estimates for the primary study were higher on the right of the mean vertical line of effect estimates than on the left, indicating publication bias. Because the distribution of effect estimates is more to the right of the vertical line in the funnel plot, which is in the direction of the diamond image in the forest plot (figure 3) which is also to the right of the null hypothesis vertical line, the publication bias

tends to overestimate the actual effect (Overestimate).

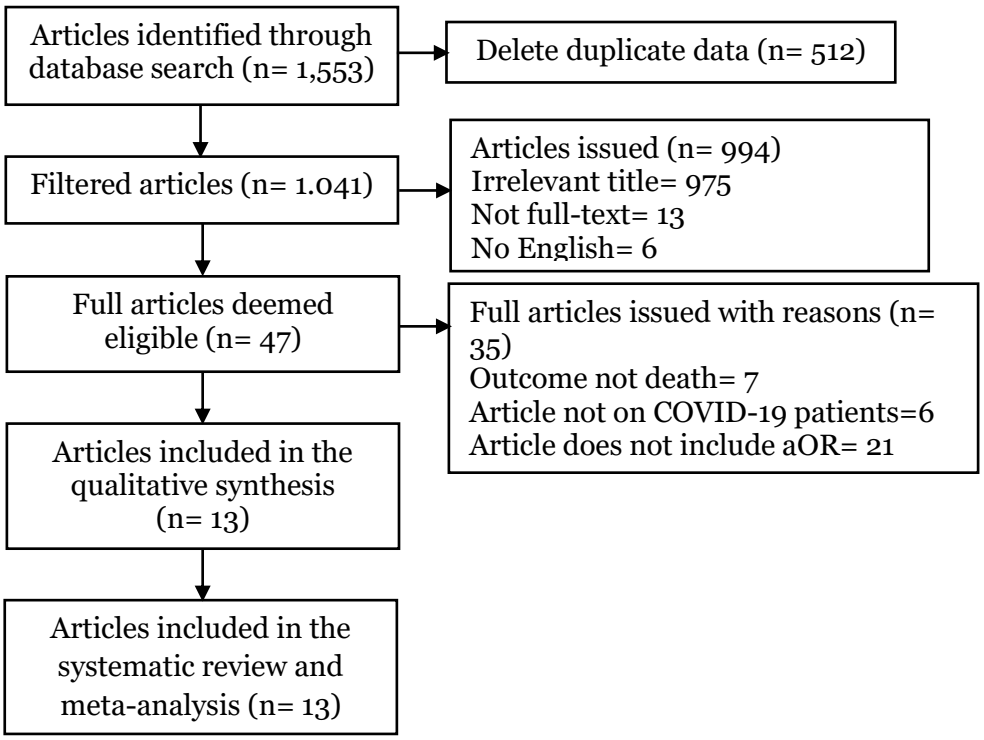

Figure 1. PRISMA Flowchart

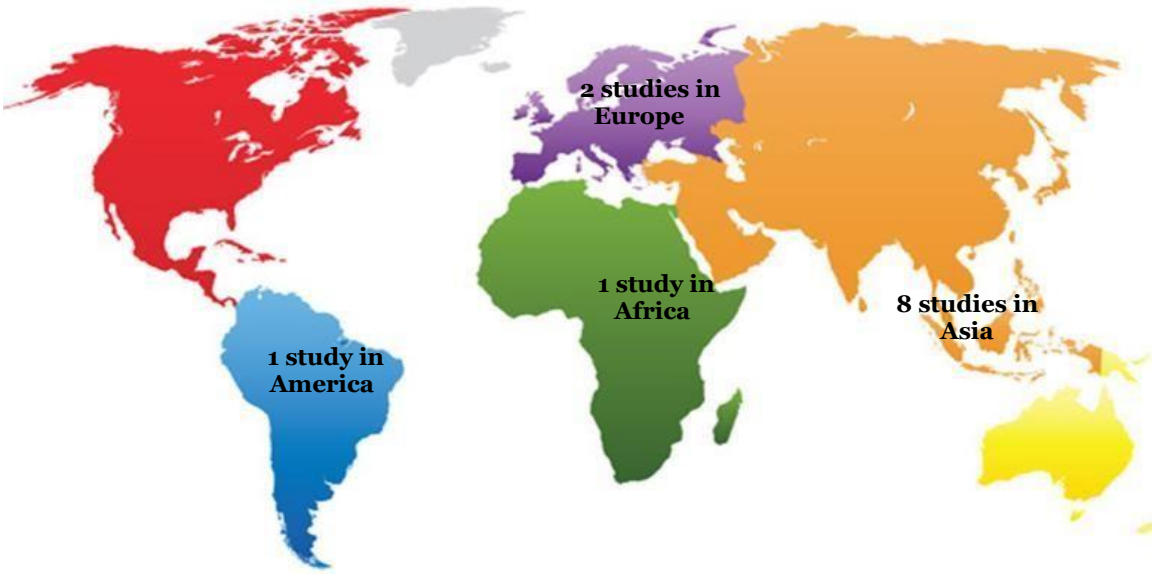

Figure 2. Map of study area

Table 1. Assessment of study quality published by the Critical Appraisal Skills Program (CASP)

No	Indicators	Publication (Author and Year)					
		Wang et al. (2009)	Yan et al. (2017)	Kwon et al. (2014)	Choi et al. (2014)	Naini et al. (2012)	Tok et al. (2020)
1	Does this research address a clearly focused problem?	2	2	2	2	2	2
2	Was the group recruited in an acceptable way?	2	2	2	2	2	2
3	Is exposure accurately measured to minimize bias?	2	2	2	2	2	2
4	Was the outcome (death status) accurately measured to minimize bias?	2	2	2	2	2	2
5	Did the author identify all the important confounding factors? Has the author taken into account any confounding factors in the design and/or analysis?	2	2	2	2	2	2
6	Was the subject follow-up complete enough? Was the follow-up of the subject long enough?	2	2	2	2	2	2
7	Are the results of this study reported in aOR?	2	2	2	2	2	2
8	How precise is the result?	2	2	2	2	2	2
9	Are the results reliable?	2	2	2	2	2	2
10	Can the results be applied to the local population?	2	2	2	2	2	2
11	Are the results of this study consistent with other available evidence?	2	2	2	2	2	2
12	What are the implications of this research for practice?	2	2	2	2	2	2
	Total	**24**	**24**	**24**	**24**	**24**	**24**

Note: 2: Yes; 1: Can't tell; 0: No

Table 1. Cont

No	Indicator	Publication (Author and Year)					
		Atif et al. (2014)	Degner et al. (2017)	Evangelista et al. (2020)	Pradipta et al. (2018)	Montes et al. (2021)	Kebede et al. (2021)
1	Does this research address a clearly focused problem?	2	2	2	2	2	2
2	Was the group recruited in an acceptable way?	2	2	2	2	2	2
3	Is exposure accurately measured to minimize bias?	2	2	2	2	2	2
4	Was the outcome (death status) accurately measured to minimize bias?	2	2	2	2	2	2
5	Did the author identify all the important confounding factors? Has the author taken into account any confounding factors in the design and/or analysis?	2	2	2	2	2	2
6	Was the subject follow-up complete enough? Was the follow-up of the subject long enough?	2	2	2	2	2	2
7	Are the results of this study reported in aOR?	2	2	2	2	2	2
8	How precise is the result?	1	2	2	2	1	1
9	Are the results reliable?	2	2	2	2	2	2
10	Can the results be applied to the local population?	2	2	2	2	2	2
11	Are the results of this study consistent with other available evidence?	2	2	2	2	2	2
12	What are the implications of this research for practice?	2	2	2	2	2	2
Total		**23**	**24**	**24**	**24**	**23**	**23**

Note: 2: Yes; 1: Can't tell; 0: No

Table 2. Description of the primary studies included in the meta-analysis primary studies

Author (Year)	Country	Study Design	Sample		Population	Intervention	Comparison	Outcome	aOR (95% CI)
			TBC	DM					
Wang et al. (2009)	Taiwan	Retrospective Cohort	217	74	Tuberculosis patients with positive cultures who are undergoing treatment	Diabetes mellitus comorbidity	No comorbid diabetes mellitus	Death	2.56 (1.10 to 6.10)
Yan et al. (2017)	China	Retrospective Cohort	1,313	157	Tuberculosis patients undergoing treatment	Diabetes mellitus comorbidity	No comorbid diabetes mellitus	Death, Requires mechanical ventilation	1.54 (1.11 to 2.671)
Kwon et al. (2014)	Korea	Retrospective Cohort	2,481	345	Tuberculosis patients undergoing treatment over 65 years	Diabetes mellitus comorbidity	No comorbid diabetes mellitus	Death	3.64 (1.37 to 2.63)
Choi et al. (2014)	Korea	Retrospective Cohort	669	-	Tuberculosis patients undergoing treatment between 20 years to 50 years and over	Diabetes mellitus comorbidity	No comorbid diabetes mellitus	Death	2.57 (1.46 to 4.52)
Naini et al. (2012)	Iran	Retrospective Cohort	715	1,299	Tuberculosis patients undergoing treatment	Diabetes mellitus comorbidity	No comorbid diabetes mellitus	Death	9.70 (2.90 to 32.00)
Tok et al. (2020)	Malaysia	Retrospective Cohort	97,503	17,551	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid diabetes mellitus	Death	1.90 (1.03 to 1.13)
Atif et al. (2014)	Malaysia	Retrospective Cohort	336	131	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid diabetes mellitus	Death	2.02 (0.97 to 4.15)
Degner et al. (2017)	Taiwan	Retrospective Cohort	2,416	669	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid chronic diabetes mellitus	Death	1.91 (1.51 to 2.40)
Evangelista et al. (2020)	Brazil	Retrospective Cohort	708,429	260	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid diabetes mellitus	Death	1.15 (1.10 to 1.20)

Tabel 2. Cont.

Author (Year)	Country	Study Design	Sample		Population	Intervention	Comparison	Outcome	aOR (95%CI)
			TBC	DM					
Pradipta et al. (2018)	Netherland	Retrospective Cohort	45,674	268	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid diabetes mellitus	Death	2.02 (1.03 to 3.97)
Montes et al. (2021)	Guetemala	Retrospective Cohort	3,945	527	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid diabetes mellitus	Death	4.13 (2.04 to 8.35)
Kebede et al. (2021)	Ethiopia	Retrospective Cohort	465	180	Tuberculosis patients undergoing treatment	Comorbidities of diabetes mellitus	No comorbid diabetes mellitus	Death	5.70 (1.50 to 23.7)

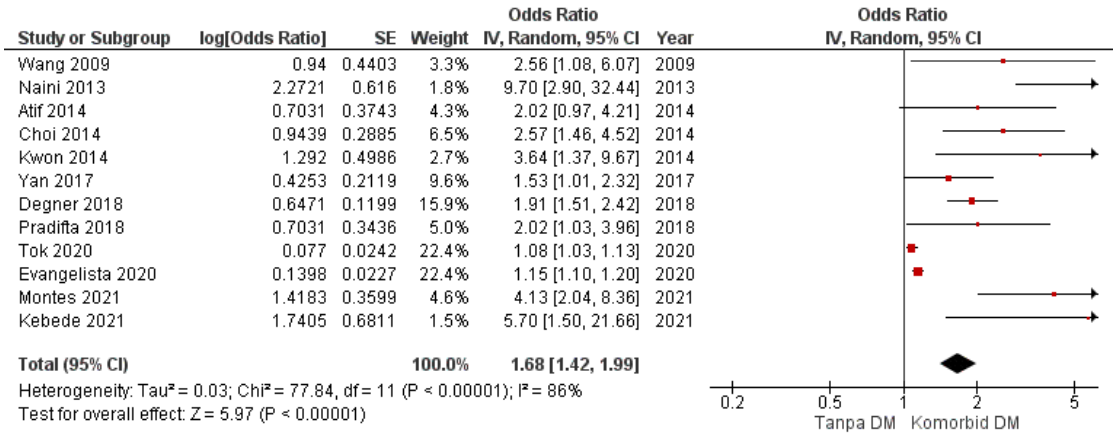

Figure 3. Forest plot of risk of death in tuberculosis patients undergoing treatment with comorbid diabetes mellitus

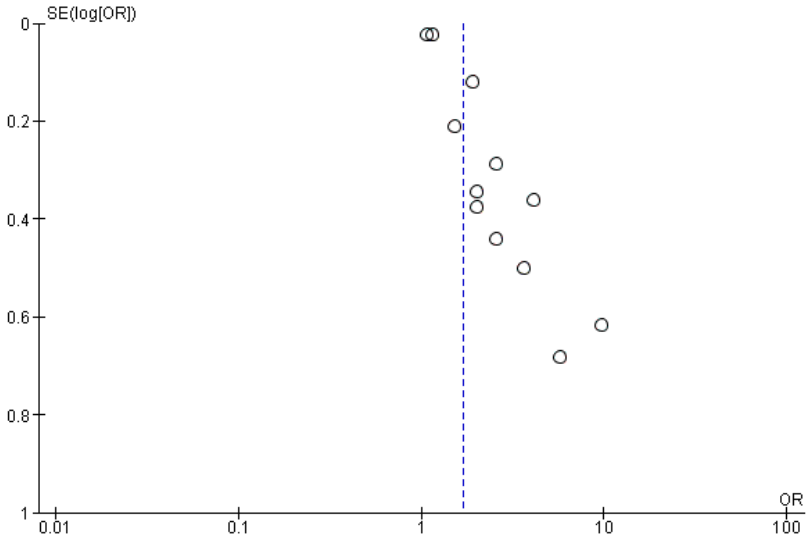

Figure 4. Funnel plot of risk of death in Tuberculosis patients undergoing treatment with comorbid diabetes mellitus

DISCUSSION

This systematic study and meta-analysis of research raised the risk of death in tuberculosis patients undergoing treatment 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 aggravate and cause death in Tuberculosis patients undergoing treatment.

Wang 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 (12.2% vs. 4.2%; OR= 3.16; 95% CI= 1.08 to 9.25). Another finding from a retrospective cohort study of the Province of China 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 revealed that of the 2,481 patients who received TB treatment in eight hospitals from January 2009 to December 2010 there were treatment failures including death and the case occurred in 148 patients (6.0%). In multivariate analysis, age, gender, 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 for the death of TB patients undergoing treatment (Kwon et al., 2014).

Tuberculosis patients undergoing treatment with comorbid diabetes mellitus will experience pathological changes, including thickening of the alveolar epithelial walls and the basal lamina of the pulmonary capillaries. The process which is secondary to complications of microangopathy is the same as that of retinopathy and nephropathy. Neuropathic disorders of the autonomic nerves can be in the form of central hypoventilation and sleep apnea. In addition, there can also be a decrease in lung recoil elasticity, a decrease in the diffusion capacity of carbon monoxide, 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 blood sugar levels. This is because the use of rifampin as an anti-tuberculosis drug (OAT) will reduce the effectiveness of oral anti-diabetic drugs (sulfonyl urea) so that the dose of oral antidiabetic drugs needs to be increased. While isoniazid dada is a P450 enzyme inhibitor, so it can reduce the effect of rifampin.

Enforcement of the diagnosis in patients with tuberculosis accompanied by diabetes mellitus is the discovery of Mycobacterium tuberculosis complex which is identified from clinical specimens (tissue, body fluids, throat swab, etc.) and culture. In countries with limited laboratory capacity to identify M. tuberculosis, pulmonary TB cases can be established 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 treated with complete guidelines and duration of treatment (Indonesian Lung Doctors Association 2009).

Baghaei (2013) states that from several hypotheses, DM causes depression of cellular immunity, alveolar macrophage dysfunction, decreased interferon gamma, pulmonary microangiopathy and micronutrient deficiency. In DM patients, defects in insulin secretion (insulin deficiency) and insulin work disorders (insulin resistance) result in blood glucose not being able to enter muscle cells and fat tissue. As a result, to obtain an energy source for survival and carry out their functions, muscle and fat tissue will break down the energy reserves contained within themselves through the process of glycogenolysis and lipolysis. The continuous process of glycogenolysis and lipolysis ultimately causes muscle mass and fat tissue to decrease and weight loss occurs.

TB patients with DM are more difficult to treat. People with diabetes who

receive TB therapy are more likely to fail therapy and are more likely to die during therapy than those without comorbid DM. The relationship between TB and DM requires intervention in both diseases. To improve detection and prevent diabetes or tuberculosis-related complications, diabetic people should be checked for tuberculosis, as well as for tuberculosis people should be checked for diabetes (IDF, 2012). TB patients with comorbid DM have a higher risk of death during therapy as well as an increased risk of recurrence after treatment, which can also provide a greater risk of transmission (Dooley et al., 2009). In this study, it was stated that the risk of death was increased in Tuberculosis patients with comorbid diabetes mellitus who were undergoing treatment. The limitations of this study are that there is a language bias because it only uses English articles, a publication bias shown in the funnel plot results, and a search bias because it only uses three databases.

AUTHOR CONTRIBUTION

Hakim Anasulfalah is the main researcher who selects the topic, searches for and collects research data. Didik Gunawan Tamtomo and Bhisma Murti analyzed data and reviewed research documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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