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Research

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Type 2 Diabetes Mellitus is the Risk Factor for Multi-drug Resistance Tuberculosis: A Meta-Analysis

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) has a significant risk of developing active Tuberculosis (TB) and complicates its treatment. There is no conclusive evidence on whether TB-T2DM comorbidities are associated with an increased risk of Multidrug Resistant Tuberculosis (MDR-TB). The study aims to analyze and estimate the relationship of T2DM to MDR-TB incidence and to estimate the size of the combined effect.

Subjects and Method: This study was a meta-analysis with PICO, Population: patients actively undergoing MDR-TB treatment. Intervention: Patients with comorbid Type 2 Diabetes Mellitus. Comparison: Tuberculosis patients without comorbid Type 2 diabetes mellitus. Output: MDR-TB (Multidrug Resistant Tuberculosis). The articles used in this study were obtained from databases with keywords to search for articles were ("Diabetes Mellitus, Type 2" OR "diabetic" OR "diabetes") AND "tuberculosis" AND ("Tuberculosis, Multidrug-Resistant" OR "drug resistance" OR "multidrug-resistant" OR "multidrug resistant" OR "multidrug resistance" OR "drug-resistant" OR "drug resistant"). Articles were selected based on inclusion criteria, is published in the form of an English full-text article from January 2015 to January 2025, reporting the relationship between T2DM and MDR-TB among TB patients. The articles were selected using the PRISMA flow diagram and analyzed using the Review Manager 5.3 application.

Results: This meta-analysis consisted of 9 articles originating from Europe, Asia, Africa and America. Results of the meta-analysis showed that the cohort study of type 2 diabetes mellitus had a 4.11 times greater risk of developing MDR-TB compared to people who did not have type 2 diabetes mellitus. In a control case study of type 2 diabetes mellitus, there was a 3.11 times greater risk of developing MDR-TB than people without type 2 diabetes mellitus, and both were statistically significant (aOR= 3.39; CI 95%= 2.05 to 8.24; p= 0.001).

Conclusion: Type 2 diabetes mellitus is a risk factor for MDR TB.

Keywords: diabetes mellitus, multidrug resistant tuberculosis, meta-analysis

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BACKGROUND

Tuberculosis (TB) is an infectious disease that is still a global public health problem till now. The definitive diagnosis of pulmonary tuberculosis is to find Mycobacterium TB germs in the sputum or lung tissue culture

(Diana et al, 2020). The global burden of TB continues to be a major public health challenge despite efforts to mitigate its impact.

In 2023, the global prevalence of TB is 10.8 (WHO, 2024). Indonesia targets in the Sustainable Development Goals "End The TB Strategy" a 90% reduction in TB incidence and a 95% reduction in TB mortality by 2030. However, global epidemiological and demographic transitions pose significant challenges to TB control programs as they change the significance of various TB risk factors (Kemenkes RI, 2023). The global epidemiological and demographic transition poses significant challenges to TB control programs as it changes the significance of various risk factors for TB.

Tuberculosis is suffered by people of all age ranges, but the prevalence will increase with age, and it will worsen if the patient is comorbid with Diabetes Mellitus (DM) (Huangfu et al., 2019). Population based cohort study published in 2020 found that people with diabetes have a three times higher risk of developing TB, while active TB worsens diabetes mellitus (Nowinski, 2023). Other study shows that comorbidities such as diabetes, alcoholism, substance addiction, immunosuppressive therapy, cancer, and smoking increase the risk of TB treatment failure (Huangfu et al., 2019).

The high prevalence of diabetes is a serious threat to the control and treatment of tuberculosis. Diabetes mellitus is one of the factors that hinders low and middle income countries from achieving a 90% reduction in TB rates (IDF, 2021). The relationship between TB and T2DM has long been known as diabetes suppresses the patient's immune response, which will further facilitate the occurrence of infection by Mycobacterium Tuberculosis (M. TB) and eventually develop into tuberculosis.

Patients with T2DM have a 2-3 times greater risk of developing tuberculosis compared to people without diabetes (Laughs et al., 2024). The length of time a person suffers from T2DM is also a risk factor for a person becoming infected with tuberculosis, based on a study (Irawan, 2020). People with T2DM for more than 10 years increase their risk of being infected with tuberculosis by 1.9 times. The length of time a person suffers from T2DM affects the risk of TB, because T2DM can reduce the immune response and worsen the body's immune system, triggering vulnerability to TB germs (Torres et al., 2019). The researchers are interested in analyzing and estimating the relationship of T2DM to the incidence of MDR-TB and in estimating the combined effect size between the variables. exposure.

SUBJECTS AND METHOD

1. Study Design

This study was a meta-analysis using the PICO model. Population: Active patients undergoing MDR-TB treatment. Intervention: Patients with comorbid T2DM. Comparison: Tuberculosis patients without comorbid Type 2 diabetes mellitus. Output: Multi-drug Resistant Tuberculosis (MDR-TB). Article searches were conducted using the PubMed database, EMBASE, Google Scholar, and Science Direct. Some of the keywords used to search for articles were ("Diabetes Mellitus, Type 2" OR "diabetic" OR "diabetes") AND "tuberculosis" AND "Tuberculosis, Multidrug Resistant" OR "drug resistance" OR "multidrug resistant" OR "multidrug resistant" OR "multidrug resistance" OR "drug-resistant" OR "drug resistant".

2. Meta-Analysis Step

The stages carried out are:

a. Formulating research questions in PICO, which involves defining the Population, Intervention, Comparison, and Outcome

b. Searching for primary study articles from online data based on Google Scholar, Scopus, ProQuest, PubMed, Elsevier, and Science Direct
c. Conducting screening by determining inclusion and exclusion criteria and conducting cross-sectional critical assessments
d. Performing data extraction and analysis using RevMan 5.3 Software
e. Interpreting the results and drawing conclusions Lemeshow.

3. Inclusion Criteria

The inclusion criteria for the study articles were full-text study articles published between 2015 and 2025 using English, had a cohort or case-control study design, the study subjects were TB patients who were undergoing active treatment and discussed the relationship between type 2 diabetes mellitus and the incidence of MDR-TB.

4. Exclusion criteria

The exclusion criteria for this research article were non research publication articles such as literature review, case reports or qualitative research. Articles that do not report methodological information clearly, such as statistical analysis methods and articles that do not include effect size.

5. Variable Operational Definition

MDR-TB is a patient who has developed resistance to anti TB drugs. The scale of measurement is categorical.

Type 2 diabetes mellitus is a chronic disease characterized by high blood sugar levels due to the body's inability to use insulin effectively (insulin resistance) or not producing enough insulin.

6. Study Instruments

This study was guided by the PRISMA flow diagram and the quality assessment of study articles was conducted using the Joanna Briggs Institute Critical.

7. Data Analysis

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

RESULTS

The article search process was carried out through several journal databases. The process of reviewing articles using the PRISMA flowchart can be seen in Figure 1.

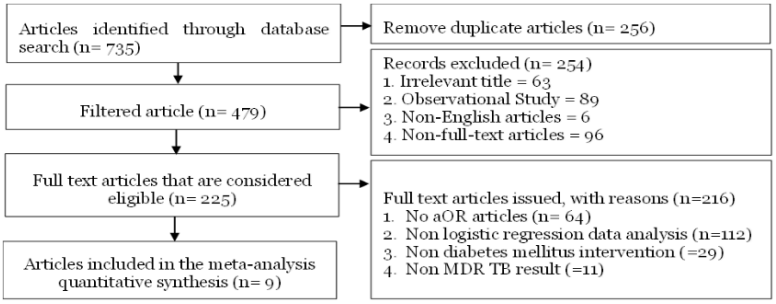

Figure 1. PRISMA flow chart

Figure 2. Map of the distribution of articles included in the Meta-Analysis

This study was carried out quantitatively and qualitatively which can be seen in Table 1 and Table 2 below. This study was conducted using the Critical Appraisal Center for Joanna Briggs Institute Critical (JBI, 2017).

Table 1. Critical Appraisal Checklist with case-control study design, Risk Factors for T2DM on the Incidence of MDR TB

Author (Year)	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Qisheng et al. (2016)	2	2	2	2	2	2	2	2	1	2	2	2	23
Lucia et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	24
Lyu et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24

Description of the question criteria:

1 = Do the control case studies clearly address clinical problems?
2 = Did the researcher use the correct method to answer the research question?
3 = Was the case selected appropriately?
4 = Was the control selected appropriately?
5 = Was exposure measured accurately (correctly) to prevent/minimize bias?
6 = Beyond the exposure that has been studied, have the researchers taken into account the influence of all the potential confounding factors in this study?
7 = Did the researchers control the influence of all potential confounders in data analysis?
8 = Is the magnitude of the exposure effect determined?
9 = Is the estimation of the effects of exposure accurate?
10 = Are the results trustworthy?
11 = Can the results be applied to the local population?
12 = Are the results of the study compatible with other available evidence?

Answer score description:

0 = No
1 = Indecisive
2 = Yes

Table 2. Critical Appraisal Checklist with cohort study design of Risk Factors for T2DM on the Incidence of MDR TB

Author (Year)	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Magee et al. (2015)	2	2	2	2	2	2	2	2	2	2	2	2	24
Muñoz-Torrico et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	24
Lee et al. (2017)	2	2	2	2	2	2	2	2	1	2	2	2	23
Antonia et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	24
Sahakyan et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	24
Adane et al. (2023)	2	2	2	2	2	1	2	2	2	2	2	2	23

Description of the question criteria:

1 = Does the research address focused issues clearly?
2 = Is the cohort research method appropriate for answering research questions?
3 = Are there enough subjects to establish that the findings were made not by chance?
4 = Is the selection of the choir based on objective and validated criteria?
5 = Does the cohort represent a specified population?
6 = Is the follow-up conducted in sufficient time?
7 = Are the criteria of objective and unbiased outcomes used?
8 = Are the methods of measuring the T2 DM intervention validated?
9 = Is the effect size practically relevant?
10 = Are there any faith interventions given?
11 = Have confounding factors been taken into account?
12 = Are the results applied to your research?

Answer score description:

0 = Yes
1 = Indecisive
2 = Yes

Table 3. Description of the Primary Study

Author (Year)	Country	Sample	P	I	C	O
Song et al. (2016)	Chinese	118 (46 cases and 72 controls)	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
Lucia et al. (2017)	Mexico	507 (183 cases and 324 controls)	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
Lyu et al. (2020)	Chinese	657 (267 cases and 390 controls)	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
Magee et al. (2015)	Georgia	318	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB

Author (Year)	Country	Sample	P	I	C	O
Muñoz-Torrico *et al.* (2017)	Mexico	73	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
Lee *et al.* (2017)	South Korea	252	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
Antonia *et al.* (2018)	Indonesia	356	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
São Paulo, Sã *et al.* (2020)	Armenia	621	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB
Adane *et al.* (2023)	Ethiopia	267	Patients actively undergoing MDR-TB treatment	Patients with comorbidity of T2DM	Tuberculosis patients without comorbidity of T2DM	MDR-TB

Table 4. AOR and confidence interval data from the case control study design articles of Risk Factors for T2DM on the Incidence of MDR TB

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Qisheng et al. (2016)	2.64	1.51	4.61
Lucia et al. (2017)	3.10	1.70	5.80
Lyu et al. (2020)	4.02	2.00	8.08

Table 5. AOR and *confidence interval* data from the cohort study design articles of Risk Factors for T2DM on the Incidence of MDR TB

Author (Year)	aOR	95% CI	
		Lower Limit	Upper Limit
Magee et al. (2015)	2.27	1.02	5.08
Muñoz-Torrico et al. (2017)	3.80	1.20	11.70
Lee et al. (2017)	1.67	1.03	2.70
Antonia et al. (2018)	6.80	2.00	23.70
Sahakyan et al. (2020)	8.99	2.51	32.23
Adane et al. (2023)	14.80	3.50	62.70

The forest plot in Figure 3 shows that DM was a risk factor for MDR TB. In the control case study, people with T2DM had a 3.11 times greater risk of developing MDR TB than people without T2DM (aOR= 3.11; CI 95%= 2.18 to 4.42; p=0.001). In the cohort study, people with T2DM had a 4.11 times higher risk of developing MDR TB than people without T2DM (aOR= 4.11; CI 95%= 2.05 to 8.24; p= 0.001 and both were statistically significant (aOR= 3.39; CI 95%= 2.31 to 4.98; p=0.001). The heterogeneity of the

study data showed I^2= 51% so that the data distribution was declared non heterogeneous (fixed effect model).

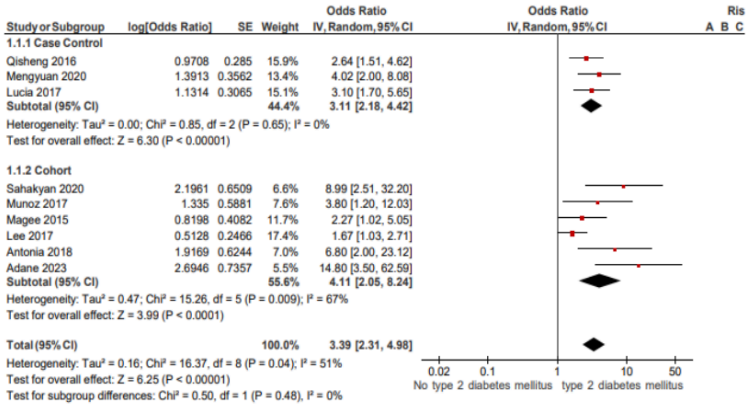

Figure 3. Forest plots of the influence of T2DM on the incidence of MDR-TB

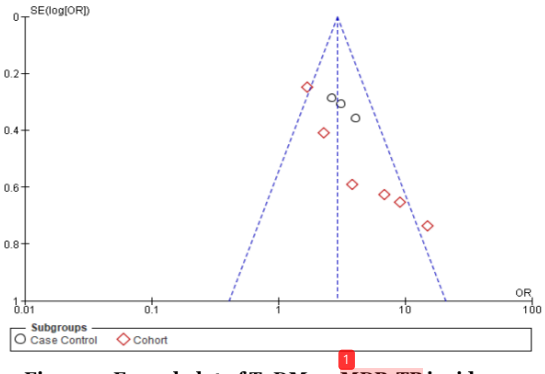

Figure 4. Funnel plot of T2DM on MDR-TB incidence

The plot funnel presented in Figure 4 shows that there was no publication bias which was characterized by the symmetry of the right and left plots, where 3 plots are on the right, 3 plots are on the left and 1 plot touches the center line. It was supported by the absence of an over-the-top tendency in the actual study or the occurrence of a balance of the distances between studies on the right and left sides of the funnel plot.

DISCUSSION

The results of meta-analyses from 9 previous studies related to T2DM on the incidence of MDR-TB provide an overview of the results that, in the case control study, people with T2DM had a 3.11 times greater risk of developing MDR-TB compared to people without T2DM. In the T2DM cohort study, people with T2DM had a 4.11 times greater risk of developing MDR TB than people without T2DM, and both were statistically significant (aOR= 3.39; CI 95%= 2.05 to 8.24; p= 0.001). The heterogeneity of the study data showed I2= 51% so that the data dissemination was declared to be high heterogeneity because many studies were conducted in the same country (random effect model).

In line with the results of a study conducted by Rehman et al., (2023) it was shown that Diabetes Mellitus has a significant influence on the occurrence of MDR-TB in comorbid TB-T2DM patients. DM may also increase the risk of developing MDR-TB in TB patients due to DM, including phagocytosis activity, chemotherapeutic response, oxidative species formation, microbial proliferation, changes in drug disposition, and non-adherence to treatment (Huangfu et al., 2019).

This is supported by the results of a study (Tegegne et al., 2018) which also states that DM is a risk factor for a person to have MDR-TB by 1.97 times, and according to (Hu et al., 2021) DM is a high risk factor for a person to experience second line drug resistance to TB by 2.51 times, generally the effect of hyperglycemia, because the condition will interfere with the function of neutrophils, monocytes, and macrophages in chemotaxis and phagocytosis as an effort of the defense mechanisms. In addition, it is estimated that there is an insulin deficiency that results in reduced bactericidal activity of leukocytes and lymphocytes in patients who have poor sugar control.

TB patients with DM also fail treatment 1.71 times more often than TB patients without DM and relapse more often, increasing the risk of MDR-TB (Liu et al., 2017). MDR-TB is the result of the failure of the body's defense system. Impaired function of the pulmonary vascular capillary endothelium, stiffness of the red blood cell corpus, and changes in the oxygen dissociation curve due to prolonged hyperglycemia conditions (Gómez et al., 2015). One hypothesis is that the katG gene plays a role in mycobacteria's protection against oxidative destruction and also in encoding enzymes that convert isoniazid into an active form. In T2DM, reactive oxygen production is impaired, so strains with KatG mutations may be able to survive (Liu et al., 2017).

Our study has several limitations; firstly, the studies taken have not been representative of the entire continent. Second, it may not be that all disruptive factors are measured or controlled, such as socioeconomic status and smoking behaviors, which can worsen TB patients in treatment. However, we believe our findings provide a reliable understanding of the current situation and highlight important risks associated with T2DM that have been significantly shown to be a risk factor for a person with MDR-TB.

AUTHOR CONTRIBUTION

Bibit Irawan, Farit Setyo Nugroho, Nine Elissa Maharai were the researchers who selected topics, searched, collected, and analyzed research data.

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CONFLICT OF INTEREST

There was no conflict of interest in this study.

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