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Predictor Factors of Multi-Drug Resistance Tuberculose on the Characteristics of Chest Radiographic Lesions

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Abstract

This research aimed to demonstrate some predictors of screening diagnosis of multi-drug-resistant tuberculosis (MDR-TB). Researchers determined several predictors as a screening diagnosis of MDR-TB, based on clinical symptoms, WHO criteria, chest radiographic lesions, and sputum smear microscopy. The method demonstrated a correlation between several factors as predictors of the MDR-TB diagnosis consisting of clinical symptoms, WHO criteria, BTA sputum, and cross-sectional chest radiograph lesions, based on examination of Gene X-pert for suspected MDR-TB. The results demonstrated a significant and positive odds ratio value of the relationship between variables: 1). Clinical symptoms (p:0.000) with the largest percentage of coughing with shortness of breath exhibiting 51.32% and coughing exhibiting 27.9%; 2). WHO criteria are among others, new patients (p:0.000; OR:3); 3). Chest radiographic lesion: consolidation (p: 0.000; OR: 3); pleural thickening (p:0.003; OR:2); Fibrosis (p:0.000; OR:6) with location on the medial right (p:0.000; OR:2) and left inferior (p:0.000; OR:3). The BTA sputum is (p:0.000; OR:8). The predictors for screening the diagnosis of MDR-TB are coughing, and shortness of breath. Other WHO criteria include radiographic lesions, fibrosis, consolidation, pleural thickening with the location of lesions either left inferior or medial right and positive smear sputum results.

Introduction

WHO Global Tuberculosis Report 2017 data indicated that multi-drug-resistant tuberculosis (MDR-TB) and Rifampicin Resistance Tuberculosis (RR-TB) cases in Indonesia reached 32,000. These cases were recorded as pulmonary TB with 11,000 per 100,000 populations. With a total of 44,000 cases, drug-resistant TB (TB RO) increased by 2.8% of new cases and 16% of previously treated TB. MDR-TB cases with laboratory confirmation reached 2,757 cases, and only 1,931 cases followed the treatment with a 51% successful rate. Patients with TB who recover and relapse can be affected by several factors, such as contact with other patients in one home/environment, poor life quality (due to smoking and drinking alcohol), nutritional status, and other diseases such as DM, HIV, AIDS, and malignancy. Further, in developing countries, MDR-TB prevalence ranges from 4.6%–22.2% and increases with each year (Zida & Nur, 2019). The risk factor for increasing MDR-TB cases is the use of fluoroquinolones in the community without medical or rational considerations. Fluoroquinolones are second-line anti-TB drugs in MDR-TB cases, so the continuous use of Fluoroquinolones causes a tendency to become resistant to this drug. As a result, TB patients who are rifampin-resistant, need to consider the choice of this second-line TB drug. The success of MDR-TB treatment is around 60% and Extensively Drug-Resistant Tuberculose (XDR-TB) (Jeong et al., 2015; Singh & Jain, 2019).

Diagnosing MDR-TB is not easy, because

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the symptoms and clinical signs are not typical. Patients with MDR-TB based on their treatment history are divided into primary and secondary groups (Zida & Nur, 2019). Medicine resistance in TB treatment, mainly MDR-TB and TB with Extensive Drug-Resistance (XDR) or XDR-TB, is a significant health problem in numerous countries, and this is an obstacle to global TB control programs (Alok, 2019). MDR-TB cases result in several losses including losses to patients, hospitals, and the government. Incurring costs by patients and the government are high. Further, one of the problems of MDR-TB is a long diagnosis (around 3 weeks to a month); therefore, M. tuberculosis bacteria transmission increases and inadequate treatment occurs as a result [2, 4, 6] (Zida & Nur, 2019; Emanuele et al., 2019).

Several studies state that the MDR-TB diagnosis based on several criteria for risk of resistant TB medicine (MDR-TB clinical sufferers): in chronic cases or patients with failing treatments with TB medicine categories II, patients with sputum examination results remaining positive after the third month with TB medicine categories II, patients who received TB treatment, including second-line TB medicine, such as quinolones and kanamycin, patients who fail treatment with TB medicine categories I, patients with sputum examination results remaining positive after insertion with TB medicine categories I, TB recurrent cases, patients returning for treatment after negligence in category I and/or category II treatment, patients with complaints of suspected TB, patients living near people with dual drug-resistant TB, including health workers of duty in the dual drug-resistant TB ward, and patients with HIV (José et al., 2017; Abu et al., 2019; Yi et al., 2018).

Thorax radiographic examination is still routinely performed on patients with TB and MDR-TB suspicion since this examination is considered affordable, easy, and available in almost all hospitals and healthcare clinics. Thorax radiographs between TB and MDR-TB generally vary and are difficult to distinguish. Some studies indicate thorax radiographic examination on MDR-TB exhibits several characteristics, namely, lesion type; these are multiple cavities with a diameter of less than 4 cm, multiple nodules with less than 3 cm, Pleural thickening; lesion location is most common in the superior lobe of the right or left lung, or the right lobe of the right lung, and lesion exhibits a large extent (Zida & Nur, 2019; Abu et al., 2019; Yi et al., 2018; Dwi et al., 2012).

Gene X-pert test is a molecular test with an automatic real-time PCR system for MTB complex DNA detection in suspected patients with TB. It can diagnose quickly and precisely; therefore, proper treatment can be performed on patients, mainly in patients with TB who are resistant to usual anti-tuberculosis medicine. This test can produce a result in less than 2 h and detect genetic mutation with rifampicin resistance. Unfortunately, Gene X-pert availability is limited only in certain hospitals in urban areas. So, MDR-TB diagnosis remains an obstacle, with a process that requires a long time (Pramanindyah & Soedarsono, 2019; Priyatam et al., 2019; Riele et al., 2019).

Based on the information above, MDR-TB incidents are increasing, while the biggest obstacle is Gene-X-pert diagnosis duration and availability, causing inadequate medication. This obstacle makes the researcher want to perform some component research as a MDR-TB diagnosis predictor including clinical aspects (risk factors) from medical record data based on WHO criteria, lesion characteristics, lesion location, and lesion area on thorax radiographic with suspected MDR-TB and Gene X results-pert. The current study demonstrates a sizeable extent of resistant cases among pulmonary TB patients. This study presaged a significant risk of Drug Resistant-TB (DR-TB) among females, young adults, unemployed, smokers, and patients with previous treatment failure and cavitation on chest X-rays. Timely identification of high-risk patients will give pronounced advantages regarding appropriate choices of prevention, treatment, and disease control (Saifullah et al., 2021).

This study aimed to find the predictor of MDR-TB, which is very important to an early screening of the suspect of MDR-TB so that he or she can be further examined by Gene X-pert. The diagnostic of MDR-TB can be conducted quickly so it will not infect other people, along with increasing the total number of recovered patients. By providing therapy treatment

immediately, the total number of recoveries from MDR-TB could be increased. The predictor, which highly contributed to faster diagnosis of MDR-TB, is based on nine clinical symptoms according to the WHO criteria and also characteristics of lesion in the thorax, type of lesion, location of lesion, and area of lesion that can b e visualized by radiography.

Methods

A cross-sectional research design was used, to obtain a relationship between MDR-TB risk factors (nine categories + additional categories), thorax radiographic characteristics lesions cover lesion type, lesion location, and lesion area with the results of Gene X-pert examination. 75 samples were included in this research, namely all patients with suspected MDR-TB with at least one risk factor, who met the inclusion and exclusion criteria at Dr. Sardjito General Hospital Yogyakarta and Sleman District General Hospital from 2015–2018. Inclusion criteria from patient medical record data are the following: patients aged >18 years old, patients with suspected MDR-TB with at least one risk factor among the nine risk factors for suspected MDR-TB, patients with thorax radiographic results, and patients with Gene X-pert results (Non-TB/TB-Resistant Rifampicin/ TB-Sensitive Rifampicin). The exclusion criteria were as follows: TB patient data with complications (malignancy, chronic metabolic diseases, and occupational diseases/ miners), thorax radiographic results, and non-TB abnormalities (mass, pneumonia, pulmonary edema, massive pleural effusion, and massive pneumothorax), as shown in Fig. 1.

This research variable consisted of independent variables: 1) Nine WHO criteria for MDR-TB risk factors; 2) thorax radiographic results (+) and thorax radiographic results (–), including lesion characteristics, location, and area. Dependent variables included Gen X-pert (+)/M tb Rif-R test results and Gen X-pert (–)/ M tb Rif-S test results. The research analysis objective was to obtain the relationship between independent and dependent variables with $\chi 2$ (chi-square) statistical analysis by determining the p-value and Relative Risk (RR).

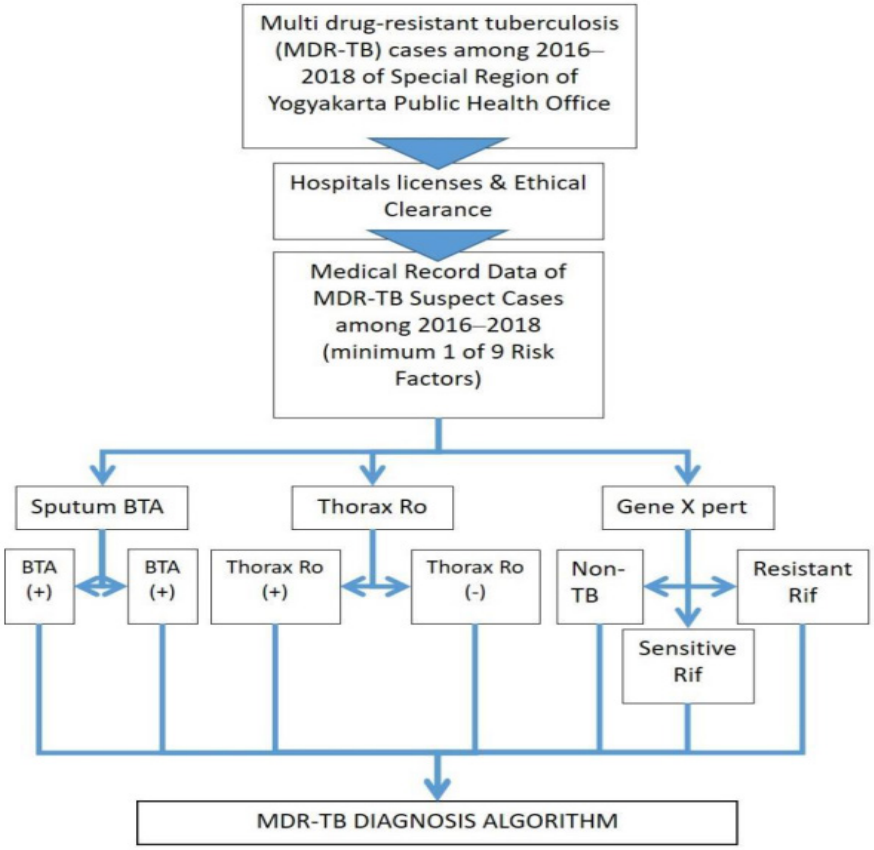

FIGURE 1. Research procedures diagram

Results and Discussion

As shown in Table 1, the research subject domicile was mostly from the special region of Yogyakarta (85.3%) and a small portion from outside the special region of Yogyakarta (14.7%). This condition occurred due to the sample came from RSUP Dr. Sardjito General Hospital Yogyakarta and Sleman District General Hospital; so, only a small portion originated from outside the special region of Yogyakarta. The age of most research subjects was adult (88.0%), followed by elderly (9.3%) and children (2.7%). The research subjects were mostly male (59.8%), with females being 40.2%.

Table 1. Research Subject Characteristics

Criteria	Result	Percentage	Number of Patients	p-value
Patients Domicile			75	
Special Region of Yogyakarta	64	85.3%		
Outside Special Region of Yogyakarta	11	14.7%		
Patients Age			75	0.000
Children	2	2.7%		
Adults	66	88.0%		
Elderly	7	9.3%		
Gender			75	0.591
Male	44	59.8%		
Female	31	40.2%		
MDR-TB Patient's Clinical Symptoms			75	0.000
Cough and shortness of breath	32	42.7%		
Cough (blood coughing, sputum coughing, dry cough)	29	38.7%		
Limp	8	10.7%		
Others (lack of appetite, thin, chest pain, etc.)	5	6.7%		
Shortness of breath	1	1.3%		
Gene X-pert result			75	
Rifampicin Resistant	33	44.0%		
Rifampicin Sensitive	40	53.3%		
Negative Gene X-pert	2	2.7%		
Diagnosis			75	
MDR-TB	33	44.0%		
TB-Sensitive Drug	39	52.0%		
NTM	3	4.0%		
Other Diagnosis				
Disorder of Mental/Psychosis/ Depression/Hallucination	7	9.3%	75	
DM	16	21.3%		
More than one disorder	11	14.7%		
Anemia	3	4.0%		
No disorder	38	50.7%		

Source: Primary Data, 2021

Furthermore, clinical symptoms in patients with MDR-TB include coughing and shortness of breath (42.7%), followed by cough (blood coughing, dry coughing) with 38.7%, limp with 10.7%, others (thin, lack of appetite, and chest pain) with 6.7%, and shortness of breath with 1.7%. The results indicate that a significant relationship (p-value < 0.005) between clinical symptoms and MDR-TB incidents is found based on Gene

X-pert, as shown in Table 1. Suspected research subjects with MDR-TB tested by Gene X-pert sensitive Rifampicin (RS) results are 52.0%, and Rifampicin resistance indicates a diagnosis of MDR-TB by 44.0% and negative 2.7%. Patients with the most suspected MDR-TB with accompanying disease are patients with DM (21.3%), as s (Table 1). Comorbid patients in this study include mental disorders/psychosis, hallucinations, and depression by 7 people (6%), and other disorders such as hearing loss, nausea, vomiting, insomnia, and others include 11 people (14.7%), as shown in Table 1.

Table 2 indicates that thorax radiographic lesions in suspected patients with MDR-TB have a significant relationship with MDR-resistant TB Rifampicin in terms of mass, consolidation, pleural thickening, and fibrosis. From the lesions with MDR-TB, the biggest predictor is fibrosis (p: 0.000 with an odds ratio value of 5.610), meaning that fibrosis lesions tend to MDR-TB 5x higher than other thorax radiographic lesions. The lesion location with a significant relationship to MDR-TB is the right medial, left superior-medial, and inferior lesion location. In addition, the lesion location with the biggest predictor is left inferior (p: 0.000 and OR: 2.632), meaning that the biggest probable factor for MDR-TB from lesion location is left inferior left lung, and the predictor is 2.672 times more likely to become MDR-TB than lesion location in other lung areas. Table 3 shows a comparison of the characteristics of the thoracic radiography lesions between the results of this study and previous studies.

Table 2. Thorax Radiographic Lesion Characteristics on MDR-TB

Thorax radiographic lesion characteristics on MDR-TB	p-value	**OR**
Lesion Type		
Infiltrates	0.000*	0.245
Cavitary	0.515	0.985
Nodules	0.038*	0.573
Mass	0.000*	2.631*
Consolidation	0.000*	2.681*
Pleural Effusion	0.099	0.681
Pleural Thickening	0.002*	2.314*
Fibrosis	0.000*	5.610*
Calcification	0.004*	0.004
Lesion Location		
Right-superior	0.000*	1.968*
Right medial	0.102	0.780
Right-inferior	0.444	0.940
Left superior	0.009*	1.606*
Left-medial	0.000*	0.508
Left inferior	0.000*	2.632*
Lesion Area	0.004*	0.000

*: significant p-value

Source: Primary Data, 2021

Table 3. Comparison of Results of Other Research Studies with the Present Research Study "Characteristics of Thoracic Radiography on MDR-TB"

The result of the research	Radiographic finding		
	Lesion	**Lesion location**	**Area**
Icksan *et al.* [19]	1. Consolidation 2. Cavity 3. Fibrosis	Lung bilateral	Large
Majdawati *et al.* [20]	nodule	upper lobe	Large
James *et al.* [23]; Yi *et al* [10]; Resta *et al.* [21]; Priyatam *et al.* [12]; Rielea *et al.* [13]	Multiple cavities with diameter Θ > 3–4 mm consolidation	upper lobe	Large
Present research	Fibrosis Pleural thickening consolidation	Upper lobe, left inferior	Large area

Source: Primary Data, 2021

Table 4. WHO Criteria by Gene X-pert Result

Clinical Symptoms based on WHO Criteria MDR-TB Suspect	**Amt**	**Percentage**	p-value, **OR**
Chronic cases or failing treatment patients with category II TB medicine	2	2.7%	*p*: 0.052
Patients with sputum test results remain positive after the third month with category II TB medicine	1	1.3%	*p*: 0.113
Patients who have received TB treatment. including second-line TB MEDICINE, such as quinolones and kanamycin	4	5.3%	*p*: 0.140
Patients who failed treatment with category I TB medicine	14	18.7%	*p*: 0.236
Patients with sputum test results remain positive after insertion with category I TB medicine	0	0%	-
Recur TB cases	16	21.3%	*p*: 0.326
Returning patients for treatment after negligence in Category I and/or Category II treatment	4	5.3%	*p*: 0.012*/ OR 0.361
Patients with TB suspicion, patients who live near people with dual medicine-resistant TB, including health workers on dual medicine-resistant TB	8	10.7%	*p*: 0.000* / OR 0.286
HIV Patients (CDK-215/ vol. 41 no. 4, yr. 2014)	4	5.3%	*p*: 0.053 OR 0.426
Other patients and new patients, outside the nine criteria	22	29.3%	*p*: 0.00 * / OR: 2.654

*: significant p-value

Source: Primary Data, 2021

Table 4 indicates 9 WHO criteria and one other criterion related to MDR-TB. From those nine criteria, the criteria with a meaningful relationship to MDR-TB are as follows: returning patients to treatment after negligence in treatment for category I and/or category II; Patients with TB suspicion complaints, patients living near people with dual medicine-resistant TB, including health workers on dual drug-resistant TB, Patients with TB-suspected complaints, patients living near people with dual drug-resistant TB, including health workers served in multiple drug-resistant TB; III) Other patients beyond nine criteria. Therefore, the biggest predictors of MDR-TB are other patients outside the 9 WHO criteria, with an OR value of 2.654.

Some references and results did not discuss trends in several patients with MDR-TB by origin, age, and gender, because some data indicated that the number of patients with MDR-TB was mostly inconsistent among the numbers based on these criteria (Riele et al., 2019). Further, the highest number of patients with MDR-TB in another study was found at the reproductive age, around 20–55 years. This has been proved by this study, where the number of MDR-TB is mostly adults (88.0%) (Rosalia et

al., 2019). Other research results demonstrate a significant relationship between age and MDR-TB; people aged 15–29 years suffered the most MDR-TB, followed by people aged 30–44 years or those of reproductive age. MDR-TB events demonstrate no association with gender, although in some studies including the results of this study, most of the patients with MDR-TB are male. Several references from 15 articles reviewed, showed that age, gender, irregularity treatment, and medication adherence are the most influencing factors occurrence of MDR-TB. (Priyatam et al., 2019; Riele et al., 2019; Singla et al., 2018; Bawonte et al., 2021).

According to a study of patients with MDR-TB with the most clinical symptoms, including blood coughing, shortness of breath, and chest pain, as indicated by thorax X-ray with the highest grading for weight category with extensive lesions (Pramanindyah & Soedarsono, 2019; Samuel et al., 2016), the frequent symptoms in this research include cough followed by shortness of breath, blood, or sputum coughing, This is aligned with some research of the clinical symptoms, which demonstrates that a significant relationship exists between MDR-TB incidence and cough and chest pain (Abu et al., 2019; Priyatam et al., 2019). The risk factor for the increased incidence of MDR-TB is also influenced by the patient's clinical symptoms, such as shortness of breath due to sequelae of lung disorders, and pleural abnormalities due to MDR-TB infection (Bawonte et al., 2021).

Researchers reported that patients with type 2 DM are more susceptible to TB MDR in Texas and Mexico. They constitute the largest population of active TB cases in Mexico and Mexican America, and this population contributes to an increase in MDR-TB cases. Type 2 DM causes a decrease in the body's immune system, and this is related to poor blood sugar control. Poor blood sugar control can cause disorders of phagocytic function, chemotaxis, reactive oxygen species, and T-cell function (Dwi et al., 2012; Repon et al., 2015). Another risk factor presented in this study was the habit of smoking. Despite increasing the risk of active TB, we have found no sufficient evidence in the literature that smoking is an important risk factor for resistance. However, studies show smoking as a factor associated with the failure of treatment of TB. The time to sputum culture conversion from positive to negative among smokers is higher than nonsmokers after the second month of the start of treatment with both first-line and second-line drugs (Fregona et al., 2017a).

Some previous studies indicated that the possibility of psychiatric disorderrelated medicine is cycloserine therapy. Sleep disturbance or insomnia might be caused by levofloxacin (Dwi et al., 2012). Some references to the side effects of MDR-TB treatment are vertigo, hearing loss, insomnia, and visual impairment. The frequent contributing factors accompanying patients with MDR-TB include DM disease, hypertension, heart disease, and Rheumatoid Arthritis (Repon et al., 2015). Previous studies found that the default or returning patients' criteria to treatment after negligence in category I and/or category II treatment demonstrate a significant relationship with MDR-TB incidents and 3.5 times higher to be classified as patients with MDR-TB (Devi & Sri, 2018). The biggest predictor of MDR-TB in this study is outside the 9 WHO criteria, namely other criteria and new patients with an OR value of 2.654. Based on WHO 2017 data, the MDR-TB rate is estimated at 2.8% of all new TB cases and 16% of TB cases with repeat treatment. The rate of MDR-TB cases in Indonesia is 32,000 out of a 100,000 population, in a year. Further, new patients and other found criteria demonstrate a 2.65 times tendency to become patients with MDR-TB, compared to patients with 1–9 WHO criteria. This number is likely occurring due to M. tuberculosis bacteria transmission, which is resistant to TB medicine and to people around them. Seeing this reality, we need to think about the increasing cases of MDR-TB seriously due to MDR-TB and RR-TB patients' transmission who do not obey the treatment of people around them (Abu et al., 2019; Icksan et al., 2018; Majdawati et al., 2019). The predictor factors in this study, of the 9 WHO criteria were new patients who were exposed to or in contact with people around them who suffered from MDR-TB, TB patients who were not regularly treated so that the possibility of relapse was very high (Fregona et al., 2017b).

In general, resistance to anti-tuberculosis medicine is divided into primary, initial, and secondary. First, the primary is if the patient never receives TB medicine treatment or receives TB medicine treatment for less than 1 month. Next, initial resistance is if we are not sure whether the patient exhibits a history of previous TB medicine treatment or not. Next, secondary is if the patient exhibits a history of TB medicine treatment for at least 1 month. Theoretically, five considered factors exist that play a role in causing MDR-TB outbreaks, namely inadequate treatment (rising to resistant M. tuberculosis mutants); late MDR diagnosis patients, then becoming a source of continuous transmission; patients with incurable TB medicine resistance will continue the transmission; Patients with TB medicine resistance, although they were treated continuously by inadequate medicine, they may cause resistant bacteria multiplication, and HIV infection facilitates primary and secondary resistances (Icksan et al., 2018). The main-factor cure for MDR-TB is treatment compliance (OR: 6.736), TB treatment history (OR: 4.198) and the suitability of the drug dose TB medicine (OR: 5.281). MDR-TB will increase 4–7 times in patients that do not correspond to those mentioned above. Moreover, regular, and orderly TB treatment as well as dosage and choice of TB medicine also affects the healing of MDR-TB (Resta et al., 2018). Irregularity in taking medication is one of the predictors of MDR-TB tendencies. This is caused by feeling lazy, forgetting to take medicine, and feeling bored from taking long-term medicine and making you feel uncomfortable (Mashidayanti et al., 2020).

Based on the research conducted, researchers concluded that from the research variables consisting of clinical symptoms, WHO criteria for suspected MDR-TB and thorax radiographic characteristics (lesion type, lesion location, and lesion area) are predictors of MDR-TB. The lesion area is significantly related to MDR-TB incidents; the wider the lesion, the more likely for MDR-TB to be present. Several studies on the community with TB endemic areas obtain that most lesions with a significant relationship to MDR-TB include consolidation, cavitary, mass/nodules, fibrosis, pleural thickening, or pleural effuse. The lesion location on most thoraxes radiographic is in the upper right lobe, followed by the upper left lobe and medial and inferior lobes. Most MDR-TB is in the area/severe category according to the degree of severity or lesion area (Icksan et al., 2018; Majdawati et al., 2019).

Some researchers who researched the characteristics of the thoracic radiographic lesions of patients with MDR-TB found that most of the lesion results on MDR-TB are cavities, multiple quantities, most locations in the superior pulmo second lobe, and occupy a wide area of more than three segments of the right and left lung (Yi et al., 2018; Priyatam et al., 2019; Riele et al., 2019; Repon et al., 2015; James et al., 2013). Other researchers from Indonesia found that most lesions on MDR-TB are fibrosis, consolidation, and thickening of the pleural (José et al., 2017; Abu et al., 2019). Researchers from Indonesia took samples from the community, not from hospitals. Moderate research has now been carried out on samples from the hospital's case proofing MDR-TB. Lung cavitary nodules or masses were more frequently observed and also showed greater extent in primary multidrug-resistant tuberculosis compared with drug-sensitive tuberculosis. Thick-walled multiple cavity lesions present the most promising radiological sign for MDR-TB diagnosis. For future studies, cavity lesion characteristics should be quantified in detail. The extent of bronchiectasis was significantly greater in primary multidrug-resistant tuberculosis than in drug-sensitive tuberculosis. Calcification, large nodules, and calcified lymph nodes were more frequent in drug-sensitive tuberculosis (Li et al., 2017;

Conclusions

Clinical symptoms with the strongest predictor value are cough accompanied by shortness of breath (42.7%) followed by blood coughing or sputum coughing (38.7%). The strongest WHO criteria predictor is other criteria and new patients (OR: 2.654), followed by default patients, for instance, those who return to treatment after negligence on category I and/or category II treatment and suspected patients with TB living near people with dual drug-resistant TB, including on-

duty health workers or in dual drug-resistant TB wards. Thorax radiographic characteristics are as follows: lesion type: mass (OR: 2.631), consolidation (OR: 2.681), pleural thickening (OR: 2.314), and fibrosis as the strongest (OR: 5.610). Lesion location: superior right (OR: 1.968), superior left (OR: 1.606), and inferior left as the strongest (OR: 2,632). The lesion area with the strongest predictor is area/weight.

Acknowledgment

All procedures performed in studies involving human participants followed the ethical standards of the institutional and/or national research committee. Moreover, our ethical standards were evaluated based on the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were received informed consent and willing to participate in this study. This research has received permission from the Ethics Commission of Dr. Sardjito-FK UGM with no ethical clearance KE/FK/0153/EC/2019. This research fund was supported by the Lembaga Pengabdian Masyarakat (LPM) Universitas Muhammadiyah Yogyakarta.

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