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Risk Factor Identification of Multi-Drug Resistant Tuberculosis

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ABSTRACT

Background: Multi-drug resistant tuberculosis (MDR-TB) is a serious health problem with high morbidity and mortality. The identification of risk factors is needed to prevent the incidence TB-MDR. **Objective**: To identify the risk factors of TB-MDR in the Special Region of Yogyakarta. **Method**: This study used a case control design to assess the risk factors for the incidence of MDR-TB. Patients diagnosed with MDR-TB compared to non-MDR TB patients were then compared to exposure to the risk factors studied. The results of the study were analyzed by calculating the mean and proportion. Next, Chi-square tests and analysis of odds ratio (OR) with 95% confidence interval (CI) were conducted using a 2x2 dummy table as an aid with multivariate logistic regression analysis. **Result**: There were 53 patients with MDR-TB as the case group and 106 non-MDR TB patients as controls. There were no significant differences between the two groups regarding the characteristics of age, sex, place of residence, and type of work (p>0.05). The multivariate analysis found the risk factors associated with an increased incidence of MDR-TB were a history of previous TB treatment (p<0.001; OR 31.82; 95%CI: 9.40-107.77) and surrounding TB (p<0.01; OR 4.45; 95%CI: 1.45-13.70), while other factors that were not significantly related to the incidence of MDR-TB included body mass index, distance of home to health facilities where taking medicine, smoking, drinking alcohol, history of BCG vaccination, education, income, medication adherence, and comorbidities (p> 0.05). **Conclusion**: The risk factors found to be associated with an increased incidence of MDR-TB in this study were the presence of surrounding TB patients and a history of previous TB treatment.

Keywords: *risk factor, TB-MDR, TB-non-MDR*

BACKGROUND

It is estimated that the number of patients with TB in Indonesia is around 10% of the total number of TB patients in the world. At the same time, the dual immunity of TB germs to anti-TB drugs is increasingly a problem due to cases that have not been successfully cured[1]. Indonesia is one of the 10 countries with the highest cases of Multi-Drug Resistant Tuberculosis (MDR-TB) globally with an estimated 1 million new TB cases. The case number of MDR-TB in Indonesia has increased from 2010-2012 to 182 cases in 2010 and 428 cases in 2012. In the Yogyakarta Special Region in 2015, out of 159 samples suspected of MDR-TB, 23 were positive for MDR-TB or the frequency of 14.46%, whereas in 2016 until June there were 19 positive MDR-TB cases from 177 people suspected of MDR-TB[2].

MDR-TB is caused by bacteria that is resistant to isoniazid and rifampicin which are the most effective anti-TB drugs, both as a result of primary infection and due to treatment in previous patients with TB. One of the causes of immunity (secondary resistance) is the result of mismanagement of patients with TB. Drug resistance is associated with a history of previous treatment. The possibility of resistance in patients with a history of previous treatment is as much as 4-fold, whereas for the occurrence of MDR-TB, it

increases by 10 times or more compared to patients who have never been treated[1].

Theoretically. there are five factors that are considered to play a main role in causing the 'outbreak' of MDR-TB, namely: (1) Inadequate treatment (causing resistant *Mycobacterium tuberculosis* mutants); (2) Patients who are slowly diagnosed with MDR, thus becoming a source of continuous transmission; (3) Patients with incurable MDR-TB which will continue transmission; (4) Patients with MDR TB despite being treated continuously but with inadequate drugs resulting in doubling of resistant mutants; and (5) HIV co-infection which facilitates primary and secondary resistance.

Research in several countries identified a variety of risk factors for MDR-TB, including previous TB treatment, poor adherence to treatment, inadequate regimens and positive BTA examinations at the end of the second or third month of treatment. Patient characteristics such as HIV co-infection, alcohol abuse, and young age are also believed to influence the occurrence of drug resistance even though information about it is still limited and controversial. The World Health Organization (WHO) includes age as a TB risk factor[3].

MDR-TB is one of the biggest problems with TB prevention and eradication with an incidence that increases significantly every year. Therefore, certain risk factors that increase the incidence of MDR-TB need to be investigated in order to reduce the cost, morbidity and mortality of MDR-TB. This study aimed to identify risk factors for MDR-TB associated with the incidence of MDR-TB in the Special Region of Yogyakarta.

METHODS

This study used a case control design with MDR-TB patients as a case group and patients with non-MDR TB as a control group. The research subjects were patients who were over 18 years old, diagnosed with MDR-TB from January 2014 to December 2016 and patients living in the Special Region of Yogyakarta, while the control group were non-MDR TB patients who lived in one area with MDR-TB patients.

The inclusion criteria were: patients with MDR-TB and non-MDR TB patients, residing in the Yogyakarta Special Region, willing to be the subjects of research. The exclusion criteria were: patients living outside Yogyakarta Special Region and where the patient's residence was not found due to relocation. The study sample was selected using a total sampling method with 56 patients as the case group and the control group was twice the number of the case group.

TB researchers and/or programmers conducted the data retrieval by looking at data on TB 01 and questionnaires given to the research subjects. Anamnesis was done with a questionnaire on the research subjects' characteristics related to age, sex, height and weight, education, income, employment, residence, smoking, drinking alcohol, surrounding TB patients, BCG vaccination, history of previous TB treatment, adherence to taking medication, and comorbidities. Data were analyzed using the SPSS computer program.

The researcher guarantees the confidentiality of the data concerning the subjects of the study. Ethical clearance was issued by Medical and Health Research Ethics Committee (MHREC) from the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada.

RESULTS

There were 56 cases of MDR-TB in the Special Region of Yogyakarta between January 2014 to December 2016, but only 53 cases were included in the study because 2 patients refused to take the study and 1 patient did not meet the inclusion criteria because he resided outside the Special Region of Yogyakarta. The ten criteria of suspected MDR-TB (Ministry of Health Republic of Indonesia, 2014) are: 1) TB patients failed treatment category; 2) Non-converted category 2 treatment TB patients (remain positive) after 3 months of treatment; 3) TB patients who have a history of non-standard TB treatment and use quinolones and second-line injection drugs for at least 1 month; 4) Patients with failed category 1 TB treatment; 5) TB patient who remains positive after 3 months of treatment category 1; 6) Relapse case of TB patients with categories treatment 1 or 2 ; 7) TB patients who return after loss to follow-up (negligent treatment/default); 8) Suspected TB who has a history of close contact with MDR TB patients; 9) TB-HIV coinfected patients who do not respond to drug administration; 10) Patients other than the above criteria (TB smear + new or TB Child). This picture below shows the numbers of each category of suspected MDR-TB. The most common criteria for suspected MDR-TB in the case group were MDR-TB caused by relapses of category 1 or 2. There were no suspicious criteria for MDR-TB in TB-HIV co-infection patients who did not respond to drug administration.

The characteristics of patients with MDR-TB and the non-MDR TB patients did not show significant differences.

Risk factors that show significant differences between patients with MDR-TB and non-MDR TB patients are education, income, medication adherence, drinking alcohol, presence of comorbidities, history of TB treatment, and surrounding TB.

Education, income, obedience in taking medicine, smoking, drinking alcohol, comorbidities, TB treatment history, and surrounding TB have a relationship with TB-MDR incidence.

The multivariate logistic regression analysis identified a history of TB treatment and the presence of surrounding TB patients were the significant risk factors for MDR-TB.

DISCUSSION

Age as a risk factor in this study was not related to the incidence of MDR-TB. The average age of MDR-TB patients is in the productive age of 42 y.o. Another study with similar results found that the prevalence of MDR-TB was more common at ages 36-64 y.o[4]. Some studies have shown that age factors have an independent relationship with MDR events and an increase in their proportions at

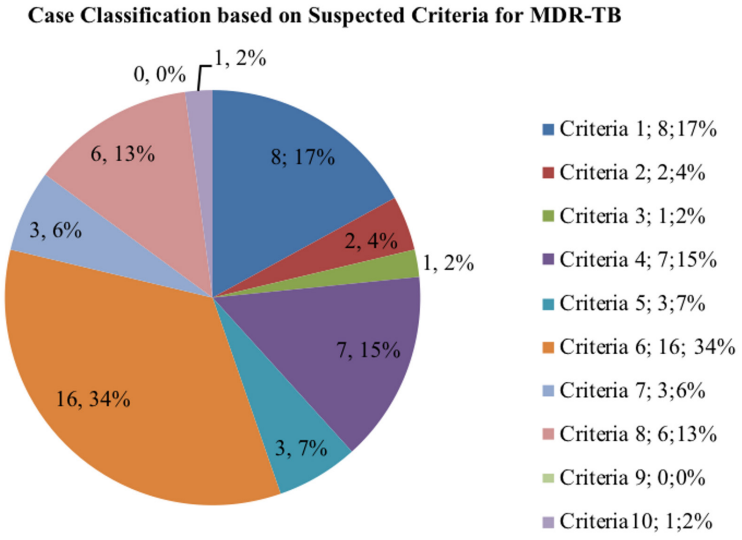

Figure 1. Case Classification Based on Suspected Criteria for MDR-TB.

Table 1. Characteristics of Research Subjects

	TB-MDR (n = 53)	TB non-MDR (n = 106)	*p*-value
Age. year. *mean*±SD			
Mean (year)	42.43±13.08	42.15±13.41	0.99
Gender.n (%)			
Male	33 (62.3)	64 (60.4)	0.82
Female	20 (37.7)	42 (39.6)	
Job.n (%)			
Housewife/Unemployment	20 (37.7)	37 (34.9)	0.61
Student	3 (5.7)	4 (3.8)	
Farmer/Trader	13 (24.5)	31 (29.2)	
Health Employee	1 (1.9)	0 (0)	
Unhealth Employee	16 (30.2)	34 (32.1)	
Residence.n (%)			
City	15 (28.30)	32 (30.2)	0.81
Village	38 (71.70)	74 (69.8)	

ages 45-64 y.o[5].

The number of male patients with MDR-TB was more than women even though it is not related to the incidence of MDR-TB. The same results were found in patients with MDR-TB in Europe. MDR-TB was more likely in men even though male sex was not a risk factor for MDR-TB[6]. In a study in Ethiopia, male was a risk factor for MDR-TB, while the same study in Nigeria showed the same results and found most treatment failures occurred in men. This is hypothesized because women are more disciplined and regularly take medicine[7].

Low education is significantly associated with the incidence of MDR-TB. This result is the same as research conducted in Bangladesh[8]. Several results from other studies that analyze risk factors for MDR-TB are consistent with these results.

In this study, the income below the UMP was associated with the incidence of MDR-TB. Some studies also showed that family opinion is low and the absence of health insurance is associated with MDR-TB. Patients with low income may have limited access to health services and health costs[9]. In this study the work was not related to the incidence of MDR-TB. Gomes' research et al. showed the same results. Patients with low social status/income or low education were not significantly associated with the incidence of MDR-TB[10].

Drug disobedience in this study was a risk factor associated with the incidence of MDR-TB. In a meta-analysis, the poor adherence to medication is a risk factor for MDR-TB in China[11]. Giving inadequate TB therapy will cause resistant mutants. This is what causes resistance to first-line OAT. Factors that cause inadequate TB therapy include long-term treatment of more than 6 months so that patients get bored, side effects of drugs so that treatment is not finished, provided the wrong medicine, improper dosage of drugs and/or procurement of medicines was cut off[12].

Smoking was not a significant risk factor for MDR-TB in this study. Different results from other studies have shown a significant relationship between smoking and MDR-TB[8]. The number of patients with MDR-TB who have a history of smoking in this study is large, which is 59%. These results are similar to studies conducted in Georgia that found there were more cases of patients with MDR-TB who were smokers. Patients with MDR-TB who are smokers and properly treated for MDR-TB have an outcome risk 3 times worse than non-smokers[13].

Table 2. The Results of Bivariate Analysis of Risk Factors with Diagnosed MDR-TB

Risk Factor	TB-MDR n (%)	TB-non-MDR n (%)	*P*	OR	CI 95%
Education					
≤ JHS	29 (54.7)	40 (37.7)	0.04	1.99	1.02-3.89*
≥ SHS	24 (45.3)	66 (62.3)			
Income					
< Provincial Minimum Wage/UMP	36 (67.9)	51 (48.1)	0.02	2.28	114-4.55*
≥ Provincial Minimum Wage/UMP	17 (32.1)	55 (51.9)			
BMI					
Thin	26 (49.1)	58 (54.7)	0.50	079	0.41-1.54
≥ Normal	27 (50.9)	48 (45.3)			
Obedience in Taking Medicine					
Disobedient	10 (18.9)	1 (0.9)	0.00	24.41	303-196.64*
Obedient	43 (81.1)	105 (99.1)			
Distance of Home to Health Facilities					
< 3 km	17 (32.1)	27 (25.5)	0.38	1.38	0.67-2.84
≥ 3 km	36 (67.9)	79 (74.5)			
Smoking					
Yes	29 (54.7)	46 (43.4)	0.18	1.57	0.81-3.06
No	24 (45.3)	60 (56.6)			
Drinking Alcohol					
Yes	9 (17.0)	2 (1.9)	0.00	10.63	2.20-51.24*
No	44 (83.0)	104 (98.1)			
Comorbidities					
Yes	21 (39.6)	12 (11.3)	0.00	5.14	2.27-11.61*
No	32 (60.4)	49 (88.7)			
DM Disease					
Yes	8 (15.1)	7 (6.6)	0.08	2.51	0.859-7.358
No	45 (84.9)	99 (93.4)			
TB Treatment History					
Never	36 (67.9)	5 (4.7)	0.00	42.77	14.71-124.37*
Ever	17 (32.1)	101 (95.3)			
BCG Vaccination History					
Never	25 (47.2)	53 (50.0)	0.74	0.89	0.46-1.73
Ever	28 (52.8)	53 (50.0)			
Surrounding TB					
Yes	25 (47.2)	17 (16.0)	0.00	4.67	2.21-9.88*
No	28 (52.8)	89 (84.0)			

* Statistically significant.

Table 3. The Results of Multivariate Logistic Regression Analysis of Risk Factors for MDR-TB

Variable	*P*	OR	95%CI
Education	0.49	1.43	0.51-3.96
Income	0.13	2.26	0.79-6.4
Obedience in Taking Medicine	0.45	2.96	0.18-48.35
Drinking Alcohol	0.29	3.26	0.38-28.25
Comorbidities	0.13	3.53	0.69-18.10
DM Disease	0.74	1.43	0.18-11.66
TB Treatment History	0.00	31.82	9.40-107.77*
Surrounding TB	0.01	4.45	1.43-13.71*

* Statistically meaningful

The consumption of alcohol in this study was not a significant risk factor with the incidence of MDR-TB. Other studies provide different results, indicating alcohol as a risk factor for MDR-TB[14].

Diabetes mellitus (DM) in this study was not significantly associated with the incidence of MDR-TB. The same results were shown in a study in Malaysia where DM was not significantly associated as a risk factor for MDR-TB[15]. The results of this study are different from other studies which mention DM as an independent risk factor associated with the incidence of MDR-TB[10].

Previous history of suffering from TB was statistically significantly related to the incidence of MDR-TB. Some studies have shown similar results, indicating previous TB history or previous history of TB treatment are risk factors for MDR-TB. Although MDR-TB can be transmitted among individuals (primary resistance), most cases occur after inadequate therapy which causes drug resistant strains to become dominant. Some studies found that resistance tends not to occur if TB treatment is done with the DOTS program[10]. The WHO and International Union Against Tuberculosis and Lung Disease (IUATLD) have conducted surveillance for OAT resistance, and reported that the prevalence of occurrence in primary MDR is only 1.4%

while it is 13% in patients with treatment. The prevalence is 10 times higher in cases of resistance of patients who have received prior treatment[3].

The risk of drug resistance is increased in cases with a history of treatment. Accordingly, the frequency of MDR-TB increases in the risk group of patients with TB, namely chronic TB patients, TB treatment failure, TB relapse, and TB patients with a history of dropout / default. In addition to the group of patients with a history of treatment, resistance was also suspected in patients with TB who were not converted after initial/intensive treatment. and TB patients who had close contact with patients with MDR-TB. As a result, it is important in practice to identify whether there is a history of previous treatment and monitor treatment response to identify the presence or absence of conversion after initial/intensive treatment or after insertion[16].

The BCG vaccine history was not significantly associated with the incidence of MDR-TB. Some studies provide the same results, indicating the BCG scale is not related to the incidence of MDR-TB[8]. BCG is effective in preventing miliary TB, severe pulmonary TB, and TB meningitis in children, but not for pulmonary TB in adults, especially in developing countries. This is due to the protective effect of the BCG vaccine given when the baby survives up to 10 years, but it is not known whether there is still a protective effect after this period[17].

In this study a history of contact with TB patients was significantly associated with the incidence of MDR-TB. This study found the same results of several studies indicating contact history with MDR-TB patients as a risk factor that is significantly associated with the incidence of MDR-TB. The relationship of contact history with patients with MDR-TB and MDR-TB strains was caused by patients who developed primary resistant to drugs[18]. Other studies have identified significant differences in the history of close contact in the MDR-TB group and while the history in the non-MDR TB group was not significantly different[19,20].

CONCLUSIONS

A history of previous TB treatment and the presence of surrounding TB patients are risk factors that are significantly associated with the incidence of MDR-TB.

Suggestions

Suggestions in this study are (1) Carrying out the slogan "Find Obedience to Heal" in all patients with TB to prevent transmission and resistance to OAT by increasing the discovery of TB patients with active selective case finding in the community by activating the role of health cadres; (2) Perform early detection of TB suspects by conducting microscopic examination of sputum in patients with cough for more than 2 weeks; (3) Tighter monitoring of TB treatment by optimizing the role of the Drugs Supervisor, especially in TB patients with DM and HIV/AIDS; (4) Increasing Public Private Mix (PPM) starting with Hospital DOTS Linkage (HDL) activities involving hospitals. Based on consideration of the great potential in TB control programs, the aim of the PPM is to improve the quality of treatment for patients with TB in preventing MDR-TB cases, increasing access and even distribution of TB services, and reducing the cost burden for TB patients in Indonesia.

REFERENCES

1. Directorate General of Disease Control and Environmental Health. National Guidelines for Controlling Tuberculosis. Jakarta: Ministry of Health Republic of Indonesia; 2014.
2. Disease Control Section. Report on Disease Control Section. Yogyakarta: Yogyakarta Health Office; 2014.
3. World Health Organization. WHO Teatment Guidelines for Drug-Resistant Tuberculosis. 2016 October. Available from: https://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf.
4. Espinal MA, Laserson K, Camacho M, Fusheng Z, Kim SJ, Tlali E, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. The International Journal of Tuberculosis and Lung Disease. 2001;5(10):887-93.
5. Herlina L. Tuberculosis and risk factors for the incidence of multidrug resistant tuberculosis (mdr tb/multi-drug resistance). Bandung: Padjadjaran University; 2007.
6. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax. 2006;61(2):158-63.
7. Hirpa S, Medhin G, Girma B, Melese M, Mekonen A, Suarez P, et al. Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study. BMC Public Health. 2013;13(1):782.
8. Barman N, Ghosh D, Rahman MQ, Uddin MN, Ahmed S, Paul D, et al. Assessment of risk factors of multidrug resistant tuberculosis with emphasis on serum zinc. Bangladesh Medical Journal. 2014;43(1):3-8.
9. Chen S, Huai P, Wang X, Zhong J, Wang X, Wang K, et al. Risk factors for multidrug resistance among previously treated patients with tuberculosis in eastern China: a case–control study. International Journal of Infectious Diseases. 2013;17(12):e1116-20.
10. Gomes M, Correia A, Mendonça D, Duarte R. Risk factors for drug-resistant tuberculosis. Journal of Tuberculosis Research. 2014;2(03):111.
11. Zhao Y, Xu S, Wang L, Chin DP, Wang S, Jiang G, et al. National survey of drug-resistant tuberculosis in China. New England Journal of Medicine. 2012;366(23):2161-70.
12. Soepandi PZ. Diagnosis and factors that influence the occurrence of MDR-TB. Indonesian Tuberculosis Journal. 2010;7(2):16-9.
13. Gegia M, Magee MJ, Kempker RR, Kalandadze I, Chakhaia T, Golub JE, et al. Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. Bulletin of the World Health Organization. 2015;93:390-9.
14. Kendall EA, Theron D, Franke MF, Van Helden P, Victor TC, Murray MB, et al. Alcohol, hospital discharge, and socioeconomic risk factors for default from multidrug resistant tuberculosis treatment in rural South Africa: a retrospective cohort study. PLoS One. 2013;8(12):e83480.
15. Elmi OS, Hasan H, Abdullah S, Jeab MZ, Alwi ZB, Naing NN. Multidrug-resistant tuberculosis and risk factors associated with its development: a retrospective study. The Journal of Infection in Developing Countries. 2015;9(10):1076-85.
16. Sutoyo DK. Multi-drug resistance (MDR) in tuberculosis. J Respir Indones. 2010;30(2):72-74.
17. Rosandali F, Aziz R, Suharti N. Relationship between BCG vaccine scar formation and the incidence of tuberculosis infection. Andalas Health Journal. 2016;5(2).
18. Mulu W, Mekkonnen D, Yimer M, Admassu A, Abera B. Risk factors for multidrug resistant tuberculosis patients in Amhara National Regional State. African Health Sciences. 2015;15(2):368-77.
19. Liew SM, Khoo EM, Ho BK, Lee YK, Mimi O, Fazlina MY, et al. Tuberculosis in Malaysia: predictors of treatment outcomes in a national registry. The International Journal of Tuberculosis and Lung Disease. 2015;19(7):764-71.
20. Workicho A, Kassahun W, Alemseged F. Risk factors for multidrug-resistant tuberculosis among tuberculosis patients: a case-control study. Infection and Drug Resistance. 2017;10:91.