Original Article

Delayed Treatment and Adverse Effects of Drug Resistance Tuberculosis Impact on Outcome, Survival and Quality of Life

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Abstract

Background: Global TB Report 2020 states that 78% of tuberculosis patients experience drug resistancy with a global treatment success rate of 57%. Drug resistance tuberculosis (DR TB) patients whom experience side effects such as arthralgia and hyperuricemia with inadequate treatment will affect the treatment result.

Methods: Retrospective cohort study to DR TB patients who underwent treatment from January 2015 to August 2020 at RSUD dr. Moewardi Surakarta. Survival analysis using Kaplan Meier method and Cox regression test for the effect of risk factors on the safety and survival of TB RO patients. Quality of life analysis using Mann Whitney test.

Results: From 372 patients, delayed treatment factor (OR=2.906; 95% CI=1.890-4.469; *P*≤0.001) and arthralgia factor (OR=1.775; 95% CI=1.148-2.744; *P*=0.010) were variables that had a significant effect on recovery of DR TB patients. Delayed treatment and arthralgia have risk (2,906 times and 1.775 times) for non-recovered DR TB patients. Delayed treatment factor with HR=14.772 (95% CI=13.381-16.163), arthralgia with HR=15.170 (95% CI=13.960-16.379), and anemia with HR=15.304 (95% CI=14.074-16.535; *P*=0.002) affect on the survival of DR TB patients. Anemia affect on the quality of life DR TB patients.

Conclusion: Delayed treatment for more than 14 days and arthralgia that is not treated adequately can affect the recovery of DR TB patients. The survival and quality of life of DR TB patients can be increased by monitoring the time of taking medication, monitoring side effects of drugs such as arthralgia, and adequate nutritional intake so that anemia does not occur.

Keywords: anemia, arthralgia, delayed treatment, drug resistant TB, hyperuricemia, quality of life, recovery, survival

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INTRODUCTION

Global TB report 2020 states that there are 465,000 cases of *rifampicin resistant* (RR) tuberculosis which 78% of them are drug-resistant TB (DR TB). The number of patients receiving DR TB treatment was 177,099 in 2019, this number increased by 10% from the previous year. The death rate due to tuberculosis is still a problem in Indonesia, especially when *Mtb. bacilli* strain appeared that are resistant to several types of drugs. The decline in health services and the increase in drug resistance will exacerbate TB deaths.[1–5]

Individuals who are susceptible to physical, biological, psychological, and socio-economic stressors can exacerbate TB mortality. Depression, anxiety, drug use, stigma, discrimination, and psychological distress are considered to be the most commonly reported psychological and social problems among TB patients. Azam et al in 2020 did the research about the correlation between depression and gender. Almost 40% women and 16.7% man had depression (OR=7.6; 95% CI=1.79-32.21). Drug side effects also higher in subject with depression due to perception and stigma from community.[1–5]

Delay in diagnosis and delay treatment can increase the severity of the disease, increased transmission time, and poor treatment outcomes up to death. Asres et al's study (2018) in Ethiopia assessed the effects of treatment delay on TB outcome. Treatment success in 735 TB patients differed between patients starting treatment within 30 days and after 30 days of diagnosis. TB patients starting treatment in 30 days after diagnosis had 94.2% treatment success and the mortality rate is 1.9%. TB patients who started treatment more than

30 days after diagnosis had 88.4% treatment success with a mortality rate of 4.8%. Delay in starting treatment will increase the risk of transmission, morbidity, and mortality high in the patient. Arthralgia or joint pain is a side effect that often occurs after gastrointestinal disorders. Research by Reviono et al in 2014 in Surakarta stated that the third most common side effect in the treatment of DR TB was arthralgia in 90 (78.9%) patients.[6,7]

The World Health Organization (WHO) recommends nutritional assessment to be an integral aspect of TB care. Anemia in pulmonary TB patients can be caused by several causes including: the result of chronic disease, increased blood loss from hemoptysis, decreased red blood cell production, and anemia due to malnutrition. The 2019 Holden, et al study in Denmark examined 1188 TB patients of which 640 patients (53.87%) were anemic at the time of diagnosis. Unfavorable outcomes associated with male gender, alcohol abuse, a history of mental disorders, and anemia. Anemia is associated with slowed sputum conversion, worsening of the disease and death. Research by Bhargava, et al in 2020 in India found that anemia occurs in 75% of TB patients and can cause morbidity and mortality in as much as 5% due to TB.[1,8–13]

Treatment of DR TB in Indonesia are a constraint both from the patient and the health care system. There is no comprehensive report on the timing of delay in treatment initiation and its predictors in Indonesia. The results of this study are expected to evaluate the side effects of treatment and delay in treatment so as to increase the resilience and quality of life of DR TB patients. This research is expected to help the national program to control drug-resistant tuberculosis to take appropriate action to achieve zero TB.

METHODS

A retrospective cohort study was conducted at the drug-resistant TB outpatient clinic at RSUD Dr. Moewardi Surakarta from June–August 2021. This study used primary data and medical record data by taking 372 DR TB patients who had received treatment from January 2015 to August 2020 and declared completed at RSUD Dr. Moewardi Surakarta. This study used a total sampling method (consecutive sampling). Inclusion criteria were DR TB patients, who received treatment from January 2015 to August 2020, who had finished receiving DR treatment, age >18 years, complete medical records related to the data needed in this study. Exclusion criteria for DR TB patients with blood disorders, patients in pregnancy who had not finished treatment, prior history of anemia and arthralgia, incomplete medical record data related to this study, patients who refused to be interviewed and or fill out a questionnaire.

The basic data were processed descriptively. Statistical analysis has been done with resistance and quality life of DR TB patient as the dependent variable. Delay on treatment, arthralgia, hyperuricemia, and anemia were independent variables. Estimation of the magnitude of the association of two variables with relative risk. Survival analysis to analyze data with time until the occurrence of a certain event as a response variable. Survival rate and median survival using survival analysis and Log Rank test to know the difference between the two survival curves (Kaplan Meier). Quality of life scores were analyzed using the Mann Whitney Test. The relationship between the independent variable and the dependent variable used the Chi square test followed by Cox regression analysis (multivariate). The statistical test used 95% confidence limit value (95% *Confidence Interval*) or a significance limit value of $P<0.05$. Data analysis using computer program SPSS 21 for windows.

RESULTS

Baseline characteristic data was obtained at the beginning of the TB treatment, while the data about arthralgia, anemia, and hyperuricemia was taken during the TB treatment. The primary data taken is the data on the quality of life of DR TB patients. The purpose of this study was to determine the effect of delay in treatment, arthralgia,

hyperuricemia, and anemia on healing, survival, and quality of life of drug-resistant TB patients.

The results of recording the medical records of drug-resistant TB patients obtained as many as 397 drug-resistant TB patients, but those used in this study were 372 patients, because as many as 25 patients did not have complete data. The results of the characteristics of research subject data characteristics based on the results of research on 372 DR TB patients can be seen in Table 1 as follows.

Table 1. Basic Characteristics of Research Subjects (N=372)

Variable	Frequency	%
Gender		
Male	232	62.3
Female	140	37.7
Age		
18–40 years	154	41.3
41–60 years	179	48.1
>60 years	39	10.6
Healed		
Cured	215	57.8%
Not cured	157	42.2%
Died		
Alive	282	75.8%
Died	90	24.2%
Late treatment		
No	205	55.1%
Yes	167	44.9%
Hyperuricemia		
No	76	20.4%
Yes	296	79.6%
Arthralgia		
No	165	44.4%
Yes	207	55.6%
Anemia		
No	177	47.6%
Yes	195	52.4%

Among 327 patients who are selected as the subjects of this study, most of the patients were male (62.3%) and aged between 41–60 years (48.1%). Baseline characteristic data showed that 57.8% of patients were cured at the end of TB DR treatment and 75.8% of patients were still alive.

The data about delay in DR TB treatment among the patients was obtained. Among 327 patient, 44.9% patients were failing to receive a TB DR treatment before 14 days after they diagnosed with TB DR. Based on the data, 79.6% patients had hyperuricemia, 55.6% had arthralgia, and 52.4% had anemia.

Table 2. Multivariate analysis of variables that affect the recovery of DR TB patients

Variable	OR (95%CI)	*P*
Treatment delay	2.906 (1.890-4,469)	<0.001*
Arthralgia	1.775 (1.148-2.744)	0.010*
Treatment delay	2.906 (1.890-4,469)	<0.001*

Based on logistic regression analysis, it was found that treatment delay (OR=2.906; 95% CI=1.890-4.469; *P*≤0.001) and arthralgia (OR=1.775, 95% CI=1.148-2.744; *P*= 0.010) is a variable that has a significant effect on the recovery of DR TB patients. Delay in treatment has a higher risk (2.906 times) of non-healing DR TB patients compared to arthralgia (1.775 times).

Because there are 3 variables that have a significant effect on the *outcome of* death, namely delay in treatment (OR=2.385; 95% CI=1.467–3.879); *P*≤0.001), arthralgia (OR=2.563; 95% CI=1.529–4.299; *P*≤0.001) and anemia (OR=2.178; 95% CI=1.325–3.579; *P*=0.002) then followed by multivariate regression analysis logistics as follows.

Table 3. Multivariate analysis of variables that affect the *outcome* of DR TB patients

Variable	OR (95%CI)	*P*
Delay in Treatment	2.309 (1.402–3.802)	0.001*
Arthralgia	2.302 (1.349–3.928)	0.002*
Anemia	1.817 (1.084–3.047)	0.024 *

Note: Logistic regression test = *Significant at *P*≤0.05

The effect of delay in treatment, arthralgia, hyperuricemia, and anemia on the quality of life of DR TB patients involved 103 recovered patients. The effect of delay in treatment, arthralgia, hyperuricemia, and anemia on the quality of life of DR TB patients in this study used a different independent t-test if the data met the assumption of normality.

If the data does not meet the assumption of normality, then use the Mann-Whitney test, this is because the quality of life data (SF-12 score) is in the form of numerical data. The results of statistical analysis of the effect of delay in treatment, hyperuricemia, arthralgia and anemia on the quality of life of DR TB patients can be seen in Table 4 as follows.

Table 4. Effect of delay in treatment, arthralgia, hyperuricemia and anemia on quality of life of cured DR TB patients (N=103)

Variable	N	Score SF-12 (Quality of Life)		
		Mean±SD	Mean Difference	*P*
Late Treatment				
No	68	40.04±5.57	0.66	0.525
Yes	35	39.82±4.50		
Hyperuricemia				
No	22	37.82±6.38	2.74	0.082
Yes	81	40.56±4.72		
Arthralgia				
No	52	40.60±5.29	-1.26	0.131
Yes	51	39.33±5.10		
Anemia				
No	55	41.00±4.93	-2.21	0.021*
Yes	48	38.79±5.32		

Note: Whitney-Mann test = *Significant at *P*≤0.05

Based on table 16 it is known that treatment delay (diff mean = -0.66; *P*=0.525), arthralgia (diff mean = -1.26; *P*=0.131) and hyperuricemia (diff mean = 2.74; *P*=0.082) did not show a significant effect on the SF-12.

Anemia (diff mean = -2.21; *P*=0.021) showed a significant effect on the SF-12 score (Quality of Life). Where DR TB patients who do not have anemia (41.00±4.93) have a better quality of life compared to DR TB patients with anemia (38.79±5.32).

Survival analysis has been done in this study to see the effect of delay in treatment, arthralgia, hyperuricemia, and anemia on DR TB patient survival. The overall survival rate of 90 died patients among 372 subjects who are selected in this study is 75.8%, and the average survival is 17.364 (95% CI=16.510–18.218) months.

Table 5 shows the overall survival analysis of DR TB patient who were delayed in treatment and had certain medical condition such as hyperuricemia, arthralgia, and anemia. Among 205 patients who were not delayed in the DR TB treatment, 35 patients died. The survival rate is 82.9% and the average survival is 18.887 (95% CI=17.919–19.855) months.

The analysis also has been done based on the prior history of arthralgia, hyperuricemia, and anemia. Approximately 65 patient died among 207 patients without arthralgia, with survival rate 68.6% and average survival is 15.170 (95% CI=13.960–16.379) months. The survival rate of 75 deceased patients with hyperuricemia is 74.7%, with average survival 16.362 (95% CI=15.426–17.298) months. Sixty deceased patients with anemia has survival rate approximately 69.2%, and the average of survival is 15.304 (95% CI=14.074–16.535) months.

Table 5. Effect of delay in treatment, arthralgia, hyperuricemia and anemia on DR TB patients' survival

Variable	Total N	N of events	Mean	95% CI
Late Treatment				
No	205	35	18.887	17.919–19.855
Yes	167	55	14.772	13.381–16.163
Hyperuricemia				
No	76	15	18.422	16.746–20.098
Yes	296	75	16.362	15.426–17.298
Arthralgia				
No	165	25	19.230	18.195–20.266
Yes	207	65	15.170	13.960–16.379
Anemia				
No	177	30	18.916	17.867–19.964
Yes	195	60	15.304	14.074–16.535
Overall	372	90	17.364	16.510–18.218

Note: Log rank = *Significant at *P*≤0.001

Log rank analysis has been done to know the significancy of patient's survival in each group. It comes to the conclusion that there is a significant difference of survival rate between DR TB patient who were had the treatment on time and the patient who were delayed in treatment (Log Rank = 16.582; *P*≤0.001). The same result also found in two other variables. There is significant difference of survival rate between two groups of each medical condition, Arthralgia (Log Rank = 14.390; *P*≤0.001) and Anemia (Log Rank = 9.297; *P*=0.002). Based on the result of the analysis, there is no significant difference between survival rate of DR TB patient with and without Hyperuricemia (Log Rank = 0.951; *P*=0.329).

DISCUSSION

The characteristics of drug resistant tuberculosis patients in this study during the period January 2015 – August 2020 as many as 372 patients, after exclusion in as many as 25 patients Gender DR TB patients in this study are predominantly male (62.3%). In this study 48.1% patients were aged 41–60 years. The male gender tends to be at higher risk of being infected with DR TB because many men work outside the home and interact with the community, while not all of the

female gender work outside, many also work as housewives. In productive age, humans tend to have more mobility so that they have a higher possibility of exposure to Mtb germs.

In this study, delays in treatment with *outcomes* did not heal as much as (59.9%). Treatment delay (OR=2.902; 95% CI=1.895–4.444; *P*≤0.001) in this study was a risk factor for the non-healing of DR TB patients. Most of the DR TB patients are patients with secondary resistance. Patients with a history of drug-sensitive TB who have already undergone TB treatment with all the side effects that arise, when diagnosed with DR TB patients may feel discouraged and not eager to seek treatment. Moral support from the psychological side can play a role since the patient is diagnosed with DR TB and before starting treatment to be able to accompany DR TB treatment.

The delay in treatment (OR=2.385; 95% CI=1.467–3.879; *P*≤0.001) in this study is a risk factor for the death outcome of DR TB patients. Patients with delay in treatment are at risk of dying 2.385 times greater than patients who do not experience delays in treatment. Statistical tests showed that there was a significant effect between delay in treatment and the outcome of dying of DR TB patients. One of contributing factor to delay in treatment is the never-ending bureaucracy and administration due to tiered healthcare insurance system. It is possible that the patient's lack of education and knowledge about drug-resistant tuberculosis contributed to the delay in treatment. Delay in treatment can cause DR TB patients tend to experience clinical deterioration with opportunistic infections to severe complications and cause death based on the Adiwinata's research in 2018, the national health insurance rules for tuberculosis treatment had to step by step from primary healthcare facilities. This rules also take the important step of delay in treatment and diagnosis.[6,12,14]

The survival of 207 patients who experienced arthralgia, there were 65 patients died with the survival rate of 68.6%. DR TB patients who died with arthralgia had an average survival of 15.170 months. The Log Rank test showed that there was a significant difference in patient survival between those without arthralgia and patients with arthralgia (Log Rank = 14.390; *P*≤0.001). Arthralgia has a significant effect on the survival of DR TB patients. Patients with arthralgia have lower survival because there are disturbances in daily activities that affect the psychology of DR TB patients. Arthralgia in this study was not the main cause of death. Arthralgia is a factor that can aggravate the patient's condition, resulting in clinical deterioration or death. There are many factors associated with a direct effect on the survival of DR TB patients.[8,13]

Hyperuricemia (OR=1.324; 95% CI=0.788–2.227; *P*=0.289) in this study was not a risk factor for non-healing DR TB patients. There was no significant effect between hyperuricemia and recovery in DR TB patients (*P*>0.05). In the classification of antitubercular medications of DR TB for individual regimens, they are divided into 3 groups, group A which is considered the main drug with the best efficacy, group B and group C. The fluoroquinolones (levofloxacin, moxifloxacin) are included in group A which is in the treatment of individual TB therapy. The DR must consist of at least 5 drugs with the division of 3 drugs from group A and 2 drugs from group B. Group C is additional if there is one class A or B drug that cannot be given.[1,3,7,8]

In group C treatment, Ethambutol is the first choice while Pyrazinamide is the third choice, thus increasing the possibility of hyperuricemia caused by antitubercular medications. In the short-term therapy regimen according to WHO 2020 guidelines, treatment is given for 9–11 months where levofloxacin, pyrazinamide and ethambutol are continued during treatment. If hyperuricemia is controlled and does not cause complaints, it is not necessary to change the treatment regimen. Hyperuricemia can cause disturbing joint pain symptoms, which is one indication of changing the regimen to an individual regimen. The patient's recovery had no effect on increased uric acid levels.[1,3,7,8]

Based on the incidence of hyperuricemia (OR=1.380; 95% CI=0.740–2.572; *P*=0.309) in this

study was not a risk factor for the death outcome of DR TB patients. There was no significant effect between hyperuricemia and the outcome of DR TB patients (*P*>0.05). Hyperuricemia is associated with high blood pressure, atherosclerosis, kidney failure, and diabetes mellitus so that the outcome of death is not directly caused by hyperuricemia. In cardiac disorders, hyperuricemia is a risk factor that causes vascular endothelial damage through the mechanism of ROS formation.

The survival rate of DR TB patients who did not experience hyperuricemia was 80.3% with an average survival of 18.422 (95% CI=16.746–20.098) months. The average survival was 16.362 (95% CI=15.426–17.298) months, or it can be said that DR TB patients who died and experienced hyperuricemia had an average survival of 16.362 months. The Log Rank test showed that there was no significant difference between the survival of DR TB patients between patients who did not have hyperuricemia and had hyperuricemia (Log Rank = 0.951; *P*= 0.329). Hyperuricemia has no significant effect on the survival of DR TB patients.

The use of Pyrazinamide has been shown to increase the rate of sputum conversion. The success and cure of therapy depends on the patient's tolerance and medication adherence. Factors that cannot be controlled by researchers are the consumption of foods or diets that are high in purines, which can affect uric acid levels. The research subjects in this study were included in the criteria for hyperuricemia by looking at the increase in uric acid levels during baseline blood tests and when taking antitubercular medications. Hyperuricemia can be divided into a*symptomatic hyperuricemia* and *symptomatic hyperuricemia*. Hyperuricemia that causes symptoms can affect *activities of daily living and* affect survival. In this study, researchers did not distinguish between symptomatic and asymptomatic hyperuricemia. There is no significance of hyperuricemia on survival.[7,8]

According to the Guideline: *Nutritional care and support for patients with tuberculosis* from WHO, malnutrition in TB patients can be caused, among others: polypharmacy, decreased appetite, decreased oral intake, nausea, vomiting, abdominal pain, diarrhea and vomiting. catabolic reaction. TB infection and malnutrition are related. Patients with malnutrition or undernutrition will reduce their immunity so that they are easily infected with TB disease or reactivation of TB infection.[1,3]

Anemia (OR=2.178, 95% CI=1.325–3.579; *P*=0.002) in this study is a risk factor for the death outcome in DR TB patients. Patients with anemia risk of dying 2.178 times greater than patients without anemia. Anemia in this study was associated with chronic inflammatory disease and inadequate nutritional intake. This is in line with the research by Fantaw et al, in 2018 which stated that DR TB patients who had a lower initial body weight had 56% higher risk of dying. Multivariate Cox-regression analysis in this study assessed anemia as a significant predictor of mortality among drug-resistant TB patients. Malnutrition that triggers anemia is associated with drug toxicity which can contribute to default and eventually lead to death.[8–11,15]

Log Rank test in this study showed that there was a significant difference in the survival of DR TB patients between those who were not anemic and anemic (Log Rank = 9.297; *P*=0.002). Anemia has a significant effect on the survival of DR TB patients. Patients with anemia has lower survival. Economic support and nutritional intervention can reduce the mortality of DR TB patients.

Tuberculosis is a disease that can reduce the patient's quality of life. Long-term treatment, polypharmacy therapy, toxic reactions and drug side effects, medication adherence, social support, social and family acceptance, lifestyle changes, marital status, level of access to health care services, socioeconomic status, knowledge of patients and families about the disease, treatment, as well as complications of the disease mutually influence the quality of life of DR TB patients. According to WHO there are four aspects of quality of life, namely: 1) physical health which includes daily activities; 2) psychological well-being which includes self-image and appearance, spirituality, thinking, learning, memory and concentration; 3) social relationships

which include personal relationships and support social; 4) relationship with the environment which includes financial resources, freedom, physical security and health insurance. In this study, anemia (diff mean = -2.21; *P*=0.021) showed a significant effect on the SF-12 score. DR TB patients who did not have anemia (41.00±4.93) had a better quality of life than DR TB patients who had anemia (38.79±5.32).[8,16,17]

Some of the patients that we contacted and some of the patients who came to the DR TB polyclinic still felt tired quickly and were unable to carry out strenuous activities even though they had been declared cured, thus affecting the patient's daily activities and the quality of life of the patient. The social aspect has not changed much because DR TB patients who have recovered have received a certificate of completion of treatment and are declared cured. Drug side effects due to hyperuricemia are not felt by many patients after recovering. Arthralgia side effects some of the patients still feel especially in some patients suffering from TB with diabetes. A side effect that is quite disturbing until after recovery is hearing loss which we did not investigate further in this study.[8,18]

LIMITATION

Limitations in this study are secondary data regarding the date time for treatment, complaints of joint pain, uric acid levels, hemoglobin levels that do not complete data collection can be difficult. A lot of phone number data which has changed and the latest telephone number data is not included so that the researcher was unable to contact to ask for a quality of life questionnaire. When this research took place, it coincided with a spike in the number of the incidence of covid and restrictions on community activities were carried out so that some research subjects could not come to the workshop.

CONCLUSION

Delay in treatment, arthralgia, affects the recovery of TB RO patients. Treatment delay, arthralgia, and anemia affect the survival of RO TB patients. Anemia affects the quality of life of TB RO patients.

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CONFLICT OF INTEREST

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