Original Article

The Impact of Comorbidities on Drug-Resistant Tuberculosis Treatment Success at Dr. Soebandi Hospital Jember 2018-2022

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Abstract

Introduction: *Drug-resistant tuberculosis (DR-TB) is a major health concern in Indonesia, where treatment success rates remain low. Comorbidities such as diabetes mellitus (DM) and human immunodeficiency virus (HIV) may worsen patient outcomes by complicating disease management and increasing the risk of treatment failure. This study aimed to assess the impact of comorbidities on treatment success among DR-TB patients at dr. Soebandi Hospital Jember.*
Method*: An analytic observational study was conducted on 228 DR-TB patients at RS dr. Soebandi in 2018-2022 who had completed treatment, selected using total sampling. Data were analysed using bivariate analysis to examine associations between comorbidities and treatment outcomes.*
Results*: The overall treatment success rate was 36.8%. Comorbidities were present in 37.3% of patients and were associated with a significantly lower success rate compared to those without comorbidities (21.2% vs. 46.2%; p=0.000; OR=3.19). DM (p=0.018; OR=2.17) and HIV (p=0.026; OR=9.31) each significantly reduced treatment success. A combination of DM and hypertension also showed a significant association (p=0.041; OR=9.44).*
Conclusion*: Hypertension alone, chronic kidney disease, and chronic hepatitis were not statistically related to treatment success. Comorbidities, particularly DM, HIV, and the combination of DM with hypertension, significantly affect DR-TB treatment success. Addressing these conditions could improve patient outcomes and enhance treatment programs.*

Keywords: *Comorbidites, DR-TB, Treatment outcome.*

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Pengaruh Penyakit Komorbit dengan Keberhasilan Terapi Tuberkulosis Resisten Obat pada pasien DR-TB di Rumah Sakit Dr Soebandi Tahun 2018-2022

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Abstrak

Pendahuluan: *Tuberkulosis resistan obat (DR-TB) merupakan masalah kesehatan serius di Indonesia, dengan angka keberhasilan pengobatan yang masih rendah. Penyakit penyerta seperti diabetes melitus (DM) dan HIV dapat memperburuk kondisi pasien serta mempersulit penatalaksanaan. Penelitian ini bertujuan untuk mengetahui pengaruh komorbiditas terhadap keberhasilan pengobatan pasien DR-TB di RS dr. Soebandi Jember.*
Metode*: Penelitian ini merupakan penelitian observasional analitik ini melibatkan 228 pasien DR-TB di RS dr Soebandi tahun 2018-2022 yang telah menyelesaikan pengobatan. Subyek dipilih dengan metode total sampling. Analisis data dilakukan secara bivariat.*
Hasil*: Angka keberhasilan pengobatan keseluruhan adalah 36,8%. Sebanyak 37,3% pasien memiliki komorbiditas, dengan tingkat keberhasilan lebih rendah dibandingkan pasien tanpa komorbiditas (21,2% vs 46,2%; p=0,000; OR=3,19). DM (p=0,018; OR=2,17), HIV (p=0,026; OR=9,31), serta kombinasi DM dan hipertensi (p=0,041; OR=9,44) berhubungan signifikan dengan keberhasilan pengobatan.*
Kesimpulan*: Hipertensi, penyakit ginjal kronis, dan hepatitis kronis tidak menunjukkan hubungan yang bermakna. Komorbiditas berpengaruh terhadap keberhasilan pengobatan DR-TB, terutama DM, HIV, dan kombinasi DM dengan hipertensi. Penanganan komorbiditas secara optimal dapat meningkatkan keberhasilan terapi DR-TB.*

Kata Kunci*: Penyakit komorbit, DR-TB, Keberhasilan terapi.*

Introduction

Tuberculosis (TB) is an infectious disease with the highest mortality rate in the world. TB is caused by an infection from the *Mycobacterium tuberculosis* (M.tb). The M.tb can mutate into a strain that is resistant to antituberculosis drugs, thus becoming drug-resistant TB (DR-TB). According to a WHO report, out of all TB cases worldwide, approximately 450,000 cases are DR-TB. It is estimated that Indonesia has around 28,000 cases of DR-TB, ranking it fourth among countries with the highest number of DR-TB cases worldwide.[1] DR-TB treatment, which is more complex, affects the treatment success rate. In Indonesia, the treatment success rate for DR-TB patients in 2019 was 47%. This figure is still below the global success rate of 60% and significantly lower than the national target of 80%.[2] The persistently low success rate has led to an increase in the number of DR-TB cases each year. The main reasons for the low treatment success rate include the more challenging treatment regimen for DR-TB, longer treatment duration, and higher treatment costs compared to drug-sensitive TB.[3] Several other factors that can affect DR-TB treatment success include age, gender, previous TB treatment history, and comorbidities.[4]

Comorbidities such as diabetes mellitus (DM), human immunodeficiency virus (HIV) infection, and chronic kidney disease (CKD) have been found to influence the treatment success of DR-TB.[4] Other comorbidities, such as hypertension and hepatitis, also negatively affect the treatment success of drug-sensitive TB.[5,6] On the other hand Nurfa

et al. reported that comorbidities do not have an impact on the treatment success of DR-TB.[7] Bastard et al. also reported no difference in treatment success between patients with comorbid HIV and those without comorbid HIV for DR-TB.[8] Based on the background above, there are still differences in research findings regarding the relationship between comorbidities and the treatment success of DR-TB. Therefore, this research is necessary to provide information about the relationship between comorbidities and the treatment success of DR-TB patients, particularly in Jember Regency.

Materials and Methods

This research was an observational analysis study. The data collected includes medical records of DR-TB patients at dr. Soebandi Hospital in Jember from 2018 to 2022, comprising anamnesis results, physical examination findings, and laboratory test results. 228 patients met the study criteria using the total sampling method. The inclusion criteria for this study were all DR-TB patients who had completed treatment from 2018 to 2022. The exclusion criteria were patients with comorbidities other than those being studied and patients with incomplete data on comorbidities in their medical records.

The independent variables in this study are the comorbidities of DR-TB patients. Patients will be grouped into two comorbidity groups: DR-TB patients with comorbidities and DR-TB patients without comorbidities. Furthermore, patients will also be grouped based on the comorbidities they possess, including DM, HIV, hypertension, CKD, and chronic hepatitis. The dependent variable in this study is the treatment success of DR-TB patients. Treatment success is categorized into two groups: patients who succeed in treatment with a cured outcome and patients who do not succeed in treatment with outcomes such as failure, death, loss to follow-up, incompleted treatment, or not evaluated according to the DR-TB management guidelines in Indonesia.

Data on gender, age, and educational level are also collected from the patient's medical records. The data collected will be analyzed using the Statistical Package for the Social Sciences (SPSS) with bivariate analysis. This research obtained ethical approval from the ethics committee of the Faculty of Medicine, Jember University, with registration number 325/UN25.1.10.2/KE/2024.

Result

Based on the data obtained, which can be seen on table 1, out of 228 patients sampled, 138 patients (60.5%) were male, a higher number compared to females. Regarding age groups, patients were predominantly in the age range of 41-60 years, with 103 patients (45.2%). The educational level of most patients was at the elementary school level, with a total of 59 patients (25.9%). However, there were 107 patients (46.9%) whose educational data were not recorded in the medical records. Most patients did not have comorbidities, comprising 143 patients (62.7%). However, there were 72 patients (31.6%) with one comorbidity and 13 patients with more than one comorbidity. Overall, the treatment success rate for DR-TB patients sampled was 36.8%.

Table 1. Characteristics of Sample

Characteristic	Amount (N)	Percentage (%)
Gender		
Male	138	60.5
Female	90	39.5
Age group		
<21 years old	18	7.9
21-40 years old	85	37.3
41-60 years old	103	45.2
>60 years old	22	9.6
Educational level		
No schooling	2	0.9
Elementary school	59	25.9
Middle school	21	9.2
High school	33	14.5
College	6	2.6
No data	107	46.9
Comorbiditas status		
No comorbid	143	62.7
1 comorbid	72	31.6
>1 comorbid	13	5.7
Therapy success		
Successful	84	36.85%
Unsuccessful	144	63.2%

Comorbid Distribution can be seen on table 2. A total of 85 DR-TB patients have comorbidities. Among all patients with comorbidities, the most common comorbidity is DM, with 60 patients (70.6%). Patients with multiple comorbidities are distinguished

from those with only one comorbidity. The most common combination of comorbidities among patients is DM and hypertension, with a total of 5 patients (5.9%).

Table 2. Comorbidities Distribution

Comorbid	Amount (N)	Percentage (%)
DM	60	70.6
HIV	6	7.1
Hypertension	1	1.2
CKD	2	2.4
Chronic hepatitis	3	3.5
DM and HIV	1	1.2
DM and hypertension	5	5.9
DM and chronic hepatitis	3	3.5
HIV and chronic hepatitis	2	2.4
Hypertension and CKD	1	1.2
DM, hypertension, and chronic hepatitis	1	1.2

with DR-TB patients without DM (28.3% vs. 46.2%; p=0.018; OR=2.17). DR-TB patients in the HIV group also showed lower treatment success compared with non-HIV patients (0% vs. 46.2%; p=0.026; OR=9.31). This indicates that overall comorbidities including DM and HIV are associated with the treatment success of DR-TB patients. However, comorbidities such as hypertension (p=1.000), CKD (p=0.501), and chronic hepatitis (p=1.000) statistically not associated with the treatment success of DR-TB patients.

Patients with more than one comorbidity are grouped according to their respective combinations to avoid bias among comorbidities. The results of bivariate tests are listed in Table 3. Only the combination of DM and hypertension (p=0.041; OR=9.44) is associated with the treatment success of DR-TB patients, whereas other combinations of comorbidities are not associated.

Table 3. Result of Bivariate Analysis

	Successful	Unsuccessful	Total	p-value	OR
Comorbid Status					
Positive	18	67	85	0.000	3.19
Negative	66	77	143		
DM	17	43	60	0.018	2.17
HIV	0	6	6	0.026	9.31
Hypertension	0	1	1	1.00	-
CKD	0	2	2	0.501	-
Chronic hepatitis	1	2	3	1.00	-
DM and HI	0	1	1	1.00	-
DM and hypertension	0	5	5	0.041	9.44
DM and chronic hepatitis	0	3	3	0.299	-
HIV and chronic hepatitis	0	2	2	0.533	-
Hypertension and CKD	0	1	1	1.00	-
DM, hypertension, and chronic hepatitis	0	1	1	1.00	-

Correlation Between Comorbidities and DR-TB Treatment Success

The results of the bivariate tests for each comorbidity regarding treatment success are presented in Table 3. The treatment success rate was lower in DR-TB with comorbidities overall compared with DR-TB patients without comorbidities (21.2% vs. 46.2%; p=0.000; OR=3.19). Furthermore, for each comorbidity, the treatment success rate was lower in DR-TB patients with DM compared

Discussion

Most patients do not have comorbidities, but comorbidities can facilitate the progression of TB to DR-TB by disrupting immune function and increasing the bacterial load.[9] The overall treatment success rate of DR-TB patients in this study is 36.8%. The treatment success rate in this study is still below the global target of 60% and the Indonesian national target of 80%.[2]

Comorbid Distribution

DM is the most frequently encountered non-communicable disease in the DR-TB patient population.[10] DM is one of the risk factors that can increase the incidence of DR-TB in patients with previous TB, likely due to hyperglycemic conditions that can disrupt the absorption of anti-TB drugs. Impaired anti-TB drug absorption leads to reduced treatment effectiveness, thereby increasing the risk of anti-TB drug resistance in M.tb bacteria.[11] Tegegne et al. also explain that DM is associated with an increased risk of DR-TB occurrence.[12]

Immune system dysregulation is common in DM patients, characterized by cytokine secretion disturbances. The function of neutrophils, macrophages, NK cells, and several other innate immune components is disrupted due to metabolic changes in DM patients. In the early phase of the body's defense against infection, innate immune components secrete proinflammatory cytokines to attract additional leukocytes to the site of infection to combat M.tb bacteria. This will be followed by the emergence of adaptive immune components, largely mediated by CD4+ and CD8+ T lymphocytes. The entire population of immune cells will express different cytokines to limit and eliminate M.tb infection.[13] When immune system dysregulation occurs, the body cannot effectively combat existing infections, making DM patients more vulnerable to bacterial infections, and disease progression accelerates. Therefore, controlling DM conditions that can worsen M.tb bacterial infections is necessary.

Correlation Between Comorbidities and DR-TB Treatment Success

Based on the data obtained, it can be inferred that the presence of comorbidities is significantly associated with the treatment outcomes of DR-TB. Nowiński et al. also reported that DR-TB patients with comorbidities have lower treatment success rates and higher mortality rates.[14] DR-TB patients with comorbidities are more likely to experience adverse treatment reactions, prescription limitations for drug combinations, and treatment discontinuation due to drug side effects.[15]

Correlation between DM and DR-TB Therapy Outcome

The findings of this study showed that DM is associated with the treatment success of patients with DR-TB. These results are similar to a study conducted by Soeroto et al., which showed that DM affects the success of DR-TB treatment with a p-value of 0.006.[4] Another study by Xu et al. also explains that there is a correlation between comorbid DM and the success of DR-TB patient treatment.[16]

Diabetes mellitus also leads to a higher bacterial burden and faster progression.[16] DR-TB patients with comorbid DM will experience an increased level of proinflammatory cytokines, both before and during treatment. Consequently, there will be significant clinical implications as excessive and prolonged inflammation leads to increased mortality and morbidity in TB patients. This situation can be exacerbated if the patient's DM condition is not controlled.[17]

The simultaneous use of TB drugs and DM drugs can result in pharmacodynamic and pharmacokinetic interactions, leading to the ineffectiveness of the drugs in the body.[18] Some TB drugs interacting with DM drugs cause a decrease in diabetes mellitus drug concentration in the plasma.[19] In DM patients using pyrazinamide with higher levels of HbA1c, there is a risk of not achieving therapeutic effects from pyrazinamide due to increased xanthine oxidase levels. The use of ethambutol also requires dose adjustment in DM patients with decreased kidney function. Second-line drugs, bedaquiline, and delamanid are highly bound to plasma proteins. Thus they may compete for binding sites on plasma proteins and affect the concentration of free drugs when used concurrently with sulfonylureas, glinides, or SGLT-2 inhibitors.[19]

The use of anti-TB drugs also presents side effects that make DR-TB patients uncomfortable. These side effects may be exacerbated by the presence of complications in DM. Some commonly occurring side effects overlapping with DM conditions include diabetic retinopathy overlapping with ocular toxicity from ethambutol, which can lead to permanent visual impairment.[20] Anti-TB drugs with neuropathy-inducing effects, such as linezolid, will exacerbate patients with diabetic neuropathy.[19] Several side effects of anti-TB drugs, when combined with the condition of DM patients, can worsen clinical conditions and make patients uncomfortable, rendering them susceptible to discontinuing DR-TB treatment.[21]

Correlation Between HIV and DR-TB Therapy Outcome

The results of this study indicate that the presence of HIV as a comorbid condition is related to the treatment success of DR-TB patients. Roseno et al. also reported that comorbid HIV independently affects the success of DR-TB treatment with a p-value of 0.039 and an OR of 2.74.[22]

HIV and M.tb are two intracellular pathogens that can evade innate and adaptive immune defense mechanisms, allowing them to survive and replicate. Patients with HIV will experience a depletion of CD4+ lymphocytes and create a chronic inflammatory environment that promotes M.tb proliferation. HIV infection in macrophages in the lungs, including alveolar macrophages, will directly impact lung immunity because its effects will impair innate immune responses and the phagocytic function of alveolar and interstitial macrophages.[23] Moreover, in HIV comorbidity, there is an increase in catabolism to meet the energy demands used in fighting infection. Compared to patients without HIV comorbidity, patients with HIV comorbidity exacerbate TB infection synergistically through increased inflammation and mitochondrial damage due to antiretroviral therapy usage. This factor adversely affects energy availability, weakening the body and resulting in poorer outcomes in patients with HIV comorbidity.[24]

The simultaneous use of anti-TB-drug and antiretroviral may lead to detrimental drug interactions. Human immunodeficiency virus can increase the number of adverse drug reactions (ADR) due to overlapping treatment toxicities and poor clinical conditions.[25] Moxifloxacin has been found to have lower concentrations in the body in HIV patients using efavirenz. Bedaquiline is also metabolized by cytochrome P450, thus it can be influenced by antiretroviral that modulate the isoenzyme. Ritonavir can cause an increase in bedaquiline concentration, potentially leading to increased drug toxicity, especially QT interval prolongation. Conversely, efavirenz can reduce the concentration of bedaquiline in the body, thereby not working optimally.[26]

Correlation Between Hypertension and DR-TB Therapy Outcome

In this study, hypertension was not found to be associated with treatment success of DR-TB patients, possibly due to the limited sample size. There was only one patient with comorbid hypertension, and this patient failed in treatment.

In the study by Chidambaram et al., hypertension was associated with increased oxidative stress. Angiotensin II is known to increase ROS production through NADPH oxidase. The risk of treatment failure for TB resulting in mortality in that study might be attributed to elevated levels of interleukin, NADPH oxidase, and ROS in patients.[27] Several cases of hypertension drug resistance had been reported during TB treatment. Blood pressure in hypertensive patients becomes uncontrolled, possibly due to the concurrent use of antihypertensive drugs with rifampicin, which is a cytochrome P450 inducer.[28]

Correlation Between CKD and DR-TB Therapy Outcome

This study found no significant association between CKD comorbidity and treatment outcomes among DR-TB patients. The statistical analysis did not reveal any association, potentially attributable to the limited sample size. On the other hand, Jo et al. demonstrated a correlation between CKD and the efficacy of DR-TB treatment, with a p-value of 0.019. However, out of the two patients with comorbid CKD, both did not succeed in treatment.

A remarkable increase in proinflammatory cytokine levels usually characterizes patients with CKD. The continuous activity of innate immune effectors in CKD patients does not mean that patients will be protected from pathogens. On the contrary, infections in CKD patients may exacerbate in severity. T cells in CKD patients can also be affected, thereby influencing the patient's body in eliminating intracellular pathogens.[29] Patients with TB-CKD comorbidity are expected to experience a decline in renal function. This phenomenon has implications for the course of TB treatment, which is predominantly cleared through the kidneys and includes medications with nephrotoxic effects. First-line drugs such as ethambutol and pyrazinamide require dosage adjustments based on renal function to mitigate excessive renal side effects. Adjustment of anti-TB-drug dosage in DR-TB patients with CKD is essential for safety and better outcomes. The study conducted by Saito found that adjusting the TB treatment dosage in patients with CKD is an efficient measure, resulting in therapy outcomes similar to those in patients without CKD.[30]

Correlation Between Chronic Hepatitis and DR-TB Therapy Outcome

The data analysis showed that chronic hepatitis was not associated with treatment success among DR-TB patients. DR-TB patients with chronic hepatitis are more sensitive to the hepatotoxic effects of anti-TB-drug because chronic hepatitis causes damage to the liver, making it more susceptible to drug-induced damage.[31] Several first-line antituberculosis drugs that can cause hepatotoxicity include isoniazid, rifampicin, and pyrazinamide. DR-TB patients with chronic hepatitis can receive anti-TB-drug if it is not a severe case of chronic hepatitis.[32]

Correlation Between More than One Comorbid and DR-TB Therapy Outcome

Based on the statistical test conducted, it was found that only the combination of comorbid DM and hypertension had a statistically significant association with the successful treatment of DR-TB. Other combinations of comorbidities are not associated with the successful treatment of DR-TB.

Comorbidities in DR-TB patients pose a challenge in the treatment process due to the increased disease burden and the complexity of the patient's immune conditions. Therefore, the greater the number of comorbidities in patients, the more complicated the treatment becomes due to impaired immune function, increased risk of drug toxicity, and unfavorable drug interactions. As a result, the number of comorbidities can affect the success of DR-TB patient treatment.

Conslusion

This study demonstrates that comorbidities significantly influence the treatment outcomes of drug resistant patients. The presence of comorbid conditions, particularly diabetes mellitus and human immunodeficiency virus, is associated with a markedly lower treatment success rate. Patients with diabetes mellitus exhibited impaired treatment response, likely due to altered immune responses, pharmacokinetic drug interactions, and metabolic dysregulation. human immunodeficiency virus comorbidity showed the strongest negative association with treatment outcomes, potentially due to immunosuppression, mitochondrial dysfunction, and adverse drug interactions between antiretroviral and anti tuberculosis regimens.

Conversely, comorbidities such as hypertension, chronic kidney disease and chronic hepatitis did not show statistically significant associations, though this may be attributed to limited sample sizes. Among combination comorbidities, only the coexistence of diabetes mellitus and hypertension demonstrated a significant impact on treatment failure.

These findings underscore the necessity for integrated, comorbidity-conscious clinical management in drug resistant tuberculosis patients. Tailored pharmacological regimens and vigilant monitoring of adverse events are imperative to improve therapeutic efficacy and achieve global treatment success benchmarks.

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