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# Diabetes Mellitus and History of Tuberculosis Treatment as Risk Factors of Developing Multidrug-Resistant Tuberculosis at TB Polyclinic Dr. Soetomo General Hospital 2019 - 2020

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**Abstract.** Multidrug-Resistant Tuberculosis (MDR TB) is a condition when *Mycobacterium tuberculosis* were resistant to Isoniazid and Rifampicin simultaneously, with or without being followed by other first-line Anti-Tuberculosis Drugs. Diabetic patients who also have TB are more susceptible to drug resistance. There is ample evidence noting that a history of previous TB treatment is one of the main factors contributing to the development of MDR TB. This study was a case-control study. The sample of this study was all patients from TB Polyclinic Dr. Soetomo Hospital who were diagnosed with pulmonary TB by pulmonologists on January 1, 2019 – December 31, 2020, who met the inclusion criteria. The data obtained were analyzed using the IBM SPSS Statistics 23 application with a binary logistic regression test.There were 178 samples of this study. MDR TB (65.8%) was the dominant resistance type in Drug-Resistant Tuberculosis (DR TB) patients. Patients with DM were 2.2 times more likely to develop MDR TB than patients without DM. Patients with histories of previous tuberculosis (TB) treatment tended to be three times more likely to develop MDR TB than new patients. Other factors such as age, sex, BMI, history of alcohol consumption, and history of smoking did not show a significant relationship with the incidence of MDR TB. Diabetes Mellitus comorbidity and history of previous Tuberculosis treatment were significant risk factors for developing MDR TB.

**Keywords:** Diabetes mellitus; History of tuberculosis treatment; Tuberculosis; Multidrug-resistant; Previous tuberculosis treatment

## INTRODUCTION

Tuberculosis (TB) is a global health problem becoming the second leading cause of death from infectious diseases after the Human Immunodeficiency Virus (HIV). According to World Health Organization (2020), it was stated that as many as 10 million people suffer from TB and 1,5 million people die from TB every year. The high incident rate (IR) and case fatality rate (CFR) in TB disease are the biggest challenges for various countries, especially for developing countries such as Indonesia. Improper handling or transmission of TB from one person to another can trigger *Mycobacterium tuberculosis* (MTB) to develop resistance to antimicrobial drugs consumed, namely Multidrug-Resistant Tuberculosis (MDR TB). MDR TB is a condition when *Mycobacterium tuberculosis* were resistant to Isoniazid and Rifampicin simultaneously, with or without being followed by other first-line Anti-TB drugs (Kemenkes RI, 2020). In 2019, it was estimated that there would be 465,000 cases of Drug-Resistant TB worldwide. In addition to substantial TB cases, Indonesia was listed as the 7$^{th}$ country with the heaviest MDR TB burden globally (WHO, 2020).

Worldwide, type 2 diabetes (DM) prevalence is increasing, especially in developing countries where TB is endemic. Diabetes Mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Patients with DM had decreased immune systems. These patients were highly susceptible to bacterial infections, especially *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa, and Mycobacterium tuberculosis* (Schaible et al., 2007). Diabetic patients were more susceptible to infection by resistant strains (Fisher-Hoch et al., 2008). TB patients with DM complications often experience delayed sputum conversion by culture method, an increased risk of MDR TB, recurrence, and even death. Pharmacological interactions between rifampicin and anti-diabetic drugs were also suspected to be the cause of poor outcome of TB patients with DM comorbid (Nijland et al., 2006). A study in Taiwan by Chang et al. (2011) showed that TB patients with DM had more severe infections, higher MTB loads, higher rates of treatment failure, delayed elimination of MTB, and was more probably to progress to MDR TB than TB patients without Diabetes. TB patients with DM were at risk of having a poor prognosis. In addition, the presence of comorbid DM can also reduce the effectiveness of Anti-TB drugs. This phenomenon was explained in a study that showed that plasma levels of Rifampicin in TB patients with comorbid DM were 53% lower (Pasipanodya et al., 2012), which may affect the treatment outcomes. Resistant strains were more likely to develop in DM patients with compromised immune systems (Fisher-Hoch et al., 2008). A study showed that decreased IFN-Ɣ production in DM patients was associated with the decreased immune response to MTB infection and decreased IL-12 response to MTB stimulation in leukocytes from TB patients with DM, resulting in

decreased innate immune response (Chang et al., 2011). Higher MTB loads may cause the incidence of MDR TB in DM patients, changes in Anti-TB drugs pharmacokinetics, and low medication adherence (Wang K. et al., 2014).

History of TB treatment was recognized as the most significant risk factor that can cause MTB resistance to first-line of Anti-TB drugs. The prevalence of MDR TB was estimated to be ten times higher after the failure of previous treatment. In Europe, history of TB treatment was also the most significant risk factor for MDR TB (Faustini A. et al., 2006). MDR TB in previously treated TB patients usually results from exposure to drugs suppressing the growth of drug-sensitive MTB but allowing the multiplication of previous drug-resistant strains. MDR TB patients with history of TB treatment could be divided into the isoniazid and rifampicin mechanisms. Mutation of the katG gene in MTB was an essential process in the mechanism of isoniazid resistance. This gene contributed to the protection of bacteria against oxidative stress but also encoded catalase-peroxidase enzyme converting isoniazid into the active form (Gagneux et al., 2006). Rifampicin resistance occured due to mutations at a frequency of 10-7/-8, but the current study showed higher mutation frequency (Zhang, 2015).

## METHODS

This study was a correlation study with a case-control design. This study was conducted from October 2020 until May 2021 and approved by the Medical Ethics Committee of Dr. Soetomo General Hospital Surabaya. Observations were made through the patient's medical records at the TB Polyclinic Dr. Soetomo General Hospital regarding DM comorbid, TB treatment history, and socio-demographic data. The population of this study was all patients from the TB Polyclinic Dr. Soetomo General Hospital who were diagnosed with Drug-Resistant pulmonary TB by a pulmonologist in the period January 1, 2019 – December 31, 2020. The study samples were patients who met the inclusion criteria, such as those older than or equal to 18 years, resistance at least to Isoniazid and Rifampicin, and complete medical records. The exclusion criteria were incomplete medical records. The sample size in this study was calculated using the Epi Info 7 application with a two-sided confidence level of 99.99%, power 90%, a ratio of controls to cases 1. Following the previous study by Mi et al. (2014), the prevalence of Rifampicin-resistant (RR) and MDR in new cases was 10% and 6.2%, respectively, while the prevalence of RR and MDR in cases with a history of treatment was 12% and 62.3%h, therefore the percent of controls exposed used was 12%. The percent of cases with exposure was 62.3%. The minimum sample size required was 100, which was divided into 50 cases and 50 controls. The dependent variable of this study was the incidence of Multidrug-Resistant Tuberculosis. Diabetes Mellitus comorbid and history of TB treatment became the independent variables of this study. In this study, patients would be categorized into two groups, RR TB, which became the control group, and the case group was MDR TB, including MDR TB, Extensively Drug-resistant (XDR) TB, and pre-XDR TB. The data obtained were analyzed using the IBM SPSS Statistics 23 application with a binary logistic regression test, with a significant $p<0.05$. The possibility of the variables causing MDR TB was assessed by an Odd Ratio.

## RESULTS

Two hundred eighty-six patients were diagnosed with Drug-Resistant TB in 2019 - 2020; 178 patients fulfilled the inclusion criteria and became samples of this study. There were 61 RR TB patients (34.2%) and became control group, 93 MDR TB patients, 22 Pre-XDR TB patients, and 2 XDR TB patients. MDR TB, Pre-XDR, and XDR TB patients were grouped into the MDR TB variable, which amounted to 117 patients (65.8%) and became the case group in this study. The highest number of patients based on age were adults; 155 patients (87.1%). The average age of Drug-Resistant (DR) TB patients was 44.3 years. Based on gender, the number of male DR TB patients was more than female DR TB patients; 91 male DR TB patients (51.1%) and 87 women (48.9%). The majority of DR TB patients had history of TB treatment, as many as 120 patients (67.4%). The Body Mass Index (BMI) of DR TB patients was thin primarily (43.3%) and average (43.8%). More than half of DR TB patients had no DM comorbid (57.3%), history of smoking (69.3%), and history of alcohol consumption (84.3%). The relationships between independent variables and MDR TB was obtained by comparing MDR TB patients' medical records with RR TB patients at the TB Polyclinic Dr. Soetomo General Hospital 2019 - 2020 through binary logistic regression test. Diabetes Mellitus comorbid ($p=0.022$) and history of TB treatment ($p=0.002$) had a significant relationship with MDR TB. The odds ratio method was used to assess the likelihood of risk factors causing MDR TB. Patients with DM tended to be 2.2 times more likely to develop MDR TB than patients without DM. Patients with a history of TB treatment had three times greater tendency to progress to MDR TB than new patients.

According to the binary logistic regression test results in Table 2, it was found that age, sex, nutritional status, smoking history, and alcohol consumption history did not show a significant effect ($p>0.05$) on the incidence of MDR TB.

**Table 1.** Sample Characteristics

| Subject characteristics Resistance type | Amount (n=178) | Percentage (%) |
|---|---|---|
| RR | 61 | 34.2% |
| MDR | 93 | 52.2% |
| Pre-XDR | 22 | 12.4% |
| XDR | 2 | 1.1% |
| Gender | | |
| Man | 91 | 51.1% |
| Woman | 87 | 48.9% |
| Status Umur | | |
| Adolescent (11-19 years) | 4 | 2.2% |
| Adult (20-60 years) | 155 | 87.1% |
| Elderly (>60 years) | 19 | 10.7% |
| Nutritional Status (BMI) | | |
| Thin (<18,5) | 77 | 43.3% |
| Normal (18.5-25.0) | 78 | 43.8% |
| Obese (>25.0) | 23 | 12.9% |
| History of TB treatment | | |
| Yes | 120 | 67.4% |
| No | 58 | 32.6% |
| Diabetes Mellitus (DM) | | |
| Yes | 76 | 42.7% |
| No | 102 | 57.3% |
| Smoking history | | |
| Yes | 70 | 30.7% |
| No | 108 | 69.3% |
| Alcohol consumption | | |
| Yes | 28 | 15.7% |
| No | 150 | 84.3% |

Source: Processed Data

**Table 2.** Risk Factors of MDR TB

| Variable | Significance (p) | Odds Ratio (OR) |
|---|---|---|
| Age | 0.952 | 0.971 |
| Gender | 0.16 | 0.472 |
| Comorbid DM | 0.022 | 2.262 |
| Body Mass Index (BMI) | 0.186 | 0.716 |
| History of TB treatment | 0.002 | 3.055 |
| Smoking History | 0.687 | 1.258 |
| Alcohol Consumption | 0.48 | 0.694 |

Source: Processed Data

The relationships between independent variables and MDR TB was obtained by comparing MDR TB patients' medical records with RR TB patients at the TB Polyclinic Dr. Soetomo General Hospital 2019 - 2020 through binary logistic regression test. Diabetes Mellitus comorbid (p=0.022) and history of TB treatment (p=0.002) had a significant relationship with MDR TB. The odds ratio method was used to assess the likelihood of risk factors causing MDR TB. Patients with DM tended to be 2.2 times more likely to develop MDR TB than patients without DM. Patients with a history of TB treatment had three times greater tendency to progress to MDR TB than new patients. According to the binary logistic regression test results in Table 2, it was found that age, sex, nutritional status, smoking history, and alcohol consumption history did not show a significant effect (p>0.05) on the incidence of MDR TB.

## DISCUSSION

*Characteristics of Drug-Resistant TB Patients*

Based on Table 1, from 178 DR TB patients, 34.2% RR TB patients and 65.8% MDR TB patients were found. This result differed from studies by Tirtana & Musrichan (2011) and Adiwinata et al. (2018), which stated that monoresistance to rifampicin was the most common resistance pattern. It might be because isoniazid and rifampicin are the first-line active drugs in TB therapy. Therefore, the possibility of isoniazid and rifampicin being used as monotherapy or in combination with other antibiotics was higher (Putri et al., 2015). This study found that male DR TB patients were more than the number of female DR TB patients, 91 male (51.1%) and 87 female (48.9%). This result was concordant with a German study period 2008-2017 which found more male patients with DR TB (61%) (Glasauer et al., 2019). This result was also in line with a study by Sinha et al. (2017) in India period May 2012 - February 2014, which found a more significant number of male patients with DR TB than women (59%). This event could be caused by several factors, such as men who were more vulnerable due to social contact, exposure to dust, smoking habits, and alcohol consumption (More et al., 2017).

The patients' age groups were classified according to WHO (2020), which consisted of adolescents (10-19 years), adults (20-60 years), and the elderly (>60 years). The highest number of DR TB patients were adult patients (20-60 years). This result was in line with a study conducted in Belarus, Iran, which showed that the most common age group found in patients with first-line OAT resistance was the 25-44 year age group with 318 patients (34%) (Surkova et al., 2012). This result was also under a study by Cao et al. (2019) in China, which showed that patients with the highest number of first-line Anti-TB drugs resistance were 35-55 years with 72 patients (39%). Based on the explanation above, it could be seen that the highest age group was found in the working-age group. The working-age population itself is the population aged 15-64 years (OECD, 2021). This age group was mainly exposed to TB cases, which might be why this age group was considered more vulnerable (Sinha et al., 2017). In addition, high-risk behavior and the tendency to stop TB treatment could also affect the resistance in the working-age group (Adane et al., 2015). The nutritional status of DR TB patients was assessed by dividing weight (kilograms) by height squared ($m^2$) and finally getting Body Mass Index (BMI). The BMI threshold value uses the Indonesian Ministry of Health (2019) classification, which consists of thin (BMI <18.5 $kg/m^2$), standard (BMI 18.5-25.0 $kg/m^2$), and obese (BMI >25.0 $kg/m^2$). Based on Table 1, from 178 patients with DR TB, 43.3% were classified as thin, 43.8% normal, and 12.9% obese. The results of this study were supported by a study by Adiwinata et al. (2018), which found that 28.6% of patients had lean BMI status, 25% of patients had normal BMI status, and 3.6% of patients had obese BMI status. The large number of DR TB patients who were thin was related to a study by Park et al. (2016) showing that low BMI status (<18.5 $kg/m^2$) was an independent risk factor for failure of sputum culture conversion within three months in patients with DR TB.

This study revealed that 67.4% of DR TB patients had a history of taking Anti-TB drugs, and 32.6% were new cases. These results were consistent with a study in Malaysia showing that 66.7% of DR TB patients had a history of TB treatment, and 33.3% were new patients. The high number of DR TB patients who had a history of TB treatment might be due to poor patient compliance, so that it could increase the probability of secondary drug resistance. These phenomena were proved by a study in Iran which showed that MDR TB infected a group of patients with a history of TB treatment due to poor medication adherence, lack of surveillance during treatment, inappropriate drug prescription, problems in drug supply, and poor infection control in the treatment stage (Merza et al., 2011). In this study, 42.7% of RR TB and MDR TB patients had Diabetes Mellitus comorbid. This result was in line with Adiwinata et al.'s (2018) study, which showed that 42.9% of MDR TB or RR TB patients had comorbid Diabetes Mellitus. The high number of DR TB patients who had DM was associated with a decreased immune response in DM patients, causing an increased susceptibility to infection with resistant bacteria (Fisher-Hoch et al., 2008). This study found that DR TB patients without a history of smoking and alcohol consumption were greater than DR TB patients who had a history of smoking and alcohol consumption. The results of this study were in line with studies by Adiwinata et al. (2018) and Shariff et al. (2016). This result was also reinforced by BPS (2020), showing that alcohol consumption by people aged 15 years and over in Indonesia had decreased since 2018-2020. In 2018, alcohol consumption in Indonesia was recorded at 0.48 liters per capita and will become 0.39 liters in 2020.

*Risk Factors of MDR TB*

According to Table 2, Diabetes Mellitus comorbid had a significant relationship with the incidence of MDR TB ($p = 0.022$). Patients with DM comorbid tended to be 2.2 times more probably to develop MDR TB than patients without Diabetes. These results were consistent with a study in Malaysia by Shariff et al. (2016) that diabetic patients were twice as likely to develop MDR TB as those without this metabolic disease. These results are also supported by a study in Taiwan by Chang et al. (2011), which showed that TB patients with comorbid DM had more severe infections, higher MTB loads, higher rates of treatment failure, delayed elimination of MTB, and were more likely to develop MDR TB than TB patients without DM. MDR TB patients with Diabetes Mellitus were at risk of having a poor prognosis. In pulmonary TB patients with DM comorbid, a higher number of bacteria was found at the start of therapy. There was a higher possibility of mutations and the incidence of MDR TB with a higher number of bacteria. Therefore in these patients, more prolonged therapy was needed (Rumende, 2018). Resistant strains were more likely to develop in diabetic patients because they had weakened immune systems, so the prevalence of primary MDR TB was higher in these patients. Higher MTB loads might cause secondary MDR TB in DM patients, changes in OAT pharmacokinetics, and low medication adherence (Wang et al., 2014).

According to many studies, the most common risk factor for the incidence of MDR TB was history of TB treatment. In this study, history of tuberculosis treatment was associated with the incidence of MDR TB ($p = 0.002$), and patients with a history of TB treatment tended to be three times more probably developing MDR TB than new patients. These results were in corcondance with a study in China by Liang et al. (2012), showing that patients with a treatment history were 5.48 times more likely to develop MDR TB than new patients. Another study also stated an association with a greater likelihood of medication history and the incidence of MDR TB, which was 8.1 times (Eshetie S. et al., 2017). In line with the results of this study, Mekonnen et al. (2015) found that history of TB treatment was the only risk factor that significantly associated with the incidence of MDR TB. Nawas et al. (2010) also explained that Anti-TB drugs resistance was an artificial phenomenon. These events were caused by human activities, including inadequate treatment (regimen, dosage, rough treatment, monotherapy, and others), resulting in resistant bacteria from mutations that occurred in small numbers, then became the dominant population, multiplied, and finally had an impact on patients clinical conditions. In patients with a history of TB treatment, the incidence was increased because of the frequent interactions of bacteria with anti-TB drugs. It was because prior exposure to Anti-TB drugs could only suppress the growth of susceptible bacilli. However, on the other hand, it could allow suitable conditions for the growth of pre-existing drug-resistant strains (Colijn et al., 2011). It was the most common type of resistance to first-line Anti-TB drugs. Non-standardized drug prescribing could also lead to treatment failure and increase drug-resistant strains type (Sharma & Mohan, 2006).

This study found that age, gender, BMI, alcohol consumption history, and smoking history did not show significant relationships with the incidence of MDR TB. The results of this study were supported by a study by Günther et al. (2015) stating that there was no relationship between the incidence of MDR TB and abnormal BMI (<18 or >25). The results of this study were also consistent with a meta-analysis by Samuels et al. (2018), which showed that there was no clear relationship between smoking history and the incidence of MDR TB. The results of this study were also in line with a study by Akaputra et al. (2008), showing that there was no significant relationship between gender and the incidence of MDR TB. In line with the results of this

study, a study in Ethiopia by Mekonnen et al. (2015) found that gender, age, smoking history did not have a significant relationship with the incidence of MDR TB. Other factors such as residence, occupation, ethnicity, education level, BCG vaccination status, ethnicity, history of imprisonment, HIV status, fasting, and occupation also did not show a significant relationship. However, the results of several other studies contradicted our study results. A study in Bangladesh by Rifat et al. (2014) showed that patients aged 18-45 years and with a history of smoking were related with MDR TB. A case-control study also found that a history of alcohol consumption and patients aged <26 years had a significant relationship with the incidence of MDR TB (Mulu et al., 2015).

## CONCLUSION

Diabetes Mellitus comorbid and history of Tuberculosis treatment were significant risk factors of developing MDR TB. Our study found that other factors, such as age, gender, BMI, alcohol consumption history, and smoking history, did not show significant relationships with the incidence of MDR TB. It is necessary to improve education, support, and supervision efforts for TB and DR TB patients to improve patient compliance and achieve successful treatment. Further research with a cohort design is needed to determine the incidence of MDR TB in Diabetic patients and patients with history of TB treatment.

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