Determinants of Multidrug-Resistant Tuberculosis among Retreatment Tuberculosis Patients in South Sulawesi Province: A Case-Control Study

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global concern including in Indonesia. The estimated cases of multidrug-resistant tuberculosis in this country were 6,900 cases in which new MDR-TB cases were 1.9% and recurrent MDR-TB cases were 12%. For such a reason, the aim of this study was to identify the determinants of MDR-TB incidence in retreatment tuberculosis patients at the Labuang Baji General Hospital in Makassar Municipality. The research design in this study was a case-control study which located at the Labuang Baji General Hospital as the referral hospital for multidrug-resistant tuberculosis cases. A total number of samples in this study were 160 cases with a 1:1 ratio. Case was MDR TB patients who was confirmed RMP resistant using geneXpert test, and it was then confirmed from culture test and drug sensitivity test (DST) of resistant to both RMP and INH . Control was presumptive MDR TB patient that result of geneXpert test was RMP sensitive. Data were collected by structured interview questionnaire. Multivariate logistic regression analysis was computed to determine the risk factors associated with MDR TB. Results of this study indicated that low level of education (AOR=0.59; 95% CI: 0.38-0.94), low income (AOR=3.97; 95% CI: 1.65-9.51) and health facilities for the non-DOTS group (AOR=3.45; 95% CI: 1.42-8.37) were the risk factors of MDR TB in retreatment tuberculosis patients.

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Conclusion of study is determinants of MDR TB in retreatment tuberculosis patients analyzed in this study significantly indicated high risk level of MDR TB. Consequently, there should be a strengthening effort in formulating and implementing directly observed therapy (DOTS) policy plans at health facilities to improve medication compliance among patiens in achieving exhaustively tuberculosis treatment and focusing medical treatment by giving priority to the accessibility of geneXpert test, culture test dan drug sensitivity test (DST) at laboratory facilities.

Key words: tuberculosis; MDR TB; retreatment tuberculosis patients; DOTS.

1. Introduction

Drug-resistant TB poses a major threat to the control of TB worldwide. Multidrug-resistant tuberculosis is a form of drug resistant TB to at least both isoniazid and rifampicin [1,2]. At global scope, new MDR-TB cases were estimated at 3.3% (95% CI: 2.2– 4.4%) and recurrent MDR-TB cases were 20% (95%CI:14–27%) in 2014 [3]. Multidrug-resistant tuberculosis is indeed a new challenge in medical treatment on how to formulate and implement adequate health care programs to control tuberculosis due to the difficulty of diagnostic assertion, high frequency of theraupetic failure and mortality. The estimated cases of multidrug-resistant tuberculosis in Indonesia for the year 2004 were 8,900 cases [4]. Higher prevalence of multidrug-resistant tuberculosis cases are mostly takes place in patients with previously diagnosed multidrug-resistant tuberculosis. A total number of multidrug-resistant tuberculosis cases in South Sulawesi for the year 2014 were 87 cases. The rate of MDR-TB cases in this province shows an ascending trend from year to year in which multidrug-resistant tuberculosis cases achieve 46 patients in 2012 and 83 patients in 2013 [5, 6]. Patients with previously diagnosed multidrug-resistant tuberculosis have four times more likely resistant to a variety of drugs and a ten-fold risk having multidrug-resistant tuberculosis than those with newly diagnosed multidrug-resistant tuberculosis. Although patients with newly diagnosed multidrug-resistant tuberculosis have lower risk to multidrug-resistant tuberculosis than those with previously diagnosed multidrug-resistant tuberculosis, prevalence of patients with newly diagnosed multidrug-resistant tuberculosis are higher than those with previously diagnosed multidrug-resistant tuberculosis [2,7]. Patients who experience a prior treatment history are the foremost risk factor to multidrug-resistant tuberculosis [8, 9]. In developing countries, its main determinants that relate to irregular use of medication and lost to follow up in tuberculosis patients are socioeconomic factors, behavioral factors, lack of health service officers and HIV status [10,11,12]. Socioeconomic factors consist of age, gender, nutritious food intake, poor transportation, lack of social support and status of employment, whereas, behavioral factors comprising negative stigma, uncomfortable feelings after having treatment in the duration of several weeks, smoking habits and alcoholism. Besides these two primary determinants, communication gap between patients and health officers, poor accessibility to reach primary health care facilities and side effects of treatment in TB HIV patients relate also with irregular use of medication and lost to follow up [13,14,15]. In the current time, prevalence of multidrug-resistant tuberculosis cases shows an increasing rate and it is mostly affected by inadequate tuberculosis treatment either in terms of the implementation of regime standard or the use of its doses. This reality becomes a medical challenge in giving health services due to low medication compliance of patients and an ascending rate in the implementation of inadequate standard of tuberculosis drugs. In addition, other problems are unevenly coverage of health facilities and lack of instruments used to test multidrug-resistant

Mycobacterium tuberculosis strains and disobedience of patients to adhere tuberculosis treatment. Such conditions provide for primarily potential transmission of tuberculosis to healthy individuals in a short period of time. Regarding to such reasons, this study aims to identify the determinants of multidrug-resistant tuberculosis among retreatment tuberculosis patients in South Sulawesi Province.

2. Methods of the Study

2.1   Research design

A case-control study was used in this study as one of the types of observational study. The study period was conducted from Agustus 2015 until July 2016 at the Labuang Baji General Hospital as the referral hospital for multidrug-resistant tuberculosis cases.

2.2 Samples of the study

Samples analyzed in this study were retreatment tuberculosis patients as the referral cases to conduct diagnosis of patients that resistant to rifampicin. Case was MDR TB patients who was confirmed rifampicin resistant by geneXpert testing and the strains were resistant to at least isoniazid and rifampicin by drug susceptibility testing. Control was presumptive MDR TB patients that the strains were still sensitive to rifampicin by geneXpert testing. A total number of samples in this study were 160 cases with a 1:1 ratio (80 cases of the case group and 80 cases of the control group). Compilation of samples was conducted using consecutive sampling technique.

2.3 Data collection

Screening multidrug-resistant tuberculosis patients was done using geneXpert instrument at the laboratory of the Labuang Baji General Hospital in Makassar to analyze patients with *Mycobacterium tuberculosis strains resistant to* rifampicin. After patients were confirmed resistant to this drug, the subsequent tests were performed using culture test and drug densitivity test (DST) for both the first-and second-lines of antituberculosis drugs at the Hasanuddin University Medical Research Center (HUMRC). This study was reviewed and approved by the Research Ethics Committee of Hasanuddin University. Collection of data was conducted using structured questionnaire and interview was done among the selected patients.

2.4 Statistical analysis

Data were analyzed and processed using SPSS version 21statistical software. Analysis of bivariate was carried out for categorical variables and odds ratios with 95% CI were used to quantify the level of correlation among variables. The cut-off point for statistical significance was determined at a *p*-value of less than 0.05. Multivariate logistic regression analysis was carried out to determine which independent variables categorized as the predictor of multidrug-resistant tuberculosis.

3. Results

3.1 Sociodemographic characteristic of study participant

A total of 80 cases and an equal number of controls were included in the study. Higher proportion of multidrug-resistant tuberculosis cases was identified in male patients amounted to 56.3%. In view of age, most MDR-TB cases were at a 15-to-54 year scale in the category of productive working age either in the case group (78.8%) or the control group (67.5%). Detail characteristics of the study participants are presented in Table 1.

Table1: Sociodemographic characteristics of MDR TB cases and control in Labuang Baji Hospital, 2016

Variables	Cases (n = 80)	Percentage	Control (n = 80)	Percentage
Sex				
Male	45	56.3	53	66.25
Female	35	43.8	27	33.75
Age category (years)				
15-54	63	78.8	54	67.5
≥ 55	17	21.3	26	32.5
Marital status				
Single	11	13.8	14	17.5
Married	69	86.3	66	82.5
Educational status				
Tidak sekolah	3	3.8	4	5
SD	17	21.3	24	30
SMP	10	12.5	13	16.3
SMU	44	55.0	30	37.5
PT	6	7.5	9	11.3
Continued Table 1.				
Occupation				
Tdk Bekerja/IRT	29	36.25	25	31.25
PNS	3	3.75	11	13.75
Karyawan Swasta	8	10	2	2.5
Wiraswasta	20	25	17	21.25
Pelajar/Mahasiswa	6	7.5	2	2.5
Lainnya	14	17.5	23	28.75
Monthly income				
< Rp2000.000,-	71	88.8	55	68.8
≥ Rp2000.000,-	9	11.3	25	31.3

3.2 Tuberculosis related conditions

Previous tuberculosis related conditions are presented in Table 2. The estimated proportion of patients in the case group who had multidrug-resistant tuberculosis that referred to its classification criteria was highest in the category of recurrent patients amounted to 40 patients (50%) and the lowest proportion was observed in the category of unconverted patients amounted to 4 patients (5%). The proportion of multidrug-resistant tuberculosis for patients with previously diagnosed multidrug-resistant tuberculosis for the non-DOTS group was 30%, whereas, the proportion of patients with newly diagnosed multidrug-resistant tuberculosis was 11.3%. Multidrug-resistant tuberculosis patients who had prior irregular tuberculosis treatment history had highest proportion compared with other remaining groups of patients which amounted to 55% and the proportion of tuberculosis patients who underwent medication in the duration of tuberculosis treatment of less than 6 months amounted to 52.5%. In addition, the number of medication was only one time in patients who previously undertook tuberculosis treatment either in the case group or the control group.

Table 2: Tuberculosis disease related conditions in MDR TB cases and controls in Labuang Baji Hospital, 2016

Variables	Cases (n = 80)	Percentage	Control (n = 80)	Percentage
Ever smoked cigarettes				
Yes	35	43.8	42	52.5
No	45	56.3	38	47.5
Category of TB MDR Suspect				
Treatment failure	17	21.25	15	18.75
No Conversion	4	5	1	1.25
Continued Table 2.				
Non DOTS	10	12.5	2	2.5
Relaps	40	50	42	52.5
Default	9	11.25	20	25
Place of previous TB treatment				
Non DOTS	24	30	9	11.3
DOTS	56	70	71	88.7
History of TB treatment				
Irreguler	44	55	28	35
Reguler	36	45	52	65
Number of previous treatment				
1 time	41	51.2	67	83.8
2 times	25	31.3	11	13.8
> 2 times	14	17.5	2	2.5
Duration of first time TB treatment				
< 6 months	42	52.5	27	33.8
6-8 months	35	43.8	53	66.3
> 8 months	3	3.8	0	0

3.3 Results from logistic regression analysis

Relationship among all observed risk factors were determined in the category of confounding factors, as shown in Table 3, and then the risk factors associated with treatment failure and multidrug-resistant tuberculosis were examined that consisted of level of education (AOR=0.59; 95% CI: 0.38-0.94), low income (AOR=3.97; 95% CI: 1.65-9.51) and the accessibility of health facilities for the non-DOTS group (AOR=3.45; 95% CI: 1.42-8.37).

Results of logistic regression analysis indicated that age, level of education, status of employment, prior tuberculosis treatment history and smoking habits had significant correlation with multidrug-resistant tuberculosis.

Table 3: Determinants of multidrug resistant tuberculosis from logistic regression model

Variables	Case Number	Control Number	COR (95% CI)	AOR (95% CI)	*p-value*
Age category (years)					
15-54	63	54	1.78 (0.88-3.63)	0.70 (0.31-1.59)	0.39
≥ 55	17	26	1	1	
Sex					
Male	45	53	1.53 (0.81-2.89)	0.79 (0.21-2.98)	0.73
Continued Table 3.					
Female	35	27	1	1	
Educational status					
Low	30	41	1.75 (0.93-3.29)	0.59 (0.38-0.94)	0.03
High	50	39	1	1	
Occupation					
No	35	27	0.66 (0.35-1.24)	0.63 (0.19-2.05)	0.44
Yes	45	53	1	1	
Monthly income					
< Rp2000.000,-	71	55	0.27 (0.12-0.65)	3.97 (1.65-9.5)	0.002
≥ Rp2000.000,-	9	25	1	1	
Place of previous TB treatment					
Non DOTS	24	9	0.29 (0.13-0.69)	3.45 (1.42-8.37)	0.006
DOTS	56	71	1	1	
History of TB treatment					
Irreguler	44	28	0.44 (0.23-0.83)	1.80 (0.84-3.87)	0.13
Reguler	36	52	1	1	
Ever smoked cigarettes					
Yes	35	42	1.42 (0.76-2.65)	0.61 (0.20-1.87)	0.39
No	45	38	1	1	

4. Discussion

A case-control study in this study was conducted by collecting data of patients with the similar ratio between the case group and the control group who previously underwent the first-line antituberculosis treatment. A total number of samples were 160 patients and instigates this study to identify determinants of the incidence of multidrug-resistant tuberculosis. The significant determinants related with the incidence of multidrug-resistant tuberculosis were level of education, low income and poor accessibility of health facilities for the non-DOTS group. In addition, variables of the study that consisted of age, gender, status of employment, prior tuberculosis treatment history and smoking habits did not have significant correlation with the incidence of multidrug-resistant tuberculosis. The findings in this study are in line with other studies in several countries [23,24,] in which sociodemographic factors that include age, gender, and marital status did not have significant correlation with the incidence of multidrug-resistant tuberculosis. There were 43.8% female patients who indicated multidrug-resistant tuberculosis and this proportion gives an important direction in formulating and implementing medical treatment at health facilities due to its impact to the pregnancy of females who are in the category of productive working age and those are in the status of nurturing their children.

Results of this study showed that level of education had statistically significant correlation with the incidence of multidrug-resistant tuberculosis (p=0.03) with the value of AOR=0.59 (CI=0.383-0.94). A previous study gave a similar result in which level of education in tuberculosis patients had significant correlation with multidrug-resistant tuberculosis amounted to 76 patients (56.7%) with the value of AOR=3.7[16]. Another study also reported that level of education indicated significant risk factor to the incidence of multidrug-resistant tuberculosis with the value of AOR=1.87 [17].

A study conducted in Ethiopia reported different results in which TB RO patients were mostly occurred in patients who had low level of education with the value of AOR=1.6 (95% CI=0.65-3.68)[18], and it is consistent with the study conducted by Yanni Sun et.al (2015) [19] that the probability of TB RO patients was mostly taken place in patients who had low level of education with the proportion value was 55.9% and it proved the significant correlation between low level of education and mortality in TB RO patients. Tuberculosis patients who are in the category of low level of education have less understanding in gaining health services, especially in fulfilling the need of tuberculosis medication. Results of a health survey of tuberculosis prevalence in 2004 that analyze level of knowledge, attitude and behavior indicated that 96% households has taken care their family members who experienced tuberculosis and 13% households did not report their family members who had tuberculosis. Although 76% households had been previously informed on tuberculosis and 85% of all observed households knew that tuberculosis could be recovered, only 26% households could only at least mention two main symptoms of tuberculosis [20]. A study conducted in India reported individuals with low illiteracy rate/level of education of less than primary school had misunderstanding on the subject of tuberculosis. Another study in India revealed that some physicians who treated tuberculosis patients had insufficient knowledge on the management and procedure of tuberculosis treatment. Another study performed in the United States of America among homeless individuals indicated that more than 60% respondents had misinterpretation on tuberculosis spreading, and a study conducted among the users of NAPZA revealed that they did not entirely know that HIV-TB could be recovered and 70% of them supposed that positive results of skin test meant that they were infected

by tuberculosis germs [21].

Education has significant impact to learning and teaching process. The higher level of education of individuals, the easier they grab important health information. Individuals who have high level of education will tend to absorb useful information either from other individuals or mass media. More knowledge can be obtained from various sources, including the knowledge of health sciences. Lack of information derived from health services leads to higher risk to multidrug-resistant tuberculosis that will in turn prompt disobedience of individuals to compliant medication and lost to follow up.

Level of individual income has high correlation with their quality of life. In view of health aspect, individuals will always fufill their health demand through adequate intake of nutritious food and they tend to seek sufficient access of quality health services. Results of this study proved significant correlation between level of income and MDR TB (p=0.002) with the value of AOR=3.97; 95% CI: 1.65-9.51. According to Mulu.W et.al [18], socioeconomic factor is one of the foremost factors to the incidence of TB RO for the group of patients with low socioeconomic status. This is due to low fulfillment of tuberculosis medication because of poor income level of households and limited access to gain health services that leads to potential spreading of tuberculosis in healthy individuals at a wider scale.

Socioeconomic status affects access of information on the subject of tuberculosis. This condition encourages certain communities decide to select health facilities and gaining qualified medication. Tuberculosis is a common disease in poor communities. A study conducted in India indicated a significant high correlation between income level of individuals and tubeculosis. In a study carried out in a district in this country indicated that individuals who had income with less than US$ 7 per month had two times more likely having tuberculosis compared with individuals with income of more than US$ 20 per month. In developing countries, poor communities have deprived access to gain health services and lead to lag of diagnostic assurance and they are more probably gain inconsistent treatment or irregular tuberculosis medication [21]. According to Yoga T (2005)[22], there are several reasons for the failure of tuberculosis treatment that include poverty level of patients, difficulty to reach primary health facilities due to remote and isolated areas, lack of health officers, expensive price of drugs, and excessively bureaucratic procedures. A study carried out by Tupasi T et.al [26] indicated that 93.4% of all poor individuals defaulted to access tuberculosis medication.

Access for health service cannot only involve on the consideration of the association between individual income and tuberculosis incidence, but should also regard the impact of environment and condition of household of tuberculosis patients. Tuberculosis disease is certainly affected by poor physical layout of a house, such as inadequate room temperature, poor ventilation and lighting, level of moisture, inadequate sanitation as well as household crowding.

Another significant determinant identified in this study was location of tuberculosis treatment where tuberculosis patients were firstly diagnosed in both the DOTS and non-DOTS groups. Results of this study indicated significant correlation between recurrent tuberculosis and multidrug-resistant tuberculosis (p=0.006) with the value of AOR=3.45; 95% CI: 1.42-8.37. Tuberculosis medication for the non-DOTS group was

difficult to monitor vigorously due to poor documentation and tendency of patients to partially discontinue their tuberculosis medication as long as no any adequate education on tuberculosis among tuberculosis patients.

The current challenge in giving health service is most health facilities do not comprehensively involve in tuberculosis control. Based on the provincial data in 2012 in Indonesia, 100% Community Lung Health Centers and 98% of all Community Health Centers have implemented DOTS strategy. However, only 38% of all hospitals (the Government, State-Owned Companies, Indonesian National Armed Forces, Police and Private Companies) implemented DOTS strategy. In private sector, DOTS strategy has not been yet implemented systematically [25]. One of the weaknesses in implementing DOTS strategy at hospitals is low supervision during medication of patients concerning most hospitals do not have health service zones with result that tuberculosis patients decide to discontinue their medication. This situation prompts hospitals settle on this problem by giving health information to public health officers who take health job duties located at residence zones of tuberculosis patients. This situation leads to a great deal of reports that patients decide to discontinue their medication who previously been treated at hospitals.

5. Conclusion

This study delivers importat information on the risk factors of MDR TB among retreatment tuberculosis patients that consist of level of education, level of income and health facilities for the non-DOTS group. These risk factors had significant correlation with multidrug-resistant tuberculosis incidence. Results of this study can be used as the consideration in formulating and implementing medical treatment efforts to the control of multidrug-resistant tuberculosis in South Sulawesi Province. Consequently, there should be a strengthening effort in formulating and implementing directly observed therapy (DOTS) policy plans at health facilities to improve medication adherence of patiens in achieving exhaustively tuberculosis treatment and focusing medical treatment by giving priority to the accessibility of medical treatment using geneXpert test, culture test dan drug sensitivity test (DST).

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Competing Interest

The authors declare that they have no competing interests.

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