A Survival Analysis of Successful and Poor Treatment Outcome Among Patients with Drug-Resistant Tuberculosis and the Associated Factors: A Retrospective Cohort Study

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ABSTRAK

Latar belakang: *Tuberkulosis dan resistensinya merupakan masalah kesehatan global yang utama di dunia. Peningkatan insiden dan kematian tuberkulosis di Indonesia masih menjadi masalah kesehatan masyarakat yang besar khususnya di Provinsi DKI Jakarta. Tidak ada penelitian yang dipublikasikan yang berfokus pada penilaian hasil pengobatan resistensi tuberkulosis baik dalam keberhasilan maupun kematian. Oleh karena itu, penelitian ini bertujuan untuk menilai hasil kesembuhan dan kematian serta faktor-faktor penentu yang mungkin mempengaruhi resistensi obat TB di Provinsi Kota Jakarta antara tahun 2010 dan 2015.* ***Metode:*** *penelitian ini menganalisis register elektronik tuberkulosis nasional (e-TB Manager) Provinsi Jakarta pada tahun 2010 hingga 2015. Semua pasien dewasa yang tinggal di provinsi Jakarta dan didiagnosis dengan TB-MDR (multidrug-resistant tuberculosis) dan TB resistan obat ekstensif (XDR-TB) memenuhi syarat untuk penelitian. Kurva kelangsungan hidup Kaplan Meier digunakan, bersama dengan uji log-rank dan uji Chi-Square (X2) untuk analisis deskriptif. Analisis regresi Cox dijalankan untuk menentukan faktor risiko potensial. Beberapa faktor risiko dianalisis dalam penelitian ini, termasuk usia, jenis kelamin, tempat tinggal, status HIV, status resistensi, dan riwayat pengobatan sebelumnya.* ***Hasil:*** *secara keseluruhan, 553 sampel yang memenuhi syarat dianalisis dalam penelitian ini. Resistensi obat tuberkulosis meningkat secara bertahap selama tahun 2010 hingga 2015, dimana masing-masing 248 dan 67 pasien yang termasuk dalam penelitian ini sembuh dan meninggal. Ada perbedaan tingkat kelangsungan hidup dengan pengobatan yang berhasil (sembuh) antara pasien yang didiagnosis dengan MDR-TB dan XDR-TB. Perawatan yang buruk (kematian) di antara pasien diprediksi oleh usia lebih dari 60 tahun (HR 3,48; 95% CI 1,48 – 8,38, p-value = 0,004).* ***Kesimpulan:*** *ada perbedaan angka kelangsungan hidup antara keberhasilan pengobatan (sembuh) dan pengobatan yang buruk (kematian) selama enam tahun pengamatan. Usia pasien adalah prediktor tunggal dalam kelangsungan hidup kematian. Sedangkan status HIV dan status resistensi merupakan prediktor kelangsungan hidup orang yang sembuh.*

Kata kunci**:** *MDR, XDR, Tuberkulosis, resistensi, analisis kesintasan.*

ABSTRACT

Background: *Tuberculosis and its resistance are a major global health problem in the world. The increased incidence and mortality of tuberculosis in Indonesia remain a big public health issue especially in Jakarta Province. No published studies have focused on assessing the outcome treatment of tuberculosis resistance both in success and death. We aimed this study to assess the survival of cured and death outcomes as well as the determinant factors which might influence drugs resistant tuberculosis in Jakarta between 2010 and 2015.* ***Methods:*** *this study analyzed the national electronic tuberculosis register (e-TB Manager) of Jakarta province in 2010 to 2015. All adult patients who lived in Jakarta province and were diagnosed with multidrug-resistant tuberculosis (MDR-TB)*

and extensively drug-resistant tuberculosis (XDR-TB) were eligible for the study. Kaplan Meier survival curve was used, together with log-rank test and Chi-Square (X^2) test for descriptive analysis. Cox regression analysis helped determine the potential risk factors. Several risk factors were analyzed in this study, including age, gender, residency, HIV status, resistance status, and history of previous treatment. ***Results:*** *we analyzed 553 samples in this study. The drug-resistant tuberculosis cases increased gradually from 2010 to 2015. Of all cases, 248 and 67 patients were cured and death, respectively. There was a difference in survival rate between patients diagnosed with MDR-TB and XDR-TB with successful treatment. Poor treatment outcome (death) among patients was predicted by age greater than 60 years old (HR 3.48; 95% CI 1.48 – 8.38, p-value = 0.004).* ***Conclusion:*** *there was a difference survival rates between success treatment (cured) and poor treatment outcome (death) during six years of observation. Age of patients is a single-predictor in survival of death. While, HIV status and resistance status were predictors in survival of cured.*

Keywords**:** *MDR, XDR, Tuberculosis, resistance, survival analysis.*

INTRODUCTION

Tuberculosis (TB) remains one of the major global health challenges in the world. In 2018, it was estimated that tuberculosis mortality rates were 11 per 100,000 among HIV-negative people and 0.31 per 100,000 among HIV-positive people.[1] World Health Organization (WHO) also reported that 43% and 83% of bacteriologically confirmed TB cases tested for Rifampicin resistance as new cases and previously treated cases in 2018, respectively[1]. Furthermore, there were 5,584 multidrug-resistant tuberculosis (MDR/RR-TB) cases confirmed by laboratory and 4,566 cases of them started on treatment[1]. On the other hand, 122 cases of extensively drug-resistant tuberculosis (XDR-TB) were detected and 100 of them started on treatment. The treatment success rate for new cases of MDR-TB/RR-TB and XDR–TB reached 65% and 37%, respectively.[1]

Indonesia is one of ten countries that account for 75% of the global gap between treatment enrolments and the estimated number of new cases of MDR/RR-TB in 2018. Based on Indonesian national health survey in 2018, the prevalence of lung tuberculosis reached 42%. Treatment outcomes of tuberculosis in Indonesia for new, relapsed (previously treated, excluding relapsed in 2016), MDR-TB (2015 cohort), and XDR-TB (2015 cohort) were reported as 86%, 71%, 47%, and 28%, respectively.[1] Jakarta had the highest number of tuberculosis cases in Indonesia with 37,114 cases in 2018.[2] The Jakarta Province Health Office [3] reported that new cases of tuberculosis in 2017 was 12,880 which around 10,709 received anti-tuberculosis treatment.[4] From those who had anti-tuberculosis treatment, forty-eight percent completed the treatment, and the success rate was 77%, while 465 deaths (four cases per 100,000 population) were attributed to tuberculosis in Jakarta.[4] This circumstance might occur due to the Jakarta's population density in 2018 which was 17,200/km^2 (the WHO standard of population density is 9,500/km^2).[5] Studies pointed out that population density are the key factor that influences the transmission of tuberculosis.

Treatment of resistant tuberculosis requires a long duration and high cost, but previous studies showed highly successful outcomes in some countries.[6-8.] Several factors were significantly associated with the treatment outcomes of resistant tuberculosis. These included patient characteristics, such as age, sex, socio-economic status, patient compliance during treatment, nutritional status, smoking, alcohol consumption, comorbidities, anti-tuberculosis treatment side effects, and additional nutrients (vitamin D, vitamin C, Potassium and others) during treatment.[9-17]

Although several studies showed that individual treatment regimens among patients with MDR tuberculosis could achieve profitable outcomes in more than 60% of cases,[6-8] only few studies assessed the risk factors of outcome treatment in both positive and negative result among TB patient through retrospective data in Indonesia. Due to the large population,

high density, and multicultural population of Indonesia, the results of previous studies cannot be simply applied to Indonesian condition. Therefore, we aimed to assess success treatment (cured) and poor treatment outcome (death) and factor associated of resistant tuberculosis in patients in Jakarta City province between 2010 and 2015.

METHODS

An observational retrospective cohort study was conducted in Jakarta, which consists of five cities and one district. The observation was documented from 2010 to 2015 in all areas, including South Jakarta, West Jakarta, North Jakarta, East Jakarta, Central Jakarta and Kepulauan Seribu. The observation started from diagnosis after sputum culture result and ended when a final event occurred (cured or deceased) or after 30 months of treatment. The factors that observed including characteristic demography, resistance status, tuberculosis treatment regimen, and duration of tuberculosis treatment. The outcomes were cured and deceased as success or failure of treatment during the observation period.

Data Sources and Measurement

This study was the continuation of our previous study "Determinant factors of drop out among multi drugs resistance Tuberculosis (MDR TB) patients at Jakarta Province from 2011 to 2015", published in the Indonesian Journal of Tropical and Infectious Disease in September 2018. The national electronic tuberculosis register (e-TB Manager) of Jakarta province in 2010 to 2015 was used as the data source. These data are the national tuberculosis surveillance system in Indonesia and consist of demographic and clinical information along with initial assessment and follow-up during antimicrobial treatment using sputum culture test and GeneXpert as the rapid test.

Participants

All adult patients (> 18 years old) living in Jakarta province and were diagnosed with drug-resistant tuberculosis between 2010 and 2015 were eligible for the study. Only patients with MDR-TB and XDR-TB were included. Those who were diagnosed with mono-resistance and poly-resistance were excluded. All patients were evaluated from diagnosis to the end of treatment (cured or deceased) started from 2010 to 2015. Totally, there were 630 eligible patients who were diagnosed with MDR-TB and XDR-TB living in DKI Jakarta and received tuberculosis treatment.

Variables

Variables were observed, including sex, age, and residency, HIV status, drug-resistance, and history of previous treatment. The age groups consisted of the following five categories: less than 30 years old, 30 to 39 years old, 40 to 49 years old, 50 to 59 years old, and greater than 60 years old. MDR-TB was defined as tuberculosis resistance to at least isoniazid and rifampicin with or without one of the first-line drugs (streptomycin), and XDR-TB was defined as MDR-TB with additional drug resistance to at least one of the injectable second-line drugs (kanamycin, amikacin, and ofloxacin).

Previous treatment refers to a patient history of any previous tuberculosis treatments before starting the current treatment. Incomplete treatment consists of new patients (received tuberculosis treatment for less than two months/ less than 28 doses or never), default treatment (stopped treatment before completion of treatment), and lost to follow-up after at least two months of treatment. Complete treatment consists of failed treatment in first-line or second-line (conversion test after treatment still positive) and relapsed patients (patients who were already cured who returned with resistant tuberculosis infection). The unknown category includes patients without a clear history of previous treatment.

The outcomes of this study were successful treatment (cured) and poor treatment outcome (death). Patients with a negative conversion test result between 0 and 30 months of treatment are considered cured or having had successful treatment. The conversion test used monthly sputum culture. Poor treatment outcome (death) refers to patient death during the treatment and observation periods (30 months).

Statistical Methods

The time variable is time to cure or death measured from admission to date of an event and coded as one (cure or death). Data were transferred to SPSS version 20.0 from Excel version 2017. The variables were then cleaned and coded, and the presence of missing values and influential outliers was checked. Kaplan Meier survival curve was used, together with log-rank test and Chi-Square (X^2) test, for descriptive analysis. Goodness-of-Fit test was used for the presence of different risks in the incidence of cured and deceased among the groups during treatment/ observation. The results of Goodness-of-Fit test indicated that Cox regression proportional hazard analysis could be applied for the survival of poor treatment outcome (death), while successful treatment used an extended Cox regression analysis. The incidence of cure and death with respect to person-time at risk was calculated. The association between variables was summarized by using adjusted hazard ratio, p-value <0.05, and statistical significance tested at 95% confidence interval (CI).

Ethical Clearance

The study used the existing routine information of MDR-TB and XDR-TB treatment that already had permission from the DKI Jakarta Health Office, letter of permission number 1713/ SDK/XI/2017. There was no direct contact with the patients, and informed consent was not obtained from the patients. However, ethical approval was obtained from the previous study that was provided by the Ethical Committee of Public Health Faculty, Universitas Indonesia, number 08/UN2.F10/PPM.00.02/2018.

RESULTS

A total of 553 of 630 eligible patients with a diagnosis of MDR-TB or XDR-TB were analyzed, giving a participation rate of 88% (**Figure 1**). Sixty and 17 patients were diagnosed with mono-resistance and poly-resistance, respectively. **Table 1** shows that about 60% of the patients were men, of which 44% were cured and 10% died during and/or after treatment. The rate of tuberculosis resistance in patients with a history of complete treatment, including failed and relapsed, was 78%. All patients showed resistance to isoniazid and rifampicin, and more than 50% had resistance to streptomycin. Only 1% of the patients were diagnosed as HIV-positive, while the others were HIV-negative (43%) or had unknown status (56%).

The percentage of tuberculosis resistance appears to increase from 81 cases in 2010 to 116 cases in 2015. The following are the six outcomes of tuberculosis resistance treatment between 2010 and 2015: cured after treatment, stopped before completion of treatment, no progress in result of conversion test during and/or after completion of treatment (failed), completion of treatment but no information available related to conversion test, and lost to follow-up (**Table 2**). In this study, the focus was on successful treatment (cured) and poor treatment outcome (death) only. There was a fluctuation in the number of events of cured and deceased during the six years. Overall, survival of cured and death reached 58% and 84%, respectively. While, The median survival time of patients previously treated between 2010 and 2015 were significantly differences of survival of cured and death (**Figure 2** and **3**).

There was a slight difference between treatment for less than 20 months and treatment for greater than 20 months from 2010 to 2015. It was also shown that treatment for greater than 20 months was more likely to be not successful than treatment for less than 20 months. Other variables that can predict survival by successful treatment were resistance status after 20 months of treatment (HR 0.33, 95% CI 0.13 – 0.81), HIV status between zero and before 20 months (HR 0.55, 95% CI 0.39 – 0.78), sex (HR 1.16, 95% CI 1.01 – 1.33) and age during treatment (HR 0.89, 95% CI -.79 – 0.99) (**Table 3**).

Table 4 shows that age greater than 60 years significantly predicted tuberculosis mortality (HR 3.48; 95% CI 1.48 – 8.38 P-value = 0.004), while the area of treatment, history of previous treatment, resistance status, and HIV status were not proven statistically as predictors of tuberculosis mortality.

Table 1. Characteristic demography of MDR-TB and XDR-TB.

Variables	Successful Treatment (Cured)	Poor Treatment Outcome (Death)	Other Outcomes*	Total (n=553)
Sex				
- Male	148 (44.3)	35 (10.5)	151 (45.2)	334 (60.4)
- Female	84 (38.4)	32 (14.6)	103 (47.0)	219 (39.6)
Age (years)				
- < 30	72 (52.6)	12 (8.8)	53 (38.7)	137 (24.8)
- 30 – 39	53 (37.6)	23 (16.3)	65 (46.1)	141 (25.5)
- 40 – 49	60 (42.0)	9 (6.3)	74 (51.2)	143 (25.9)
- 50 – 59	38 (41.3)	12 (13.0)	42 (45.7)	92 (16.6)
- > 60	9 (22.5)	11 (27.5)	20 (50.0)	40 (7.2)
Residency (City/District)				
- South Jakarta	26 (33.8)	9 (11.7)	42 (54.5)	77 (13.9)
- West Jakarta	30 (39.0)	8 (10.4)	39 (50.6)	77 (13.9)
- North Jakarta	23 (30.3)	8 (10.4)	45 (59.2)	76 (13.7)
- East Jakarta	91 (46.0)	17 (8.6)	90 (45.5)	198 (35.8)
- Central Jakarta	29 (46.8)	11 (17.7)	22 (35.5)	62 (11.2)
- Kepulauan Seribu	33 (52.4)	14 (22.2)	16 (25.4)	63 (11.4)
Previous treatment				
- Incomplete	31 (42.5)	6 (8.2)	36 (49.3)	73 (13.2)
- Complete	187 (43.0)	52 (12.0)	196 (45.1)	435 (78.7)
- Unknown	14 (31.1)	9 (20.0)	22 (48.9)	45 (8.1)
Resistance Status				
- MDR-TB	216 (45.2)	55 (11.5)	207 (43.3)	478 (86.4)
- XDR-TB	16 (21.3)	12 (16.0)	47 (62.7)	75 (13.6)
Drug Resistance				
- Isoniazid	232 (42.0)	67 (12.1)	254 (45.9)	553 (100)
- Rifampicin	232 (42.0)	67 (12.1)	254 (45.9)	553 (100)
- Streptomycin	127 (42.6)	43 (14.4)	128 (43.0)	298 (53.9)
- Kanamycin	2 (9.1)	5 (22.7)	15 (68.2)	22 (4.0)
- Amikacin	2 (11.1)	4 (22.2)	12 (66.7)	18 (3.3)
- Ofloxacin	14 (21.2)	10 (15.2)	42 (63.6)	66 (11.9)
HIV Status				
- Negative	79 (33.5)	24 (10.2)	133 (56.4)	236 (42.7)
- Positive	2 (33.4)	2 (33.4)	2 (33.4)	6 (1.1)
- Unknown	151 (48.6)	41 (13.2)	119 (38.3)	311 (56.2)

**Default, failed, and loss to follow-up.*

Table 2. Percentage of the outcome of treatment of MDR-TB and XDR-TB.

Outcome	Frequency	Percent
Cured	248	44.8
Default	156	28.2
Failed	31	5.6
Death	67	12.1
Complete treatment	11	2.0
Loss to follow-up	40	7.3
Total	553	100.0

DISCUSSION

Overall, the survival of successful treatment (cured) and poor treatment outcome (death) were 58% and 84%, respectively. The resistance status after 20 months of treatment, HIV status before 20 months of treatment, sex, and age during treatment were the predictor variables for the survival of successful treatment (cured). While, having elderly patient (>60 years old) was the only predictor variable of poor treatment outcome (death).

The presence of MDR-TB and XDR-TB are predictive factors related to successful treatment. A previous study in Tehran, Iran showed similar results with success rates for treatment of MDR-TB and XDR-TB being different (76.5% and 41.7%, respectively).[18] A study in Hunan, China also had similar results, with MDR-TB having a higher percentage of successful treatment than XDR-TB (38% and 30%, respectively).[19] Conversely, Balabanove et al.[20] did not suggest significant difference in survival of patients with

Table 3. Prediction of successful treatment (cured) among resistant Tuberculosis (Extended Cox Regression analysis).

Covariate	HR (95% CI)	p-value
Sex	1.16 (1.01 – 1.33)	**0.03***
Age (years)	0.89 (0.79 – 0.99)	**0.03***
Area		
- < 20 (months)	1.07 (0.93 – 1.23)	0.53
- ≥ 20 (months)	0.96 (0.85 – 1.10)	0.35
Previous treatment		
- < 20 months	0.85 (0.56 – 1.27)	0.42
- ≥ 20 months	0.72 (0.49 – 1.05)	0.09
Resistance status		
- < 20 months	0.61 (0.31 – 1.18)	0.14
- ≥ 20 months	0.33 (0.13 – 0.81)	**0.01***
HIV status		
- < 20 months	0.55 (0.39 – 0.78)	**0.001***
- ≥ 20 months	1.01 (0.72 – 1.40)	0.98

** p-value < 0.05*

Table 4. Prediction of poor treatment outcome (death) among resistant tuberculosis patients (Cox Regression analysis).

Covariate	HR (95% CI)	p-value
Sex (ref: male)	1.50 (0.92 – 2.54)	0.09
Age (years) (ref: <30)		
- 30 – 39	1.71 (0.83 – 3.52)	0.14
- 40 – 49	0.64 (0.64 – 0.27)	0.32
- 50 – 59	1.56 (1.56 – 0.69)	0.29
- > 60	3.48 (1.48 – 8.38)	**0.004***
Area (ref: South)		
- West Jakarta	0.81 (0.31 – 2.13)	0.68
- North Jakarta	0.94 (0.35 – 2.48)	0.89
- East Jakarta	0.82 (0.36 – 1.88)	0.64
- Central Jakarta	1.65 (0.66 – 4.13)	0.28
- Kepulauan Seribu	1.94 (0.69 – 5.39)	0.20
Complete	1.47 (0.62 – 3.46)	0.38
Unknown	2.45 (0.81 – 7.39)	0.11
Resistance status (ref: MDR-TB)	1.25 (0.65 – 2.45)	0.49
Positive	3.20 (0.69 – 14.93)	0.14
Unknown	2.00 (0.89 – 4.48)	0.09

** p-value < 0.05*

MDR-TB and XDR-TB during treatment (HR = 1.29; 95% CI 0.91 – 1.81, p-value = 0.15). The obvious explanation is the fact of many patients in this study were 'MDRTB plus' with resistance to many other SLD, which made less difference between MDR and XDRTB.

Our analysis also revealed that gender is one of predictor variable for successful treatment (cured), which female was more likely to had experience of successful treatment (cured) than male. This is in line with a previous study from Ethiopia, which found that male MDR-TB patient had tendency to have longer recovery time compared to female. It was hypothesized that male patient was linked to higher tendencies toward alcohol and drug abuse and interruption of their medication. [21] In regards to interruption of medication, a study assessed the influencing factors of non-attendance of health facility for tuberculosis clinical evaluation among household contact. This study found that males were less likely to visit public health facility for Tuberculosis screening compared to women due to the purporting that men visiting clinics are not masculine.[22] Apart from that, Chida et al claimed that gender was not a risk factor for default treatment, because both men and women have similar condition related to economic burden, which affect to their tuberculosis treatment. [23]

There is a difference in survival of successful treatment (cured) among patients with positive, negative, and unknown HIV status. This study showed that HIV diagnosis as a co-infection predicted survival due to successful treatment. Patients diagnosed as HIV-positive and/or unknown status has a higher risk of being non-survivors (unsuccessful treatment) than patients who are HIV-negative.[20,24,25] Girum et al.[25] showed that HIV-positive patients had 3 times higher mortality risk compared with HIV-negative patients. This may be cause HIV status is known as an aggravating comorbidity in tuberculosis patients, and it can influence the treatment outcome [26,27] A previous study in a rural area of South Africa also found that 52 of 53 HIV-positive patients with XDR-TB died, with a median survival of 16 days from the time of diagnosis.[28]

Poor treatment outcome (death) among patients was predicted by age greater than 60 years old (HR 3.48; 95% CI 3.47 – 1.48, p-value = 0.004). Previous studies showed a similar result with patients aged 55 years and older having an almost eight times higher risk of death than patients aged 15 to 34 years.[15,20] Other study suggested age as one of independent predictors of mortality during tuberculosis treatment.[29] A possible explanation is that the elderly population was more likely to have adverse experience of drug reactions to tuberculosis treatment, which may affect treatment outcome.[23] Other than that, age related factors also have impact on poor outcome among elderly people such as multi-

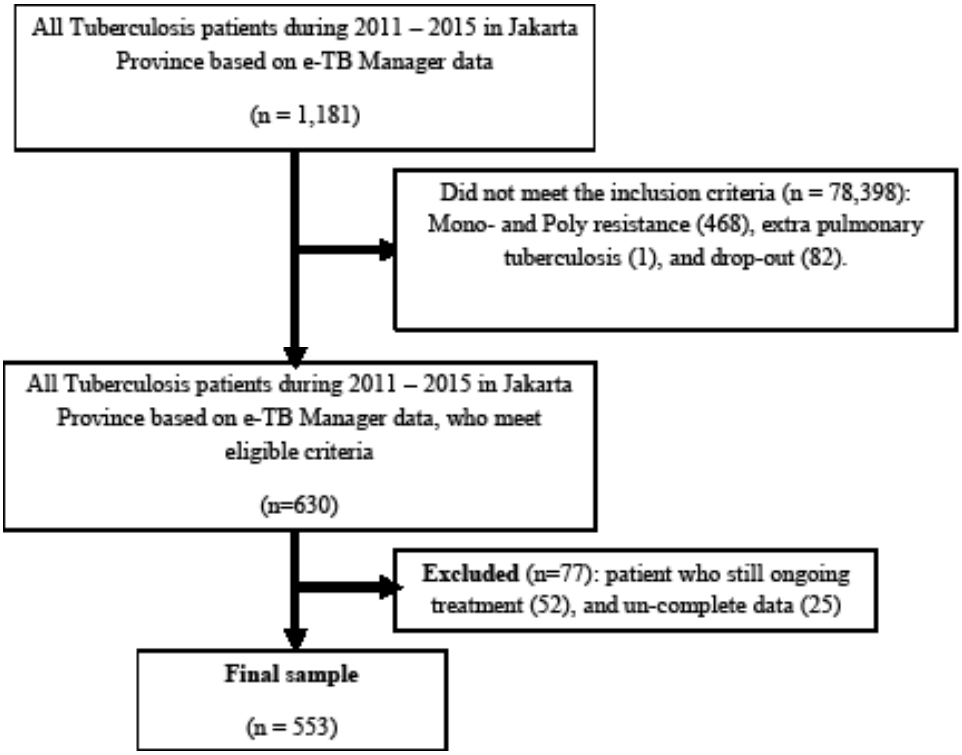

Figure 1. Flow chart of participant selection for the study.

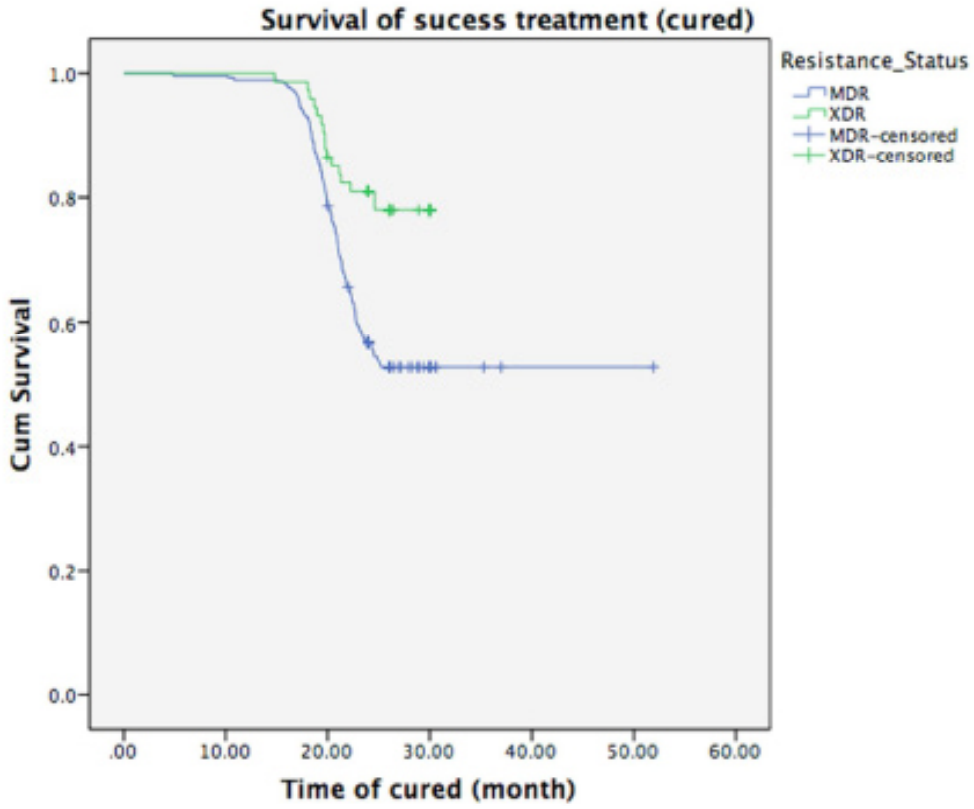

Figure 2. Kaplan-Meier estimates of survival of success treatment or cured among resistant Tuberculosis.

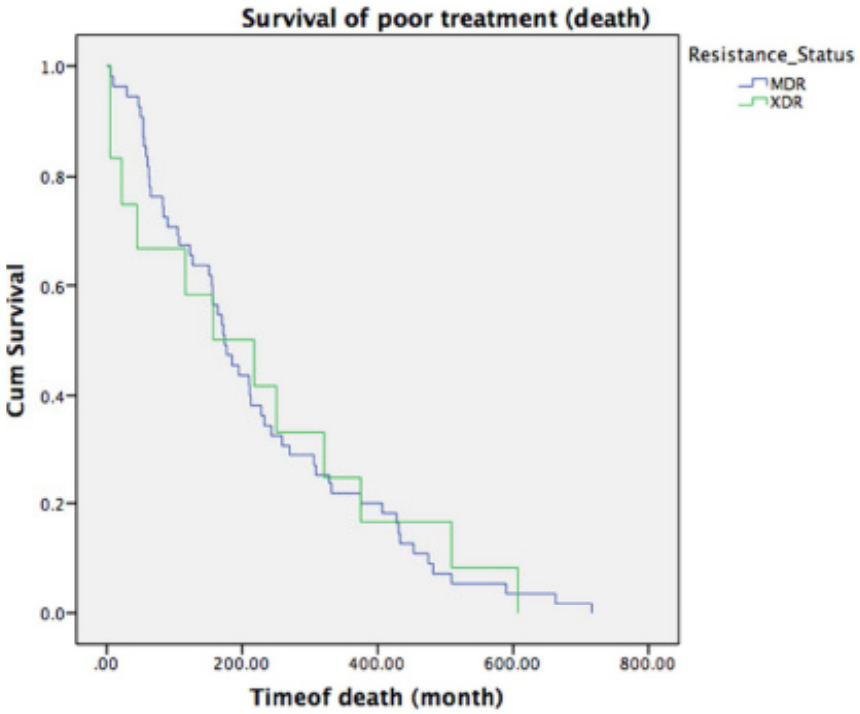

Figure 3. Kaplan-Meier estimates of survival of poor treatment (death) among resistant Tuberculosis.

pathology, cognitive impairment, and economic status. [30]

Some factors could not be assessed due to data limitations. First, this retrospective cohort study did not consider variability over time among the independent variables. Second, several factors also predict the outcomes of treatment outcome (cure and death) include socio-economic nutritional status and/or baseline of weight smoking and alcohol consumption, side effects during treatment, diabetic status, and additional micronutrient consumption during treatment.[9,10,12-14,16,20,25,31-41] Third, this study only involved pulmonary tuberculosis, while extra pulmonary tuberculosis may also be a significant predictor of treatment outcome.[15,20,29,42] However, we believe that potential selection bias was low because of the small drop out percentage (7%) and high rate of participation (88%), so that the study results have generalizability for others population.

CONFLICT OF INTEREST

No conflicts of interest declared.

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