

Meta-Analysis: Smoking and Proverty as Risk Factors of Tuberculosis Multidrug Resistance

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ABSTRACT

Background: The financing burden for tuberculosis treatment is increasing along with the increasing number of cases of Multidrug Resistant Tuberculosis (MDR-TB). The main problems that arise in MDR-TB patients are difficult and expensive treatment, high mortality rates and the potential to transmit resistant bacilli to others. The purpose of the study was to estimate the magnitude of the influence of smoking behavior and poverty on the incidence of MDR-TB.

Subjects and Method: This was a meta-analysis with PICO, population: active patients on TB treatment. Intervention: Smoking behavior and poverty. Comparison: not smoking and not poor. Result: MDR TB. The articles used in this study were obtained from three databases, namely Google Scholar, Pubmed, and Science Direct. Keywords to search for articles are “poverty” OR “smoking” AND “multidrug resistant tuberculosis”. Articles included are full-text English from 2012 to 2022. Articles were selected using a PRISMA flow diagram. Articles were analyzed using the Review Manager 5.3 application.

Results: A total of 12 articles came from the continents of Asia (China India, Indonesia), Africa (Sudan, Ethiopia, Tanzania), North America (Georgia), and South America (Peru). The results of this meta-analysis showed that smoking increased the risk of MDR TB 1.94 times compared to those who did not smoke (aOR = 1.94; 95% CI = 1.64 to 2.30; p = 0.005), and poverty increased the risk of MDR TB 1.85 times compared to those who did not. not in poverty (aOR= 1.85; 95% CI= 1.35 to 2.53; p= 0.004), and both results were statistically significant.

Conclusion: Smoking behavior and poverty increase the risk of MDR TB.

Keywords: smoking behavior, poverty, MDR TB.

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BACKGROUND

The financing burden for tuberculosis treatment is increasing along with the increasing number of cases of Multidrug Resistant Tuberculosis (MDR-TB). Tuberculosis is transmitted through splashes of phlegm or saliva containing germs from TB patients which are spread through the air when the

TB patient is coughing, talking, or sneezing which is then inhaled by other people (Kemenkes RI, 2018). TB treatment causes selective inhibition of the Mtb population so that sensitive Mtb bacteria are killed, while the mutant population will reproduce and cause resistance to Anti-TB drugs (Eva-mawanti, 2021).

MDR-TB is the biggest problem in eradicating TB in the world and in Indonesia. The main problems that arise in MDR-TB patients are difficult and expensive treatment, high mortality rates and the potential to transmit resistant bacilli to others (Kemenkes RI, 2018).

Geographically, in 2020 the most TB cases will be in Southeast Asia (43%), Africa (25%) and the Western Pacific (18%), with a smaller share in the Eastern Mediterranean (8.3%), America (3.0%) and Europe (2.3%). The highest burden is on adult men, who accounted for 56%, adult women accounted for 33% and children for 11% of all TB cases in 2020. Globally, the global burden of MDR-TB comprises 3.6% of new cases and 17% TB cases were re-treated.

Studies show a positive relationship between smoking as a risk factor for TB incidence, smoking can also increase the risk of TB patients becoming MDR-TB. As many as 78.3% of TB patients are active smokers. Smoking increases the risk of suffering from TB with a risk of 1.92 times higher than non-smokers (Viswanathan, 2012). The risk of people who smoke is 30-40% higher for TB than people who don't smoke (Thapa et al, 2015).

Low income/poverty has a risk impact on meeting family food needs, so that family members do not get adequate nutritional intake to meet daily nutritional needs. Thus, people who have poverty levels will have an impact on low body immunity. Low income will also go hand in hand with unfavorable environmental conditions so that it will be able to increase TB patients suffering from MDR-TB (Mahfuzhah, 2014).

Based on the description above, the presence of various risk factors for a TB patient suffering from MDR TB reported by several previous researchers prompted researchers to conduct a systematic study

and/or meta-analysis. Researchers are interested in combining and analyzing the results of existing studies and draw conclusions from studies that discuss smoking behavior and poverty on the incidence of MDR-TB in the world. The purpose of the study was to estimate the magnitude of the influence of smoking behavior and poverty on the incidence of MDR-TB.

SUBJECTS AND METHOD

1. Study Design

This was a meta-analysis study with PRISMA flow chart guidelines. Article searches were performed using the PubMed database. Some of the keywords used are: "poverty" OR "smoking" AND "multidrug resistant tuberculosis".

2. Inclusion Criteria

The inclusion criteria for this research article were full paper articles with a study design in the form of cohort and case-control, articles using English, research subjects in the form of active TB patients. The selected articles provide intervention on smoking behavior and poverty on the incidence of MDR TB.

3. Exclusion Criteria

The exclusion criteria for this research article were articles that were not in English, research designs other than using RCTs and articles that were not full text and articles published between 2012 and 2022.

4. Operational Definition of Variables

The articles included in this study were PICO-adjusted. The search for articles was carried out by considering the eligibility criteria determined using the following PICO model: Population= patients treated for tuberculosis, Intervention= smoking behavior and poverty, Comparison= not smoking and not poor, Outcome= multi-drug resistant tuberculosis.

Smoking behavior is the activity of burning tobacco mixed with tar and

nicotine in paper then sucking and exhaling it through the mouth or nose. The measurement scale is categorical.

Poverty is a condition in which a person cannot fulfill his basic right to maintain and develop a dignified life. The measurement scale is categorical.

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

5. Instruments

This study uses PRISMA flow diagrams and assessment of article quality using the the Critical Appraisal Skills Program (CASP, 2018).

6. Data Analysis

The collected articles were then processed using the Review Manager (RevMan 5.3).

Data processing is done by calculating aOR. Forest plots and funnel plots are used to determine the size of the relationship and the heterogeneity of the data.

RESULTS

Process of searching article was carried out by searching several journal databases Pub-Med and Google Scholar it can be seen using the PRISMA FLOW flowchart shown in Figure 1.

The initial search process resulted in a total of 1079 articles, after deleting the duplicated articles, 830 articles were found, of which 554 articles were eligible for a full text review. A total of 14 articles that meet the criteria according to the quantitative synthesis meta-analysis.

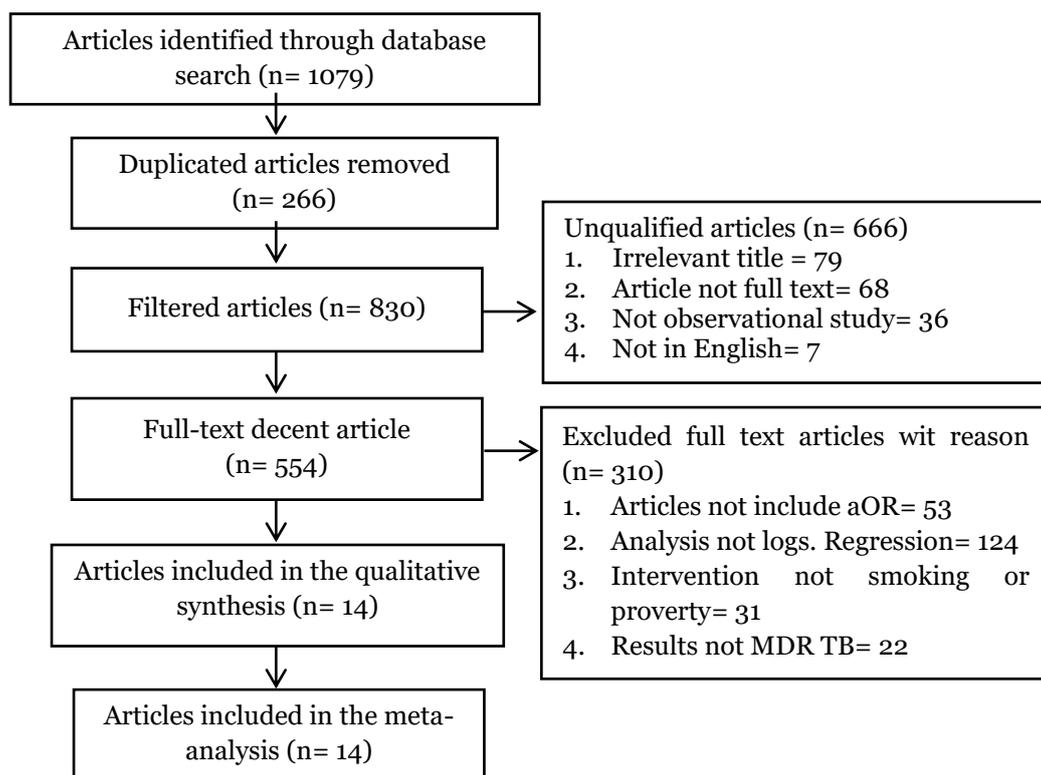


Figure 1. Results of Prisma Flow Diagrams



Figure 2. Research Distribution Map

It can be seen in Figure 2 that the research articles come from fourth continents such as Asia, Africa, South America, and North America.

An assessment of the quality of the articles with case-control study design used in this study can be seen in table 1, and quality of the articles with cohort study it can be seen in table 2.

Then Table 3 showed that 8 articles from case-control study. Table 4 showed that 6 cohort study provide risk factors for smoking behavior on the incidence of MDR TB.

Table 5 it can be seen about the details of the articles provide risk factors for smoking behavior on the incidence of MDR TB used in this study, such as the study population, intervention, comparison, and the results of each study.

Table 6 it can be seen about the details of the articles provide risk factors for proverty on the incidence of MDR TB used in this study, such as the study population, intervention, comparison, and the results of each study.

a. Forest plot smoking against MDR TB

The forest plot in Figure 3 shows that smoking behavior is a risk factor for MDR TB. In a cohort study of smoking behavior, the risk of developing MDR TB was 1.50 times compared to non-smokers. In the case control study, smoking behavior had a risk of developing MDR TB 2.17 times compared to non-smokers and both were statistically significant (aOR= 1.94; 95% CI= 1.64 to 2.30; p= 0.005). The heterogeneity of the research data shows I2 = 31% so that the distribution of the data is not heterogeneous (fixed effect model).

b. Funnel plot smoking against MDR TB

The funnel plot presented in Figure 4 shows no publication bias as indicated 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. This is reinforced by the absence of a tendency to overestimate in the actual study or a balance between the distances between studies on the right and left sides of the funnel plot.

Table 1. Assessment of study quality case-control study.

No	Indicator	Publication (Author and Year)							
		Zhang et al. (2016)	Ali et al (2019)	Workie et al. (2021)	Lalwani et al. (2019)	Li et al. (2015)	Setiyadi et al. (2019)	Li et al. (2015)	Lalwani et al. (2019)
1	Does the case-control study clearly address the clinical problem?	2	2	2	2	2	2	2	2
2	Did the researcher use the correct method to answer the research question?	2	2	2	2	2	2	2	2
3	Is the case selected the right way?	2	2	2	1	2	2	2	2
4	Are the controls selected the right way?	2	2	2	2	2	2	2	2
5	Is exposure measured accurately (correctly) to prevent/minimize bias?	2	2	2	2	2	2	2	2
6	Apart from the exposures that have been studied, have the researchers taken into account the influence of all potential confounding factors in this study?	2	2	2	2	2	2	2	2
7	Did the researcher control for the influence of all potential confounders in the data analysis?	2	2	2	2	2	2	2	2
8	Is the magnitude of the exposure effect determined?	2	2	2	2	2	2	2	2
9	What is the precision of the exposure effect estimate?	1	2	2	2	2	2	2	2
10	Are the results reliable?	2	2	2	2	2	2	2	2
11	Are the results applicable to the local (local) population?	2	2	2	2	2	2	2	2
12	Are the results of the study compatible with other available evidence?	2	2	2	2	2	2	2	2
Total		23	24	24	23	24	24	24	24

Table 2. Assessment of study quality cohort study.

No	Indicator	Publication (Author and Year)					
		Tao et al. (2021)	Leverl et al. (2019)	Salindri et al. (2016)	Cheng et al. (2021)	Wingfield et al. (2014)	Salindri et al. (2016)
1	Does the research address a clearly focused problem?	2	2	2	2	2	2
2	Is the cohort research method appropriate to answer the research question?	2	2	2	2	2	2
3	Are there enough subjects to establish that the findings did not occur by chance?	2	2	2	2	2	2
4	Was the cohort selection based on objective and validated criteria?	2	2	2	2	2	2
5	Is the cohort representative of the defined population?	2	2	2	2	2	2
6	Was the follow-up done in sufficient time?	2	2	1	2	2	1
7	Were objective and unbiased outcome criteria used?	2	2	2	2	2	2
8	Are the smoking and poverty behavioral intervention measurement methods validated?	2	2	2	2	2	2
9	Are effect sizes practically relevant?	2	2	2	2	2	2
10	Are any belief interventions provided?	2	2	2	2	2	2
11	Have confounding factors been taken into account?	2	2	2	2	2	2
12	Do the results apply to your research?	2	2	2	2	2	2
Total		24	24	23	24	24	23

Table 3. Description of Primary Research included in the Meta-Analysis provide risk factors for smoking behavior on the incidence of MDR TB.

No	Author (Year)	Country	Study Design	Sample	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	aOR (95 % CI)
1	Zhang et al. 2016	China	case control	287 cases and 291 controls	TB patient	age, gender, occupation, education degree, distance to health facilities, alcohol smoking, room ventilation, knowledge of MDR-TB, previous TB treatment, and contact with MDR-TB patients	Non-smoking patient	To describe the characteristics and risk factors associated with MDR-TB	2.07 (1.66-3.19)
2	Ali et al. 2019	Sudan	case control	76 cases and 107 controls	TB patient	age, gender, occupation, education, place of residence, number of members, income, smoking, drugs, comorbid diseases	The patient does not have a smoking habit	To ensure predictors of MDR-TB in Sudan to provide future guidance	4.00 (1.20-13.02)
3	Workie et al. 2021	Ethiopia	case control	82 cases and 167 controls	TB patient	gender, age, marital status knowledge, alcohol, smoking, HIV, TB treatment support,	Patient does not smoke	To determine risk factors for MDR-TB . treatment	2.82 (1.14-6.94)
4	Lalwani et al. 2021	India	Control case	247 cases and 494 controls	TB patient	gender, age, education, occupation, HIV and DM status, smoking, alcohol, other substances, migration for work, income, and marital status	The patient does not have a smoking habit.	To determine risk factors for the development of MDR-TB	2.56 (1.19-3.26)
5	(Tao et al. 2021)	China	Cohort	1,703	TB patient	age, sex, BMI, smoking, symptoms, TB contacts	The patient does not have a smoking habit.	To summarize characteristics of host status and identify risk factors for MDR-TB.	1.69 (1.19-2.39)

No	Author (Year)	Country	Study Design	Sample	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	aOR (95 % CI)
6	(Leverit et al. 2019)	Tanzania	Cohort	332	TB patient	age, gender, place of residence, HIV status, history of TB that has been treated, smoking status, alcohol use, drug resistance pattern.	Patient does not smoke	To determine the proportion of treatment outcomes and their predictors among MDRTB patients in Tanzania	0.74 (0.32-1.77)
7	(Salindri et al., 2016)	Georgia	Cohort	268	TB patient	age, gender, education, income, smoking, alcohol, close contacts with MDR-TB patients, BMI, DM status, HIV	Patient never smoked	To assess risk factors for MDR-TB/	1.52 (0.50-4.59)

Table 4. Description of Primary Research included in the Meta-Analysis provide risk factors for poverty against MDR TB

No	Author (Year)	Country	Study Design	Sample	Population (P)	Intervention (I)	Comparison (C)	Outcome (O)	aOR (95 % CI)
1	Li et al. 2015	China	Control case	146 cases and 146 controls	TB patient	age, gender, education, marital status, occupation, income, area of work, house size, and house floor	Patients with high income	MDR-TB	9.90 (2.00-4.81)
2	Li et al. 2015	China	Control case	110 cases and 110 controls	TB patient	sociodemography, income, environment, diet, behavior, and other potential factors	Patients with high income (2000 per capita/year)	MDR-TB	5.32 (1.22-23.22)
3	Lalwani et al. 2019	India	Control case	247 cases and 494 controls	TB patient	gender, age, education, occupation, HIV and DM status, smoking, alcohol, other substances, migration for work, income, and marital status	Patient has income >2000 per capita/year	MDR-TB	1.82 (1.21-2.59)
4	Setiyadi et al. (2019)	Indonesia	Control case	81 cases and 228 controls	TB patient	gender, length of treatment, continued TB treatment, low monthly income, and education level.	Patients have high monthly income	MDR-TB	2.86 (1.18 -6.92)
5	Cheng et al. (2021)	China	Cohort	673	TB patient	age, gender, nationality, occupational risk, education, place of residence, family income, and type of MDR-TB diagnosis	The patient's family has middle to upper income	MDR-TB	1.34 (1.06- 1.66)
6	Salindri et al (2016)	Georgia	Cohort	268	TB patient	age, gender, education income, smoking, alcohol, close contact with MDR-TB sufferers, BMI, DM status, HIV and hypertension	Patients with monthly income <59 USD	MDR-TB	3.51 (1.56-8.20)
7	(Wingfield et al. 2014)	Peru	Cohort	93	TB patient	age, gender, education, number of householders, BMI, monthly income, duration of symptoms, and debt	Patients are classified as not poor	MDR-TB	1.25 (1.15-1.36)

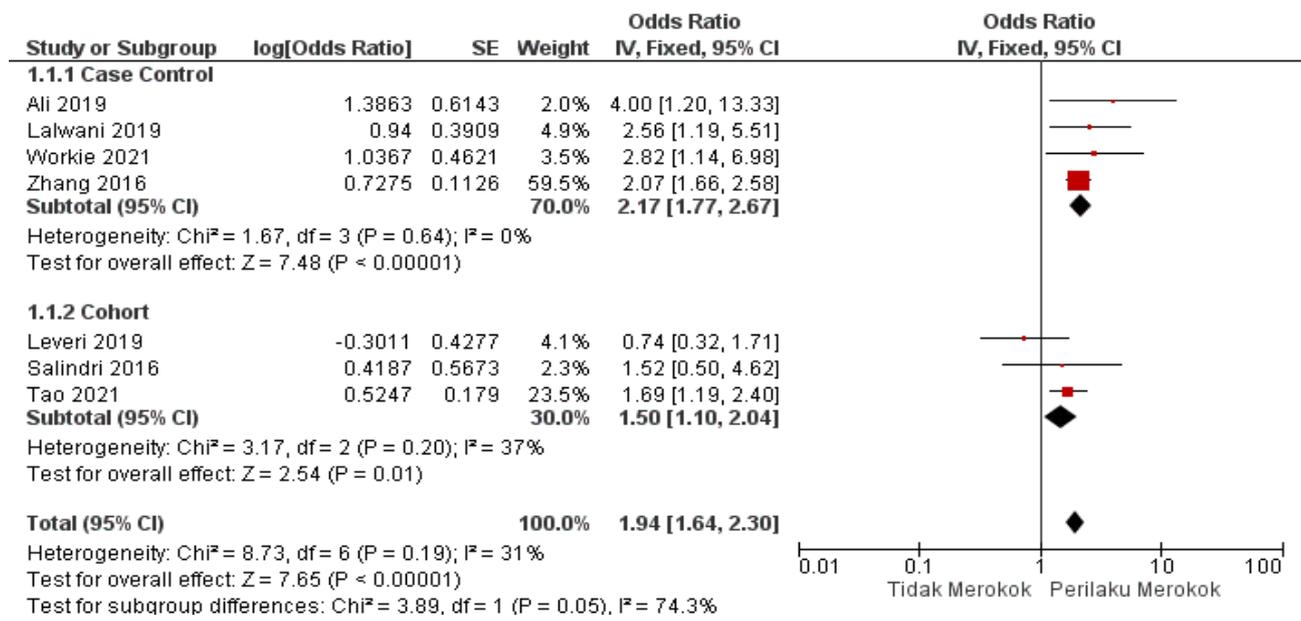


Figure 3. Forest plot Smoking against MDR TB

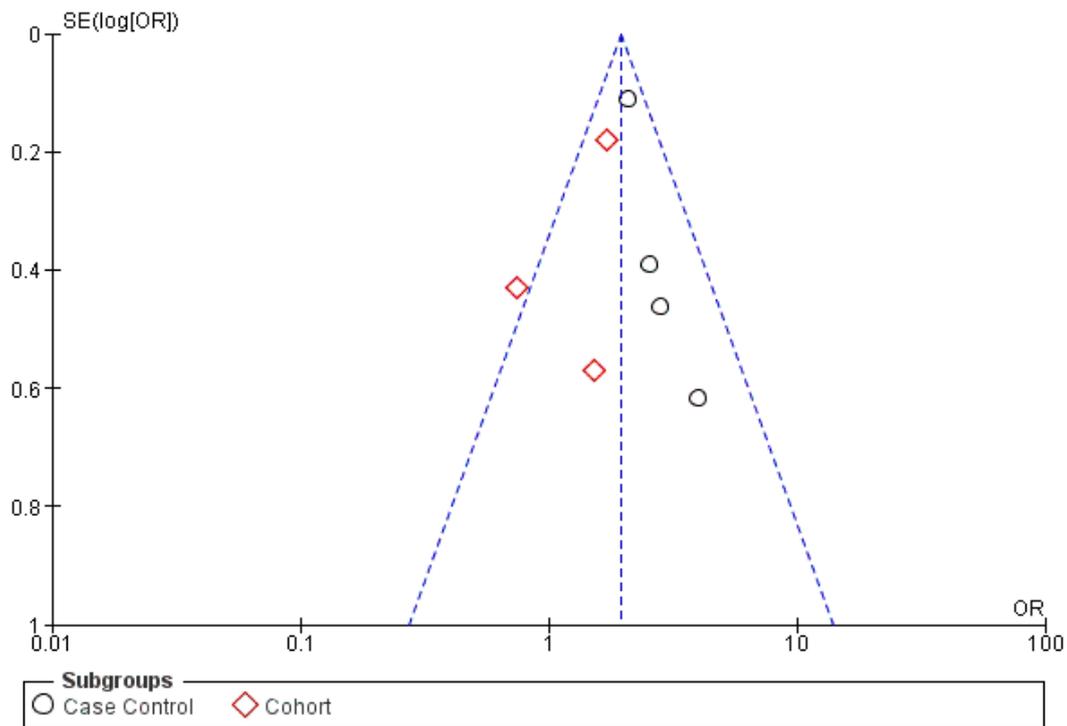


Figure 4. Funnel plot Smoking against MDR TB

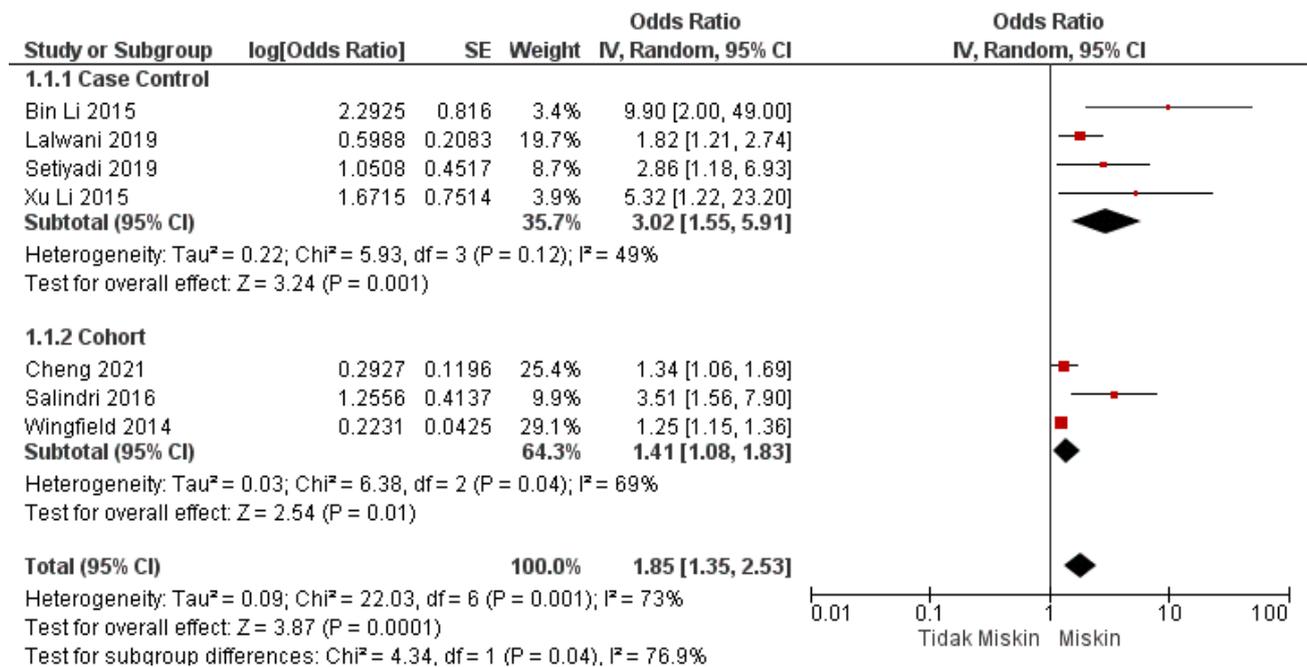


Figure 5. Forest plot poverty against MDR TB

The forest plot in Figure 5 shows that poverty behavior is a risk factor for MDR TB. In the cohort study, poor people have a 1.41 times risk of developing MDR TB compared to people who can afford it. In the case-control study, poor people had 3.02 times the risk of developing MDR TB

compared to people who could afford it and both were statistically significant (aOR= 1.85; 95% CI= 1.35 to 2.53; p=0.004). The heterogeneity of the research data shows I²= 73% so that the distribution of the data is declared heterogeneous (random effect model).

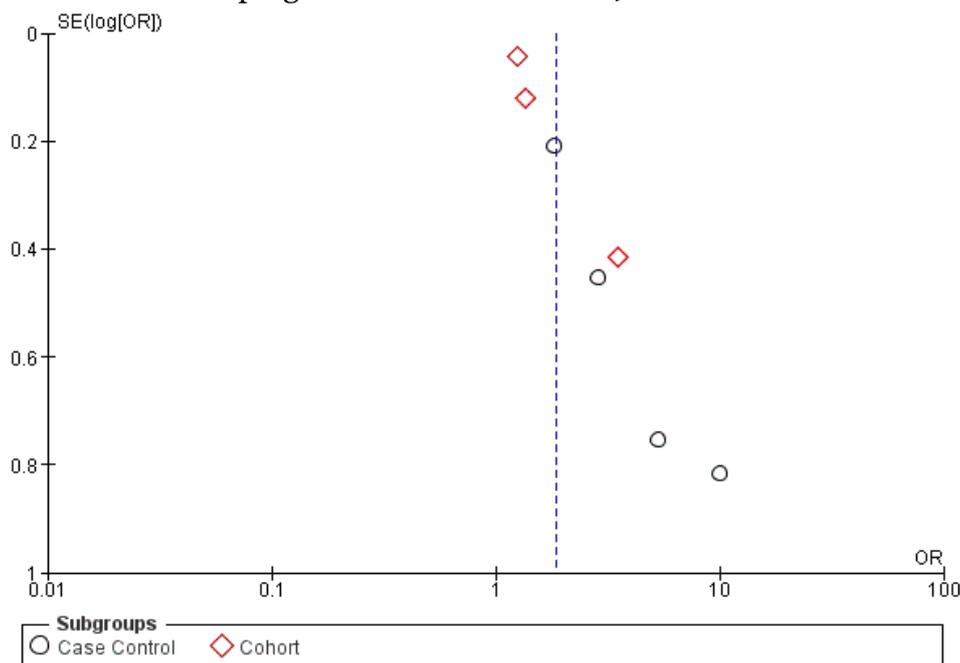


Figure 6. Funnel plot poverty against MDR TB

The funnel plot presented in Figure 6 shows a publication bias which is indicated by the asymmetry of the right and left plots where 4 plots are on the right, 2 plots are on the left and 1 touches the middle axis. The plot on the right of the graph shows 4 studies tend to be larger than the average aOR is smaller, this publication bias is a tendency to overestimate the actual study or is called an overestimate.

DISCUSSION

Theme of risk factors for smoking behavior and poverty on the incidence of MDR TB. This study focuses on the smoking behavior of patients undergoing TB treatment and living in poverty. The independent variables in this study were smoking behavior and poverty. The dependent variable in this study was MDR TB.

This systematic study as well as this meta-analysis used controlled studies for confounding factors that could be seen from the inclusion study requirements, namely multivariate analysis, and statistical results were reported by adjusted odds ratio (aOR). The combined estimation of smoking behavior and poverty on the incidence of MDR TB was processed using RevMan 5.3 with the generic inverse variance method.

The results of the systematic study and meta-analysis are presented in the form of forest plots and funnel plots. The forest plot provides an overview of each study examined in the meta-analysis, and an estimate of the overall outcome (Murti, 2018). The funnel plot shows visually the amount of variation (heterogeneity) (Murti, 2018). Funnel plots show the relationship between the study effect sizes and the sample sizes of the various studies studied, which can be measured in a number of different ways.

Previous studies that met the criteria regarding smoking behavior and poverty on the incidence of MDR TB were 12 articles spread across several continents, namely 7 articles from the Asian continent (China, India and Indonesia), 3 articles from the African continent (Sudan, Ethiopia and Tanzania), 1 article from North America (Georgia), 1 article from South America (Peru).

In the retrospective case control and cohort studies used in this study, it was explained in the primary study that smoking behavior and poverty factors in tuberculosis patients undergoing treatment, 11 of the 12 previous research articles stated that both factors significantly influenced the incidence of MDR TB. Smokers used as research subjects are active patients for treatment and have smoking behavior as well as subjects who are classified as under the poverty line.

1. Risk factors of smoking behavior on the incidence of MDR TB

The results of a systematic study and meta-analysis of 7 previous studies related to smoking behavior on the incidence of MDR TB provide an overview of the results that smoking behavior in the case control study aOR= 2.17 times and in the cohort study the aOR= 1.50 times can increase the risk factors for the occurrence of MDR TB. The results of the meta-analysis above as a whole show that smoking behavior can increase the incidence of MDR TB by 1.94 times compared to people who do not have smoking habits with statistical significance (aOR = 1.94; 95% CI = 1.64 to 2.30; p = 0.005). The heterogeneity of the research data shows $I^2 = 31\%$ so that the distribution of the data is not heterogeneous (fixed effect model).

In line with the results of research conducted by Welekidan et al. (2020) in Ethiopia stated that smoking habits are

more at risk of developing MDR TB than non-smokers. This relationship is closely related to patients who are non-adherent to anti-TB treatment, lack of treatment supervision or poor program quality, inappropriate drug regimens and inadequate drug supply can potentially lead to genetic mutations in bacteria and patients will become drug resistant.

This is supported by research from Semunigus et al. (2016) also stated that active smokers more than 5 years were 10.1 times more likely to have smear positive than those who smoked less than 5 years, this would increase the susceptibility to the risk of developing active TB or MDR TB. Bad habits of patients with smoking will cause a decrease in mucosal function which will detect incoming TB bacteria and then be killed, but their non-functioning will make MTB bacteria grow quickly and if the treatment is not carried out with good management, it will have the potential to become MDR TB.

2. Risk factors of poverty against MDR TB

The results of a systematic study and meta-analysis of 7 previous studies related to poverty on the incidence of MDR TB provide an overview of the results that poverty in the case control study aOR= 3.02 times and in the cohort study the aOR = 1.41 times can increase the risk factors for the occurrence of MDR TB. The results of the above meta-analysis as a whole show that poverty can increase the incidence of MDR TB by 1.85 times compared to people who are not in the poor category level with statistical significance (aOR = 1.85; 95% CI= 1.35 to 2.53; p= 0.004). The heterogeneity of the research data shows $I^2= 73\%$ so that the distribution of the data is declared heterogeneous (random effect model).

Research on poverty risk factors for the incidence of MDR TB is in line with research that has been done (Zhao et al. 2012) which states that poverty increases the risk of contracting MDR TB in living conditions that are densely populated, poor, periods of infection in the long term and lack of medical and health services. health care in areas in the poor category. People in the poor category will have an effect on the lack of knowledge and awareness in orderly carrying out treatment, treatment failure is closely related to previous treatment they have taken because they have stopped taking medicine because of far access to health.

In a study conducted (Tola et al. 2015) poverty or low economic status will affect the psychological pressure of patients undergoing MDR TB or first-line TB treatment. The psychological pressure of non-poor patients will have high motivation to recover, while patients who have low or poor economic status will be much more complex in the management of motivation to recover, besides affecting their low knowledge, they also occupy homes that do not meet the requirements of healthy homes such as poor lighting, damp floors and ventilation access for limited air exchange all of which will affect the easy spread of MDR TB bacteria in family clusters.

Patients with smoking behavior and being in the poverty line may be at greater risk of transmitting the disease with drug-resistant TB types to others (Zhao et al., 2012). Drug-resistant TB can occur when the drugs used to treat TB are not taken as prescribed. This can occur when a patient misses a dose or does not complete a full course of treatment. Other things that can trigger treatment failure are health care providers prescribing the wrong medication, the wrong dose, or the wrong length of

time to take medication, effective drugs are not available, and poor-quality drugs MDR-TB requires a treatment period of two to four times longer than drug-susceptible TB (Sejahwit et al., 2013).

AUTHOR CONTRIBUTION

Bibit Irawan is the main researcher who selects the topic, searches for and collects research data.

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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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