ORIGINAL RESEARCH

TREATMENT OUTCOMES OF MULTIDRUG RESISTANT TUBERCULOSIS PATIENTS IN EAST JAVA FROM 2014 TO 2017

Hasil Akhir Pengobatan Pasien Tuberkulosis Multidrug Resistan di Jawa Timur Tahun 2014─2017

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ABSTRACT

Background: Multidrug resistant tuberculosis (MDR TB) is a major public health problem marked by the Mycobacterium tuberculosis strain that is resistant to first line anti TB drugs, including rifampicin and isoniazid simultaneously. A patient confirmed as having MDR TB can transmit this form of TB to other individuals. Therefore, treatment success is the main target when addressing MDR TB. **Purpose:** This study aimed to assess the treatment outcomes of MDR TB patients in East Java Province from 2014 to 2017. **Method:** This is a quantitative-descriptive study using the secondary data of drug resistant TB patients sourced from the e-TB Manager website in the East Java Province Health Office. **Results:** The results show that the average MDR TB patients was 47 years old, 57.44% were male, 37.52% had a negative HIV status, 44.87% were relapse patients, 71.95% had undergone two or less previous treatments, and 69.24% had sputum culture conversion. The treatment outcomes included 161 patients (31.14%) confirmed as cured, 27 patients (5.22%) completing treatment, 174 patients (33.65%) defaulting, two patients (0.38%) confirmed as having failed treatment, and 59 patients (11.41%) dying during the treatment period. **Conclusion:** The treatment success rate was low and the number of defaults was high. Therefore, it is hoped that there will be support from those closest to the patient and health workers who will maintain and increase the patient's motivation to complete the treatment.

ABSTRAK

Latar Belakang: *Tuberkulosis Multidrug Resistan (TB MDR) merupakan masalah kesehatan masyarakat utama yang ditandai dengan kondisi Mycobacterium tuberculosis kebal terhadap OAT lini pertama yaitu rifampisin dan isoniazid secara bersamaan.*

Pasien yang telah terkonfirmasi TB MDR dapat menularkan kuman tersebut pada individu lainnya, sehingga keberhasilan pengobatan merupakan target utama dalam pengobatan TB MDR. **Tujuan:** *Penelitian ini bertujuan untuk menilai hasil akhir pengobatan pasien TB MDR di Provinsi Jawa Timur tahun 2014-2017.* **Metode:** *Desain penelitian ini merupakan studi deskriptif-kuantitatif dengan menggunakan data sekunder pasien TB resisten obat yang bersumber dari website Sistem Informasi e-TB Manager Dinas Kesehatan Provinsi Jawa Timur.* **Hasil:** *Hasil penelitian menunjukkan bahwa rata-rata pasien TB MDR berumur 47 tahun, 57,44% pasien laki-laki, 37,52% merupakan pasien dengan status HIV negatif,, 44,87% pasien kambuh, 71,95% merupakan pasien dengan ≤ 2 kali pengobatan sebelumnya, dan 69,24% pasien telah memiliki konversi biakan dahak. Hasil akhir pengobatan pasien TB MDR meliputi 161 pasien (31,14%) telah dinyatakan sembuh, 27 pasien (5,22%) merupakan pengobatan lengkap, 174 pasien (33,65%) default, 2 pasien (0,38%) telah dinyatakan gagal pengobatan, dan 59 pasien (11,41%) meninggal dalam masa pengobatan.* **Kesimpulan:** *Angka keberhasilan pengobatan masih rendah dan jumlah pasien defaults masih tinggi. Oleh karena itu, diharapkan adanya upaya yang dapat menjaga dan meningkatkan motivasi pasien untuk menyelesaikan pengobatannya secara tuntas.*

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the Mycobacterium tuberculosis bacteria and transmitted from one individual to another. In 1993, WHO designated TB as a global emergency. This was due to the worsening TB situation, especially in countries with a high TB burden. A country's TB burden increases with the emergence of double resistant or multidrug resistant (MDR) strains of the disease, due to the failure of recuperation efforts (Ministry of Health RI, 2013).

MDR TB is identified by TB bacteria resistant to the most effective first line anti TB drugs, namely rifampicin and isoniazid, with or without resistance to other first line anti TB drugs. This type of TB has two causes—inadequate treatment or direct transmission from an individual with MDR TB (Ministry of Health RI, 2016). Based on surveillance data of anti TB drug resistance, in 2016, only 130,000 of 490,000 cases received MDR TB treatment. Of the patients starting treatment in 2014, 54% were treated successfully, while 8% were declared to have failed treatment, 16% died, 15% defaulted (failed to follow up/dropped out) and 7% were not evaluated (WHO, 2017).

The number of Multidrug or Rifampicin Resistant of TB (RR/MDR-TB) cases in Indonesia increased from 2009 to 2014. In 2009, there were 148 suspected cases examined and 66 were confirmed as being RR/MDR TB. This number increased each year up to 2014, which saw 1,715 of 9,422 suspect cases being confirmed as RR/MDR TB (Ministry of Health RI, 2017). East Java was one of three provinces with the largest distribution of MDR TB cases in Indonesia (Ministry of Health RI, 2016). According to the e-TB Manager data from the East Java Provincial Health Office, only 46% of MDR TB cases detected in 2015 were treated successfully, as 12% died, 39% defaulted and 3% failed treatment.

The high number of drug resistant TB cases is a major public health problem, as it can strain the success of TB control. The management of drug resistant TB cases is more complicated and requires more attention than the management of drug sensitive TB. MDR TB treatment lasts approximately 20-26 months and is much more expensive; anti TB drugs have more diverse side effects and patients require more complex treatment, which makes it more difficult to control (Ministry of Health RI, 2016).

WHO developed the directly observed treatment short-course (DOTS) strategy as an

effort to tackle TB cases, especially drug resistant TB. Indonesia began MDR TB treatment in 2009, which was implemented under the Integrated Management of Drug Resistant Tuberculosis (MTPTRO) program. This aimed to improve treatment outcomes, as one of five actions to improve treatment success (Ministry of Health RI, 2013). Research related to treatment outcomes of MDR TB patients is not common in Indonesia, especially in East Java, which was one of provinces with the highest prevalence of MDR TB. The purpose of this study is to assess the outcomes of MDR TB patients receiving treatment in East Java between 2014 and 2017, to evaluate the MTPTRO program in the East Java Provincial Health Office.

METHOD

This study used a descriptive design, gathering secondary data from all MDR TB patients treated by East Java health care services between 2014 and 2017. The inclusion criteria of this study were patients with pulmonary MDR TB, over 14 years of age, domiciled in East Java Province, and who had complete evaluations and records in the e-TB Manager on the East Java Provincial Health Office website. This study did not use a sample size calculation because it used the total population that fulfilled the inclusion criteria (n = 517). Data was collected on February 22, 2019 by download from the e-TB Manager website.

Treatment outcomes were divided into six categories: cured, treatment completed, defaulted/failed to follow up/dropped out, failed treatment (category 1 and category 2), died, and not evaluated. Patients were categorized as cured if they completed the MDR TB treatment; this was supported by at least three negative culture results in a row at the advanced stage, with a minimum deviation per culture test of 30 days. Patients were categorized as having completed treatment if they fulfilled the treatment requirements, but were not categorized as failed or cured. Patients were categorized as defaulted/failed to follow up/dropped out if they started MDR TB treatment and dropped out from treatment for two or more consecutive months. Patients were categorized as having failed treatment if they stopped treatment or permanently required new combinations of at least two anti TB drugs. This was probably caused by one or more conditions: sputum smear test results were positive until the end of eighth month in the early stage; sputum culture test results were

positive (reverse) for two consecutive tests in the advanced stage after a negative in a previous test; there was additional resistance to second line injection or fluoroquinolone class anti TB drugs; or there were severe side effects causing treatment to be stopped permanently. Patients were categorized as having died if they died during the treatment period, regardless of the cause. Patients were categorized as having not been evaluated if they did not have a treatment outcome. This included patients who moved to other regions or where treatment (Ministry of Health RI, 2016).

RESULTS

Initially, the number of MDR TB patients registered in the e-TB Manager of the East Java Provincial Health Office between 2014 to 2017 was 905. The total final sample after applying the inclusion criteria was 517 patients. Figure 1 shows the trend prevalence of MDR TB patients in this study. Figure 1 also shows that the prevalence of MDR TB patients in East Java Province from 2014 to 2017 tended to fluctuate. The highest prevalence of MDR TB patients was in 2017 (37.33%) and the lowest was in 2014 (17.79%). The majority of MDR TB patients in East Java Province were aged between 45 and 64 (48.93%), were male (57.44%), had an unknown HIV status (62.47%), were relapse patients (44.87%), had a history of two or more previous treatments (71.95%), and had negative sputum culture tests (69.24%) (Table 1).
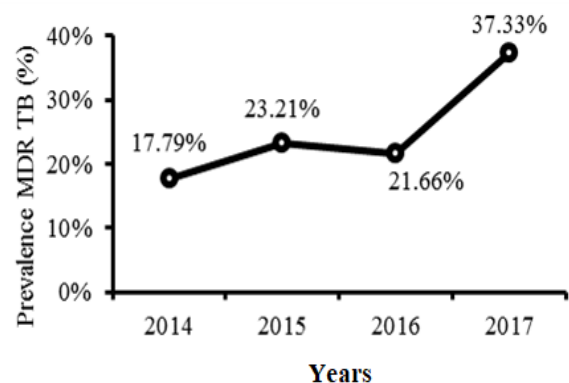

Figure 1 Trends of MDR TB Patients in East Java Province from 2014 to 2017

The cured rate of MDR TB patients in East Java Province from 2014 to 2017 tended to fluctuate. The highest rate of cured MDR TB patients was in 2014 (55.43%) and the lowest was in 2017 (5.70%). The treatment completion rate

was the highest in 2015 (10%) and the lowest in 2014 (0%) (Figure 2).

Table 1 shows that the treatment success rate (cured and treatment complete) of MDR TB patients was low, at 36.36%. Of the 188 patients who were successfully treated, 85 patients (45.21%) were aged 25 to 44, 102 (54.25%) were male, 86 (45.74%) had a negative HIV status, 80 (42.55%) relapsed, 180 (95.74%) had a history of two or more previous treatments, and 185 (98.40%) had negative sputum culture tests.

MDR TB patients with a defaulted treatment outcome increased in 2015, then declined in 2016 and 2017 to 30.57% (see Figure 2). The default rate among MDR TB patients tended to decrease with a more than 10% decline annually. The patients with MDR TB who defaulted tended to be 45 to 64 years of age (37.15%) and male (37.07%), with an unknown HIV status (42.10%), a history of defaulting (39.74 %), an unclear previous TB treatment history (34.05%), and a positive sputum culture test (71.07%) (Table 1; Figure 2).

The number of MDR TB patients who failed treatment tended to be low, with the highest percentage of failed patients at 0.89%. MDR TB patients who died during the treatment period tended to increase, with the highest percentage of patients dying in 2017 (12.95%) and the lowest in 2016 (1.79%) (Figure 2).

Table 1 shows that the poor treatment rate (failed treatment and died) of MDR TB patients in East Java province between 2014 and 2017 was quite high, at 11.79%. Of the 61 patients who were declared as having poor treatment, 34 were aged 45 to 64 (55.74%), 27 (44.26%) were women, 42 (68.85%) had an unknown HIV status, 30 (49.18%) relapsed, 40 (65.57%) had a history of more than two previous treatments, and 36 (59.02%) had positive sputum culture tests.

In this study, approximately 18.18% of the MDR TB patients were not evaluated. The highest proportion of MDR TB patients who were not evaluated was recorded in 2017 (Figure 2).

DISCUSSION

This study aimed to describe the treatment outcomes of MDR TB patients who were registered in the e-TB Manager in the East Java Provincial Health Office. The average age of MDR TB patients was 47; the youngest patient was 15 years old and the oldest was 85. A previous study at Dr. Moewardi General Hospital Surakarta found the highest proportion of MDR TB patients were more than 41 years of age (Reviono, Kusnanto, Eko, Pakiding, & Nurwidiasih, 2014).

According to the Technical Guidelines for Integrated Management of Drug Resistant Tuberculosis Treatment, the success of drug resistant TB treatment is divided into two categories—patients who experienced treatment success (cured or treatment complete) and patients who did not complete treatment (Ministry of Health RI, 2017). MDR TB treatment occurs in two stages—the early stage and the advanced stage. Early treatment is begun after a sputum culture conversion, with an estimated time of up to eight months. Indicators of a response to MDR TB treatment are based on sputum culture conversion. Culture conversion is the change of culture test results from positive to negative at least three times in a row, with a minimum deviation per culture test of 30 days (Ministry of Health RI, 2016). In the results of this study, it was known that the majority of MDR TB patients with treatment success had negative sputum culture test results. It can be concluded that sputum culture conversion of patients can determine the outcome of MDR TB treatment. This study was supported by Kurbatova et al (2015) who found that patients with a shorter average sputum conversion time had significantly better treatment success rates.

This study in East Java Province found that the MDR TB treatment success rate was low, at less than 60%. Some previous studies showed higher numbers than the results of this study. Lu et al (2017), who found that patients with a shorter average sputum conversion time had significantly better treatment success rates. This study in East Java Province found that the MDR TB treatment success rate was low, at less than 60%. Some previous studies showed higher numbers than the results of this study. Sun et al (2019), showed a success rate of 82.40%. A study in India, conducted by Kumar, Sharma, Agarwal, & Purohit (2016), found that the success rate of MDR TB was only 48%, while a study in Indonesia found a success rate of 80.90% in RSUP Persahabatan (Soepandi, 2014). A study of MDR TB on global scale showed that, from the 129,689 MDR TB patients who started treatment, only 70,032 patients (53.99%) experienced treatment success (Gandhi, Brust, & Shah, 2017).

This study found that 46.91% of MDR TB patients were declared cured. In a European study involving 380 MDR TB patients, the cure rate was 31% (Günther et al., 2016). A study by Yasin, Abu Bakar, & Abdul Muttalif (2014) in Kuala Lumpur found a cure rate of 34.50%. One previous study

showed a higher rate than this study, in China and Ethiopia, with a cure rate of 57% (Alene et al., 2018). Another study also showed that treatment outcome recorded in Ethiopia with cure rate of 64.9% (Shibabaw, Gelaw, Wang, & Tessema, 2018).

The percentage of MDR TB patients with a failed treatment outcome (0.38%) or who died (11.41%) was lower compared to results in other Asian countries. In a previous study in India, the success rate was 47.80%, the failure rate was 7.30%, and the mortality rate was 27.50% (Akshata & Chakrabarthy, 2016). The few failed patients of MDR TB treatment in this study were not the good results because the treatment success rate was low and the default rate was high.

The default rate in this study was 33.65%. This is in line with a study in Gresik Regency, which found a default rate of 33.70% (Ghithrif,

2016). A similar study in DKI Jakarta Province had a higher default rate of 44.6% (Farihatun & Machmud, 2018). The problem that can arise from the unsuccessful treatment of MDR TB is second line anti TB drug resistance (resistance to kanamycin, amikacin, or quinolone), which can lead to extensively drug resistant (XDR) TB cases. XDR TB treatment has a low success rate and a high treatment failure rate (Ministry of Health RI, 2016).

This study showed that MDR TB patients with poor treatment results included a fairly high proportion of patients with a relapsed treatment history, requiring re-treatment. Most patients did not have sputum conversion during MDR TB treatment, the HIV status of most patients was unknown, and most patients had undergone two or more previous treatments. (Ministry of Health RI, 2017).

Table 1
Treatment Outcomes by Patient Characteristics in East Java Province from 2014 to 2017

| Variable	Treatment Success		Default		Poor Treatment		Not evaluated		n	%
	n	%	n	%	n	%	n	%		
Age (years)										
15-24	17	50	7	20.58	1	2.94	9	25.47	34	6.76
25-44	85	40.47	61	29.04	22	10.47	40	19.04	210	40.61
45-64	83	32.80	94	37.15	34	13.43	44	17.39	253	48.93
>64	3	15	12	60	4	20	1	5	20	3.67
Sex										
Female	86	38.09	64	29.09	27	12.27	43	19.54	220	42.55
Male	102	34.34	110	37.07	34	11.44	51	17.17	297	57.44
HIV Status										
Negative	86	44.32	38	19.58	19	9.79	51	26.28	194	37.52
Positive	0	0	0	0	0	0	0	0	0	0
Unknown	102	31.57	136	42.10	42	13	43	13.31	323	62.47
Type of Patient										
New	8	17.39	17	36.95	8	17.39	13	28.26	46	8.89
Relapse	80	24.48	71	30.60	30	12.93	51	21.98	232	44.87
Defaulter	27	34.61	31	39.74	11	14.10	9	11.53	78	15.08
Failed category 1	59	45.73	45	34.88	7	5.42	18	13.95	129	25.95
Failed category 2	8	50	5	31.25	2	12.5	1	6.25	16	3.09
Other	6	37.50	5	31.25	3	17.75	2	12.5	16	3.09
Number of Previous TB Treatments										
≤2	180	48.38	125	33.60	40	10.75	27	7.25	372	71.95
>2	2	28.57	2	28.57	3	42.85	0	0	7	1.35
Unclear	6	4.34	47	34.05	18	13.04	67	48.55	138	26.69
Sputum Culture Test										
Negative	185	51.67	61	17.03	25	6.98	87	24.30	358	69.24
Positive	3	1.88	113	71.07	36	22.64	7	4.40	159	30.75
Total	188	36.36	174	33.65	61	11.79	94	18.18	517	100.00
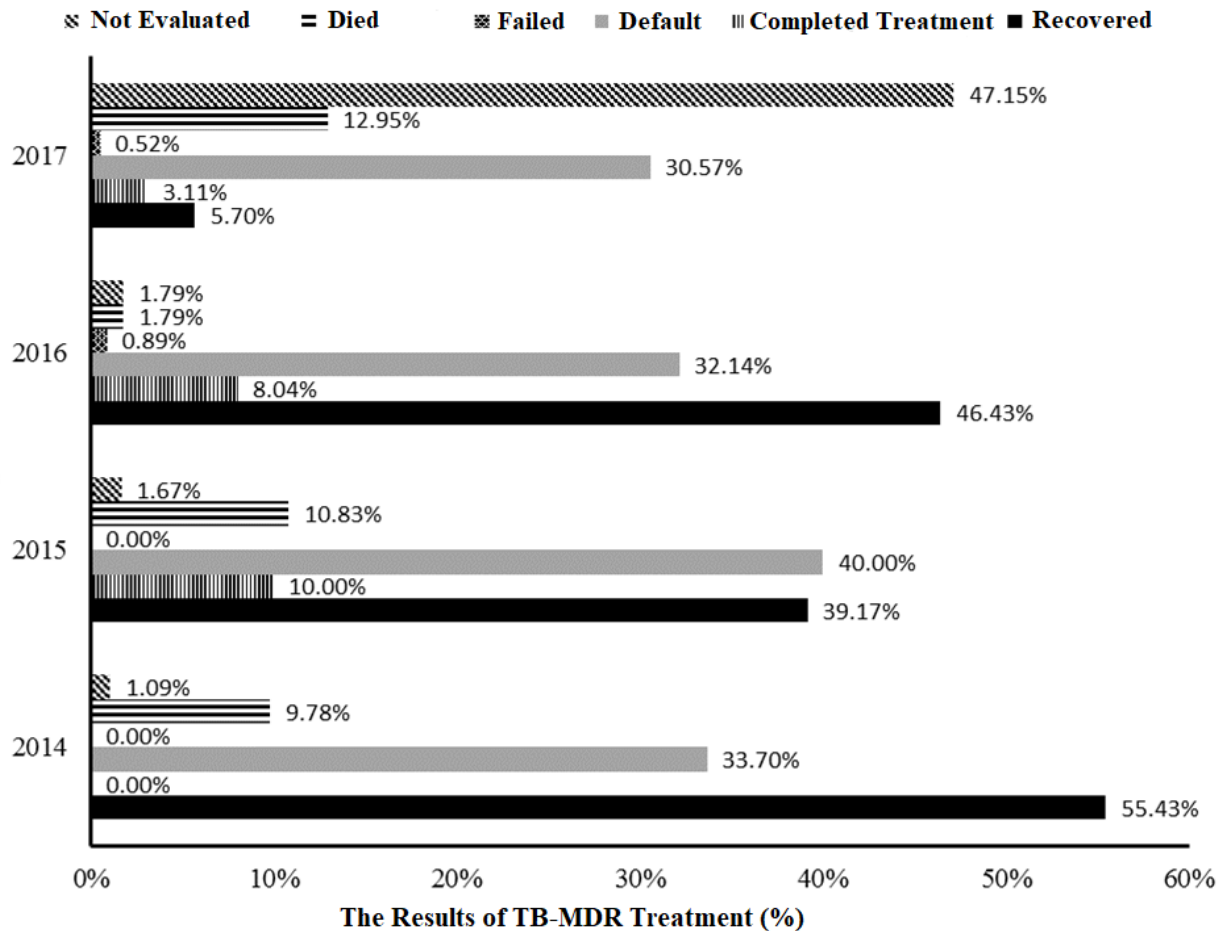
Figure 2 Treatment Outcomes of MDR TB Patients in East Java Province from 2014 to 2017

In fact, most MDR TB patients in Indonesia have a history of previous TB treatment. Treatment of patients with a previous treatment history with first line anti TB drugs requires the use of second line anti TB drugs. The management of second line anti TB drug can be more complicated and they have more frequent and more significant side effects than first line anti TB drugs (Ministry of Health RI, 2017). According to the International Standards for Tuberculosis Care (ISTC), the treatment standard guide for patients confirmed with MDR TB is 6 Km – E – Etho – Levo – Z – Cs / 18 E – Etho – Levo – Z – Cs (Mardhiyyah & Carolia, 2016).

Based on existing theories, the important factor that has a significant correlation with treatment success, but could not be investigated in this study, was the side effects of anti TB drugs. Side effects are observed after the consumption of anti TB MDR drugs when there were no existing symptoms caused by previous side effects. Data on the side effects of anti TB drugs can be obtained from medical records of patients with drug resistant TB. The study conducted by Widyasrini,

Probandari, & Reviono (2017) were significantly related to the treatment success of MDR TB patients in Surakarta, with a crude OR value of 4.83 (95% CI = 2.06 – 0.24; p <0.01) and an adjusted OR value of 6.84 (95% CI = 2.50 – 18.74; p <0.01). This is in line with the study conducted by Deshmukh et al (2015) who found that many factors affect the compliance of MDR TB patients, including the presence of side effects. According to a study on TB patients by Seniantara, Ivana, & Adang (2018) the more significant the side effects of the drugs, the lower the treatment compliance of patients. Side effects cause patients to be reluctant to continue regular TB treatment.

The majority of MDR TB patients in this study were not evaluated because they were still in the treatment period or had moved to different treatment regions. Overall, this study showed that the treatment outcomes of MDR TB patients in East Java Province from 2014 to 2017 were 31.14% cured, 5.22% treatment complete, 33.65% default, 0.38% failed, and 11,.41% died. Several studies regarding treatment outcomes, such as in the Hunan Chest Hospital, China and Gondar

University Hospital, Ethiopia, found that 57% of patients recovered, 3% completed treatment, 18% died, 12% failed, and 25% defaulted (Alene et al., 2018). A study in north-west Ethiopia found that 54% of patients recovered, 9% completed treatment, 13% died, 2% failed, 11% defaulted, 2% changed treatment, and 8% were continuing treatment (Alene, Viney, McBryde, Tsegaye, & Clements, 2017). A study in Italy found that the percentage of successful trials was 68.40%, while 22.80% of patients defaulted, 1.80% died, and 3% changed treatment (Gualano et al., 2016).). A study in Japan found that 65.40% of patients experienced treatment success, 3.70% defaulted, 2.50% failed, 20.10% died, and 8.10% changed treatment (Kobayashi, Hattori, Akter, Mizoue, & Ohta, 2017). The difference in these numbers shows that treatment success is influenced by several factors, including geography and environment.

Research Limitation

This study used cohort registration data from the e-TB Manager; the evaluated characteristics in this study were based on available variables that were recorded completely in the e-TB Manager. Using secondary means that there is data that not reported to e-TB Manager, resulting in a proportion that was different from previous studies (under-reporting).

CONCLUSION

The average age of MDR TB patients was 47 years old, with a majority of male patients. The treatment success rate of MDR TB patients was low, the poor treatment rate was below 10%, and the default rate was high.

CONFLICT OF INTEREST

The authors declare that no conflict of interest in this study.

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