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Path Analysis of The Determinants of MDR-TB in Indonesia

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ABSTRACT

Multidrug resistant tuberculosis (MDR-TB) has a tendency to increase as the number of tuberculosis cases (TB) increases with the prevalence of 1.8% of TB cases in Indonesia that currently is second ranks highest of TB cases in the world. This study aimed to determine the knowledge, income, social capital, health belief model, quality care, adherence and history of previous TB treatment factors on MDR-TB. This was an analytic observational study with a case-control design from August to December 2017. A total of 309 study subjects including 81 respondents with MDR-TB (case) and 228 volunteers without MDR-TB (control). MDR-TB data was collected by medical record with moleculer examination confirmation (GenExper). The data were analyzed by path analysis model. The risk of MDR-TB increased with history of previous TB treatment >2 (b=2.58; 95% CI= 1.55 to 3.61; p-value <0.001). The risk of MDR-TB decreased with adherence (b=-4.99; 95% CI= -6.53 to -3.44; p-value <0.001), and high montly income (b=-0.91; 95% CI= -1.72 to 0.09; p-value 0.028). The social capital increased with cues to action >6 (b=6.04; 95% CI= 4.03 to 8.04; p-value <0.001). The cues to action increased with adherence >3 (b=3.34; 95% CI= 1.24 to 5.44; p-value 0.002). The knowledge increased with perceived quality care (b=3.00; 95% CI= 2.38 to 3.61; p-value <0.001). The quality of care perceived increased with adherence >2 (b=2.01; 95% CI= 1.29 to 2.72; p-value <0.001). The self efficacy increased with adherence >1 (b=1.14; 95% CI= 0.35 to 1.93; p-value 0.004).

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1. Introduction

Almost all countries in the worldwide are affected by one of the 10 leading diseases that cause death: tuberculosis (TB) [1]. Prior studies have shown that incidence and death rates in middle-income countries, particularly emerging ones, can attain 90% [2- 4]. Indonesia currently has the second-highest rate of TB cases globally, with a prevalence of 1.8%. MDR-TB is thought to have evolved in 20% of previously

treated TB cases, even though pharmacokinetic research and advances have identified optimal dosages and treatment regimens [3]. In addition, the MDR-TB plus was described as resistant to fluoroquinolone and at least one of kanamycin, capreomycin, and amikacin. MDR-TB was classified as resistance to isoniazid, rifampin, and linchpins [5].

Social determinants, including low education, low income, and alcohol addiction, contributed to the rise in MDR-TB [6- 8]. According to a cross-sectional study on non-adherence to TB treatment conducted in Indonesia, a multitude of variables, such as insufficient and inaccessible TB services, non-standardized case finding and diagnosis, limited and uneven drug availability, failure to conduct continuous monitoring, inaccurate recording and reporting, misconceptions about the advantages and efficacy of BCG vaccination, and poor health infrastructure, can lead to MDR-TB [9]. All explanations for these factors were derived from the study using regression analysis, so they did not distinguish between direct and indirect factors associated with the incidence of MDR-TB.

Various studies employ regression analysis that focuses on the relationship between the dependent and the independent variable, identifying several causes of MDR-TB [10]. Regression analysis, however, has been unable to pinpoint and clarify direct and indirect influences on the impact variable. To obtain a thorough understanding of the relationship between variables, the path analysis method helps address, clarify, and differentiate between three different types of influences: direct, indirect, and total effects [11].

Forming decisions concerning MDR-TB control programs in Indonesia would probably be built more straightforward with the identification of factors that are both, directly and indirectly, related to MDR-TB, as well as the relationship between health belief models and their application.

2. METHODS

2.1 Research Area

This study was in part of Indonesia, Central Java which is located in the middle in Java Island. The area is 32,800.69 km^2 and 33,753,023 populations approximately lived. The cases was collected from a referral hospital for MDR-TB, and the control of tuberculosis smear positive was obtained from Surakarta city, Sukoharjo district, Wonogiri district, Boyolali district, and Kudus district. This reserach was conducted from August 2017-February 2018.

2.2 Study design

This study id quantitative study using observational analytic design with case control approach. The number of study subjects was 309 subjects. The number of study subjects for MDR-TB was 81 subjects, while the number of TB patients was 228 subjects with random sampling techniques.

Endogenous variables included medication adherence, implementation of DOTS treatment, MDR-TB. Exogenous variables included perceptions of vulnerability, perceptions of seriousness, perceptions of benefits, perceptions of barriers, availability of OAT and nutritional status. Drug compliance was the patient's willingness to obey the rules of medical treatment routine and complete. The perception of vulnerability was a positive or negative assesment of the risk experiencing MDR-TB. The perception of seriousness was the individual's subjective perception of how severe the physical and social consquences of the illness were. Perceiving benefits was the patient's perceived belief in the benefits of treatment to reduce the risk of MDR-TB. Perception of barriers was a belief that was a constraint or hindrance of patients to undergo treatment. The implementation of DOTS treatment was a strategy implemented basic health

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services to detect and cure TB patients. Nutritional status was the assesment of the patient's nutritional status based on antrhopometric assesment. All variable used a dichotomy scale. Data collection techniques used questionnaires. The multivariate analyis used was path analysis in order to estimate the direct and inderect effects among independent variables

2.3 Eligibility criteria and operational definitions

The eligibly criteria for both cases and controls were: The subject had provided signed informed consent to participate in the study and the subject was able to speak and understand Bahasa, could provide reliable information, and was both well enough and sufficienttly intact cognitively to respond to the interview questions. This criterion was determined by the trained interviewed.

Cases

The following additional eligibly criteria were used to define an individual as a MDR-TB cases:

1. Indonesian citizen
2. Confirmed with moleculer test (geneExpert) and culture examination
3. Intensive phase of MDR-TB treatment
4. Registered in Moewardi Hospital
5. They are ≥18 years old

Control

The following additional eligibly criteria were used to define an individual as a MDR-TB controls:

1. Indonesian citizen
2. Confirmed with not resistant of rifampicin and isoniazid
3. Intensive phase of TB treatment.
4. Registered in PUSKESMAS
5. They are ≥18 years old

Ethical clearence

First, this study was aprroved by the Khon Kaen University Ethics Committe for Human Research on Declaration of Helsinki, Reference No. HE.602085. Second, this research was approved by Health Research Ethics Committe A Hospital of Dr. Moewardi Surakarta and School of Medicine Sebelas Maret University Surakarta, Reference No 487/ VI/ HREC/ 2017. Informed consent will be conducted from all participants, and then all information belonging to the respondent will be kept confidential. The results will be used only for the purpose as stated in the study. No information will be published which will be break the autonomy of the respondents

3. RESULTS

3.1 Baseline characteristic

Table 1. Baseline characteristics

Variable Name	Cases		Control	
	n=81	%	n=228	%
Residence				
Rural	67	82.7	195	85.5
Urban	14	17.3	33	14.5
BMI				
Underweight (<19.00)	53	69.7	101	47.4
Normal range (19.00-22.99)	23	30.2	93	43.6
Overweight and obesity (>=23.00)	0	0	19	8.9

<=19	53	65.4	101	44.3
>19	28	34.4	127	55.7
Mean height ± SD	19.4±3.3			
Median (min:max)	19(11.9:33.3)			
Gender				
Male	52	64.2	130	57.0
Female	29	35.8	98	43.0
Marital status				
Single	15	18.5	35	15.4
Married	66	81.5	157	84.6
Educational status				
Primary school and below	27	33.3	125	54.8
Junior high school	26	32.1	32	14.1
Senior high school and above	28	34.6	71	31.1
Occupation				
Unemployed	32	39.5	79	34.6
Own business	31	38.2	86	37.7
Employee	18	22.2	63	27.6
Monthly income				
Low <$USD 100	70	86.4	165	72.4
High ≥$USD 100	11	13.6	63	27.6
Low (<district min salary)	48	59.3	72	31.6
High (≥district min salary)	33	40.7	156	68.4
Mean Income ± SD ($USD)	73.3±89.0			
Median (min:max) ($USD)	37.0(3.7:777)			
Smoking				
No	59	72.8	189	82.8
Yes	22	27.2	39	17.2
Alcohol use				
Never	67	82.7	199	87.3
Ever	14	17.2	29	12.7
Comorbidities				
No	40	49.4	169	67.1
Yes	41	50.62	59	32.9
Lenght of TB treatment (month)				
<5	57	29.6	82	64.0
>=5	24	70.4	146	36.0
Mean ± SD	6.0±5.0			
Median (min:max)	5(1:25)			

3.2 Multivariate analysis in path analysis

Results of data processing using path analysis with the help of STATA obtained the following results:

1. Model spesification

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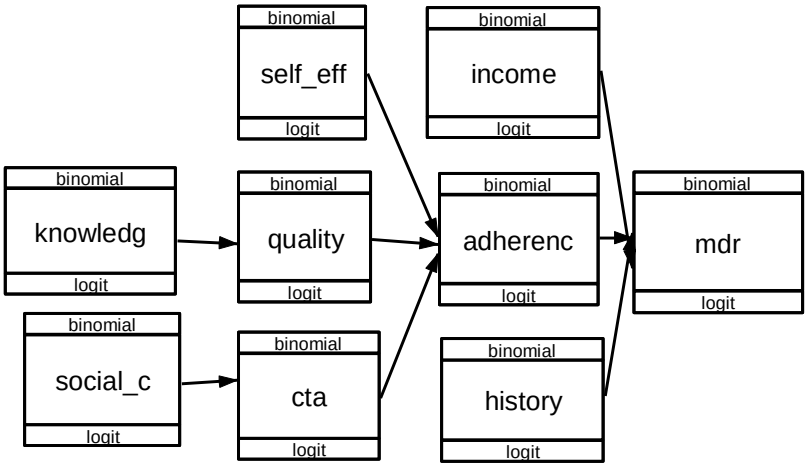

Figure. 4.1. Model specification of path analysis

This figure shows the relationship value each variable signifying the exogen and endogen variables. The variables included in the model were knowledge, social capital, self-efficacy, perceived quality of care, cues to action, income, treatment adherence, history of TB treatment and multi-drug resistance tuberculosis.

2. Model identification

This stage will be done the identification of the number of variables measured, the number of endogenous variables, exogenous variables, and parameters to be estimated. At this stage the degree of freedom (df) is calculated which shows the path analysis can be done or not as below:

Number of measurable variables: 9

Endogenous variables: 4

Exogenous variables: 5

Number of parameters: 9

Formulas degree of freedom as follows:

df = (number of measured variables x (number of measurable variables + 1) / 2 - (endogenous variable + exogenous variable + number of parameters)

= (9x (9+1)/2 - (4+5+9)

= (90/2) - 18

= 45 - 18 = 27

Path analysis can be done if df ≥ 0, while in model identification in path analysis this time gets value df is 27 and called analysis of path over identified which means path analysis can be done.

3. Confirmatory model and parameter estimation

Path analysis model was made by the researchers based on the theory checked/ tested that refers to the model of the best variable relationships made based on sample data collected researchers.

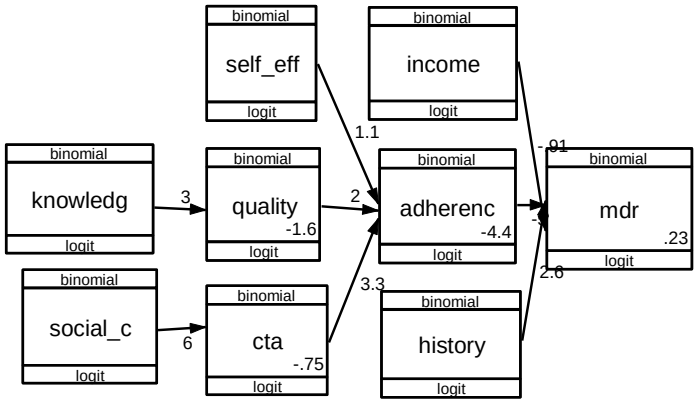

Figure 4.2. Confirmatory model and parameter estimation

Dependent variable		Independent variable	B	95% CI		p-value
				Lower	Upper	
Direct effect						
MDR-TB	←	monlty income	-0.91	-1.72	-0.09	0.028
MDR-TB	←	Adherence	-4.99	-6.53	-3.44	<0.001
MDR-TB	←	History of previous TB treatment	2.58	1.55	3.61	<0.001
Indirect effect						
Adherence	←	Self efficacy	1.14	0.35	1.93	0.004
Adherence	←	Perceived quality of care	2.01	1.29	2.72	<0.001
Adherence	←	Cues to action	3.34	1.24	5.44	0.002
Quality of care	←	Knowledge	3.00	2.38	3.61	<0.001
Cues to action	←	Social capital	6.04	4.03	8.04	<0.001
n observation =		309				
Log Likehood =		-406.81277				

The table above shows that the calculation results using statistical software STATA 13, there was a relationship between the History of previous TB treatment to increase the risk logit of the occurrence of MDR-TB. On the other hand, there were the relationship between High monetary income, Adherence decreases the risk logit for MDR-TB occurrence and the relationship is statistically significant.

4. Model re-specification

The model in this study is in accordance with the sample data used by the saturation model and also the regression coefficient which is worth more than zero and very significant, it is not necessary to recreate the analysis model as the model corresponding to the sample data

4. DISCUSSION

4.1 Relationship between montly income and MDR-TB

TB treatment which takes a long time makes the patient have to spend a lot of money to buy drugs, transportation, treatment costs and other costs which may be a burden to the family if they do not have insurance or guarantees, either private or government. Another study reported that a monthly family income below 100 euros would increase the risk of MDR-TB up to 3.7 times and was statistically significant (OR = 3,71; 95% CI = 1,22-11,28) [12]. This makes governments in various countries pay special attention to TB patients who have a correlation with poverty, poor living conditions, various social causes of vulnerability, lack of access and availability of health services [13].

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Various studies have reported strategies for public health programs that can be implemented to increase the success of TB treatment and deal with patients' financial problems, including: (1) financial incentives or programs to offset treatment costs, (2) improve coordination and logistics regarding the supply and delivery of TB treatment, (3) training for health service providers and providers. Another strategy is to address gaps in knowledge, attitudes and behavior around adherence to TB treatment [14], [15]. Based on the results of the path analysis that we carried out, it was reported that people with relatively high monthly income have the potential to reduce the likelihood of MDR-TB occurring by 0.91 units and this is statistically significant (B = -0.91; 95% CI = -1.72 to -0.09; p-value 0.028).

4.2 Relationship between adherence on TB-drug and MDR-TB

Maintaining patient adherence to medication is a challenge for all health care professionals, given the complexity, simple tolerability, and long duration of currently available treatment regimens. So that adherence is a direct factor that influences MDR-TB and also has various intermediary or indirect factors that significantly affect adherence. Various studies have reported that low adherence increases the risk of adverse outcomes, including treatment failure, relapse, and the development or strengthening of drug resistance [15], [16].

The most commonly used adherence-enhancing efforts include direct observation therapy (DOT) and via video (VOT), in which health workers, family members, or community members observe patients who are undergoing TB treatment. [17], In addition, the reminder system includes: reminder letters, telephone calls, home visits, short message service technology (SMS) and targeted electronic pillboxes to help patients keep appointments and take action when patients miss appointments. Psychological intervention through psychological or emotional counseling or peer social networks as a way to increase adherence to TB treatment [18], [19].

A meta-analysis study has reported that TB treatment outcomes will improve along with the success of comprehensive adherence improvement interventions such as providing health education and counselling, material support, psychology, reminders, trackers, and digital health technology. DOT given by trained health workers will give much better results compared to DOT performed by family members or untrained lay workers. Community-administered DOT provides better treatment outcomes than clinic-based DOT. VOT may be an appropriate alternative if the resources for its use are available [15]. However, it is very important to note that various interventions to improve adherence will be optimal if the assessment is in accordance with the circumstances and needs of the patient or is patient-centered. Thus interventions may vary according to setting, resources, and local TB epidemiology (eg, prevalence of co-morbidities, including HIV co-infection) [15], [20].

4.3 Relationship between history of previous treatment and MDR-TB

The results of this study stated that a history of previous TB treatment could increase the likelihood of MDR-TB 2.59 times. The same result was also reported that patients with a history of previous TB treatment are likely to experience MDR-TB up to 5 times higher than patients without a history of treatment. It is most likely caused by a recent infection and developed into resistance through a gene mutation [21], [22].

These results are also consistent with various systematic reviews conducted in Europe on risk factors associated with MDR-TB and surveys conducted in several countries by WHO (23,24). Even a study reported that a history of previous TB treatment could increase the likelihood of MDR-TB up to 12 times (AOR: 11.9, 95% CI: 6.8–21) this was because initially patients underwent first-line TB treatment until

finally they were considered treatment failures and experienced MDR- TB. Thus, ensuring the success of treatment and patient adherence when TB is first diagnosed is very important [23].

4.4 Relationship between self-efficacy and MDR-TB through adherence variable

This study also reports the existence of various factors related to behavior, namely the relationship between self-efficacy and adherence. Patients with high self-efficacy are more likely to have obedient behavior 1.14 higher than respondents with low self-efficacy (β = 1.44; 95% CI = 0.35-2.77; p-value 0.004). Self-efficacy can stimulate various patient behaviors such as adherence to treatment programs, keeping the environment clean, not forgetting to take medication on time, being able to adjust to drug side effects, conducting sputum examinations, getting enough rest, and checking yourself if there are complaints that aggravate the disease [26]. Previous studies reported that the use of HBM theory in the analysis of TB patient adherence centralized the emphasis on self-efficacy. So it must be considered by related health workers to develop programs that can motivate TB patients through this factor. Medical interventions to increase self-efficacy will result in patients receiving greater benefits from treatment and being more compliant with the program [25]. Self-efficacy has also been recognized as a factor influencing the success of treating long-term or even life-long diseases such as HIV [26] and asthma [27].

4.5 Relationship between perceived quality of care and MDR-TB through adherence variable

The respondent who high of the perceived quality of care, on average had adherence odd log of 2.01 higher than who were low self-efficacy (b = 2.01; 95% CI = 1.29-2.72; p-value <0.001). Previous research also reported that data from 137 countries estimated that 50% of 900,000 TB sufferers died due to poor quality of care [28].

Various barriers to obtaining good quality of service include: (1) Diagnosis takes a long time to establish which results in patients not returning for their follow-up clinic visits, and sometimes delaying the initiation of treatment [29]. Expanding the use of enhanced molecular diagnostics such as the use of Xpert MTB/RIF may contribute to timely diagnosis especially for MDR-TB. (2) health workers who are still lacking in competence, this makes continuous training for health staff about screening TB patients and their treatment must be expanded and improved in quality and quantity, to ensure patients are screened, diagnosed and treated properly for TB [30]. (3) the number of health cadres who come from ordinary people who give short lectures about TB is still very limited, contact tracing programs and outreach about community-based education and awareness formation are very important in the success of TB and MDR-TB alleviation programs [31]. However, another challenge is that the longer a person becomes a cadre is not a guarantee that the cadre will become better at conveying information and providing counseling [32].

4.6 Relationship between cues to action and MDR-TB through adherence variable

Based on the results of this study, respondents who had high cues to action (cues or awareness to act) had an average compliance of 3.34 higher than those with low cues to action (β = 3.34; 95% CI = 1.24 -5.44; p-value 0.002). These results are in line with research which reports that cues to act independently can predict adherence, the higher a person's cues to action in taking medication, the better predicted adherence [33]. Literature review on non-adherence in chronic disease shows that predictors of non-adherence arranged in the psychological theory of the health believe model include: perceived vulnerability, expectations of positive outcomes, perceived barriers to treatment such as costs, and cues to action that reduce forgetting [34].

Current research suggests that cues to action can be internal (eg, perception of one's own physical condition) or external (information from the media, communication between MDR-TB patients and doctors,

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fellow sufferers, or family). Cues to action activate readiness to trigger appropriate pro-health behaviors so that effective cues to action can drive intentions to comply with recommended health behaviors [35].

4.7 Relationship between knowledge and MDR-TB through perceived quality of care and adherence variable

There is a relationship between knowledge and increased logit risk of perceived service quality. Respondents with high knowledge on average had a perception of quality of care 3.0 higher than respondents with low knowledge (β=3.0; 95% CI = 2.38-3.61; p-value <0.001). Good knowledge about the dangers of MDR-TB makes patients have the opportunity to choose a better health service. so that they can get adequate treatment and recover from regular TB disease. The combination of good knowledge and appropriate health care facilities will certainly increase patient compliance [36]. Patients will be aware and feel that their recovery is a top priority and must be fought for.

4.8 Relationship between social capital and MDR-TB through cues to action and adherence variable

There is a relationship between social capital and a logit increase in the risk of action cues. Respondents who have high social capital have an average cues to action log odd of 6.04 higher than respondents who have low social capital (β= 6.04; 95% CI = 4.03-8.04; p-value <0.001). Social capital is divided into structural and cognitive components. Structural social capital refers to observable behaviors and actions such as patterns of social participation, while cognitive social capital refers to values, attitudes, norms and beliefs [37].

People with high social capital are proven to have a healthier lifestyle, they will consume nutritious food for endurance, buy supplements. This is consistent with research which reports that social capital directly impacts a healthy lifestyle in the long term, this lifestyle includes increased physical activity and nutritional intake [37].

Social capital is also one of the factors that influence compliance in patients with chronic diseases. High social capital can increase adherence in taking medication, eating nutritious foods such as fruit, vegetables, cereals and fish [38]. In this context, high social capital will make patients take TB drugs more routinely without the need to think about the cost of accessing health services, because the whole family and the surrounding environment support them.

5. CONCLUSION

The respondent with a history of previous TB treatment had an MDR-TB odd log of 2.59 points higher than patients who did not have previous TB treatment history (β= 2.58; 95% CI = 1.55-3.61; p-value <0.001).

On the other hand, The respondent with low monthly incomes had an MDR-TB odd log of 0.91 points lower than those with high monthly incomes (β= -0.99; 95% CI = -6.53-3.44; p-value 0.028). The respondent who were obedient in taking tuberculosis medication, on average had an MDR-TB odd log of 4.99 points lower than patients who did not adhere to taking tuberculosis drugs (β= -4.99; 95% CI = -6.35-3.44; p-value <0.001).

Against the adherence factor, there were the relationship between the self-efficacy, perceived quality of care, cues to action to increase the risk logit of adherent behavior. The respondent who high self-efficacy, on average had adherence odd log of 1.14 higher than who were low self-efficacy (β= 1.44; 95% CI = 0.35-2.77; p-value 0.004). The respondent who high of the perceived quality of care, on average had adherence odd log of 2.01 higher than who were low self-efficacy (b = 2.01; 95% CI = 1.29-2.72; p-value <0.001).

The respondent who high of cues to action, on average had adherence odd log of 3.34 higher than who were low of cues to action (β= 3.34; 95% CI = 1.24-5.44; p-value 0.002).

There was a relationship between the knowledge to increase the risk logit of the perceived quality of care. The respondent who high of knowledge, on average had perceived quality of care odd log of 3.0 higher than who were low of knowledge (β= 3.0; 95% CI = 2.38-3.61; p-value <0.001).

There was a relationship between the social capital to increase the risk logit of cues to action. The respondent who high of social capital, on average had cues to action odd log of 6.04 higher than who were low social capital (β= 6.04; 95% CI = 4.03-8.04; p-value <0.001).

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