Factors Associated with Delayed 2-Month Sputum Smear Conversion in MDR-TB Patients Treated with All-Oral Regimen at Persahabatan Hospital

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Abstract

Background: The emergence of multidrug-resistant tuberculosis (MDR-TB) presents significant challenges in achieving treatment success. Sputum conversion time, an essential indicator of treatment progress, varies among patients and may be influenced by demographic and clinical factors. This study aimed to identify factors associated with sputum conversion time in MDR-TB patients treated with all-oral regimens at Persahabatan Hospital during the 2021–2022 period.

Method: This retrospective cohort study analyzed data from 154 MDR-TB patients treated with all-oral regimens at Persahabatan Hospital. Patients were categorized by sputum conversion time (≤2 months or >2 months). Independent variables included age, sex, diabetes mellitus, anemia, previous TB treatment, pulmonary cavitation, education level, marital status, and initial sputum AFB results. Inclusion criteria were primary pulmonary MDR-TB patients confirmed via sputum culture, aged ≥20 years, and treated per Indonesian national guidelines. Logistic regression analyses identified significant factors.

Results: Among the nine factors studied, four significantly influenced sputum conversion time: elderly age, anemia, pulmonary cavitation, and initial sputum AFB results. Older age (≥60 years) was protective against delayed conversion, while anemia, pulmonary cavitation, and higher initial sputum AFB results were associated with prolonged conversion times.

Conclusion: Factors such as anemia, pulmonary cavitation, and initial sputum results are associated with delayed sputum conversion, with elderly age as a protective factor against delayed sputum conversion.

Keywords: drug resistant, risk factors, sputum conversion, tuberculosis

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) remains a significant public health challenge worldwide, particularly in low- and middle-income countries. The burden of drug-resistant tuberculosis (DR-TB) in Indonesia is one of the highest globally. In 2022, there were an estimated 24,666 cases of DR-TB in Indonesia, with a national treatment success rate of 51% (target: 80%). In the same year, Jakarta recorded only 50%.[1]

Despite advancements in diagnostic tools and treatment protocols, achieving optimal treatment outcomes continues to be hampered by delays in sputum smear conversion, a critical milestone in the management of TB. Sputum smear conversion time, defined as the duration required for a patient's sputum to convert from positive to negative, serves as a surrogate marker for treatment efficacy and reduction in transmissibility. It is crucial to identify the factors linked to delayed sputum smear conversion to enhance tuberculosis treatment outcomes.

The World Health Organization recently updated its guidelines for drug-resistant tuberculosis treatment, shifting away from the long-standing use of injectable agents and recommending all-oral, longer regimens instead.[2] Since 2020, DR-TB treatment in Indonesia has adopted an all-oral drug cocktail based on bedaquiline as the primary antibiotic. This regimen replaces the injectable regimen and eliminates the need for antibiotic injections during the intensive phase of DR-TB treatment.[3] The bedaquiline-based all-oral MDR-TB regimen has been shown to improve treatment success rates and enable faster sputum smear conversion compared to injection-based treatments.[4]

Previous studies have identified a range of factors influencing sputum smear conversion time, including patient demographics, comorbidities, and disease severity. However, limited data exist on these factors in the context of all-oral regimens, which have become the standard of care for MDR-TB in line with global health recommendations.[5,6]

The goal of this study was to identify factors related to delayed sputum smear conversion time (≤2 months or >2 months) in MDR-TB patients undergoing all-oral regimen treatment at Persahabatan Hospital from 2021 to 2022. Sputum smear conversion at the end of the 2-month intensive phase has been recognized as a prognostic indicator of achieving timely and complete therapy in patients with pulmonary tuberculosis.[5,6]

METHOD

This retrospective cohort study was conducted at Persahabatan Hospital, a national referral hospital for patients with TB-MDR. This study has been approved by Persahabatan Hospital with ethical clearance No.0245/KEPK-RSUPP/11/2024. The study population included all adult patients (≥20 years old) diagnosed with MDR-TB and treated with all-oral regimens from 2021 to 2022.

All confirmed pulmonary MDR-TB patients who were registered at Persahabatan Hospital from 1 January 2021 to 31 December 2022 and treated with the new all-oral regimen based on Indonesian national guidelines were included in the study. Patients were included if they had primary pulmonary MDR-TB confirmed via sputum culture and complete medical records. Patients undergoing ongoing or incomplete tuberculosis treatment were excluded.

A total of 154 patient medical records were analyzed. Data were extracted from hospital medical records, including demographics (age, sex, education level, marital status), clinical characteristics (diabetes mellitus comorbidity, anemia, pulmonary cavitation), previous TB treatment history, and initial sputum acid-fast bacilli (AFB) results.

The dependent variable was sputum conversion time, categorized as ≤2 months or >2 months. Sputum smear conversion refers to cases of smear-positive pulmonary TB that become smear-negative following anti-TB treatment, confirmed by at least two consecutive negative sputum AFB smears taken 30 days apart.[7,8] Both univariate and multivariate logistic regression analyses were conducted to determine the key factors linked to delayed sputum conversion.

RESULT

A total of 154 patients met the inclusion criteria of this study. Among them, 101 patients (65.6%) experienced

sputum conversion within ≤2 months, while 53 patients (34.4%) required more than 2 months. The baseline characteristics of patients are written in Table 1.

Table 1. Baseline Characteristics of TB-MDR patients

Variables	n	%
Age		
<60	129	83.8
≥60	25	16.2
Gender		
Male	85	55.2
Female	69	44.8
Education Level		
Below High School	38	24.7
High School Equivalent and Higher	116	26.6
Marital Status		
Not Married	23	14.9
Married	131	85.1
DM		
No	83	53.9
Yes	71	46.1
Anemia		
No	79	51.3
Yes	75	48.7
Cavity on chest X-ray		
Non-Cavitary	113	73.4
Cavitary	41	26.6
Previous history of TB treatment		
New TB patient	85	55.2
Treated previously	69	44.8
Sputum AFB results		
<2+	91	59.1
≥2+	63	40.9

Most patients were under 60 years of age (83.8%). The proportion of males was slightly higher than that of females (55.2% vs. 44.8%). A large proportion of patients had an education level equivalent to high school or higher (75.3%), and the majority were married (85.1%). Over half of the patients did not have diabetes mellitus (53.9%), and a total of 51.3% of patients

did not have anemia.

Most exhibited non-cavitary lesions on chest X-ray (73.4%), and a slightly higher proportion were newly diagnosed with tuberculosis (55.2%). Sputum AFB results were categorized according to the IUATLD classification. Results of Negative, Scanty, or 1+ were grouped as <2+, while results of 2+ or 3+ were grouped as ≥2+. Based on this classification, 59.1% of patients had AFB results in the <2+ category, and 40.9% had results in the ≥2+ category.

Univariate analysis was performed (Table 2). Delayed sputum smear conversion (>2 months) was associated with anemia (OR=2.055; P=0.036), pulmonary cavitation (OR=2.500; P=0.013), and sputum bacillary load of ≥2+ (OR=3.441; P=0.0001). Elderly age has a negative association with delayed sputum smear conversion (OR=0.311; P=0.034).

Table 2. Univariate analysis of patient characteristics with sputum smear conversion time.

Variables	Early sputum conversion ≤2 months (n=101)	Delayed sputum conversion >2 months (n=53)	P	OR (95% CI)
Age				
<60	80 (62.0)	49 (38.0)	0.034	0.311 (0.101-0.960)
≥60	21 (84.0)	4 (16.0)		
Gender				
Male	58 (68.2)	27 (31.8)	0.442	1.299 (0.666-2.532)
Female	43 (62.3)	26 (37.7)		
DM				
No	56 (67.5)	27 (32.5)	0.595	1.198 (0.615-2.333)
Yes	45 (63.4)	26 (36.6)		
Previous history of TB treatment				
New TB patient	56 (65.9)	29 (34.1)	0.931	1.030 (0.528-2.009)
Treated previously	45 (65.2)	24 (34.8)		
Anemia				
No	43 (57.3)	32 (42.7)	0.036	2.055 (1.044-4.046)
Yes	58 (73.4)	21 (26.6)		
Cavity on CXR				
Non-Cavitary	21 (50.0)	21 (50.0)	0.014	2.500 (1.204-5.191)
Cavitary	80 (71.4)	32 (28.6)		
Education Level				
Below High School	24 (63.2)	14 (36.8)	0.717	0.868 (0.405-1.863)
High School Equivalent and Higher	77 (66.4)	39 (33.6)		
Marital Status				
Not Married	86 (65.6)	45 (34.4)	0.986	1.019 (0.402-2.585)
Married	15 (65.2)	8 (34.8)		
Sputum AFB results				
<2+	70 (76.9)	21 (23.1)	0.0001	3.441 (1.719-6.888)
≥2+	31 (49.2)	32 (50.8)		

Table 3. Multivariate analysis of predictors of sputum smear conversion time.

Variables	B	SE	P	OR	95% CI
Age					
Non-elders (<60) (ref)					
Elderly Age (≥60)	-1.246	0.619	0.044	0.288	0.085 − 0.968
Pulmonary cavitation in chest x-ray					
No pulmonary cavitation (ref)					
Pulmonary cavitation present	0.851	0.416	0.039	2.363	1.046 − 5.337
Anemia					
No Anemia (ref)					
Anemia Present	0.860	0.376	0.024	2.343	1.121 − 4.896
Sputum bacillary load					
<2+ (ref)					
≥2+	0.955	0.377	0.011	2.598	1.241 - 5.441

Variables with a significance value of P<0.250 in the univariate chi-square analysis became candidates for multivariable analysis. These variables include age, anemia, pulmonary cavity, and sputum AFB results.

On multivariate analysis, logistic regression was performed (Table 3). Elderly age (OR=0.288; P=0.044), pulmonary cavitation (OR=1.046; P=0.039), anemia (OR=2.055; P=0.024) and sputum AFB results (OR=2.598; P=0.011) were found to be significant factors affecting sputum smear conversion time.

DISCUSSION

In this study, 65.6% of patients experienced sputum smear conversion within ≤2 months, while 34.4% required more than 2 months. This finding is comparable with existing literature, such as the study by Meshesha, which reported that 69.66% of MDR/RR TB patients achieved sputum smear conversion within ≤2 months.[6] In contrast, Assemie et al.

observed a higher sputum conversion rate of 75.4% at 2 months.[9]

The results of this study showed that anemia, pulmonary cavity, and pre-treatment sputum AFB results are the significant factors that increase the odds of delayed sputum smear conversion, while elderly age (≥60 years) was found to have lower odds of delayed sputum conversion. Sputum smear conversion serves as a critical marker in tuberculosis treatment and is the primary indicator of treatment efficacy in TB management.[8]

Patients with a higher bacillary load (≥2+) during the pre-treatment phase were found to be a strong predictor of delayed sputum smear conversion. Multiple studies across diverse settings report that patients with higher pre-treatment sputum bacillary loads have significantly increased odds of delayed sputum smear conversion.[10–12] Patients with a higher bacillary load, often seen in those with extensive tuberculosis lesions, experience a significant accumulation of dead bacilli. As a result, more time is needed to clear this large bacillary burden.[13]

Cavitary lesions observed on chest x-rays were identified as significant predictors of prolonged sputum smear conversion time. Previous studies have linked pulmonary cavitation as a key risk factor for delayed sputum smear conversion.[14,15] Cavitation slows sputum conversion by harboring a high bacillary load in a protected environment with poor drug penetration. The necrotic debris in cavity walls further serves as a reservoir for bacilli, delaying their clearance and prolonging treatment response.[6,16]

Anemia emerged as a significant predictor of delayed sputum conversion in this study. Defined according to WHO criteria, anemia is characterized by hemoglobin (Hb) levels below 12.0 g/dL in women and below 13.0 g/dL in men.[17]

Anemia in TB is often multifactorial, commonly arising from chronic inflammation (anemia of chronic disease), nutritional deficiencies (e.g., iron, folate, vitamin B12), or bone marrow suppression.[18] Previous studies have linked anemia with a higher likelihood of persistent positive sputum smears after two months of tuberculosis treatment.[18–20] However, Kumar et al reported no significance between anemia and sputum conversion.[20]

Previous studies have theorized that older age is associated with a weaker immune response, which can hinder effective clearance of bacilli.[21,22] Additionally, delays in seeking timely medical care are more common among older individuals, contributing to poor treatment progress.[23]

In contrast to previous research, elderly patients were more likely to achieve early sputum conversion than younger patients. Although the reason is unclear, several explanations are possible. Some studies have reported that older individuals tend to present with less cavitary pulmonary involvement and a lower bacillary burden compared to younger patients.[24–26]

In our analysis, pulmonary cavitation was independently associated with delayed conversion, suggesting that the lower prevalence of cavitary lesions in elderly patients may contribute to their earlier smear negativity. Improvements in patient-centered care, which tailors treatment to individual needs, may play a role, as patient-centered care often demonstrates better adherence.[21,27]

Although cavitary lesions were independently associated with delayed conversion in our model, it is possible that additional unmeasured age-related differences in disease phenotype, host immune response, or healthcare engagement contributed to this association. Further research may be needed to confirm this finding.

This study has several limitations that warrant consideration. Although total sampling was used, only 154 of 236 patients had complete data, raising the risk of selection bias and limiting generalizability. While the use of total sampling minimizes sampling bias, the reduction in analyzable cases may have limited the statistical power to detect smaller, yet clinically significant

associations. Consequently, the generalizability of the findings may be somewhat constrained. Future studies with larger, more complete datasets and prospective designs are recommended to confirm and build upon the results of this study.

CONCLUSION

The majority of MDR-TB patients treated with the all-oral regimen successfully achieved sputum conversion within the first two months of treatment. Anemia, pulmonary cavitation, and high sputum AFB load (≥2+) were independent predictors of delayed sputum conversion, while older age (≥60 years) was protective.

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