Index Predictive of Drug Resistant Tuberculosis (MDR-TB) on Tuberculosis Patients

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Abstract: The resistance of the M. Tuberculosis germ to anti-tuberculosis drugs is a state in which germs can no longer be killed by first-line medicine, such as isoniazid and rifampicin. Indonesia is in 8th place out of 27 countries that have a high burden of MDR-TB. Gresik district is not among the top 10 districts in East Java, which have the highest TB incidence, but Gresik was a district with the highest proportion of MDR-TB cases among TB cases in East Java in 2015. Purpose of this research is to developed index to predictive risk factor of MDR – TB on Tuberculosis Patients. The research design of this study is case control. The sampling technique is simple random sampling. Based on the analysis using multiple logistic regression, the index of incidence of MDR-TB obtained as Drugs Swallowing Control p= 0.002, regularity p= 0.000, side effects of drugs p= 0.001, the result of previous treatment p= 0.000 and DM p= 0.001. This prediction index can predict the risk of MDR-TB occurring in Gresik with 90.2% sensitivity and 78.9% specificity with measurement accuracy is 84.1%. It can be concluded that the index of incidence of MDR-TB is 4.359 + 2.137 (Drugs Swallowing Control) + 2.885 (regularity) + 2.094 (drug side effects) + 1.926 (previous treatment) + 2.013 (diabetes mellitus).

1 INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. Tuberculosis bacteria commonly affects the lungs, but can also attack other body parts such as the kidneys, bones, and brain (CDC, 2016). Although tuberculosis is a treatable and curable disease, it is the second leading cause of death from infectious diseases in the world (Dyer, 2010). Germs that cause tuberculosis may become resistant to anti-tuberculosis drugs. The resistance of *M. tuberculosis* to the anti-tuberculosis drug (TB-MDR) is a condition when it can no longer be killed by first-line medicine, isoniazid and rifampicin. TB-MDR faced new challenges in TB control programs due to difficult diagnosis, high rates of treatment failure and mortality (Ministry of Health RI, 2011).

Since the Global Anti-TB Resistant Drug Surveillance project in 1994, MDR-TB data has been systematically collected and analyzed in 144 countries worldwide (74% of 194 WHO member countries). At the global level, the proportion of new cases with MDR-TB by 2013 is 3.5%, and this has not changed from the previous few years. MDR-TB cases are estimated to be 3.5% coming from new cases and 20.5% coming from previously treated TB patients. More than half of the world's MDR-TB cases are in India, China and Russia (WHO, 2014).

Indonesia is 8th out of 27 countries in the world with a high amenability of MDR-TB. The MDR-TB amenability in these 27 countries is 85% of the global MDR-TB amenability. In 2013, WHO estimates that, in Indonesia, 6,800 new cases of MDR-TB happen every year. An estimated 2% of new TB cases and 12% of TB re-treatment cases and over 55% of MDR-TB patients have not been diagnosed or treated properly (Riskesdas, 2010). Indonesia always has MDR-TB cases every year. In 2010, there was an increase in MDR-TB cases in East Java. MDR-TB cases in East Java are mostly new cases (84%), while the remaining (16%) is TB re-treatment cases. By contrast, data from surveys conducted in Surabaya showed that MDR-TB patients comes from a group of patients that failed re-treatment using category-2 (31.4%), relapse patients, either category 1 or 2-drug treatment (23.2%), patients that failed treatment category-1 (13.2%), and 9.8% of patients were treated outside the facility that apply the DOTS strategy (Ministry

of Health RI, 2014). MDR-TB cases in Gresik have increased from 2014 to 2015. In 2014, the proportion of MDR-TB cases among TB patients was 8 MDR-TB patients in every 100 cases of TB, whereas in 2015, Gresik is the highest proportion of MDR-TB in East Java, where there were 10 MDR-TB patients in every 100 TB cases in Gresik.

The causes of germ resistance are the inadequate TB treatment and late diagnosis, and these will cause the spread of drug resistance strains for longer. Short-term MDR-TB medicine therapy with *monotherapy* will also lead to more resistant medicine (Ministry of Health RI, 2011). MDR-TB continues to emerge and the spread is due to the errors in the implementation of TB treatment and person-to-person transmission. TB patients should acquire regular treatment for six months with support and supervision. Incorrect use of medicine or bad drug effectiveness (such as single drug use, bad quality drugs or bad drug storage conditions) and early treatment discontinuation may lead to drug resistance, which can be transmitted, especially in densely populated areas (WHO, 2015).

2 METHOD

2.1 Research Method

The design of this research is case-control.

2.2 Sample

The case population in this research is all recorded patients of MDR-TB who lived in Gresik in 2015, which is 80 people. The control population in this research are all TB patients who had completed treatment and were stated as non-TB-MDR in Gresik in 2015, which is 120 people.

2.3 Sample Size

From the calculation of the formula, the size of the samples obtained are 40. Because this research uses case-control research design, then the comparison of cases with the control is 1:1, so that the minimum sample size to be studied is 80 respondents.

2.4 Sampling Technique

The sampling technique used a Probability Sampling Technique by Simple Random Sampling.

2.5 Matching

Matching is used in this research in the health facility. Thus, the control group was taken on the basis of the similarity in which TB treatment was received before the patient was diagnosed with MDR-TB. That sampling method can improve the efficiency of assessing the effect of the disease. The TB treatment was implemented in a local health center. Using the matching of a health center in this research can reduce the bias of the research variable.

2.6 Analysis

The analysis of influence between independent variables to dependent variables uses bivariate and multivariate analysis. Bivariate analysis takes the *Chi Square* test. Multivariate analysis takes multiple logistic regression to predict the value of a dependent variable through independent variables (Sugiyono, 2012). Multiple logistic regression test can figure out the value of OR and the best index (fit) to make the approximate value of a dependent variable or response variable through an independent variable or a predictor variable. The analysis uses the Receiver Operating Characteristic (ROC) curve to test the performance (sensitivity and specificity) of the indexes produced in this research (Dahlan, 2014). The coefficient of Cohen's kappa aims to measure the level of agreement between the evaluation results of two measuring instruments when the measuring instrument is used for the same subject (Yamin and Kurniawan, 2014). In this study, the coefficient of Cohen's kappa was used to measure the level of agreement between the occurrence indexes of MDR-TB with gold standard, the X-pert gene that is commonly used in determining TB status in TB patients.

3 RESULT

Results of the Bivariate Analysis of Research Variables Affecting MDR-TB occurrence in Gresik, East Java:

The bivariate analysis in this research was used to select variables that are eligible for multivariate analysis.

Table 1: Results of bivariate variables analyzed in research of occurrence Index of Drug Resistant Tuberculosis (MDR-TB) in patients with tuberculosis in Gresik, 2015.

No	Variable	p – Value	Conclusion
Respondent Characteristic			
1.	Age	0.377	Not a multivariate analysis candidate
2.	Sex	0.377	Not a multivariate analysis candidate
3.	Level of Education	0.179	Candidates multivariate analysis
4.	Occupation	0.641	Not a multivariate analysis candidate
5.	Income	0.026	Candidates multivariate analysis
	Treatment History		
6.	Regularity	0.000	Candidates multivariate analysis
7.	Drug's side effect	0.001	Candidates multivariate analysis
8.	Previous treatment result	0.000	Candidates multivariate analysis
Comorbidities			
9.	DM	0.001	Candidates multivariate analysis
10.	HIV	0.314	Not a multivariate analysis candidate
Drugs swallowing control Existence			
11.	Drugs swallowing control	0.002	Candidates multivariate analysis
Health Service Access			
12.	Travel time	0.027	Candidates multivariate analysis
Healthy Behaviour			
13.	Smoking	0.067	Candidates multivariate analysis
14.	Alcohol	0.500	Not a multivariate analysis candidate
15.	BCG history	0.370	Not a multivariate analysis candidate
Contact History			
16.	Contact history	0.658	Not a multivariate analysis candidate

From Table 1, it can be seen that there are nine variables that are eligible to be candidates for multivariate analysis and 12 variables are not eligible for multivariate analysis because $p<0.25$. There are five variables which are the model of MDR-TB occurrence index in Gresik 2015.

Table 2: Distribution of variables into occurrence modeling of MDR-TB in Gresik year 2015.

No	Variable	p Value	OR	CI95%
1	Drugs swallowing control a. Presence (reference) b. Absent	0.009	8,470	1,704 – 42,096
2	Regularity a. Regular (reference) b. Irregular	0.000	17.905	3,704 – 86,553
3	Drug's side effects a. Exist(reference) b. Absent	0.015	8.115	1,503 – 43,822
4	Previous treatment result a. Recovered, full treatment (reference) b. Unrecovered, drop out	0.014	6.860	1,480 – 31,790
5	DM a. Not exist (reference) b. Exist	0.016	7.486	1,465 – 38,253

4 DISCUSSION

Based on the findings in the field, the variables cannot be analyzed because the results of the data collection of these variables are homogeneous. Cured TB patients and TB patients who become MDR-TB have similar characteristics, including unhealthy habits (e.g. drinking alcohol and BCG history) and the healthy home criteria result is homogeneous.

The existence of drugs swallowing control is one of the factors of MDR-TB occurrence. Patients with

TB who do not have Drugs Swallowing Control are 4,626 times more likely to become MDR-TB compared with TB patients who have Drugs Swallowing Control. The same results were also generated from a study conducted by Wulandari (2013), in that there is a relationship between Drugs Swallowing Control and MDR-TB incidence. Patients with TB who do not have Drugs Swallowing Control are 19 times more likely to become MDR-TB than those without Drugs Swallowing Control.

Irregular medicine consumptions by TB patients have 13,886 times more chance of experiencing MDR-TB compared with those who regularly consume medicine. In interviews conducted with MDR-TB patients, the irregularity or non-compliance of respondents in medicine consumption is caused by respondents often forgetting to take the medicine. This is similar to a study conducted by Barrosso et al. (2003), which states that irregular consumption of TB medicine has a risk which is 5.14 times greater than the regular consumptions on TB medicine of becoming MDR-TB.

TB patients who experienced side-effects from the medicine have 5,624 times greater risk of becoming MDR-TB than people with TB who experience no side effects from the medicine. This is in line with research conducted by Andrianti (2013) by conducting a literature study which states that the side effects of medicine are risk factors for MDR-TB.

People with TB who also have a history of diabetes mellitus have 5.635 times greater risk to be MDR-TB than people with TB who have no history of diabetes mellitus. This is in line with research conducted by Sembiring (2008) which stated that the occurrence of MDR-TB in patients with TB with diabetes mellitus is 11.3 times greater than patients with TB without diabetes mellitus.

TB patients who failed in TB treatment had a risk of 8.235 times greater than those with TB who complete TB treatment. This is in line with research conducted by Mulissa (2015), which states that failure of previous TB treatment was associated with the incidence of MDR-TB. TB patients who failed TB treatment have 3.5 times greater risk than those who complete TB treatment.

On the results of multivariate analysis using multiple logistic regression, the most influential factors on MDR-TB occurrence in Gresik are:

- the availability factor of Drugs Swallowing Control;
- regularity in consuming medicine;
- side effects of medicine;
- previous TB treatment;
- accompanying diseases such as diabetes mellitus.

These five factors are indicators in the preparation of MDR-TB occurrence index. The MDR-TB occurrence index formula is:

$$\text{Index} = -4{,}359 + 2{,}137(\text{drugs swallowing control}^{(\text{absent})}) + 2{,}885\ (\text{regularity}^{(\text{irregular})}) + 2{,}094\ (\text{drug's side effects}^{(\text{positive})}) + 2{,}013\ (\text{diabetes mellitus}^{(\text{exist})} + 1{,}926\ (\text{previous treatment result}^{(\text{unrecovered}/\textit{drop out})})$$

This prediction index can predict the risk of MDR-TB occurrence in Gresik with 90.2% sensitivity and 78.9% specificity with a measurement accuracy of 84.1%. Based on that, the MDR-TB risk management that can be done is to identify the most-at-risk variables to TB patients. The findings in this research can be applied to the MDR-TB prevention program by intervention socialization of the most influential factors on the occurrence of MDR-TB. The application of an MDR-TB occurrence index can be used by officers both at health service level and health department by using the MDR-TB occurrence index algorithm. The index is expected to prevent TB patients becoming MDR-TB, thereby the incidence of MDR-TB decreases.

Implementation of the results of this research uses the MDR-TB occurrence index algorithm that can be used by everyone, i.e. both community and health workers. To predict whether a person with TB has a high or low risk of becoming MDR-TB, the user of this algorithm is required to follow the flow of the scheme, starting from aspects of Drugs Swallowing Control availability, regularity of medicine-taking, side effects of medicine, previous and last TB treatment, and the presence of diabetes mellitus.

4.1 Sample Case

If there is a TB patient with no drugs swallowing control, who is receiving treatment regularly, experiencing disruptive side effects when taking medicine, has a history of diabetes mellitus and has previous TB treatment outcomes which have failed or dropped out, then the TB patient has a high risk of experiencing MDR-TB.

5 CONCLUSION

Based on the results of the analysis, the occurrence indicators of MDR-TB are:

- Drugs Swallowing Control;
- regularity;
- drug side effects;
- previous treatment results;
- diabetes mellitus.

The index for the occurrence of MDR-TB is: Index = -4,359 + 2,137 (drugs swallowing control (^{none})) + 2,885 (regularity (^{irregular})) + 2.094 (side effects of drugs (^{positive})) + 2.013 (diabetes mellitus (^{exist})) + 1,926 (previous treatment result ($^{failed\ /\ drop\ out}$)).

The sensitivity of the index is 90.2% and the specificity is 78% with an accuracy of 84.1%.

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