

Research

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Survival Analysis of Multi-Drug Resistant Tuberculosis Patients in North Sumatra

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ARTICLE INFORMATION	A B S T R A K
Received: June 03, 2023 Revised: June 10, 2023 Accepted: July 25, 2023 Available online: August 10, 2023	Background: The severity and ease of spread of MDR-TB have caused this disease to become an epidemic in various countries. WHO has also launched an international program "End TB" which until now has not even reached half of the
Keywords	a CFR of 0.11% and North Sumatra Province is already at the 6th highest level
MDR-TB; Survival; Risk Factors; North Sumatra	in Indonesia and the highest on the island of Sumatra.
CORRESPONDING AUTHOR	Purpose : The purpose of this study was to see the survival of MDR-TB patients in North Sumatra Province.
	Methods: The method in this study used a retrospective cohort design with
Pesona Dessritina	secondary data on MDR-TB cases for 2020 – 2022. The sample used was total
E-mail: dessritinap@gmail.com	sampling with the condition that it met the sample criteria, namely complete data
	and treatment results. The analysis was carried out using univariate, Kaplan-
	Meier, bivariate analysis using the logrank test and multivariate with full model logistic regression.
	Results: The results obtained from a total of 664 cases (26.81%) died and
	(73.19%) survived. The variables related to survival in MDR-TB patients were age ($p = 0.000$ HR (Hazard Ratio) 1.88) and HIV status ($p = 0.001$ HR 1.40). The dominant variable related to survival is age ($p = 0.000$ HR 0.64).
	Conclusion: based on statistical tests, age and HIV status had a significant
	relationship with survival, while gender, OAT resistance, history of DM, history
	of treatment and treatment delays had no significant relationship based on
	statistical tests in this study.

INTRODUCTION

In 2019, there will be approximately 9.65 million new cases of tuberculosis and 1.40 million fatalities. Despite concerted efforts by the global community to end the tuberculosis epidemic through the United Nations (UN) Millennium Development Goals by 2020, the 2020 Global Report indicates that the reduction of TB-related deaths between 2015 and 2020 is less than half of what is required to achieve the End TB strategy by 2020. The majority of studies also indicate that TB patients face a high mortality risk during and after treatment, particularly in low-income areas [2].

The complexity of the management and treatment of MDR-TB (Multidrug-Resistant) includes high medical costs, longer treatment times, and the use of extremely toxic anti-tuberculosis drugs (OAT) with the potential for side effects; it also increases treatment failure and mortality [3]. The incidence of tuberculosis in Indonesia has decreased dramatically, from 568,987 cases in 2019 to 393-332 cases in 2020. During this time period, COVID-19 entered Indonesia for the first time; since then, the number

of cases has risen progressively, from 443,235 in 2021 to 503,712 in November 2022 [4]; in 2021, the number of cases rose to 443,235; and in November 2022, it rose to 503,712.

The total number of TB cases in Indonesia has reached 969,000, including 8,268 confirmed cases of MDR (Multid-drug Resistant) TB and 5,082 cases of enrolled MDR TB, of which 42,187 were child TB cases, 8,344 cases of TB-HIV, and 15,186 TB patients died, with an 86% treatment success rate [5]. After declining from 11,463 cases in 2019 to 7,922 cases in 2020, the incidence of MDR TB cases confirmed by laboratories in Indonesia has once again increased. Nevertheless, the number of MDR TB cases increased to 8,268 in 2021 and 10,145 as of November 1, 2022 [6]. After West Java, Central Java, East Java, DKI Jakarta, and Banten, North Sumatra Province was discovered to have the sixth-highest number of tuberculosis cases in Indonesia in 2021 [7], based on TB data obtained in that year.

According to data obtained from the North Sumatra Provincial Health Office, the incidence of MDR-TB cases increased over the course of two years, with the number of cases increasing from 284 in 2020 to 347 in 2021 and to 379 as of October 21, 2022. Compared to the number of cases that are still surviving or have received complete treatment, the number of incident fatalities continues to rise. In 2020, there were 137 recovered cases and 56 incident deaths, which is almost half the ratio. In 2021, the number of MDR-TB cases that were declared cured comprised 49, while the number of MDR-TB cases that resulted in death reached 54, surpassing the number of recovered cases. Next is the number of cases in 2022 in which the mortality toll has reached 32 and no cases have recovered.

In this study, a survival analysis will be conducted on MDR TB patients in North Sumatra Province between 2020 and 2022, from the time the patient begins treatment until the final results are released from the treatment stage, by examining the attachment or relationship of several independent variables, including age, gender, history of previous treatment, HIV status, history of diabetes, drug resistance, and delay in starting treatment.

METHOD

This research is an analytic study employing a retrospective cohort design and survival analysis to examine factors associated with MDR-TB patients' survival. In this study, the population consisted of all patients with confirmed MDR-TB in the North Sumatra Provincial Health Office from 2020 to 2022, a total of 1,190, who met the inclusion criteria of having complete patient data and having been declared to have completed treatment, resulting in the collection of 664 samples. This investigation utilizes secondary data collected from agencies. This investigation was conducted in 2023 at the Health Office of the North Sumatra Province. The analysis consisted of univariate analysis to determine the distribution of each variable, bivariate analysis utilizing the log rank test method to determine the significance of the relationship between variables, and the Kaplan Meier method to determine the assumption of proportional hazard, followed by multivariate analysis utilizing the cox regression full model to determine which variables are most strongly associated with patient survival.

RESULT DAN DISCUSSION

1. Univariate Analysis

Table 1	Frequency	Distribution	of MDR-TB	Cases in	North S	Sumatra F	rovince

Variable	Frequency (f)	Percentage (%)		
Age	x x ()			
≤ 40	247	37,20		
>40	417	62,80		
Gender				
Male	432	65,06		
Female	232	43,94		
OAT Resistance				
2 OAT	441	66,42		
> 2 OAT	223	33,58		
HIV status				
Negative	341	51,36		
Positive	309	46,54		
Unknow	14	2,11		
History of Diabetes Mellitus				
Yes	181	27,26		
No	483	72,74		
Past Medical History				
New	229	34,49		
Category 1	193	29,07		
Category 2	28	4,22		
Relapse Category 1 and 2	171	25,75		
Relapse	43	6,48		
Delay in Treatment				
\leq 30 days	508	76,51		
> 30 days	156	23,49		
Survival TB-MDR				
Cencored	486	73,19		
Event	178	26,81		

There were 247 patients under the age of 40 out of 664 total patients (37.20%) and 417 patients over the age of 40 (62.80%). According to gender, there were 432 male patients out of 664 total patients (65.06%) and 232 female patients out of 664 total patients (43.94%). Based on OAT resistance, 441 out of 664 patients (66.42%) were resistant to two anti-TB medications, while 223 patients (33.58%) were resistant to more than two anti-TB drugs. Meanwhile, based on HIV status, 341 out of 664 patients (51.36%) were HIV-negative, 309 (46.54%) are HIV-positive, and 14 (2.11%) have an unknown HIV status. Based on the history of DM, 483 of the 664 patients (72.74%) did not have a history of DM, while 181 patients (27.21%) did have a history of DM. Based on the history of previous treatment of MDR-TB patients in North Sumatra Province, 229 patients out of 664 had a history of reatment for category 2 (4.22%), 171 patients had a history of treatment for recurrence categories 1 and 2 (25.75%), and 43 patients had a history of treatment for relapse (6.48%). Meanwhile, based on patient treatment delays, 508 out of 664 patients (76.51%) did not experience treatment delays, while 156 patients (23.44%) did experience treatment delays. Based on the survival status of MDR-TB patients in North Sumatra Province 486 patients who were cured or alive out of 664 patients (73.19%) and as many as 178 patients who experienced events or passed away (26.81%).

These results indicate that a greater proportion of MDR-TB patients in North Sumatra Province were cencored or alive than those who experienced events or passed away.

2. Bivariate Analysis

Variable	Cencored (%)	Event (%)	p HR	95 % CI		
Age			0,000	1,880	1,343 - 2,632	
≤ 40	41,15	26,4				
>40	58,85	73,6				
Gender			0,763	0,953	$0,\!699 - 1,\!300$	
Male	64,81	65,73				
Female	35,19	34,27				
OAT Resistance			0,219	1,210	0,891 - 1,644	
2 OAT	67,7	62,92				
> 2 OAT	32,3	37,08				
HIV status			0,001	1,400	1,072 - 1,830	
Negative	46,91	45,51				
Positive	52,26	48,88				
Unknow	0,82	5,62				
History of Diabetes Mellitus			0,893	0,977	0,701 - 1,361	
Yes	27,37	26,97				
No	72,63	73,03				
Treatment History			0,288	1,192	0,860 - 1,652	
New	36,42	29,21				
Old	63,58	70,79				
Delay in Treatment			0,166	0,766	0,524 - 1,118	
\leq 30 days	74,69	81,46				
> 30 days	25,31	18,54				

In survival analysis, the Kaplan-Meier method was used to determine the relationship between the independent variables and the dependent variable, followed by the chi-square test to determine the significance between the two groups of variables and an analysis to obtain the hazard ratio. Age and HIV status had a significant relationship with survival in MDR-TB patients, with P = 0.000 for age and P = 0.001 for HIV status, whereas gender, history of diabetes, anti-TB drug resistance, history of treatment, and delay in treatment did not. The results of the bivariate analysis conducted on MDR-TB patients in the province of North Sumatra in 2020–2022 revealed a statistically significant difference in survival between patients aged 40 years and patients aged >40 years, as indicated by the Pvalue of 0.000 (0.05). This HR value of 1.88 indicates that MDR-TB patients aged > 40 years have a 1.88-fold increased risk of mortality compared to MDR-TB patients aged 40 years. This study's findings are consistent with those of other studies, including those of Moosazadeh M, et al. (2014), Junus, AJ (2018), Firnawati AF (2017), and a number of other studies [8] [9] [10].

As indicated by the Pvalue of 0.764 (> 0.05), there is no significant correlation between gender and survival in MDR-TB patients. The HR value of 0.95 indicates that male MDR-TB patients have a 0.95-fold increased risk of death compared to female MDR-TB patients. The findings of this study are consistent with the findings of other studies, including Girum T, et al. (2017), Firnawati AF (2017), and other studies [11] [10]. The P-value of 0.220 (> 0.05) indicates that there is no significant relationship between TB resistance and survival in MDR-TB patients. The HR value of 1.21 indicates that MDR-TB patients with TB resistance > 2 are 1,21 times more likely to die than MDR-TB patients with TB resistance 2. The findings of this study are consistent with the findings of other studies, such as Girum T, et al. (2017), Machmud PB (2021), and other studies [11] [12]. The P-value of 0.001 (0.05) indicates that there is a significant difference in survival between HIV-positive and HIV-negative or unknown patients, based on the HIV status variable. The HR value of 1.40 indicates that HIV-positive MDR-TB patients have a 1.40-fold increased risk compared to MDR-TB patients who are not HIV-positive or who are unknown to survive. The findings 136 Dessritina, Pesona, *Et Al*

of this study are consistent with the findings of other studies, including Girum T, et al. (2017), Firnawati AF (2017), and other studies [11] [10].

Based on the diabetes variable, there is no significant association between diabetes mellitus (DM) and survival in MDR-TB patients, as indicated by the P-value of 0.222 (> 0.05). This HR value of 0.97 indicates that MDR-TB patients with a history of diabetes have a 0.97-fold increased risk of mortality compared to MDR-TB patients without a history of diabetes. The findings of this study are consistent with the findings of other studies, including Moosazadeh M, et al. (2014), Ranzani OT, et al. (2019), and several other studies (16). [2]. The P-value of 0.084 (> 0.05) indicates that there is no significant relationship between treatment history and survival in MDR-TB patients. This HR value of 1.19 indicates that MDR-TB patients with a treatment history have a 1.19-fold increased risk of death compared to MDR-TB patients without a treatment history. This study's findings are consistent with those of Bade AB and Mega TA (2020), Girum T, et al (2017), Olalleya, AO, and Beke AK (2016), and a number of other studies. [13] [11] [14]. The P-value of 0.068 (> 0.05) indicates that MDR-TB patients with treatment delay and survival in MDR-TB patients. This HR value of 0.97 indicates that MDR-TB patients with treatment delays are 0.97 times more likely to die than MDR-TB patients. This HR value of 0.97 indicates that MDR-TB patients with those of other studies. [13] [11] [14]. The P-value of 0.068 (> 0.05) indicates that MDR-TB patients with treatment delays are 0.97 times more likely to die than MDR-TB patients. This HR value of 0.97 indicates that MDR-TB patients with those of other studies, such as the research conducted by Firnawati AF (2017) [10]. The findings of this study differ from those of Woya AB, et al. (2019) [15].

3. Multivariate Analysis

Table 3 Modeling Results of Multivariate Cox Proportional Hazard Analysis Factors Associated with Survival in MDR-TB Patients in North Sumatra Province

Variable	Model 1		Model 2		Model 3			Model 4				
	HR	р	95% CI	HR	р	95% CI	HR	р	95% CI	HR	р	95% CI
HIV Status	0,361	0,009	0,090-0,632	0,360	0,009	0,089-0,631	0,361	0,009	0,090-0,631	0,352	0,011	0,081-0,622
Age	0,631	0,000	0,294-0,968	0,630	0,000	0,293-0,967	0,639	0,000	0,303-0,976	0,640	0,000	0,303-0,976
OAT Resistance	0,224	0,152	-0,082-0,532	0,222	0,155	-0,083-0,529	0,219	0,160	-0,086-0,526	-	-	-
Delay in Treatment	-0,00	0,849	-0,002-0,001	-	-	-	-	-	-	-	-	-

The initial comprehensive model of multivariate analysis is utilized to determine the final model. The final model is obtained by eliminating variables with a p-value greater than 0.05. Variables were eliminated in phases, beginning with the variable with the highest p-value and ending with the variable with the lowest p-value, accompanied by a confounding test. The test for confounding is conducted by examining the HR value. If the change in HR value is greater than 10%, then the variable is a confounder. Age and HIV status were found to be the variables associated with survival among MDR-TB patients in North Sumatra Province, according to the results of a multivariate analysis. In the initial modeling, all variables were accounted for. Then, variables with P > 0.25 were excluded from the second model, and further analysis was conducted. Then, in modeling, the three variables that had no relationship or P > 0.05 were excluded from the dataset, leaving age, P = 0.000 (0.640 HR), as the most influential variable in relation to MDR-TB. 95% CI 0.303 – 0.0976). After the age variable was removed from the analysis to determine whether the age variable could be a confounding variable, the HIV status variable had an HR of 0.352 before the age variable was removed, and an HR of 0.361 after the age variable was removed. According to the results obtained both before and after the release of the age variable, which did not differ by more than 10%, the age variable was not a confounding variable in this study.

Kaplan-Meier Chart







Picture 3



Picture 2



Picture 5

Picture 6



CONCLUSION

The following are the conclusions that can be derived from the results of this study, which are based on the findings of the statistical analysis and the discussion presented in the research regarding the survival of MDR-TB patients in the province of North Sumatra in 2020-2022: 486 of the 664 confirmed cases of MDR-TB that were analyzed have survived, while 178 have perished. The incidence rate is 0.0013, which corresponds to 1.3 fatalities per day per 1000 patients. The majority of the 664 MDR-TB confirmation cases analyzed were older than 40, male, resistant to two anti-TB drugs, HIV-negative, free of diabetes mellitus, had a lengthy treatment history, and were not late for treatment. Age and HIV status are variables with a significant relationship to MDR-TB patient survival. According to the statistical analyses conducted, there was no correlation between the gender variable and OAT resistance, history of diabetes, history of previous treatment, or delay in treatment. Age is the most significant factor associated with survival among MDR-TB patients in North Sumatra Province.

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