ORIGINAL ARTICLE

Diabetes Mellitus Associated with Sputum Conversion Time in Drug-Resistant Pulmonary TB Patients at Dr. Soebandi Regional General Hospital, Jember

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ABSTRACT

Introduction: Diabetes mellitus (DM) comorbidity in drug-resistant (DR) pulmonary tuberculosis (TB) patients can be associated with the treatment outcome. In DR-TB patients with DM, the immune system is impaired, which will decrease the success of treatment. Sputum conversion time is an indicator used to predict the treatment outcome. However, there is still no further study related to the association between DM comorbidity and the sputum conversion time in DR-TB patients, especially in Jember. This study aimed to determine the association between DM and sputum conversion time in DR-TB patients at Dr. Soebandi Regional General Hospital, Jember.
Methods: This was an analytic observational study with a cross-sectional design. A total of 122 samples of DR-TB patients were taken using the purposive sampling method in 2018-2023 at Dr. Soebandi Regional General Hospital, Jember. The data were analyzed using the Chi-square and logistic regression statistical test.
Results: Chi-square analysis showed that DM (p = 0.015; OR = 2.604; 95% CI 1.195-5.674) and age (p = 0.021; OR = 0.377; 95% CI 0.162-0.878) were associated with sputum conversion time. Logistic regression showed that DM was the most associated variable with the sputum conversion time (p = 0.016; OR = 2.604; 95% CI 1.195-5.674) compared to gender, age, TB resistance type, and anti-TB regimen.
Conclusion: DM is associated with prolonged sputum conversion time in DR-TB patients at Dr. Soebandi Regional General Hospital, Jember. DM was also the most associated variable with the sputum conversion time compared to gender, age, TB resistance type, and anti-TB regimen.

INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) that has developed resistance to one or more anti-TB drugs (ATDs) based on the results of drug sensitization tests. In 2019, around 78% of the total TB resistance cases were multidrug-resistant (MDR-TB), and 61% were rifampicin-resistant (RR-TB), with 206,030 cases.[1] Based on the World Health Organization (WHO) report in 2022, the estimated number of cases of DR-TB globally reached around 450,000, of which around 28,000 occurred in Indonesia.[2] In 2021, the percentage of new DR-TB cases in Indonesia reached 2.2%, while patients undergoing re-treatment reached 25%.[3] Many things can affect the success of therapy in DR-TB disease. These factors include age, gender, smoking, treatment adherence, type of anti-TB resistance, and comorbidities.[3] A study conducted at Dr. Soetomo General Academic Hospital found that 20.8% of DR-TB patients also had diabetes mellitus (DM) as comorbidities.[4] The immune system is impaired in patients with DM, especially in T cells and lymphocytes.[5] Patients with DM have a 2-3 times the

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risk of developing TB infection compared to people without it. The interaction between chronic diseases such as TB and DM deserves further attention as both conditions are often found together at around 42.1%, especially in people at high risk of TB. DM has been reported to affect the clinical symptoms of TB and is associated with slow response to TB treatment and high mortality. Increased reactivation of TB has also been noted in patients with DM comorbidity.[6] A study by Foe-Essomba, *et al*. (2021) reported that people with DM have twice the risk of being infected with TB compared to patients without DM.[7] In addition, in its progression to DR-TB, patients with comorbid DM have up to a 2.2-fold higher risk of anti-TB resistance.[8]

An indicator that can predict therapeutic success in DR-TB patients is sputum culture conversion time.[9] Sputum culture conversion is a negative result on sputum culture in two consecutive examinations with a minimum sampling period of 30 days.[1] A study by Gamachu, *et al*. (2022) showed that DR-TB patients who experienced initial conversion within 1 month showed good treatment outcomes.[10] However, on average, patients with poor treatment outcomes experienced conversion within more than 1 month.[10] Particularly in populations with DM, a study by Fauziah, *et al*. (2020) stated that MDR-TB patients with DM had a conversion time of 1.6 times longer than control patients.[11] This phenomenon also affects the success of therapy because the longer the sputum conversion time in patients, the higher the risk of therapy failure.[12] In contrast to previous findings, studies by Muñnoz-Torrico, *et al*. (2017) and Velayutham, *et al*. (2016) concluded that DR-TB patients with comorbid DM experienced faster sputum culture conversion than those without DM.[13,14]

The increase in cases of DM and comorbidity in DR-TB patients is a serious and noteworthy problem because it is related to the treatment outcome.[1] Based on the previous explanation and the absence of further study in Indonesia, especially in Jember, regarding the association between DM and the sputum conversion time of DR-TB patients, this study aimed to determine the association between DM and the sputum conversion time in patients with DR-TB at Dr. Soebandi Regional General Hospital, Jember.

METHODS

This was an analytic observational study with a cross-sectional design conducted from September to October 2023 using secondary data on medical records of drug-resistant TB patients at Dr. Soebandi Regional General Hospital, Jember, from 2018 to 2023. A total of 122 samples of drug-resistant TB patients in 2018-2023 were taken using the purposive sampling method. The inclusion criteria for this study were patients with DR-TB aged more than 18 years old (adults) who were on treatment for at least 1 month and who had completed the treatment. Exclusion criteria in this study were patients with extrapulmonary DR-TB, had a history of smoking, had a history of other comorbidities such as liver damage (chronic hepatitis or liver failure) and kidney (stage IV-V of chronic kidney disease), cancer, human immunodeficiency virus (HIV), pregnant patients, and the absence of sputum culture conversion time data.

The study subjects were drug-resistant TB patients who had complete medical record data, i.e., the results of anamnesis, physical examination results, and laboratory examination results. The independent variable was the DM comorbidity status, gender, age, TB resistance type, and ATD regimen in drug-resistant TB patients at Dr. Soebandi Regional General Hospital, Jember. The diagnosis of DM in DR-TB patients in this study data was based on the decision of the doctor in charge of the patient, who was then included in the medical record. This study did not identify how doctors diagnosed DM in the subjects. The record of DM comorbidity status in the medical record of DR-TB patients was observed and included in the subject of this study.

The dependent variable was the time of the sputum culture conversion in drug-resistant TB patients at Dr. Soebandi Regional General Hospital, Jember. The data in this study were analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) with the Chi-square and logistic regression with the Backward method statistical test. This study had received ethical clearance from the Ethics Commission of the Faculty of Medicine, Jember University, with administration number 4864/UN25.1.10/KE/2023.

RESULTS

Based on the results, the number of DR-TB patients who had DM comorbidity was 82 patients (67.20%), while DR-TB patients who did not have DM comorbidity were 40 patients (32.8%). This study also showed that 62 DR-TB patients were males (50.82%) and 61 patients were females (49.18%). In the age group, it was found that most patients were in the >40 years old range (74.59%), followed by the ≤40 years old range (25.41%). In terms of the type of TB resistance in patients, the most common type of TB resistance found was the MDR type with 112 patients (91.80%), then the non-MDR type (RR and pre-extensively drug-resistant/XDR type) with 10 patients (8.2%). Based on

the type of anti-TB regimen used by the sample patients, 80 patients (65.57%) were prescribed the long-term regimen (LTR) type, while the remaining 42 patients (34.43%) were prescribed the short-term regimen (STR) type.

Table 1. Characteristics of the study sample

Characteristics	n (%)
Diabetes mellitus comorbidity status	
Yes	67.20
No	32.80
Gender	
Male	50.82
Female	49.18
Age	
≤ 40 years old	25.41
> 40 years old	74.59
Tuberculosis resistance type	
Multidrug-resistant	91.8
Non-multidrug-resistant	8.2
Anti-tuberculosis regimen	
Long-term regimen	65.57
Short-term regimen	34.43

The data taken from the population were recorded in the medical records at the Pulmonary Clinic of Dr. Soebandi Regional General Hospital, Jember. Furthermore, as the dependent variable, this study also recorded each patient's sputum conversion time history in the selected medical record. The sputum conversion data taken was based on bacterial culture examination and categorized into two groups based on the time of conversion: early sputum conversion (the first 2 months) and late sputum conversion (more than the first 2 months). In the variable of sputum conversion time, patients with long conversion time (late) were recorded in 65 patients (53.27%), and early conversion time was recorded in 57 patients (46.73%). Data on the results of measuring each of the study variables can be seen in Table 2. The sig. <0.05 in the DM comorbidity status and age variables means that a significant correlation existed between both variables and sputum conversion time at drug-resistant TB patients at Dr. Soebandi Regional General Hospital, Jember.

Table 2. Analysis of the Chi-square test on the independent variables and the sputum conversion time

		Late (N = 65) n (%)	Early (N = 57) n (%)	Chi-square (p)	Odds Ratio	Confidence Interval 95%	
						Upper	Lower
Diabetes mellitus	Yes	76.92%	56.14%	0.015*	2.604	1.195	5.674
	No	23.08%	43.86%		1.000		
Age	>40 years old	83.08%	64.91%	0.021*	0.377	0.162	0.878
	≤40 years old	16.92%	35.09%		1.000		

*qualified for multivariate analysis (p < 0.25)

This study used binary logistic regression analysis in multivariate analysis to determine the factor most associated with the sputum conversion time. The logistic regression test analysis was performed by the Backward Stepwise method. Based on the test results, the best modeling was obtained with the DM comorbidity status variable in the sample.

In addition, based on the data on sputum conversion time in patients diagnosed with DM and DR-TB, it can be seen that most patients experienced conversion in the first month after starting treatment with ATDs, followed by more than the sixth month. The average sputum conversion time in the patient group was 4.67 months.

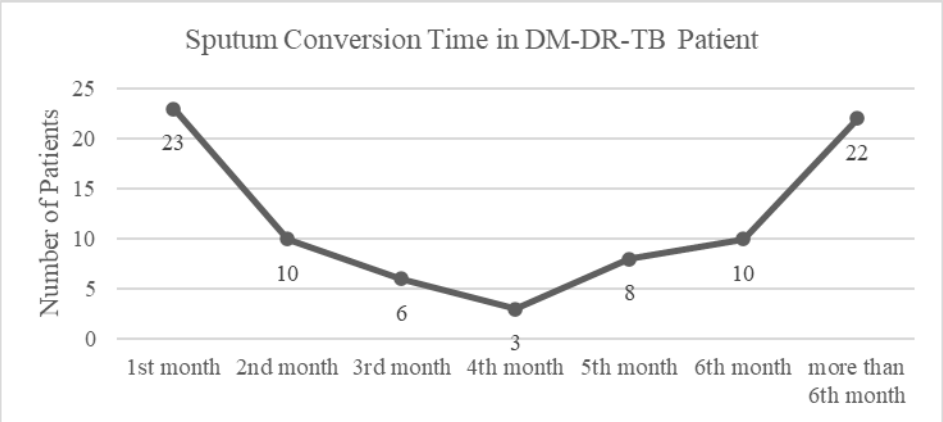

Figure 1. Sputum conversion time in DM-DR-TB patient at Dr. Soebandi Regional General Hospital, Jember

DISCUSSION

Characteristics of Study Sample

Sample characteristics in this study included DM comorbidity status, gender, age, type of TB resistance, type of anti-TB regimen used by the patients, and treatment outcome. Based on gender, it was found that the ratio between males and females was 50.82% and 49.18% (62 males and 60 females). The dominant age in the sample patients was in the age range of >40 years old, which amounted to 74.59%, while the least age range was found in the range of less than equal to 40 years old, which only amounted to 9.02%. The age range of more than 40 years old was the majority in the sample, possibly due to several other factors such as comorbidities and decreased immune system function.[15]

The type of pulmonary TB resistance found in this study sample was dominated by the MDR type, which amounted to 91.8%, followed by the non-MDR (RR and pre-XDR) type at 8.2%. This finding is similar to the WHO report in 2021, which stated that the dominance of resistance in patients with DR-TB was the MDR/RR type (often reported simultaneously), which was 84%.[2] Based on the type of anti-TB regimen prescribed to sample patients, it was found that 65.57% of patients received LTR.[2] Similar findings were also reported by Wahid, *et al*. (2022) in Pakistan, who found that DR-TB patients received more treatment with LTR, which amounted to 55%, compared to STR treatment, which was only 45%.[16] In Indonesia, the Ministry of Health report from 2022 noted that 64.5% of patients were treated using LTR.[17] In determining the anti-TB regimen, patients who received the LTR type mostly experienced more severe cases of DR-TB than usual. Thus, it can be concluded that it is likely that the sample patients experienced cases of DR-TB that fell into the severe category.[17]

Correlation between Gender and Sputum Conversion Time

Historically, DR-TB has affected males more frequently than females, with a higher incidence rate observed in many regions. Several factors, including behavioral, social, and biological differences, contribute to this disparity. Males are more likely to engage in activities that increase their risk of exposure, such as smoking and alcohol use, which also impact their overall health and immune function. A study conducted in Ethiopia found that males were significantly associated with the length of sputum culture conversion among patients with DR-TB.[18] In the male population, most patients experienced longer sputum conversion due to other factors such as smoking history, alcohol consumption, and occupation. Lifestyle factors such as smoking and alcohol can impair immune function in response to DR-TB bacterial infection, resulting in patients experiencing longer sputum conversion compared to controls. However, the relation between gender and sputum conversion time is also influenced by other factors such as lifestyle, age, body mass index (BMI), and TB treatment history.[18]

Correlation between Age and Sputum Conversion Time

In the Chi-square test results (Table 2) of the age group variable on the sputum conversion time, it was found that there was a significant relation with a p-value <0.05 (0.021). This finding is similar to a study conducted in Ethiopia, which found that patients less than 18 years old had a shorter (earlier) conversion time than those of older age.[19] However, this study did not report the impact of age on sputum culture conversion time after the first 6 months of treatment.[19] Age can be indirectly associated with the immune response to TB infection. Older individuals may have a weaker immune response, leading to slower bacterial eradication and, thus, longer sputum conversion. Age can also associated with adherence to TB treatment, with older individuals potentially experiencing non-adherence to the doctor's treatment plan, resulting in longer sputum culture conversions. Overall, evidence from a previous study suggested that age might be a factor influencing sputum culture conversion time in drug-resistant TB patients, with older age being associated with longer sputum conversion times and an increased risk of treatment failure.[20]

Correlation between TB Resistance Type and Sputum Conversion Time

Recently, no study has exclusively examined the relation between resistance type (MDR and non-MDR) and sputum conversion time of DR-TB patients. However, several factors in TB bacterial resistance patterns may influence the sputum conversion time. Different types of TB bacterial species in populations of patients in each region of the world are likely to cause various patterns of resistance to ATD regimens. This may be due to resistance mechanisms by TB bacteria involving intrinsic factors or gene mutations. For at least some ATDs, acquired drug resistance results from sequential bacterial gene mutations that gradually increase resistance, starting with the acquisition of isoniazid resistance, followed by rifampicin or ethambutol resistance. This pattern of gene mutations may, at a later stage, lead to resistance to another ATD, namely rifampicin (regardless of MTB lineage, geographic region, and/or time). This mechanism may cause TB bacteria in different geographical areas to have

different resistance patterns, which may associated with the sputum conversion time of DR-TB patients.[21] Overall, the exact reason behind the association between drug-resistant TB strains and sputum conversion time is not known in the available literature. Further study is needed to delve deeper into these relations.

Correlation between Anti-TB Regimen and Sputum Conversion Time

Following the most recent WHO recommendations, DR-TB treatment in Indonesia currently involves the use of a combination of drugs without the use of injectable medicines. There are two treatment regimens: STR for 9-11 months and LTR for 18-20 months.[1] Based on the study conducted by Mahardani, *et al*. (2022), it was found that the STR regimen was shown to provide good effectiveness in the treatment of DR-TB in terms of earlier sputum conversion and treatment success.[22] This could be due to several aspects, namely, the newer antibiotics bedaquiline and delamanid used in the STR regimen have higher efficacy than other types of ATDs.[22] In contrast, the LTR regimen requires a longer time for patients to complete treatment. Hence, the sputum conversion time is also delayed. This is also supported by the patient's condition, which is generally more severe. Therefore, it is obliged to take an LTR regimen. In summary, the duration of treatment with antibiotic regimens may be associated with a shorter time to sputum culture conversion in patients with DR-TB. However, the specific relation between antibiotic treatment duration and sputum culture conversion time may be influenced by various other factors, such as the antibiotic regimen used and the severity of drug resistance.[1] Further study is needed to fully understand the impact of antibiotic treatment duration on sputum culture conversion time in drug-resistant TB patients.

Correlation between DM and Sputum Conversion Time

The Chi-square analysis in this study (Table 2) demonstrated that DM comorbidity status had a statistically significant association ($p = 0.015$) with the sputum conversion time in sample patients. In addition, the Odd Ratio (OR) was found to be 2.604. It means that patients with DR-TB with DM had a 2.604-fold higher risk of prolonged sputum conversion time than control patients (patients with DR-TB without comorbidities). The results obtained in the analysis in this study are similar to the study conducted by Ahmad, *et al*. (2021), who found a significant association ($p = 0.034$) between DM comorbidity status and the sputum conversion time in patients with MDR-type DR-TB, especially in the second-month post-treatment culture evaluation.[9] The study also stated that MDR TB patients with DM had up to 2.7 times higher risk of experiencing longer sputum culture conversion times.[9]

The duration of sputum conversion in DR-TB patients with DM comorbidity has a variety of differences caused by many factors. One problem that can arise in this condition is related to the patient's long duration of anti-TB treatment, depending on the type of regimen, ranging from 9-24 months. Patients with this condition not only need to take anti-TB but also need to control their blood sugar with anti-diabetic drugs or insulin. This situation causes patients who experience both diseases simultaneously to have a higher risk of experiencing treatment non-adherence due to multi-pharmacy. Therefore, patients will often experience a treatment strike. Hence, the drugs are not consumed as planned. Anti-TB treatment that is not taken properly can interfere with the eradication process of MTB. Thereby, the sputum culture conversion will take longer and increase the risk of treatment failure.[23]

DR-TB patients with DM comorbidity have significantly reduced immune function. This can negatively affect the strength of the immune function in eradicating MTB. Chronic hyperglycemia in DM can cause a series of immunological changes. Elevated blood sugar levels can increase M2 polarization of macrophages, diminishing their ability to engulf MTB and resulting in higher bacterial loads. Secondly, although hyperglycemia boosts the absolute count of neutrophils, their ability to engulf pathogens decreases. Thirdly, heightened levels of NK cells secreting TNF-α, IL-2, and IL-17F contribute to increased disease severity or bacterial burden. It has also been shown that under hyperglycemia conditions, NK cells tend to secrete the cytokine IL-6, which can inhibit the maturation of Th0 cells (CD4+ T cells). Th0 cells that do not undergo maturation will result in decreased production of IL-12 cytokine (responsible for maturation into Th1 cells). Hence, bacterial eradication function is impaired. Fourthly, DM reduces the secretion of dendritic cells, diminishing stimulation to $CD4^+$ T cells and impeding adaptive immune responses. Lastly, hyperglycemia inhibits the secretion of cytokines like IFN-γ and TNF-α by Th1 T lymphocytes, reducing MTB clearance. Concurrently, decreased IFN-γ levels inhibit $CD8^+$ T lymphocyte activation by Th1 cells, resulting in reduced secretion of bactericidal substances and weakened cytotoxic T lymphocyte bactericidal capacity. In DR-TB patients with DM, successive impairment of innate and adaptive immune cell functions weakens their ability to restrain MTB, prolonging sputum conversion times.[24]

Type 1 and type 2 DM have similar impacts on DR-TB. Both types of DM are associated with an increased risk of DR-TB, including MDR-TB, which is

resistance to at least isoniazid and rifampicin.[25] However, the risk of DR-TB is higher in type 1 DM patients compared to type 2 DM patients.[26] This is likely because type 1 DM patients have a higher prevalence of MDR-TB and pre-XDR-TB compared to type 2 DM patients. Additionally, type 1 DM patients have a higher risk of developing DR-TB strains with resistance to other ATDs, such as streptomycin, kanamycin, protionamide, and levofloxacin, compared to type 2 DM patients.[8]

The treatment options for DR-TB patients with type 1 and type 2 DM comorbidity are not significantly different. The management of both DM types in patients with DR-TB is maintaining good glycemic control to ensure optimal treatment outcomes and reduce the risk of complications.[26] Until now, no further research (especially in Indonesia) has compared the two types of DM comorbidity on the sputum conversion time in DR-TB patients. Regarding the type of DM studied in this study, the type of DM (type 1 or 2) was not differentiated at the time of data collection. This was due to the unavailability of such information in the medical records of DR-TB patients at the Pulmonary Clinic of Dr. Soebandi Regional General Hospital, Jember.

In the management of patients with DR-TB with DM comorbidity, the ultimate management goal is to cure DR-TB infection while controlling blood glucose levels due to DM. Hence, it is not uncommon for these patients to be required to take anti-TB and hypoglycemic drugs simultaneously.[25] One type of anti-TB that is often used in the management of DR-TB cases is bedaquiline and delamanid. The use of these two DR-TB drugs in patients with DM requires more consideration due to potential interactions with several hypoglycemic agents. According to a review of clinical and pharmacological aspects, bedaquiline shares metabolic pathways with some oral hypoglycemic agents in the liver, while delamanid may work competitively with some oral hypoglycemic agents and insulin analogs at protein binding sites.[27] The drug liraglutide is the only drug from the glucagon-like peptide-1 (GLP-1) receptor agonist group found to possibly interact with bedaquiline and delamanid at the protein binding level. Therefore, it is important to monitor patients receiving bedaquiline and delamanide for potential drug interactions with hypoglycemic agents and insulin analogs, especially in patients with severe conditions such as those with DR-TB.[28]

The results of the multivariate test analysis showed that the variable with the potential to cause long sputum conversion is the DM comorbidity status variable. As explained, DM is associated with the sputum conversion time of DR-TB patients. DM can influence the sputum conversion time through several factors. Treatment non-adherence due to multi-pharmacy, immunosuppressive conditions in patients, and anti-diabetic drug and ATD treatment interactions are thought to be factors leading to longer sputum conversion times in patients.[24,26]

CONCLUSION

Based on the results and discussion of the study on the association of DM and the sputum conversion time, it can be concluded that DM comorbidity was associated with prolonged sputum conversion time of DR-TB patients at Dr. Soebandi Regional General Hospital, Jember. In addition, the DM variable was the most associated variable with the sputum conversion time compared to gender, age, TB resistance type, and anti-TB regimen.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Drafting the manuscript: NAR, RD, CA, YH, MAS. Collecting data, analyzing data, and preparing the manuscript: NAR, RD, CA. Compiling research design: AMR, NAR, RD, CA. Revising the final manuscript for publication: AMR, NAR, RD, CA. Giving final approval: AMR, RD, CA. All authors contributed and approved the final version of the manuscript.

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