

THE EFFECT OF CLINICAL CHARACTERISTICS OF TB PATIENTS ON THE INCIDENCE OF MDR TB AT PROF. DR MARGONO SOEKARJO PURWOKERTO HOSPITAL

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ABSTRACT

Background: MDR TB is drug-resistant tuberculosis caused by Mycobacterium tuberculosis that is resistant to rifampicin (RIF) and Isoniazid (INH) which are the most effective first-line anti-TB drugs to fight and eliminate Mycobacterium tuberculosis, so these drugs are often used as monotherapy (administration of only one type of OAT) and short therapy. Objective: This study aims to determine the effect of clinical characteristics in TB patients on the incidence of MDR TB in the Pulmonary Clinic of Margono Soekarjo Purwokerto Hospital. Methods: Descriptive analysis research with cross sectional study design using sampling technique used was total sampling of 62 patients. Data was taken by looking at the patient's medical record. Statistical data analysis using univariate test and bivariate chi square test to identify clinical characteristics that affect the incidence of MDR TB at Margono Soekarjo Purwokerto Hospital. Results: The results showed that there was an influence of clinical characteristics, namely previous TB history on the incidence of MDR TB with a p value of 0.010, while the clinical characteristics that influenced the incidence of MDR TB were 0.010. Conclusion: the clinical characteristics that most influence the incidence of MDR TB are patients with a history of previous TB disease. So it is expected that stricter monitoring of patients with this history is needed to reduce the prevalence of MDR TB in Indonesia.

Keywords: MDR TB, Treatment History, Clinical Characteristics, Margono Soekarjo

INTRODUCTION

Tuberculosis (TB) is an infectious disease transmitted through droplets by the bacterium *Mycobacterium tuberculosis*. The organs attacked by the disease are mainly the lungs. Currently, TB control in the world is facing challenges due to the spread of *M. tuberculosis*, which is resistant to standard anti-tuberculosis drugs (OAT). strains globally. This is the cause of the emergence of the spread of multidrug resistant tuberculosis (MDR TB) in the world ⁽¹⁾. There are an estimated 969,000 TB cases in Indonesia (one person every 33 seconds). There was an increase in this number from 2020, which increased by 17%, where there were 824,000 cases. Meanwhile, the incidence of TB cases in Indonesia is 354 per 100,000 population ⁽²⁾. Of the total confirmed TB cases, 10,145 were confirmed MDR/RR TB and 5,810 patients were confirmed to have started treatment ⁽²⁾. MDR TB cases in Indonesia accounted for 13% of patients treated with confirmed MDR/RO TB cases and 2.4% of all new TB patients⁽¹⁾. Multidrug resistant tuberculosis (MDR TB) is drug-resistant tuberculosis due to the presence of *Mycobacterium tuberculosis* bacteria that are resistant to rifampicin (RIF) and Isoniazid (INH), which are first-line anti-TB drugs that are considered so effective in eliminating and fighting *Mycobacterium tuberculosis*, so that these drugs are often used for short therapy and monotherapy (administration of only one type of OAT)⁽³⁾.

The causes of drug resistance in TB patients do not only stem from treatment history,

but also factors such as TB control programs, patients, and health workers. The mortality rate from TB and the success of TB treatment on the patient's side are also exacerbated by several medical conditions that the patient has previously suffered from, including impaired drug absorption due to patients suffering from comorbidities such as Diabetes Militus (DM) and HIV⁽⁴⁾.

The relationship between these two diseases has been proven. Risk factors for TB that influence the presence of disease and response to treatment are DM and HIV. The global problem of DM is increasing, especially in developing countries where TB is common. Although there is an association between TB and immune deficiency diseases such as HIV, the number of patients with a history of DM is higher⁽⁴⁾.

MDR TB does not only occur due to non-compliance with OAT use or a history of previous disease. MDR TB can also be caused by close contact with patients diagnosed with MDR TB. Significantly, patients with family members who have a history of MDR TB are at risk of developing MDR TB as well. Evidence of community and household transmission of the disease is not surprising as almost two-thirds of patients treated for TB are unaware of how TB spreads, therefore patients or families are unlikely to be aware of the various measures that can prevent the spread of TB⁽⁵⁾.

METHODS

Participants

The type of research used is descriptive analysis research with a cross sectional study design and a retrospective approach by identifying medical record data and the Tuberculosis Information System (SITB) of Margono Soekarjo Hospital. The sampling technique used in this study was total sampling by taking all samples in the population. the samples obtained in this study were 62 patients who were positive for OAT resistance and were undergoing treatment from 2021-2023.

Data collection

Data on TB patients at Margono Hospital were accessed through the SITB application and matched with the patient's medical record, then identification of previous treatment history and patient clinical characteristics consisting of DM status, HIV co-infection, and close contact history.

Data analysis process

The data obtained were then analyzed with the Chi Square test on SPSS version 26 to determine the effect of each variable on the incidence of MDR TB. Data analysis was carried out in four stages.

- 1) Data input: The researcher input the data using SPSS software,
- 2) Coding: Researchers categorized variables that needed to be grouped according to operational definitions and research objectives.
- 3) Data cleaning: Researchers conducted activities to recheck existing data that had been entered and coded.
- 4) Data were analyzed by univariate and bivariate analysis. This univariate analysis was used to determine the characteristics of the respondents. Bivariate analysis was used to determine the association between the incidence of MDR TB in each independent category. Stratification analysis used the Chi-square test and the Mantel-Haenszel test. The Mantel-Haenszel test has been used to determine the significance of the association between each parameter and the incidence of MDR TB. Parameters tested included DM, HIV co-infection, previous history of TB, close contact with the patient.

Research ethics

This study has obtained a research permit from the Ethics Committee of Prof. Dr. Margono Soekarjo Purwokerto Hospital, number 420/13104 on May 5, 2023.

RESULTS

Data collection was carried out using a total sampling technique because the number of samples taken was the same as the total population, the population and samples in this study were drug-resistant TB patients who were still undergoing treatment at the Pulmonary Clinic of Margono Hospital as many as 62 patients and met the inclusion and exclusion criteria. patients and have met the inclusion and exclusion criteria. Before the research was conducted, the researcher distributed the respondent's consent form. The measuring instruments in this study were data collection forms, patient medical record data and the hospital TB Information System. Based on this study, the following results were obtained: Table 1 Relationship between clinical characteristic and MDR TB Incidence

Karakteristik	Status TB MDR							
	TB MDR	Non TB MDR			Jumlah		P (Value)	OR
	n	%	n	%	N	%		
DM	6	14	1	5,26	7	11,29	0,778	0,778
Tidak ada DM	37	86	17	94,73	55	88,71		
Kontak Dekat	9	20,9	2	10,6	11	17,7	0,067	4,615
Tidak ada Kontak Dekat	34	79,1	17	89,4	51	82,3		
Riwayat TB	18	41,8	5	26,3	23	37		
Tidak ada Riwayat TB	25	58,2	14	73,7	39	63	0,010*	6,000

Note: * (<0,05)

Based on bivariate tests, patients who have had TB before have a significant relationship that affects the incidence of MDR TB, while patients with comorbid DM, HIV co-infection, patients who have been in close contact have no influence on the incidence of MDR TB.

Patients who had a history of TB disease previously had a 6 times higher risk of developing MDR TB compared to respondents who did not have a history of TB (OR 6.000) with the chi square test obtained a p value of 0.010 which can be interpreted as having a significant influence on the incidence of MDR TB.

DISCUSSION

Relationship between DM and MDR TB

Diabetes mellitus (DM) is a complex metabolic disorder associated with increased risk of macrovascular and microvascular disease due to defects in insulin secretion, reduced insulin sensitivity or action, or both with the main clinical description being chronic hyperglycemia⁽⁶⁾.

Several studies have examined the relationship between tuberculosis and DM. The prognosis of tuberculosis is thought to be influenced by the comorbidities that patients have, including DM⁽⁷⁾. Tuberculosis and DM are infectious diseases with high morbidity and

mortality worldwide especially if they are co-morbid. TB and DM will together cause severe symptoms and even early death.⁽⁸⁾.

According to the International Diabetes Foundation (IDF), there are 351.7 million individuals with DM, especially in developing countries. IDF data in 2019 predicted that there were 10.1 million cases of DM in Indonesia and 1.04 million of them experienced TB⁽⁹⁾.

Based on the results of the study, it did not show a significant effect between history and the incidence of MDR TB, according to the results of the chi-square statistical test obtained a value of $P = 0.778 (>0.05)$, the number of MDR TB patients with comorbid DM which was only slightly found in this study was the cause of the insignificant relationship between comorbid DM and the incidence of MDR TB.

This study is also in line with research conducted previously, the results of another study showed no significant relationship between the incidence of MDR TB and respondents who had DM and those who did not have DM, this is because most MDR TB respondents did not have DM disease⁽¹⁰⁾. A study conducted in Eastern Ethiopia, in 395 TB patients with BTA + sputum, there were only 30 patients with comorbid DM, and from the results of the chi-square test in the study, the p value was 0.77, which proves that there is no significant correlation between comorbid DM and the incidence of MDR TB⁽¹⁰⁾.

Poorly controlled DM can lead to various complications, such as increased susceptibility to infection. Diabetes increases susceptibility to tuberculosis through a number of mechanisms, such as cellular insulinopenia and hyperglycemia which have an indirect impact on macrophages⁽¹¹⁾.

The fact that DM can adversely affect the outcomes of TB patients can be due to a number of reasons:

- 1) Immunosuppressive effects of DM. DM can reduce the body's immune response, both against TB infection and in anticipation of reactivation or recurrence.
- 2) Diabetes can affect the pharmacokinetics of OAT, reducing or slowing bactericidal activity.
- 3) Drug interactions between OAT and DM drugs will affect glycemic control, worsening the outcomes of TB treatment for people with DM^(12,13).

Relationship between close contact history and MDR TB

A history of close contact is the presence of physical and non-physical contact with the patient. The risk of people who have families who are positively infected with pulmonary tuberculosis will be easily infected from the level of exposure with sputum splashes.

The results of statistical tests in this study obtained a p value of 0.067 (<0.05) which indicates that there is no significant influence between the history of close contact with the incidence of MDR TB, in this study extracting information about the history of close contact in TB patients is only observed based on medical record data and hospital SITB which may not have been updated regarding patient information so that the possibility of information bias can occur.

There are several studies that are in line with the results of this study, such as research conducted in Surakarta, Central Java, the results showed no relationship between close contact and the incidence of MDR TB, based on the results of interviews with respondents some of whom claimed not to have close contact with MDR TB patients and did not know whether the people around them had MDR TB or not⁽¹⁴⁾, based on the results of interviews with respondents some of whom claimed not to have close contact with MDR TB participants and did not know whether the people around them had MDR TB or not⁽¹⁴⁾. There are several studies that are in line with the results of this study, such as research conducted in Brebes Regency, the results of this study which showed that close contact with TB

patients did not have a significant difference with an OR value of 1.8 and a P value of 0.837⁽¹⁰⁾. Another study that is also in line with research conducted at Sardjito Hospital Yogyakarta, the results of this study did not find a significant relationship between close contact with TB patients and the incidence of MDR TB with a p value of 0.379⁽⁵⁾.

A history of close contact is significantly associated with the incidence of MDR TB because a person who often interacts with TB patients will easily be infected through the air due to sputum or splashes from family or other people with positive pulmonary TB. This is due to the high level of positivity of the sputum examination results, making the patient more contagious⁽¹⁵⁾.

However, the incidence of MDR TB due to close contact with MDR TB patients does not necessarily occur just like that, this is due to the length of the pathological process of pulmonary TB disease. It takes at least months and even years for individuals to experience the incidence of pulmonary TB despite frequent close contact with pulmonary TB patients, plus this is supported by a good immune system, so the chances of contracting in the near future are quite low⁽¹⁶⁾.

Relationship between previous TB history and MDR TB incidence

M. tuberculosis bacteria can develop resistance to common antibiotics to which the bacteria were initially sensitive. Bacteria that are already resistant in patients who have a previous history of TB are the biggest cause of MDR TB⁽¹⁷⁾.

A significant relationship was found between the history of previous TB disease and MDR TB cases. The results of the analysis with the chi square test proved a significant relationship between history and the incidence of MDR TB with a p value of 0.10. Based on the results of the analysis, the OR value = 6.000 means that respondents who have a history of TB disease are at 6 times greater risk of developing MDR TB cases than respondents who do not have a history of TB.

Previous research conducted on 395 patients in Ethiopia showed a significant association between previous TB history and the incidence of MDR TB, in this study the history of previous TB infection is an important determinant for the development of MDR TB. The risk of MDR TB acquisition among previously treated cases is likely due to mutase resistance and naturally occurring M. tuberculosis and inadequate treatment has a potential role for MDR TB⁽¹⁸⁾.

Patients with a previous history of TB will show lung damage indicated by pitting lesions in the lung and especially the residual cavity which is a significant risk factor for recurrent TB disease. Lung cavities that persist at the end of treatment have been reported to be a dominant correlate of relapsing TB in several studies. Several studies have shown residual cavitation to be a risk factor for tuberculosis relapse. The association between residual cavitation and recurrent TB has been attributed to poor penetration of anti-TB drugs into the lung wall cavity^(17,19).

Damage to the lung wall and M. tuberculosis that has been coevolving with the human host for some time and has successfully evaded immune defenses will progress to a stage of relative dormancy. Host-pathogen interaction after infection occurs until the disease extends across innate immune, adaptive immune and active replication infections and at this stage M. tuberculosis has successfully caused relapse in Tb patients⁽¹⁷⁾.

Relationship between HIV Co-infection and MDR TB Incidence

By the end of 2019, the WHO predicts thirty-eight million HIV-infected people worldwide. Two-thirds of all cases in the world come from the African region. In Indonesia, the number of HIV-infected patients is predicted to be 630,000⁽¹⁾. HIV is a virus that can cause AIDS disease which causes several symptoms resulting in weakened patient immunity because this virus attacks the human immune system, one of which becomes vulnerable to

opportunistic diseases, such as candidiasis, hepatitis, pneumonia, tuberculosis⁽²⁰⁾.

Tuberculosis is the most common opportunistic infection (40%) in HIV infection which is the most common cause in patients with comorbid HIV⁽²¹⁾. HIV-infected individuals are more susceptible to latent TB and can rapidly develop active TB because their immune systems are weakened⁽²²⁾.

The relationship between HIV infection and MDR TB co-infection is understood because there is an increased risk of MDR TB infection for HIV patients. HIV in addition to weakening the body's immune system makes patients prone to opportunistic diseases. Research has shown that *M. tuberculosis* influences the process of HIV infection and replication. *M. tuberculosis* is proven to provide a good environment for HIV growth by developing the activity of CXCR4 and CCR5 coreceptors, increasing proinflammatory cytokines and reducing CCL5 activity⁽²³⁾.

Not only that, OAT can also directly interfere with antiretroviral treatment. Rifampicin has been shown to significantly reduce serum concentrations of proteases and reverse transcriptase inhibitors present in antiretroviral drugs⁽²³⁾. HIV infection has also been shown to cause malabsorption of many OATs, especially ethambutol and rifampicin, leading to treatment failure and resistance in MDR TB cases⁽²⁴⁾. Antiretroviral drug interactions can lead to ineffective antiretroviral treatment as well as TB treatment which can result in treatment failure or poor drug absorption in TB-HIV patients⁽²⁵⁾.

CONCLUSIONS

The results of this study indicate that there is an influence between the history of previous TB disease, relapse patients and new patients with the incidence of MDR TB, so it is expected that stricter monitoring of patients with such a history is expected to reduce the prevalence of MDR TB in Indonesia.

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