Journal of Health Promotion and Behavior (2021), 06(03): 233-249
Masters Program in Public Health, Universitas Sebelas Maret

Meta-Analysis

Meta-Analysis: Risk Factors Associated with Multidrugs-Resistant Tuberculosis (MDR-TB) in Tuberculosis Patients

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ABSTRACT

Background: Today, the world not only has to face a higher number of deaths from TB every year, but other challenges arise in the form of drug-resistant TB with risk factors that can affect the incidence of MDR TB, namely treatment-related factors (direct) and other factors (not direct). direct) such as biological, social, economic, and health system factors. The aim of this study was to estimate the risk of HIV infection, smoking and previous medication history on the incidence of MDR TB, with a meta-analysis of primary studies conducted by previous authors.
Subjects and Method: This study was conducted using a systematic review and meta-analysis study design using PICO, population: Tuberculosis Patients. Intervention: Risk Factors for HIV Infection, Smoking, and History of Medication. Comparison: no HIV infection, no smoking and no history of medication, Outcome: MDR-TB incidence. The articles used in this study came from 4 databases, namely Pubmed, ScienceDirect, ProQuest and Google scholar. The article keywords are ("Risk factor" or "associated") AND ("Multidrug resistant Tuberculosis" or "MDR TB") AND “Case Control” AND (HIV or Smoke or treatment). The articles included in this study are full paper articles, case-control study designs, 2011-2021 and the size of the relationship between Adj Odds Ratio. Article selection is done using PRISMA. Articles were analyzed using the Review Manager 5.3 application.
Results: A total of 20 case-control studies with 18,790 TB patients with details of 4,220 cases and 14,570 controls from 3 America, Africa, and Asia. HIV infection had a risk of 2.05 times in TB patients becoming MDR-TB (aOR = 2.05; 95% CI = 1.03 to 4.07; p= 0.040). Smoking had a 2.2 times risk in TB patients for MDR-TB (aOR= 2.20; 95% CI= 1.87 to 2.59; p<0.001). History of TB treatment had a 9.08 times risk in TB patients to become MDR-TB (aOR=9.08; 95% CI= 5.49 to 15.03; p<0.001).
Conclusion: Risk factors for HIV infection, smoking and history of TB treatment increase the incidence of TB to MDR-TB.

Keywords: Multidrugs Resistant Tuberculosis, HIV, smoking, TB treatment history

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Cite this as:
Andriani ND, Yuliani RD (2021). Meta-Analysis: Risk Factors Associated with Multidrugs-Resistant Tuberculosis (MDR-TB) in Tuberculosis Patients. J Health Promot Behav. 06(03): 233-249. https://doi.-org/10.26911/thejhpb.2021.06.03.07.

BACKGROUND

Tuberculosis (TB) is one of the 10 infectious diseases and the biggest cause of death in the world, which is greater than HIV/AIDS every year. This causes health problems for millions of people every year. TB is an infectious disease caused by the bacterium Mycobacterium tuberculosis. This disease

attacks the lungs (pulmonary TB) but can also affect other organs (extrapulmonary TB). This disease is spread when people with pulmonary TB release bacteria into the air, for example by coughing, sneezing, talking or laughing. Although this disease is curable, it is still the second leading cause of death from other infectious diseases.

During the COVID-19 pandemic, it affected the handling of TB priority programs in several countries. Based on data from WHO in the 2021 Global Tuberculosis Report during the COVID-19 Pandemic the most obvious impact was a major global decline in the number of people newly diagnosed with TB reported falling from 7.1 million in 2019 to 5.8 million in 2020. Reduced access TB diagnosis and treatment has resulted in an increase in TB mortality. The global number of deaths from TB in 2020 is 1.3 million, almost double the number of deaths from HIV/AIDS. In 2020, WHO published estimates of causes of death globally, and TB ranks second as the single leading cause of death from infection after COVID-19 (World Health Organization, 2021).

Today, the world not only has to face a higher number of deaths from TB every year, but another challenge arises in the form of drug-resistant TB. WHO categorizes into 5 classifications of drug-resistant TB cases, namely isoniazid-resistant TB, RR-TB, Multidrug-Resistant Tuberculosis (MDR-TB), pre-extensively drug-resistant TB (pre-XDR-TB) and XDR-TB. Detection of drug resistance in TB requires bacteriological examination for confirmation of TB and drug resistance tests using rapid molecular tests, culture methods or sequencing technology (WHO, 2020). Multidrug-Resistant Tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to rifampin and isoniazid, these two first-line antituberculosis drugs which are an ongoing global public health challenge. In 2019, the World Health Organization (WHO) estimated that only about 35% of the estimated 500,000 incident cases of MDR-TB were initiated with an appropriate MDR-TB treatment regimen. Among the group of patients who underwent treatment, treatment outcomes were consistently less than optimal. In 2019, only 57% of patients who started MDR-TB treatment 2 years earlier i.e. 2017 successfully completed treatment. Deaths during MDR-TB treatment accounted for 15% of all patients who did not complete treatment. Based on WHO (2021), globally in 2020 as many as 71% or 2.1 million people diagnosed with confirmed bacteriological TB drug resistance to rifampin (World Health Organization, 2021).

A study conducted in South Africa in 2017 showed that the mortality rate of MDR-TB patients was significantly high and was more common among previously treated TB cases. Research conducted in various countries also showed the same results, namely the rate of MDR-TB was much higher in TB patients who had been treated than in new TB patients. In addition, several studies have identified risk factors associated with MDR-TB, including poor adherence to treatment, inappropriate dosing, short duration of treatment, and inadequate medication.

The risk factors that cause MDR-TB are categorized as treatment-related factors (direct) and other factors (indirect) such as biological, social, economic, and health system factors. All of these factors need to be mapped out in detail to develop an effective control strategy against MDR-TB. Based on a study conducted in India, MDR-TB is closely related to treatment failure, contact with TB patients, and related to adherence to TB treatment. While the correlation of MDR-TB with age, sex, and HIV status

shows the role of the immune system in the emergence of the MDR phenotype (Shivekar et al., 2020). In a study conducted in Bhutan, it was shown that previous TB treatment, inadequate sleep duration, and traveling by public transport were risk factors associated with MDR-TB in Bhutan. Strengthening early case detection, strengthening treatment strategies, improving treatment adherence, and raising awareness can help control the growing MDR-TB epidemic (Tenzin et al., 2020). Several of these studies have been carried out in various parts of the world including South Asian countries to determine risk factors for MDR-TB. Therefore. The aim of the study was to identify sociodemographic and clinical factors associated with MDR-TB relative to drug-susceptible TB using a meta-analysis method. With research questions in the form of: "What factors are associated with Multidrugs Resistant Tuberculosis (MDR-TB) in Tuberculosis Patients?"

SUBJECTS AND METHOD

1. Study Design

This research was conducted using a systematic review and meta-analysis study design. The articles used in this study came from various sources. Article searches were carried out comprehensively through search engines with databases of “Pubmed”, “Science Direct”, “ProQuest” and “Google scholar”.

This research started from January 2022 and is the result of searching for data from previous studies. The articles used are articles published from 2011 to 2021. The selection of articles uses a flow chart, namely the PRISMA Flow Diagram. The keywords used in the article search were ("Risk factor" or "associated") AND ("Multidrug resistant Tuberculosis" or "MDR TB") AND "Case Control" AND (HIV or Smoke or treatment).

2. Inclusion Criteria

The inclusion criteria in this study were articles in the form of full papers, articles with observational study designs, especially case-control, articles published between 2011-2021, the analysis used must be multivariate with the size of the relationship Adjusted Odds Ratio. Subjects in the study were tuberculosis patients. The intervention studied was the risk factors that caused MDR-TB in the form of infection with HIV co-morbidities, smoking and history of TB treatment. The outcome to be studied is the incidence of Multidrugs resistant tuberculosis (MDR-TB).

3. Exclusion Criteria

The exclusion criteria in this study were duplication of articles, articles published other than in English before 2011.

4. Operational Definition of Variables

An article search was conducted to consider the eligibility criteria determined using the PICO model. Population: Tuberculosis Patients, Intervention: Risk Factors for HIV Infection, Smoking, and Medication History. Comparison: no HIV infection, no smoking and no history of treatment, Outcome: MDR TB incidence.

HIV infection is a pathogen that attacks the human immune system. The instrument used is the patient's past history or by using medical records. The measurement scale is categorical.

Smoking is an activity or activity of sucking tobacco smoke that has become a cigar, then ignited using a fire. The instrument used is the patient's past history. The measurement scale is categorical.

TB treatment history was defined as treatment history based on previous history of taking OAT (Anti Tuberculosis Drugs). The instrument used is the patient's past history or by using medical records. The measurement scale is categorical.

MDR-TB (Multi Drug Resistant TB) is defined as tuberculosis mycobacteria that are resistant to at least isoniazid and rifampin. The instrument used is the patient's past history or by using medical records. The measurement scale is categorical.

5. Instruments

The instrument in this study is the PRISMA Flow diagram using a research quality assessment using predetermined criteria, namely using the Critical Appraisal Checklist.

6. Data Analysis

From the articles that have been collected, data processing is carried out using the Review Manager application (RevMan 5.3) issued by the Cochrane Collaboraton. Data processing is done by calculating the value of effect size and heterogeneity.

RESULTS

In the process of searching for articles to be synthesized, meta-analysis is carried out by searching several journal databases including Google Scholar, Pubmed, Science Direct and Proquest. In the process of reviewing and selecting articles, it can be seen using the PRISMA FLOW flowchart shown in Figure 1.

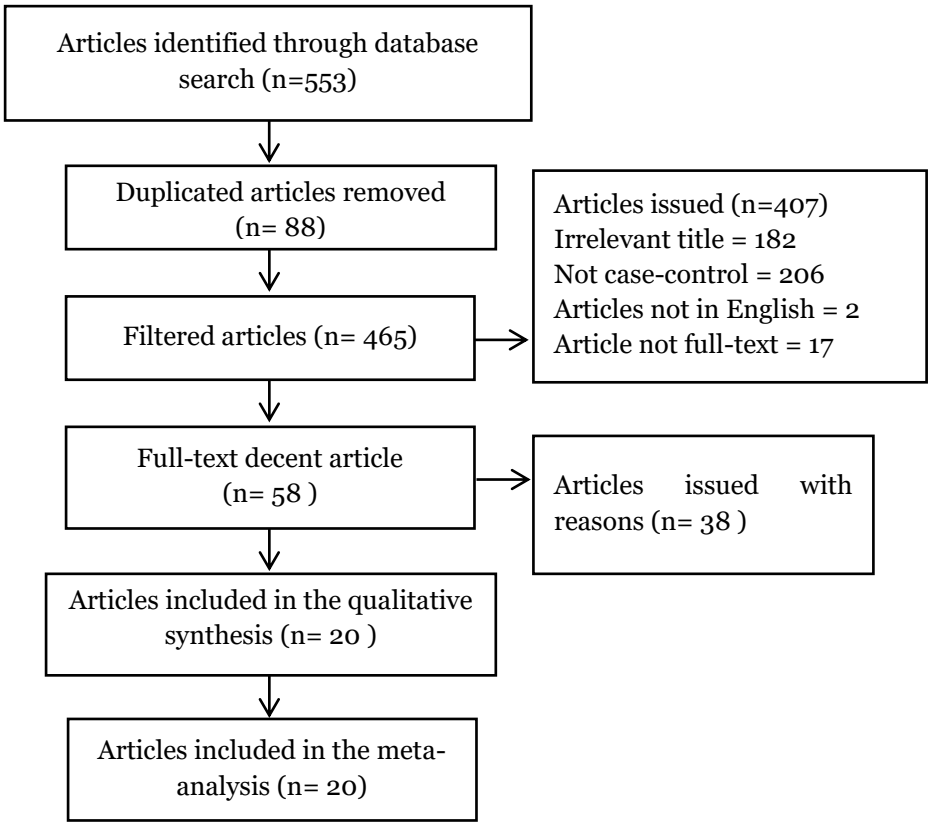

Figure 1. Results of Prisma Flow Diagrams

Figure 2. Research Distribution Map

Research related to Risk Factors associated with Multidrugs Resistant Tuberculosis (MDR-TB) in Tuberculosis Patients consists of 20 articles from the initial search process yielding 553 After deleting the duplication of articles, 465 articles were produced, then after the process of removing the duplication of articles, the next step was to check the relevance of the title and the study design used to produce 58 articles. After that, the articles were checked according to the inclusion criteria and the exclusion criteria were obtained as many as 20 articles. From the filtered articles, an assessment of the quality of the research was carried out, it was found that 20 articles met the assessment of research quality which would be included in the quantitative synthesis using meta-analysis.

Based on Figure 2, it can be seen that the research came from 3 continents, namely the African continent which consists of countries (Burundi, Ethiopia, Senegal, and Sudan), the Asian continent (Bangladesh, Bhutan, China, India, Malaysia, Pakistan and Thailand,) and the Americas. Consisting of Brazil. Table 1 shows the results of the research quality assessment process. Table 2 shows that of the 20 articles, there were 8 journal articles with Case-Control research designs showing evidence of an association between HIV infection and MDR-TB incidenceThis study deals with the effect of screen time and fast food on the incidence of obesity in children and adolescents consisting of 15 articles from 5 continents, namely 4 studies from the Asian continent and 7 studies from the African continent, a study from the America, a study from the Australian continent, and 2 studies from the European continent.

Research Quality Assessment

Assessment of the quality of research articles using the Critical Appraisal Checklist for cross-sectional study which can be seen in table 1. The criteria for evaluating articles with cross-sectional study design are as follows:

1. Does the study formulate the research question (research problem) clearly?
2. Is the cross sectional research method appropriate to answer the research question?

3. Is the method for selecting research subjects clearly described?
4. Does the sampling technique not introduce bias (selection)?
5. Is the sample representative of the research target population?
6. Is the sample size based on consideration of the results of previous studies regarding statistical power?
7. Is the minimum response rate achieved?
8. Is the instrument in determining screen time and fast food valid and reliable?
9. Has statistical significance been tested?
10. Did the researcher report confidence intervals?
11. What confounding factors have been taken into account?
12. Are the results applicable in practice or in the community?

After assessing the quality of the study, 15 articles were divided into 2 categories according to the dependent variable included in the quantitative synthesis of meta-analysis using RevMan 5.3.

Table 1. Research Quality Assessment

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Ahmad et al. (2012)	1	1	1	1	1	1	1	1	1	1	1	1	12
Garrido et al. (2012)	1	1	1	1	1	1	1	1	1	1	1	1	12
Chen at al. (2013)	1	1	1	1	1	1	1	1	1	1	1	1	12
Hirpa et al. (2013)	1	1	1	1	1	1	1	1	1	1	1	1	12
Rifat et al. (2014)	1	1	1	1	1	1	1	1	1	1	1	1	12
Mulisa et al (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Elmi et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Huai et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Jitmuang et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Shariff et al. (2016)	1	1	1	1	1	1	1	1	1	1	1	1	12
Zhang et al. (2016)	1	1	1	1	1	1	1	1	1	1	1	1	12
Workicho et al. (2017)	1	1	1	1	1	1	1	1	1	1	1	1	12
Ali et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Sharma et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Alena et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Eduma et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	1	12
Tenzin et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Nidaye et al. (2020)	1	1	1	1	1	1	1	1	1	1	1	1	12
Ambaye et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Iradukunda et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12

Table 2. Description of Primary Research included in the Meta-Analysis

No	Author (Year)	Country	Study Design	Sampel		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	aOR (95% CI)
				Case	Control					
1	Ahmad et al. (2012)	Pakistan	Case-Control	50	75	TB Patient	TB treatment history	No History of TB Treatment	Incidence of MDR-TB	4.2 (1.1 to 15.4)
2	Garrido et al. (2012)	Brazil	Case-Control	1584	9728	TB Patient	1. TB treatment history 2. HIV infection	1. No History of TB Treatment 2. No HIV Infection	Incidence of MDR-TB	1. 3.20 (2.25 to 4.57) 2. 1.62 (1.38 to 1.89)
3	Chen et al. (2013)	China	Case-Control	98	83	TB Patient	TB treatment history	No History of TB Treatment	Incidence of MDR-TB	2.18 (1.05 to 4.52)
4	Hirpa et al. (2013)	Ethiopia	Case-Control	134	134	TB Patient	Smoking	No smoking	Incidence of MDR-TB	0.4 (0.1 to 1.88)
5	Rifat et al. (2014)	Bangladesh	Case-Control	250	750	TB Patient	Smoking	No smoking	Incidence of MDR-TB	1.58 (0.99 to 2.50)
6	Mulisa et al. (2015)	Ethiopia	Case-Control	88	177	TB Patient	1. TB treatment history 2. HIV infection	1. No History of TB Treatment 2. No HIV Infection	Incidence of MDR-TB	1) 3.5 (1.57 to 6.99) 2) 1.4 (1.03-6.71)
7	Elmi et al. (2015)	Malaysia	Case-Control	105	209	TB Patient	1) TB treatment history 2) HIV infection	1) No history of TB treatment 2) No HIV Infection	Incidence of MDR-TB	1. 5.97 (2.73 to 13.04) 2. 0.22 (0.08 to 0.61)
8	Huai et al. (2015)	China	Case-Control	56	61	TB Patient	TB treatment history	No History of TB Treatment	Incidence of MDR-TB	3.82 (1.86 to 7.85)

Table 2. Continue

9	Jitmuang et al. (2015)	Thailand	Case-Control	47	141	TB Patient	HIV Infection	No HIV infection	Incidence of MDR-TB	1. 3.83 (1.02 to 14.38)
10	Shariff et al. (2016)	Ethiopia	Case-Control	134	134	TB Patient	Smoking	No smoking	Incidence of MDR-TB	0.4 (0.1 to 1.88)
11	Zhang et al. (2016)	Bangladesh	Case-Control	250	750	TB Patient	Smoking	No smoking	Incidence of MDR-TB	1.58 (0.99 to 2.50)
12	Workicho et al. (2017)	Ethiopia	Case-Control	88	177	TB Patient	1. TB treatment history 2. HIV infection	1. No History of TB Treatment 2. No HIV Infection	Incidence of MDR-TB	1. 3.5 (1.57 to 6.99) 2. 1.4 (1.03 to 6.71)
13	Tenzin et al. (2020)	Bhutan	Case-Control	79	118	TB Patient	TB treatment history	No History of TB Treatment	Incidence of MDR-TB	5.90 (2.55 to 13.64)
14	Ali et al. (2019)	Sudan	Case-Control	76	107	TB Patient	1. TB treatment history 2. HIV infection	1) No History of TB Treatment 2) No Smoking	Incidence of MDR-TB	1) 56.9 (10.2 to 319.2) 2) 4 (1.2 to 13.2)
15	Sharma et al. (2019)	India	Case-Control	247	494	TB Patient	1) TB treatment history 2) HIV infection 3) Smoking	1) No History of TB Treatment 2) No HIV infection 3) No Smoking	Incidence of MDR-TB	1) 8.86 (5.45 to 11.2) 2) 9.45 (6.80 to 15.9) 3) 56 (1.19 to 3.26)
16	Alena et al. (2019)	Ethiopia	Case-Control	242	210	TB Patient	1) TB treatment history 2) HIV infection	1) No history of TB treatment 2) No HIV Infection	Incidence of MDR-TB	1) 83.8 (40.7 to 172.5) 2) 1.10 (0.46 to 2.63)

Table 2. Continue

17	Elduma et al. (2019)	Sudan	Case-Control	430	860	TB Patient	1) TB treatment history 2) Smoking	1) No History of TB Treatment 2) No Smoking	Incidence of MDR-TB	1) 54.85 (30.48 to 98.69) 2) 3.23 (1.73 to 6.04)
18	Nidaye et al. (2019)	Senegal	Case-Control	169	507	TB Patient	TB treatment history	No History of TB Treatment	Incidence of MDR-TB	29.5 (27.3 to 30.1)
19	Ambaye et al. (2021)	Ethiopia	Case-Control	98	295	TB Patient	1. TB treatment history 2. HIV infection 3. Smoking	1. No History of TB Treatment 2. No HIV infection 3. No Smoking	Incidence of MDR-TB	1) 14.16 (7.8 to 25.4) 2) 4.39 (1.85 to 10.4) 3) 2.29 (0.79 to 6.69)
20	Iradukunda et al. (2021)	Burundi	Case-Control	60	120	TB Patient	1) TB treatment history 2) HIV infection	1) No History of TB Treatment 2) No Smoking	Incidence of MDR-TB	1) 2.16 (1.06 to 3.42) 2) 3.17 (2.06 to 5.45)

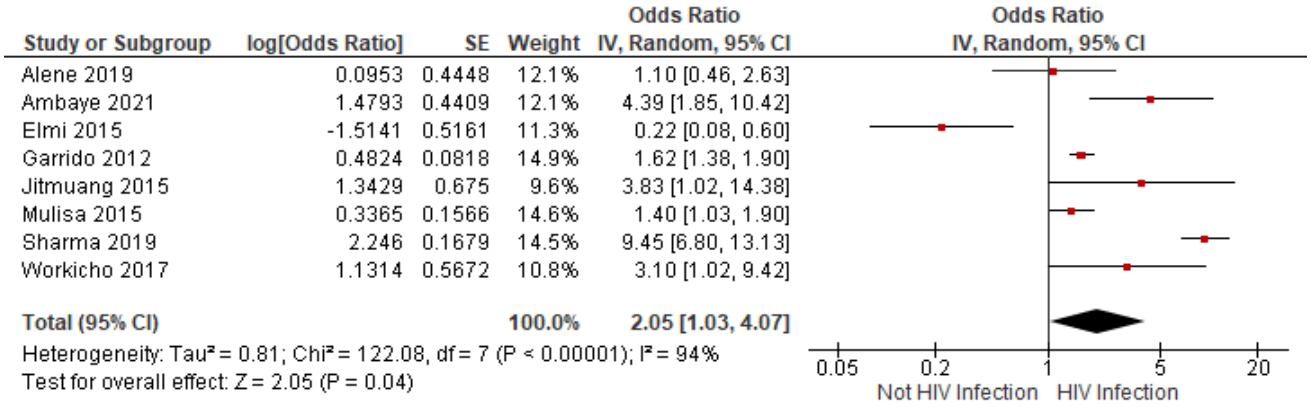

Figure 3. Forest Plot of HIV Infection Risk Factors with Incidence of MDR-TB

Based on the results of the Forest Plot Case-Control study shown in Figure 3 on the relationship between HIV infection and the incidence of MDR-TB, it shows that HIV infection has a 2.05 times risk in TB patients to become MDR-TB compared to TB patients without comorbid HIV infection (aOR = 2.05; 95% CI = 1.03 to 4.07) and the results were statistically significant (p<0.040). In the heterogeneity test in the study with risk factors for HIV infection with MDR-TB incidence, it showed I^2= 94% so that the distribution of data was declared heterogeneous Random Effect Model.

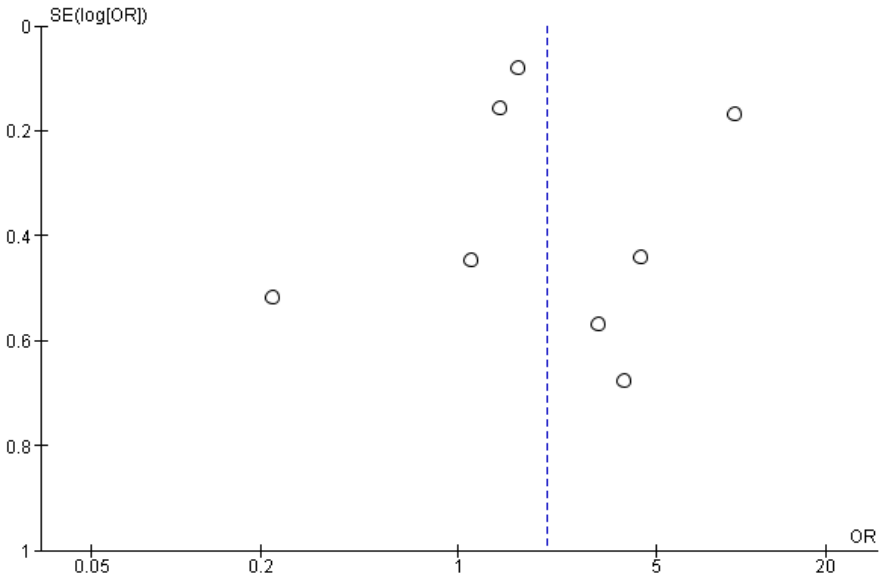

Figure 4. Funnel Plot of HIV Infection Risk Factors with the Incidence of MDR-TB

On the results of the Funnel Plot. Figure 4 shows that the distribution is symmetrical between the distributions on the right and left sides. There are 4 plots on the right, there are 4 plots on the left. The symmetrical distribution of the funnel plot indicates that there is no publication bias, and conversely, the asymmetrical shape of the funnel plot indicates the potential for publication bias (Godavitarne et al., 2018). The

plot on the right side of the graph has a standard error (SE) between 0 and 0.8. The plot on the left side of the graph has a standard error (SE) between 0 and 0.6.

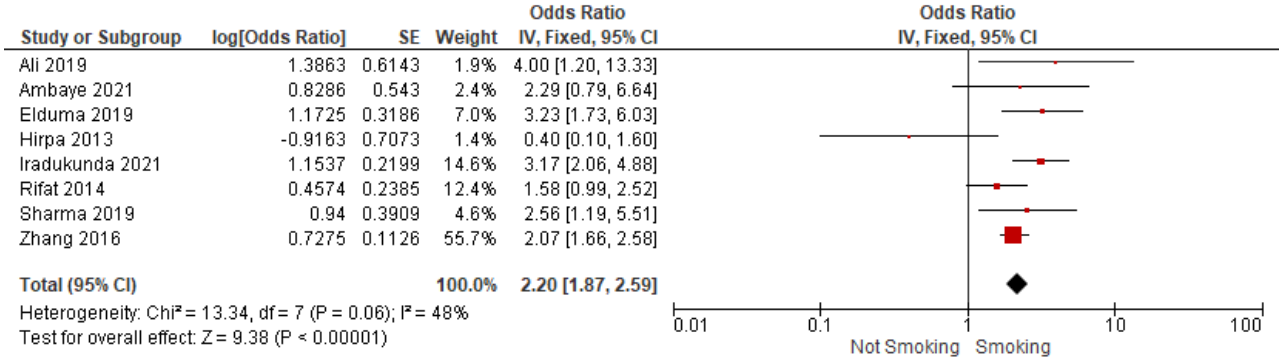

Figure 5. Forest Plot of Smoking Risk Factors with Incidence of MDR-TB

Table 2 shows that from 20 articles there are 8 journal articles with Case-Control research designs showing evidence of a relationship between smoking and the incidence of MDR-TB. The results of the Forest Plot Case-Control study in Figure 5 the relationship between smoking and the incidence of MDR-TB showed that smoking had a 2.2 times risk in TB patients to become MDR-TB compared to TB patients without smoking comorbidities (aOR= 2.20; 95% CI = 1.87 to 2.59) and the results were statistically significant (p<0.001). In the heterogeneity test in the study with smoking risk factors, the incidence of MDR-TB showed I^2= 48% so that the distribution of data was declared heterogeneous in the Fixed Effect Model.

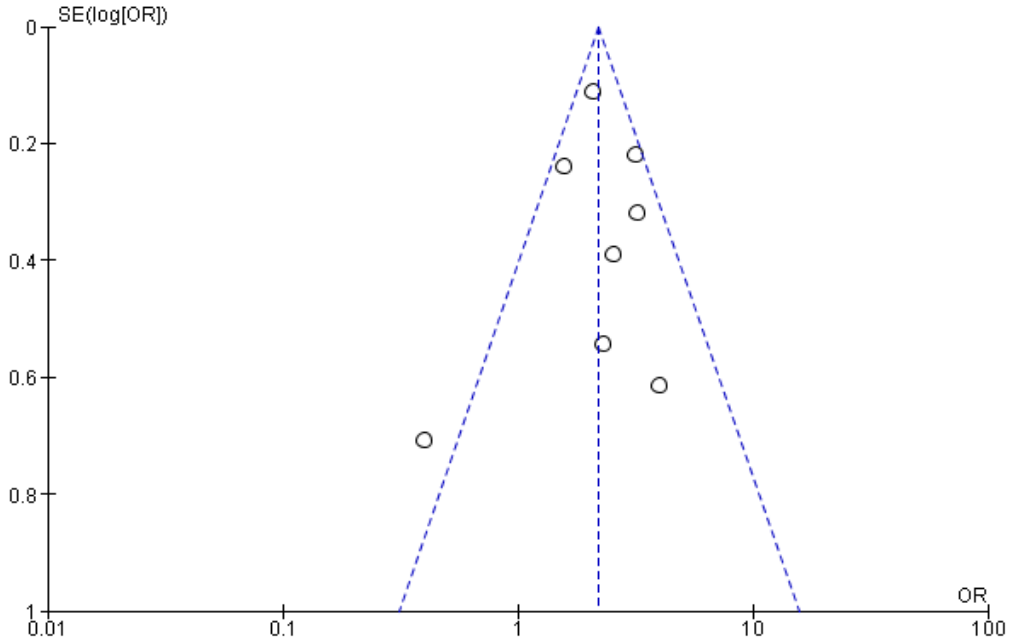

Figure 6. Forest Plot of Smoking Risk Factors with Incidence of MDR-TB

Based on the results of the Funnel plot in Figure 6, it shows that there is a possibility of publication bias by showing an asymmetric distribution between the distributions on the right and left sides. There are 5 plots on the right, 3 plots on the left and 2 plots that touch the vertical line. The plot on the right side of the graph has a standard error (SE) between 0 and 0.8. The plot on the left side of the graph has a standard error (SE) between 0 and 0.8.

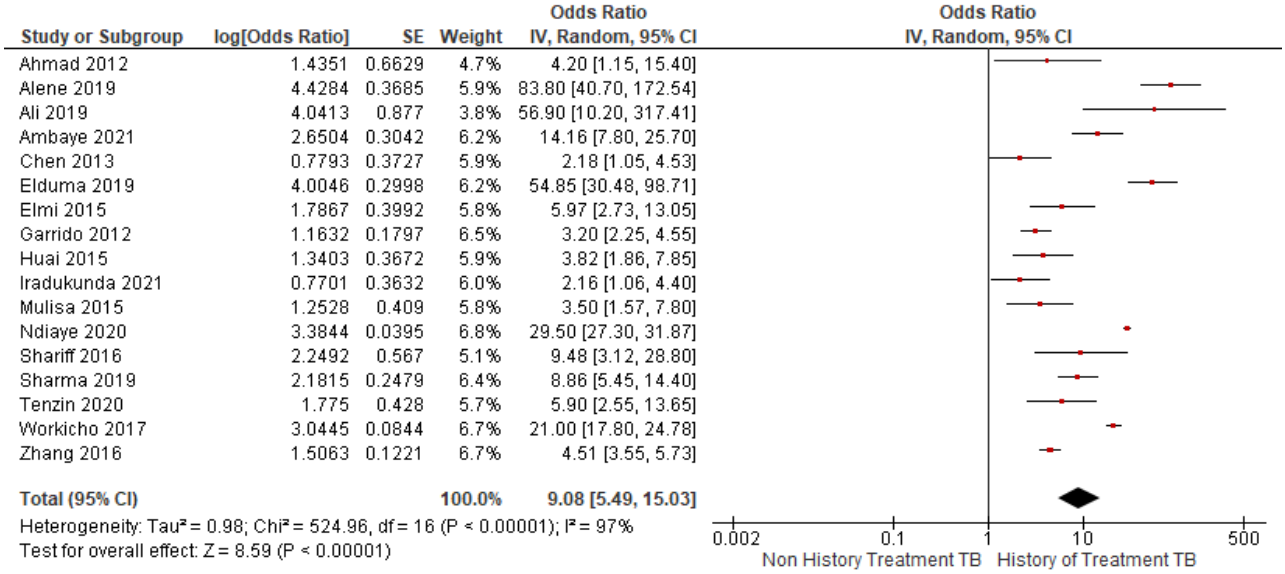

Figure 7. Forest Plot Risk Factors History of TB Treatment with the incidence of MDR-TB

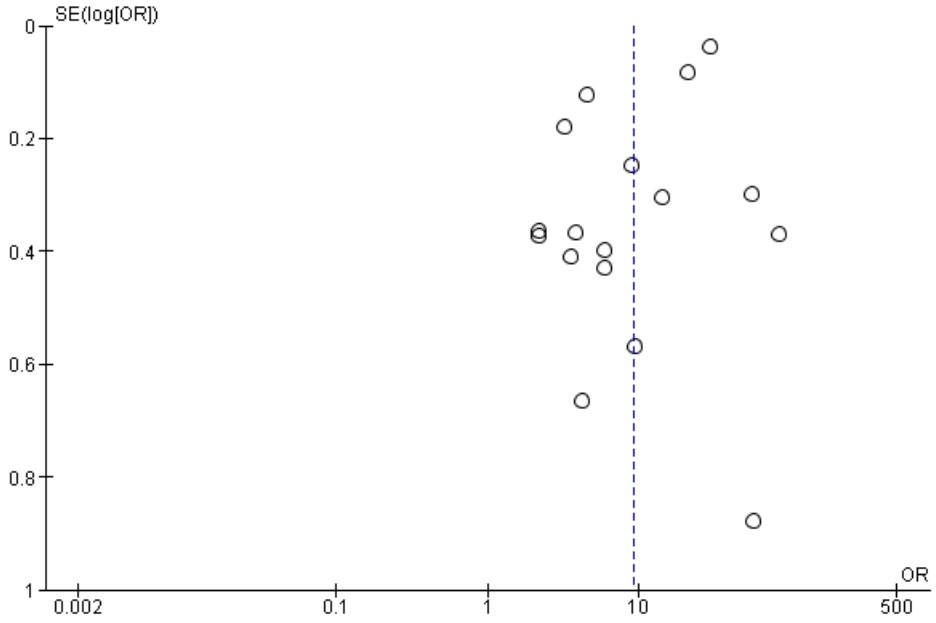

Figure 8. Funnel Plot Risk Factors History of TB Treatment with Incidence of MDR-TB

Table 2 shows that from 20 articles there are 17 journal articles with Case-Control research designs showing evidence of a relationship between TB treatment history and MDR-TB incidence. The results of the Forest Plot Case-Control study in Figure 7

of the relationship between TB treatment history and MDR-TB incidence showed that TB treatment history had a 9.08 times risk in TB patients to become MDR-TB compared to TB patients without comorbid TB treatment history (aOR= 9.08; 95%CI= 5.49 to 15.03) and the results were statistically significant (p < 0.001). In the heterogeneity test in the study with a risk factor for TB treatment history with MDR-TB incidence, it showed I2 = 97% so that the distribution of data was declared heterogeneous (Random Effect Model). On the results of the Funnel Plot.

Figure 8 shows that there is a possibility of publication bias by showing an asymmetric distribution between the distributions on the right and left sides. There are 6 plots on the right, 9 plots on the left and 2 plots that touch the vertical line. The plot on the right side of the graph has a standard error (SE) between 0 and 1. The plot on the left side of the graph has a standard error (SE) between 0 and 0.8.

DISCUSSION

Drug-resistant tuberculosis (MDR-TB) is the result of chromosomal changes due to mutations or deletions, there are several factors related to TB control programs that have a significant impact on the increase and transmission of drug-resistant TB (Mesfin et al., 2018). This systematic review and meta-analysis study identified factors associated with the incidence of MDR TB in Tuberculosis patients. This study discusses the factors of HIV infection, smoking and history of tuberculosis treatment which are considered important because they are risk factors that can be associated with the incidence of MDR TB.

HIV infection can be associated with the incidence of MDR TB. This study is in line with research conducted by (Sharma et al., 2019) that the HIV infection factor has a significant relationship to the incidence of MDR TB (aOR= 9.45; 95% CI= 6.80 to 15.9). In addition, another study (Ambaye and Tsegaye, 2021) with a sample of 244 infected with HIV was associated with the incidence of MDR TB. HIV positive increased the risk of developing MDR TB by 4.4 times compared with HIV negative TB patients (aOR = 4.39 ; 95% CI = 1.85 to 10.4). HIV and MDR TB are the reasons for the association between drug resistance and HIV infection. This may be especially important in a country with MDR-TB and a high HIV burden such as Ethiopia.

There are several epidemiological reasons that M/XDR-TB can be associated with HIV. The most important reason is the rapid disease progression due to having Drug Resistant strains, especially in the immunocompromised state compared to the immunocompetent state. In addition, malabsorption of anti-TB drugs leads to drug resistance and TB treatment failure. Susceptibility to MDR-TB infection increases when people with HIV who are immunocompromised get MDR-TB infection transmission from the surrounding environment, direct contact with MDR-TB will also increase infection in people with HIV infection. The prevalence of MDR-TB is 20% higher in HIV-positive than HIV-negative patients (Singh et al., 2020).

Most HIV-infected patients were more likely to be included in direct observation of treatment (DOTS) and more controlled during treatment. Furthermore, it is possible for these patients to stop taking all anti-TB drugs at once which will lead to treatment failure and then lead to MDR-TB. The problem is further compounded by dual treatment with a combination of two drugs, one for MDR-TB and one for HIV. Patients are more likely to discontinue treatment because the drugs they are taking have a high burden of drug toxicity or side

effects. Treatment for MDR-TB patients is complex, has low effectiveness, is toxic, and can be augmented by HIV treatment.

In this study smoking is also a factor associated with the incidence of MDR TB . This study is in line with research conducted by (Zhang et al., 2016) that smoking is a risk factor associated with the incidence of MDR TB. In this study the smoking factor had a risk of 2 times the incidence of MDR TB (aOR= 2.07; 95% CI= 1.66 to 3.19). In addition, a study conducted by Iradukunda (2021) found that smoking had a 3.1 times risk of MDR TB incidence (aOR= 3.17; 95% CI= 2.06 to 5.45). MDR-TB patients were more likely to have been tobacco smokers in the past. Smoking is a major determinant of TB and several studies have shown an association with acquired drug resistance. Another study showed that smoking is a predictor of delayed response to treatment, so smoking is one of the factors associated with the incidence of MDR TB (Rifat et al., 2014).

In a study conducted by Mollel and Chilongola (Mollel and Chilongola, 2017) suggested that smoking has a relationship with the incidence of MDR-TB, this is because smoking lowers the body's immunity to infection. The severity of smoking also increases the risk of a person's resistance to TB drugs.

In this study, a history of previous TB treatment was associated with the incidence of MDR TB. This is in line with the study conducted by Ndiaye (Ndiaye et al., 2019) that failure in the history of TB treatment in patients was significantly associated with the incidence of MDR-TB in Senegal. It can be seen that the failure of a history of treatment has a risk of 2.9 times the incidence of MDR TB (aOR= 2.95; 95% CI= 27.3 to 30.1). In addition, it is also relevant to the study conducted by Tenzin (Tenzin et al., 2020) that past history of TB treatment had a 5.9 times risk of MDR TB incidence (aOR= 5.90; 95% CI= 2.55 to 13.64).

A history of previous TB infection is an important determinant for the development of MDR TB. The high risk of MDR occurrence among previously treated cases may be due to naturally occurring mutated resistance in mycobacteria and inadequate or interrupted treatment with anti-tuberculosis agents. The association between TB treatment failure and MDR-TB may be related to lack of treatment supervision, inappropriate drug regimens, and inadequate or irregular drug supply that may have a potential role in drug resistance (Amin et al., 2021). Multidrug resistance is reported more frequently among previously treated tuberculosis patients than new tuberculosis patients, history of previous TB treatment being the strongest determinant of MDR-TB in Europe (Rifat et al., 2014).

In conclusion, our study identified risk factors for HIV infection, smoking and history of TB treatment associated with MDR-TB. Several efforts can be made, such as early detection of patients who have the potential to have MDR-TB by monitoring specific clinical manifestations. In addition, integrated and enhanced efforts are needed to provide routine diagnosis, effective treatment and high quality care for HIV and MDR-TB coinfected patients and groups of patients who are socially vulnerable and at increased risk of treatment failure.

AUTHOR CONTRIBUTION

Nurul Dwi Andriani and Resta Dwi Yuliani are the main researchers in selecting topics, finding and collecting research data and processing this research data.

FUNDING AND SPONSORSHIP

This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

ACKNOWLEDGMENT

We thank the databases used in this research, namely Pubmed, Science Direct, Google Scholar and ProQuest.

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