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Meta-Analysis

Effect of Smoking on Tuberculosis Treatment Failure: Meta-Analysis

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ABSTRACT

Background: Tuberculosis (TB) is an infectious disease that is the leading cause of health problems and death worldwide. Smoking is one of the factors that affect the outcome of TB treatment. This study aims to examine the effect of smoking on TB treatment failure.
Subjects and Method: Meta-analysis was carried out according to the PRISMA diagram using the PubMed, Science Direct, and Google Scholar databases. The keywords used ((tuberculosis OR TB) AND (smoking OR tobacco)) AND (impact OR treatment OR outcome OR effect). There were 9 studies with a cohort study design published in 2011-2021 that met the inclusion criteria. The analysis was performed with Revman 5.3.
Results: There were 9 articles consisting of 6 studies from Asia (Malaysia, Iran and Armenia), 1 study from North America (Mexico) and 1 study from South America (Brazil) which were included in this meta-analysis. Nine articles showed a significant effect of smoking on TB treatment failure (SMD= 1.88; 95% CI= 1.43 to 2.49; p< 0.001).
Conclusion: Smoking can increase tuberculosis treatment failure.

Keywords: tuberculosis, smoking, treatment, meta-analysis

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BACKGROUND

Tuberculosis (TB) is an infectious disease that is one of the leading causes of health problems and causes of death worldwide. TB is caused by the bacterium Mycobacterium tuberculosis which spreads through the air and affects both pulmonary and extrapulmonary organs. Globally, the decline in the number of deaths from TB between 2015 and 2020 was only 9.2%. The global number of deaths officially classified as caused by TB in 2020 was 1.3 million cases. Eight countries that rank first to eighth in terms of the number of cases with at least 100,000 incident cases are South Africa, India, China, Indonesia, Philippines, Pakistan, Nigeria, and Bangladesh (World Health Organization, 2021).

The determinants of TB disease related to treatment outcomes are influenced by various risk factors such as Human Immunodeficiency Virus, malnutrition, diabetes, smoking and alcohol consumption, the majority of which affect adults and more cases among men than women. Smoking is one of the factors that affect the outcome of TB treatment. Nguipdop-Djomo et al., (2020) stated that the risk of TB associated with smoking was 18% (OR= 5.67; 95% Cl= 2.68 to 11.98; p<0.001), in addition to

socioeconomic status factors (education, household density, history of homelessness and imprisonment). These results are in line with Azeez et al. (2018) that unsuccessful treatment in TB/HIV coinfected patients with treatment category is the age factor (aHR= 0.84; 95% CI= 0.69 to 1.02; p= 0.004) and smoking (aHR= 1.05; 95% CI= 0.89 to 1.23; p= 0.05).

Smoking is significantly associated with poor TB treatment outcomes. A meta-analysis conducted (Burusie et al., 2020a) found that TB treatment outcomes were poor for 21% of all study participants. Patients with poor TB treatment outcomes were 50% more exposed to smoking than patients receiving treatment (OR= 1.51; 95% CI= 1.30 to 1.75; I^2= 75.1%). Another study by (Wang et al., 2020) stated that smokers had a chance for poor TB treatment outcome (OR= 1.23; 95% Cl= 1.14 to 1.33; I^2= 48.2%), delayed smear or culture conversion (OR= 1.55; 95% CI= 1.04 to 2.07; p= 0.007), and treatment non-adherence (OR= 1.35; 95% Cl= 1.21 to 1.50; p= 0.002). These results can be useful for planning appropriate actions that impact TB control, especially on treatment outcomes, such as cognitive-behavioral approaches to smoking cessation.

These conditions indicate that smoking is one of the important factors for TB treatment outcomes. So, the authors are interested in conducting a meta-analysis research on "The Effect of Smoking on Tuberculosis Treatment Failure".

SUBJECTS AND METHOD

1. Study Design

This study uses a systematic review and meta-analysis method with secondary data from a database based on the PRISMA diagram with the question posed in this study, namely the effect of smoking on the failure of tuberculosis treatment. This research will be conducted by searching, examining, identifying and selecting secondary data from previous observational studies that are in the period 2011-2021. The research data was searched from several databases including Pubmed, Science Direct, and Google Scholar. The keywords used in the database search were ((tuberculosis OR TB) AND (smoking OR tobacco)) AND (impact OR treatment OR outcome OR effect).

2. Inclusion Criteria

The inclusion criteria in this study were full-text papers using the cohort method, the relationship size used was OR. The analysis used was multivariate with adjusted Odds Ratio (aOR). The research subjects were patients diagnosed with tuberculosis. One of the interventions is smoking. English article. Outcome is failure of TB treatment.

3. Exclusion Criteria

The exclusion criteria for this study were articles other than English and articles published before 2011 and after 2021.

4. Operational Definition of Variables

The articles in this study were adapted to PICO. The article search was carried out according to the criteria according to the PICO model. There was a PICO in this study, the population was patients diagnosed with tuberculosis, the intervention was smoking or had smoked, and tuberculosis treatment failure was the outcome.

Patients diagnosed with tuberculosis are patients with smear positive sputum and have started treatment for tuberculosis.

Smoking is a patient diagnosed with tuberculosis who smoked counted at the start of tuberculosis treatment.

Tuberculosis Treatment Failure is a TB patient who does not experience AFB sputum conversion in the last month of tuberculosis treatment or an undesirable outcome of therapy.

5. Study Instruments

This research was conducted based on the PRISMA diagram and article quality checks with the Critical Appraisal Checklist. Data collection techniques and instruments in this study are published articles that link the effects of smoking on tuberculosis treatment failure

6. Data Analysis

The research data were analyzed using the RevMan 5.3 application. The analysis was carried out by calculating the effect size and heterogeneity consistency value (I^2) from the selected research results. The results of data analysis in the form of forest plots and funnel plots.

RESULTS

The meta-analysis process was carried out using the PRISMA flow chart, which can be seen in Figure 1. The total articles obtained were 9 articles. The distribution of the articles is on 2 continents with details of 6 studies from Asia (Malaysia, Iran, and Armenia), 1 study from North America (Mexico) and 1 study from South America (Brazil), which can be seen in Figure 2. with details of Table 1 and Table 2.

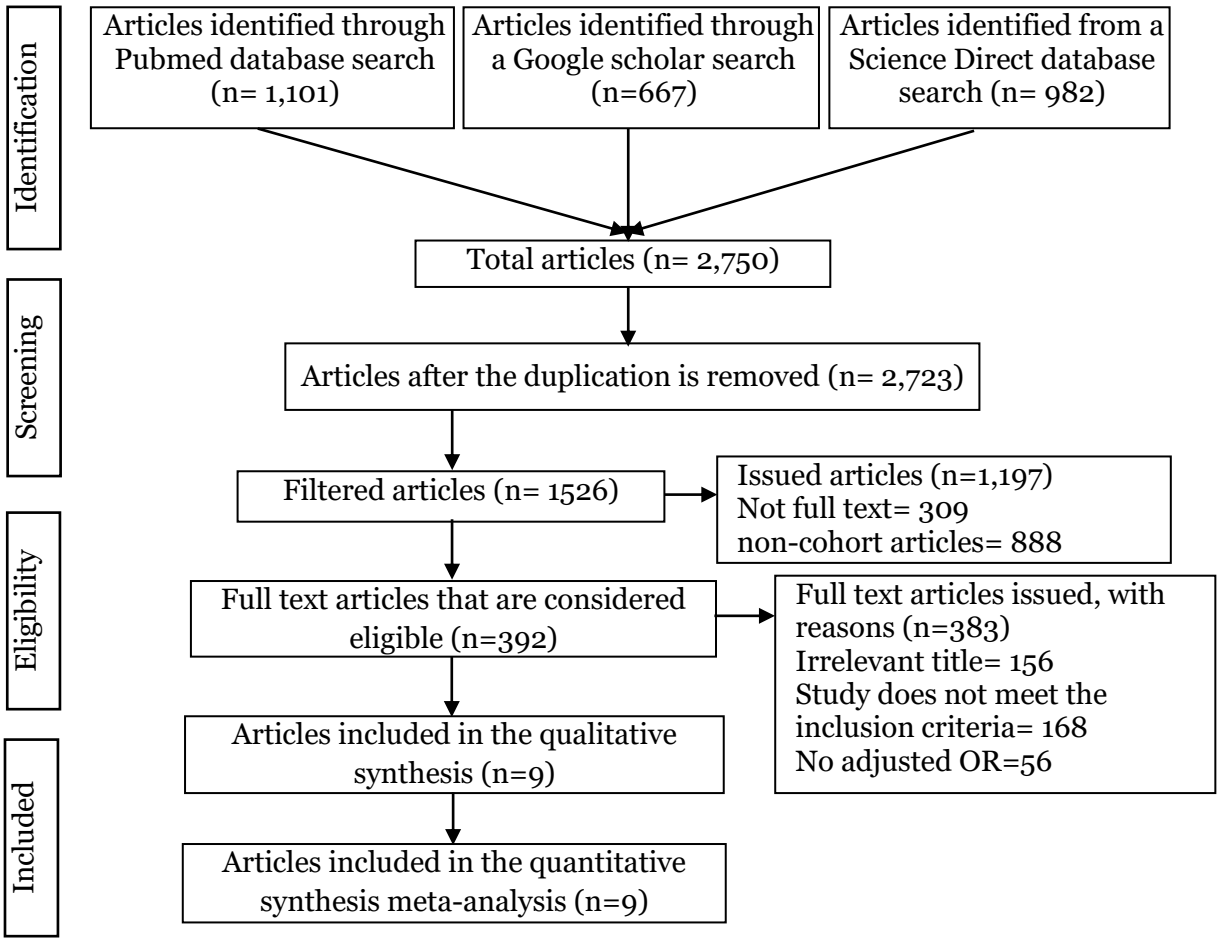

Figure 1. PRISMA Diagram

Table 1. Quality Assessment

No	Question	Atif et al. (2014)	Balian et al. (2017)	Bonacci et al. (2013)	Cailleaux-Cezar et al. (2018)	Khan et al. (2020)
1.	Are the two groups similar and come from the same population?	1	1	1	1	1
2.	Was the exposure measured equally between the exposed and unexposed groups?	1	1	1	1	1
3.	Is exposure measured in an accurate (correct) and reliable way?	1	1	1	1	1
4.	Did the researcher identify confounding factors?	0	1	1	0	1
5.	Are there strategies to control confounding factors?	1	1	1	1	1
6.	Were the groups or participants independent of the results at the start of the study (or at the time of exposure)?	1	1	1	1	1
7.	Are results measured in an accurate (correct) and reliable way?	1	1	1	1	1
8.	Is there follow-up reporting and results are obtained over a long period of time?	1	1	1	1	1
9.	Is the follow-up information complete?	1	1	1	1	1
10.	If not, is there any information regarding the failure of follow-up?	1	1	1	1	1
11.	Are there strategies for dealing with failed follow-up?	1	1	1	1	1
	Total	**10**	**11**	**11**	**10**	**11**

Note: 1: Yes; 0: No

Table 1. Cont.

No	Question	Liew et al. (2015)	Masjedi et al. (2017)	Mokti et al. (2021)	Boer et al. (2014)
1.	Are the two groups similar and come from the same population?	1	1	1	1
2.	Was the exposure measured equally between the exposed and unexposed groups?	1	1	1	1
3.	Is exposure measured in an accurate (correct) and reliable way?	1	1	1	1
4.	Did the researcher identify confounding factors?	0	1	1	1
5.	Are there strategies to control confounding factors?	1	1	1	1
6.	Were the groups or participants independent of the results at the start of the study (or at the time of exposure)?	1	1	1	1
7.	Are results measured in an accurate (correct) and reliable way?	1	1	1	1
8.	Is there follow-up reporting and results are obtained over a long period of time?	1	1	1	1
9.	Is the follow-up information complete?	1	1	1	1
10.	If not, is there any information regarding the failure of follow-up?	1	1	1	1
11.	Are there strategies for dealing with failed follow-up?	1	1	1	1
	Total	**10**	**11**	**11**	**11**

Note: 1: Yes; 0: No

Table 2. Description of the Primary Study of the Effect of Smoking on TB Treatment Failure

Author (year)	Country	Sample	Population	Intervention	Comparison	Outcome	aOR (95%CI)
Atif et al. (2014)	Penang, Malaysia	336	Patients with positive TB sputum	Smoke	Do not smoke	Extend the duration of tuberculosis treatment	2.43 (1.18 to 5.03)
Balian et al. (2017)	Armenia	992	Suspected TB patients	Smoke	Do not smoke	TB treatment failure	1.60 (1.07 to 2.42)
Bonacci et al. (2013)	Meksiko Selatan	1062	Patients with positive Mycobacterium tuberculosis sputum and receiving DOTS therapy	Smoking more than 10 cigarettes per day	Do not smoke	TB therapy failure	2.36 (1.10 to 5.05)
Cailleaux-Cezar et al. (2018)	Brazil	298	TB patients diagnosed	Smoked at the time of diagnosis of TB or smoked in the last 12 months prior to diagnosis, and have smoked at least 100 cigarettes during	Quitting smoking more than 12 months before being diagnosed or not smoking at all	TB treatment failure	6.29 (1.57 to 25.21)
Khan et al. (2020)	Malaysia	9337	All TB patients	his life	Do not smoke	TB treatment failure	1.49 (1.21 to 1.84)
Liew et al. (2015)	Malaysia	21.582	Patients enrolled in Malaysia's National TB Surveillance Database 2012	Smoke	Do not smoke	Unwanted results of TB therapy	1.15 (1.03 to 1.28)
Masjedi et al. (2017)	Iran	334	Patients with positive TB sputum	Smoke	Do not smoke	TB treatment failure	3.51 (1.95 to 6.30)
Mokti et al. (2021)	Kinabalu, Malaysia	89	Patients with positive TB sputum	Smoke	Do not smoke	TB sputum conversion delay	1.54 (1.10 to 2.10)
Boer et al. (2014)	Brazil	2641	Patients diagnosed with positive sputum	Smoke	Never smoked	Delayed conversion of sputum results at day 60 of treatment	6.90 (1.80 to 26.70)

Figure 2. Distribution of Primary Research by Continent

The interpretation of the results of the meta-analysis process can be seen through the Forest plot. Figure 3 shows that smoking increases TB treatment failure. The results of the meta-analysis showed that smoking increased the risk of TB treatment failure by 1.88 times compared to not smoking (aOR = 1.88; 95% CI = 1.43 to 2.49; p<0.001). The heterogeneity of the research data shows I^2= 77% so that the distribution of the data is said to be heterogeneous (random effect model).

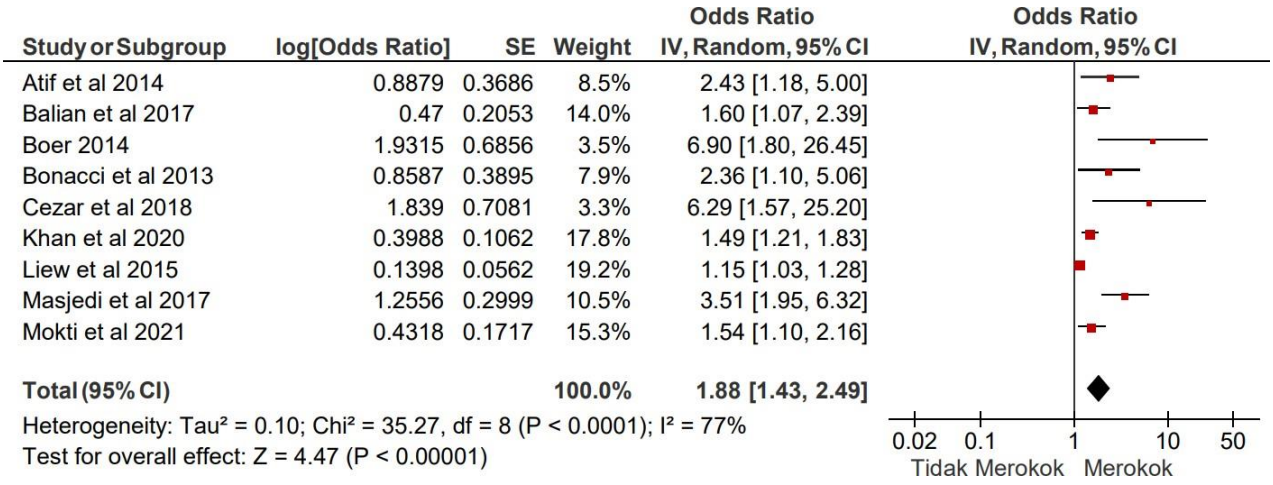

Figure 3. Forest Plot Effect of Smoking on TB Treatment Failure

In Figure 4 the funnel plot shows an asymmetric distribution of the 9 primary studies, 4 plots on the left and 5 plots on the right, indicating that there is a publication bias that tends to overestimate the true effect of smoking on TB treatment failure (overestimation).

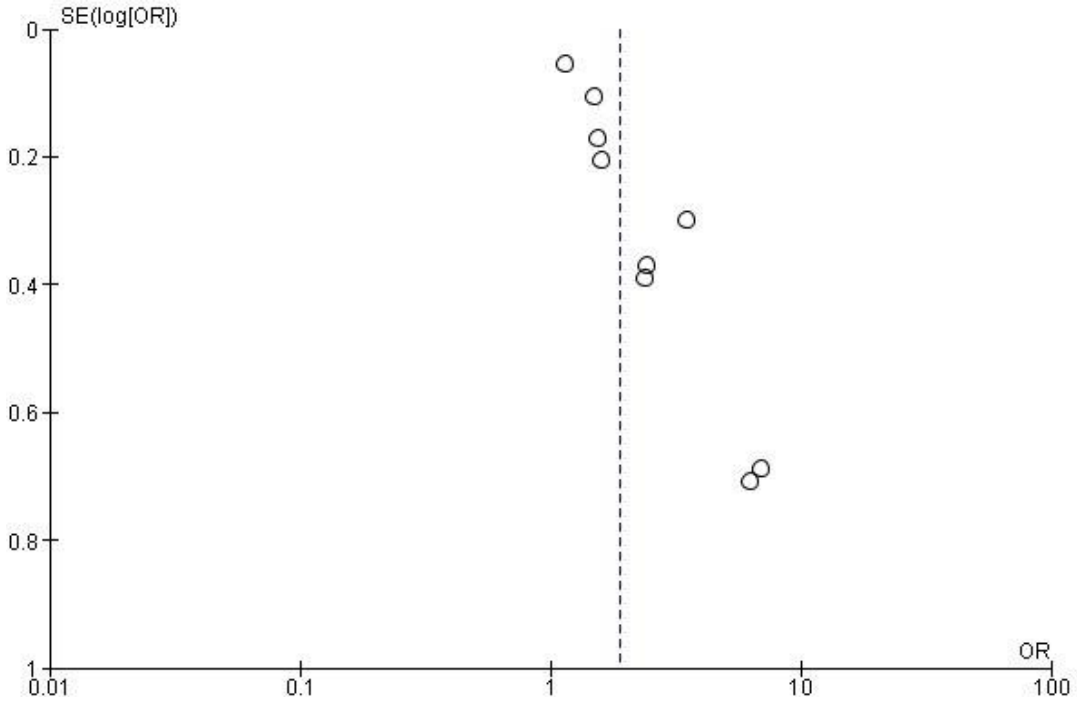

Figure 4. Funnel Plot Effect of Smoking on TB Treatment Failure

DISCUSSION

Tuberculosis (TB) is an infectious disease which is one of the leading causes of health problems and causes of death worldwide. The main determinants of TB disease are influenced by various risk factors such as smoking, malnutrition, poverty, diabetes, household air pollution (Noubiap et al., 2019; Lee et al., 2020). In addition, smoking is significantly associated with negative outcomes of tuberculosis treatment and delayed sputum conversion or negative cultures (Burusie et al., 2020b). Factors for poor TB treatment include unidentified drug resistance, inadequate support to ensure adherence to medication, weak recording and reporting systems, and inadequate prevention and management of HIV disease. including the administration of anti-retroviral treatment (Chakaya et al., 2021).

The effect of smoking on TB treatment failure is still unclear. Therefore, this study uses a systematic review study design and a meta-analysis with the aim of obtaining general conclusions as a basis for providing interventions from various similar studies that have been carried out by previous researchers examining the effect of smoking on tuberculosis treatment failure. Meta-analysis is an epidemiological study that combines and statistically combines data from primary research results that discuss the same hypothesis so that quantitative summary results are obtained (Egger and Smith in Murti, 2018).

The research results are presented in the form of forest plots and funnel plots. Forest plots can show effect sizes and 95% confidence intervals or display results from meta-analysis studies (Akobeng, 2005 in Murti, 2018). The funnel plot shows the effect size and accuracy of the effect size and makes it possible to evaluate possible publication bias in the form of a symmetrical triangular graph (Murti, 2018).

The results of this study indicate that smoking increases TB treatment failure.

Failure of TB treatment can be in the form of delays in converting examination results from positive to negative, as well as undesirable results such as treatment failure or discontinuation of treatment. Failure of TB treatment results in patients requiring further treatment which is time consuming and more expensive, in a situation that is at the same time as the risk of developing multi-drug resistance tuberculosis (MDR-TB) (Van Schayck et al., 2017).

Active smokers are more likely to experience delayed sputum or culture conversion, resulting in a prolonged potency period. This causes the duration of treatment to be longer (Wang et al., 2020). Smoking increases the presence of particles in macrophage lysosomes, which leads to reduced migration and breakdown of TB granulomas (Feng et al., 2011). The phagocytic capacity of macrophages in TB patients is reduced, namely macrophages are less able to ingest foreign bacteria than TB patients who do not smoke (Lugo-Villarino et al., 2018).

Smokers also appear to be more likely to drop out of treatment. The majority of smokers live in low-income countries where access to health services is limited (Reitsma et al., 2017). Socio-economic factors are also important to consider. Smokers tend to have lower socioeconomic status, on the other hand this creates potential financial barriers for smokers to be able to take TB treatment (Kashyap et al., 2016). Smoking also decreases overall general health and increases the risk of other diseases such as chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes, and rheumatoid arthritis (Meira et al., 2019).

The heterogeneity of study results in the odds ratio between studies may arise from clinical diversity. Clinical diversity means that the included studies have diverse participant characteristics (HIV status, susceptibility to TB drugs), TB treatment outcomes measured, research context (country income category) and study period (Gagnier et al., 2013). The results of the funnel plot show the asymmetric distribution of the main study. This shows a publication bias that tends to overestimate.

The limitations of this study are the observational nature of the data, the quality of the study, and publication bias. Several confounding variables, such as the type of TB treatment, drug resistance, and other factors were less controllable. This review uses completely free electronic study database searches, so there is still the possibility of articles being excluded.

AUTHORS CONTRIBUTION

Tsamarah Nisa as a researcher who chooses topics, searches for and collects research data. Victoria Sari analyzes data and reviews research documents.

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This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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