Original Article

Factors Affecting the Treatment Success of Short-Term Regimen for Drug Resistant Tuberculosis (DR TB) Patients at Dr. Saiful Anwar General Hospital Malang

Fahmi Adhi Prasetya[1], Yani Jane Sugiri[1], Teguh Rahayu Sartono[1], Harun Al Rasyid[2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya - RS Dr. Saiful Anwar Malang, Indonesia
[2]Laboratory of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Brawijaya, Indonesia

Abstract

Background: Tuberculosis/TB is a major health problem in the world. Indonesia ranks 3rd in TB cases and 7th in drug resistant (DR) TB cases in the world. In 2016, WHO recommended short term (9–11 month) regimen treatment with a success rate of 84% in several Asian and African countries. The purpose of this study was to determine factors that influence the success and failure of treatment using short-term regimen for DR TB patients at Dr. Saiful Anwar General Hospital Malang.

Methods: This was an analytic observational study with retrospective cohort design on 85 short-term regimen DR TB patients who started treatment on October 1, 2017 to September 30, 2018 at the DR TB ward of Dr. Saiful Anwar General Hospital Malang. Data analysis used chi square test with alternative fisher exact test and logistic correlation test.

Results: Education level had a significant correlation with treatment success (*P*=0.036; OR=2.746; CI 95%=1.053-7.165) while Pre XDR TB sputum drug susceptibility test had a significant correlation with treatment failure (*P*=0.037; OR=1.556; CI 95%=1.180-2.050). Based on logistic correlation test, the predictive variables for treatment outcomes were age, education, criteria for suspected DR TB and drug susceptibility test results of pre XDR TB.

Conclusion: The level of education affected the success treatment of DR TB short-term regimen. The results of Pre XDR TB sputum drug susceptibility test influenced the failure of DR TB short-term regimen.

Keywords: Drug Resistant TB, Short Term Regimen, Success Treatment

Corresponding Author:
Fahmi Adhi Prasetya | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya - RS Dr. Saiful Anwar Malang, Indonesia | Fahmiadhi85@gmail.com

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INTRODUCTION

Tuberculosis (TB) is one of the world's health problems and is one of the leading cause of death among the 10 most common diseases in the world. WHO data in 2018 mentioned that Indonesia ranked 3rd of highest TB case in the world after India and China.[1]

Resistance to first-line Anti-Tuberculosis Drugs (ATD) is an obstacle in achieving TB targets. About 5% of all TB cases are drug resistant (DR) TB. WHO data in 2007 stated that the percentage of primary resistance worldwide had 17.0% cases of polyresistance, 10.3% monoresistance, and 2.9% multidrug resistance (MDR). Meanwhile, in Indonesia, the primary resistance to MDR TB was 2%.[2] WHO data in 2018 pointed out that Indonesia ranked 7th of the highest DR TB prevalence in the world.[1]

Currently in Indonesia, there has been a decline in the success rate for DR TB treatment, from 67.9% (2010) to 51.1% (2013), and an increase in the rate of loss to follow-up (LFU) from 10.7% (2009) to 28.7% (2013).[3] Data at Dr. Saiful Anwar General Hospital Malang from January 2014 to December 2016 of 57 patients receiving DR TB treatment, 17 patients recovered (29.82%), 15 patients died (26.32%), and 25 patients dropped out of treatment (43.86%).[4]

The current management of DR TB takes a long time and requires high costs, both for the program and for patients. Worldwide DR TB surveillance data also showed unsatisfactory results in terms of the long-term standardized treatment success rate, which was around 62%. In 2016, WHO issued a recommendation for using standardized short-term treatment combinations of

9–11 months which indicated promising outcomes based on the results of various observational studies in several Asian and African countries with treatment success rate of 84%. Currently, there are two combinations of treatment in Indonesia, namely a combination of standard short-term treatment and a combination of individual treatment. Treatment success for DR TB patients can be seen from several factors: health workers and TB control programs, patients, drugs, economy, comorbidity factors, HIV/AIDS factors, and drug adverse effects.[3]

In general, this study aimed to determine the treatment success rate of patients with standard short-term regimen for DR TB and specifically to identify the factors that influence the success and failure of standard short-term regimen for DR TB patients at Dr. Saiful Anwar General Hospital Malang.

METHODS

This study used an analytic observational design with a cohort retrospective approach. The study subjects were all DR TB patients on short-term combination treatment who met the inclusion and exclusion criteria.

Inclusion criteria were patients aged 18 years and patients who had at least one day of treatment with a short-term combination of DR TB recorded in the MDR clinic medical record of Dr. Saiful Anwar General Hospital Malang on October 1, 2017 to September 30, 2018. Exclusion criteria were patients who did not meet the requirements for DR TB short-term combination treatment.

The study used secondary data (review of medical record documents and e-TB manager data) at the MDR TB clinic of Dr. Saiful Anwar General Hospital Malang from January 2019 to June 2019. The ethics committee had approved every procedure.

The independent variables of the study were age, gender, education level, occupation, income, domicile, criteria for suspected DR TB, nutritional status, comorbidities, smoking history, results of investigations, drugs adverse effects, and HIV status of patients with short-term standard treatment for DR TB. The dependent variable was the treatment success of patients with DR TB short-term treatment.

The recorded data were then processed, analyzed, and interpreted. The analysis used in this study were univariate, bivariate, and multivariate analysis. Chi-square test was used to evaluate the correlation between the independent and dependent variables, while the alternative Fisher exact test was used if requirements were not met. Logistic regression was applied to determine the most influential correlation between the independent and dependent variables. These measurements of variables were carried out using Microsoft Office Excel 2010 program and SPSS 25.0.

RESULTS

The sociodemographic characteristics of the study subjects and the sociodemographic correlation to the success of DR TB short-term treatment are shown in Table 1. Based on the sociodemographic characteristics of the study subjects, the majority were male (61.2%), the mean age of subjects in the treatment group was 40.08 years with a median of 42 years (Figure 1), had low education (61.2%), risk occupation group (84.7%), had low income (62.3%), domiciled outside Malang (52.9%), had a history of smoking (55.3%), had diabetes melitus (DM) comorbidity (41.2%), came from the criteria for non-relapse cases (54.1%), and had non-underweight BMI (55.3%).

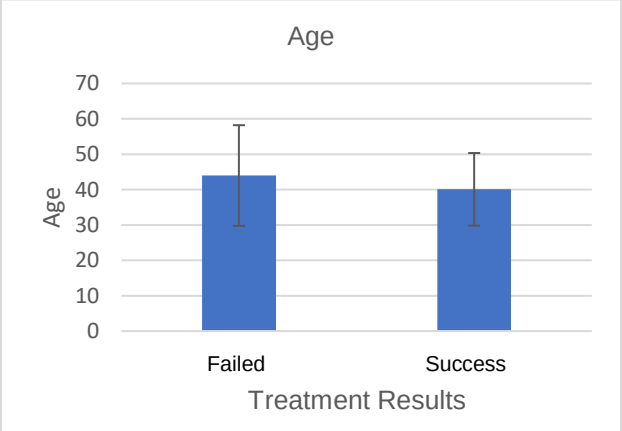

Figure 1. Age Difference in Failed Treatment and Successful Treatment Groups

Table 1. Characteristics and Sociodemographic Effects on Treatment Success

Variable		Treatment Results						*P*
		Failure		Successful		Total		
		n	%	n	%	n	%	
Occupation	No Risk	11	84.6	2	15.4	13	15.3	0.328*
	At Risk	49	68.1	23	31.9	72	84.7	
Gender	Male	39	75	13	25	52	61.2	0.262
	Female	21	63.6	12	36.4	33	38.8	
Income	Low	36	67.9	17	32.1	53	73.6	0.705
	High	12	63.2	7	36.8	19	26.4	
Education	Low	41	78.8	11	21.2	52	61.2	0.036
	High	19	57.6	14	42.4	33	38.8	
Smoking Status	Smoker	35	74.5	12	25.5	47	55.3	0.383
	Non-smoker	25	65.8	13	34.2	38	44.7	
Area	Malang	26	65.0	14	35.0	40	47.1	0.286
	Outside Malang	34	75.6	11	24.4	45	52.9	
BMI	Underweight	25	65.8	13	34.2	38	44.7	0.383
	Non-Underweight	35	74.5	12	25.5	47	55.3	
Criteria for Suspected DR TB	Relapsed	30	76.9	9	23.1	39	45.9	0.238
	Non-Relapse	30	65.2	16	34.8	46	54.1	
Comorbid	Existed	27	73	10	27	37	43.8	0.811*
	Non-existent	33	68.8	15	31.2	48	56.5	
HIV	Existed	1	100	0	0	1	1.2	1.00*
	Non-existent	59	70.2	25	29.8	84	98.8	
DM	Existed	25	71.4	10	28.6	35	41.2	0.887
	Non-existent	35	70	15	30	50	58.8	

Table 2. The Effect of Supportive Examination Results and Drugs Adverse Effects on Treatment Success

Variable		Treatment Results						*P*
		Failure		Successful		Total		
		n	%	n	%	n	%	
Sputum AFB Conversion Time	Mean	1.318		1.40		1.351		0.511*
	Median	1		1		1		
Sputum Culture Conversion Time	Mean	1.407		1.50		1.449		0.950*
	Median	1		1		1		
Chest X-Ray	Extensive	59	67.9	25	32.1	84	91.8	0.100
	Minimum	1	100	0	0	1	8.2	
Sputum drug susceptibility test	Monoresistance	0	0	1	100	1	1.6	0.379
	RR	13	60.9	9	31.7	22	36.5	0.802
	MDR	19	64.3	10	35.7	29	44.4	Reff
	Pre-XDR	11	100	0	0	11	17.5	0.037
Drugs Adverse Effects	Exist	41	66.1	21	33.9	62	72.9	0.139
	None	19	82.6	4	17.4	23	27.1	

To determine the correlation between sociodemography and the success of short-term standardized treatment for DR TB, the chi-square test and the Mann Whitney test were carried out. In this study, based on the results of the chi-square test, it was found that gender (*P*=0.262), occupation (*P*=0.328), income (*P*=0.705), domicile (*P*=0.286), smoking history (*P*=0.383), criteria for suspected DR TB (*P*=0.238), BMI (*P*=0.383), comorbid status (*P*=0,811), DM comorbidity (*P*=0.887) and HIV status (*P*=1.00) were not significantly associated with the success of short-term treatment regimen for DR TB. Meanwhile, the Mann Whitney test results indicated that age was not significantly related to the success of short-term DR TB treatment (*P*=0.218). Only the patient education variable was significantly related to the success of short-term treatment for DR TB (*P*=0.036).

The characteristics of AFB sputum conversion time and culture, chest X-ray (CXR) results, sputum examination results for first line and second line drug sensitivity tests, drugs adverse effects, and

their effects on the success of DR TB treatment can be seen in Table 2. Percentage of treatment results the effect of supporting examination results and drug side effects on success treatment: the most extensive CXR results (91.8%), the results of sputum examinations for line 1 and 2 drug sensitivity tests with the most MDR (34.1%), many have side effects of treatment (72.9%).

Table 3. Treatment Outcome, Causes of Switching to Individualized Regimens, Treatment Dropout, Drugs Adverse Effects

Parameter	n	Percentage (%)
Treatment End Result		
Complete treatment	11	12.9
Recovered	14	16.5
Dropout	26	30.6
Treatment failure	2	2.4
Died	13	15.3
Switched to individualized regimen	19	22.3
Causes of Switching to individualized regimen		
Pre XDR	11	12.9
Drugs adverse effects	8	9.4
Causes of treatment dropout		
Drugs adverse effects	20	23.5
No family supports	2	2.4
Refusing treatment	4	4.7
Drugs adverse effects		
Nausea/vomiting	56	65.9
Injection site pain	10	11.8
Weakness	2	2.4
Vertigo	12	14.1
Anorexia	3	3.5
Visual impairment	5	5.9
Hearing disorder	10	11.8
Headache	10	11.8
Electrolyte disturbance	7	8.2
Impaired kidney function	4	4.7
Arthralgia	2	2.4
Peripheral neuropathy	4	4.7
Insomnia	4	4.7

The Mann Whitney test was used to analyze the effect of AFB sputum conversion time and sputum culture conversion time on the success of DR TB treatment. On the other hand, the CXR results and sputum drug susceptibility test results affected the success of DR TB treatment, as confirmed by the Chi-Square test. AFB sputum conversion time (*P*=0.511), sputum culture conversion time (*P*=0.950), CXR results (*P*=0.100), sputum results from monoresistance drug sensitivity test (*P*=0.379), rifampicin resistance/RR (*P*=0.802) and drug adverse effects (*P*=0.139) were not significantly related to the success of DR TB short-term treatment. Only pre-XDR drug susceptibility test results were significantly associated with DR TB short-term treatment failure (*P*=0.037).

The final results of treatment, causes of switching individual regimens, causes of treatment discontinuation, and drug adverse effects of study subjects are shown in Table 3.

Most of the treatment outcome was treatment dropout (30.59%), while the most common cause of switching from standard short-term treatment regimens to individualized treatment regimens was the pre-XDR result of sputum susceptibility test in first and second lines (12.9%). The cause of treatment dropout of short-term combinations was mostly due to drugs adverse effects (23.5%), while the most common adverse effect was nausea/vomiting (65.9%).

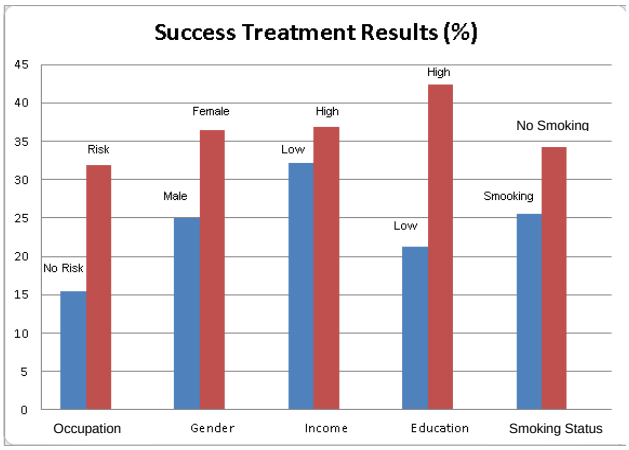

Figure 2. Successful treatment results in multiple variable groups

Table 4. Logistics Regression Test for Treatment Success of Standard Guidelines for DR TB Short-Term Regimen

Parameter	B	S.E.	Wald	df	*P*	OR	95% CI	
							Lower	Upper
Age	-0.002	0.030	0.004	1	0.950	0.998	0.941	1.059
Education	-0.309	0.825	0.140	1	0.708	0.734	0.146	3.701
Criteria for suspected DR TB	-0.470	0.801	0.345	1	0.557	0.625	0.130	3.002
Pre XDR	-20.879	12059.579	0.000	1	0.999	0.000	0.000	-
Constant	-0.045	1.577	0.001	1	0.977	0.956	-	-

The variables included in the multivariate analysis were variables with *P*-value of <0.25 in the bivariate analysis, namely age, education level, criteria for suspected DR TB and pre-XDR (Table 4).

DISCUSSION

Based on this study results, most of DR TB patients was male (61.2%), and the gender variable was not significantly correlated to the DR TB treatment success (*P*=0.262). There were no clear correlations that could explain the incidence of DR TB with gender. Men are more at risk for developing DR TB because women tend to seek health services more and are considered to be more obedient in taking medications.[5]

Descriptively, it could be seen that patients with risk of failure were in the mean age of 43.98 years with a median of 45.5 years, and for those who recovered, the mean age was 40.08 years with a median age of 42 years. From this study, it was observed that age was not associated with DR TB treatment success (*P*=0.218). This result was similar to study from Elisabeth et al. that the mean age of DR TB patients was 42.76 years. In the productive age, the rate of TB transmission is very high and extensive because the patient's interactions with other people and high work mobility might induce the patients to tend not to adhere to ATD in their previous TB treatment.[6]

Based on the occupations of DR TB patients, it was noticed that most of them had risky jobs (84.7%), and the work variable was not related to the success of DR TB treatment (*P*=0.328). Elisabeth et al. obtained no association between occupational status and treatment success, while on the contrary, patients who worked reduced the DR TB treatment success (OR=0.87; 95% CI 0.67–1.14; *P*=0.314).[7] All types of work which account study subjects to be exposed to substances that interfere with lung function and works that allow study subjects to have contact with TB patients are considered as risky jobs. A person's occupation reflects the amount of information received about illness as well as health services and helps a person to make decisions about the use of existing health services and the views about treatment.[8]

We also observed that most of the DR TB on treatment had low income (73.6%), and the income variable was not related to the success of DR TB treatment (*P*=0.705). This result was the same as study from Tirtana which stated that there was no correlation between level of income and the DR TB treatment success (*P*=1.00).[9] Resistance to ATD is broadly developed in countries with poor socio-economic conditions, where the condition of incompetent purchasing power affects the fulfillment of nutritional needs. Resistance causes M.Tb to multiply easily and ultimately inhibits sputum conversion.[10]

Based on the education status, it was observed that most of the patients with DR TB treatment had low education (61.2%), and the level of education was significantly related to DR TB treatment success (*P*=0.036). According to Kondoy et al., education level was related to medication adherence, which increased the treatment success for TB patients.[11] Higher education will support a person to understand the knowledge given.[12] Absorption of knowledge about DR TB greatly influences patients compliance behavior and leads the patient to optimize and pay more attention to their health and nutrition, including the prevention and treatment of DR TB.[13]

In this study, most DR TB patients on treatment had a history of smoking (55.3%), and the smoking history variable was not associated with the success of DR TB treatment (*P*=0.383). Khan et al. concluded that smoking was a risk factor for developing DR TB (*P*<0.05), and cases of multiple drug resistance were more common in smokers than in non-smokers. In smokers, macrophage disruption increases airway resistance and pulmonary epithelial permeability. Cigarette smoking will reduce the responsiveness to antigens. The incidence and severity of TB were related to smoking.[14]

The study subjects were DR TB patients mostly from outside Malang (52.9%), and the variable of domicile was not related to the success of DR TB treatment (*P*=0.286). It was similar to

study from Elisabeth et al. which pointed out that the distance from which the patient lived was not related to the DR TB treatment success (OR=1.01; 95% CI=0.57-1.77; *P*=0.973).[7] Most patients chose health facilities that were relatively close to their homes. The distance from home to health facilities is indeed an important factor.[15]

We also found that most DR TB patients on treatment had non-underweight BMI (55.35%), and the BMI variable was not associated to DR TB treatment success (*P*=0.383). According to Elisabeth et al., nutritional status of patients was not associated with successful treatment of DR TB (OR=2.07; 95% CI=0.47-3.02; *P*=0.718).[7] Tuberculosis patients who were underweight had a higher risk of relapse after completion of treatment. Drug resistant TB treatment has more severe side effects than drug sensitive-TB treatment, thus affecting the patient's poor nutritional status. Therefore, regular monitoring of patients' nutritional status is very important.[16]

Based on research data, the criteria for suspected DR TB were mostly non-relapse case (54.1%). The criteria for suspected DR TB were not associated with DR TB successful treatment (*P*=0.238). The incidence of DR TB is mostly caused by secondary resistance from primary resistance, and recurrence of TB patients allows drug resistance to occur. Resistant organisms can arise due to several factors, and human error is the biggest contribution.[17]

In this study, the most common comorbidity of DR TB patients was DM (41.2%), and the comorbidities variables were not related to the DR TB treatment success (*P*=0.672). According to Manurung et al., comorbidities (DM and HIV) did not affect the success rate of DR TB patients (OR=0.73; 95% CI=0.27-1.97; *P*=0.53). Comorbidities in DR TB patients cause a worse quality of life than patients without comorbidities. DM is a risk factor for DR TB, and patients with DM have deficiencies of cellular immunity.[6]

Our study obtained the mean AFB sputum conversion time of 1.351 months with a median of 1 month. There was no significant association between sputum smear conversion time with the success of DR TB treatment (*P*=0.511). The sputum culture conversion time was 1.449 months with a median of 1 month. There was also no significant association between sputum culture conversion time and the success of DR TB treatment (*P*=0.950). This result was the same as study from Sinaga which stated that among 85 study subjects, the largest AFB growth occurred in the fourth week of 43 samples (50.59%).[18]

A high conversion rate will be followed by a high cure rate.[19] Factors that could prolong sputum conversion time such as bacterial load at the start of treatment, lung cavities, smoking, chronic symptoms, age, inappropriate medication, gender, BCG score, and erythrocyte sedimentation rate, could also affect the length of conversion.[20]

Based on CXR lesions, most of the CXR lesions obtained were extensive (91.8%), and the CXR lesion variable was not associated with the success of DR TB treatment (*P*=0.100). Cha et al.mentioned that radiographic features in CXR of patients with MDR TB and XDR TB were multiple cavities, nodules, and bronchial dilatation. Both radiographic features of MDR TB and XDR TB patients were not significantly different and had various forms, which were called multiforms.[21]

The resistance pattern of the sputum results of drug susceptibility tests on first and second lines was mostly MDR (44.4%). Based on the pattern of resistance, the results of monoresistance and RR had no significant correlation to treatment success (*P*=0.379; *P*=0.802) while patients with pre-XDR pattern were associated with treatment failure for DR TB (*P*=0.037) .[22]

Marais et al. in their study pointed out that polyresistance and RR did not have significant success rate, meaning that as long as DR TB patients received the appropriate therapeutic regimen, the success rate was not much different from patients diagnosed with RR and polyresistance.[22] DR TB patients with sputum drug susceptibility test results of resistant (or intolerance) to fluoroquinolones and/or second-line injection drugs do not meet the criteria to continue short-term

standardized treatment and will be switched to individualized treatment.[23]

Most of the study subjects experienced drugs adverse effects (72.9%), and the drugs adverse effects variable was not related to the success of DR TB treatment (*P*=0.139). Deshmuck et al. expressed that many factors affected the adherence to DR TB treatment, including the adverse effects of drugs experienced by DR TB patients.[24] Management of adverse effects starts with patient education. Prior to starting treatment, patients should be well informed in detail about the potential side effects of the ATD regimen and when to report them to healthcare professionals. Even for the harmless adverse effects, the evaluation, diagnosis, and treatment should be carried out promptly.[25]

LIMITATION

This study used secondary data from patients medical records with some incomplete medical record data so that it could affect the final results of the study. The study was conducted in a limited time. The study only analyzed patients factors, investigations results, adverse effects, and HIV status on the treatment success. In contrast, microbial factors, other TB control program factors, as well as environmental and behavioral factors were not evaluated.

CONCLUSION

The success rate of short-term standardized treatment for DR TB patients was 29.4%, consisting of recovered (16.5%) and complete treatment (12.9%). The patient's education level had a significant correlation with the success of DR TB short-term treatment. Patients with pre-XDR sputum susceptibility test results of first lines and second lines had a significant correlation with DR TB short-term treatment failure (*P*=0.037). Variables that could be used as predictors of the success of short-term DR TB treatment were age, education level, criteria for suspected DR TB, and the presence of pre XDR TB.

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CONFLICT OF INTEREST

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