



Research Articles

Mapping of antibiotic resistance in multi-drug resistance tuberculosis at RSUD Arifin Achmad, Riau Province

Andralia Mayangsasati¹, Sri Sundari²

1,2) Department of Hospital Administration, Universitas Muhammadiyah Yogyakarta, DIY Yogyakarta, Indonesia

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*Correspondence:

swb191@ums.ac.id

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ABSTRACT

Tuberculosis is a disease caused by the bacteria *Mycobacterium tuberculosis*. Resistance is a condition where an antibiotic is not able to kill *Mycobacterium tuberculosis*. The type of research used is descriptive with a mixed-method approach. It was found that most MDR-TB patients were male (67.2%), aged 41-50 years (26.9%), and lived in Pekanbaru City (65.7%). There were 30 patients (44.8%) who underwent microscopic examination, 12 patients (44.4%) who had a previous medical history of TB disease who had been informed finished taking medication by their doctors. Nine patients (33.3%) with a history of inadequate TB treatment. Three patients (11.1%) were confirmed as a treatment failure. Three patients (11.1%) were primary TB and confirmed the result of laboratory tests for resistance to anti-TB drugs. MDR TB patients who smoke were nine patients (33.3%), and DM patients were two people (7.4%). So, information about the characteristics of Multi-Drug Resistance Tuberculosis is needed, and it is hoped that appropriate treatment can be given.



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INTRODUCTION

Tuberculosis is a disease caused by the bacterium *Mycobacterium tuberculosis*. This disease can affect all ages and genders. This disease worldwide shows morbidity and mortality that increases with age. (Marçôaa, Ribeiro, & I. Zãoc, 2018). The occurrence of resistance of *M. tuberculosis* to Anti Tuberculosis Drug (ATD) is a problem encountered in TB treatment. This resistance is a condition where ATD is not able to kill *M. tuberculosis* germs (Kemenkes, 2013). The resistance of TB bacteria to ATD has been around for a long time.

Indonesia is ranked 8th out of 27 countries with the highest MDR TB burden in the world with an estimated MDR TB patient in Indonesia there are 6,800 new cases of TB with Multi Drug Resistant Tuberculosis (MDR TB) every year (WHO, 2017). The MDR TB rate is estimated at 2% of new TB cases and 12% of re-treated TB cases. 55% of Multi Drug Resistant Tuberculosis (TBMDR) patients have not been diagnosed or received treatment properly (Ministry of Health, Technical Instructions for Integrated Management of Drug Resistant Tuberculosis Control, 2013). The Data and Information Center of the Ministry of Health of the Republic of Indonesia (2014) recorded that in 2009 there were 66 patients with MDR TB in Indonesia, in 2010 there were 216 patients, in 2011 there were 460 patients, in 2012 there were 696 patients, in 2013 there were 1,094 patients, in 2014 as many as 1,752 patients, in 2015 as many as 1,860 patients. The data shows an increase in the number of MDR TB sufferers every year in Indonesia (Kemenkes, 2016). The number of deaths per week is 52,000 people or every day more than 7000 people die (Rattan, Kalia, & Ahmad, 1998).

The presence of multiple drug resistance (MDR= multiple drug resistance) against *Mycobacterium tuberculosis* is reflected in the increasing number of new cases and mortality rates and the lack of successful treatment of tuberculosis. Treatment of tuberculosis requires a long and adequate time, this is a public health problem throughout the world.

METHODS

This study was done from January to March 2021. The type of research used is descriptive with a mix method approach. The mix method research is a research that uses two methods, two methods, namely quantitative, namely the prevalence of patients suffering from MDR TB and qualitative, namely the results of interviews with specialist doctors to determine the cause of resistance in a single study.

The data was processed with the help of data processing application software and analyzed univariately to describe the characteristics of the respondents (gender and education) and to determine the frequency distribution of each variable, and bivariate analysis. Then use the type of qualitative descriptive research with a phenomenological approach. Data obtained by conducting in-depth interviews. Interviews were conducted for approximately 30 minutes, conducted online in January 2021. The number of questions asked to the respondents was 39 questions.

Inclusion criterias for this research are inpatient and outpatient of RSUD Arifin Achmad with Multidrug Resistance Tuberculosis from 2020 to 2021 who are willing to be the object of research and interviewed. Meanwhile exclusion criterias are patients who are sensitive to ATD and who are rejected to be the object of research

Ethical Clearance: No: B/005/ UNI9.5.1.1.8/ UEPKK/2021



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Table 1. Characteristics of Research Subjects

Variable	Frequency	Percentage
Sex		
Male	45	67,2
Female	22	32,8
Age		
< 21 tahun	3	4,5
21-30 tahun	11	16,4
31-40 tahun	12	17,9
41-50 tahun	18	26,9
51-60 tahun	16	23,9
> 60 tahun	7	10,4
Residence		
Bengkalis	1	1,5
Indragiri Hulu	3	4,5
Kampar	10	14,9
Kodya Jakarta Timur	1	1,5
Kota Pekanbaru	44	65,7
Kota Tebing Tinggi	1	1,5
Kuantan Singingi	1	1,5
Pelalawan	2	3,0
Rokan Hilir	2	3,0
Rokan Hulu	1	1,5
Siak	1	1,5
Total	67	100,0

RESULTS

This research was conducted at Arifin Achmad Hospital, Riau Province in December 2020 - January 2021. The data of this study were obtained through recording from the medical records owned by the hospital. This study involved 67 patients as research subjects. The characteristics of the subjects of this study are shown in the table below.

It is shown in the table above that the majority of the research subjects are male age 41-50 years old and live in Pekanbaru

Theme Determination Process

The process of determining the theme in this study was obtained from the results of FGD (focus group discussion) data analysis using a qualitative data processing scheme from Creswell in 2017. Based on the results of

data analysis, 4 themes were obtained (4 or 5), Theme 1) Previous TB history, supported by 3 categories, namely primary TB, secondary TB, and suspected secondary TB. Theme 2) Risk factors for MDR TB are supported by 4 categories, namely Primary TB, Relapsed Patients, Inadequate Medication History, and Treatment Failure. Theme 3) Patient knowledge of TB treatment methods which is supported by 4 categories, namely; patients who know that if they discontinue the treatment, they have to start from the beginning, patients who do not know if they discontinue the treatment, they have to start from the beginning, patients who know that TB treatment must be complete (uninterrupted), and patients who do not know that treatment TB must be complete (uninterrupted). Theme 4) Medication compliance, which is supported by 2 categories, compliant patients and non-compliant patient. Theme 5) Patient



compliance to repeat sputum tests, supported by 2 categories namely; patients who know the need for repeated sputum tests and patients who do not know the need for repeated sputum tests.

Theme I: Medical Record/History of previous TB

A. Primary TB

The respondents are MDR TB patients who sought treatment at the Arifin Achmad Hospital. He told about his history of previous illnesses. The patient admitted that this was the first time they had TB without a previous medical history of TB disease. There were 3 patients who immediately suffered from MDR TB.

B. Secondary TB

The next respondents told about their previous medical history of TB. It was not their first time had TB. The patient had experienced a similar illness and had completed his treatment.

Patient 1 had a previous medical history of TB category 1, and had been on treatment for 6 months, but after the treatment, the patient was not advised by the doctor to do a sputum test. There is a possibility that the patient's treatment was not successful and the patient is a patient with MDR TB from the beginning.

Patient 2 had a medical record/history of previous TB category 1, but the patient performed sputum test regularly for treatment evaluation. At the end of the treatment the patient had finished taking the medicine and was confirmed cured by the test results. But in early 2020 the patient experienced similar symptoms and later developed MDR TB.

C. Secondary TB suspects

The next respondent told about his medical history of previous illnesses that had similar symptoms of TB but had never been diagnosed with TB.

Patient 3 had a medical history of a prolonged cough before, but when he went to the doctor, the patient was diagnosed with bronchitis and was programmed to take medicine for 6 months. There was no treatment for bronchitis for 6 months, which means that the patient had TB but the doctor did not tell and inform the patient the actual diagnosis and disease, and how to take medication, so the patient stopped the treatment himself after 1 month.

Patient 4 has the possibility of being misdiagnosed, she was diagnosed with the fungal disease which led to mistreatment that caused the patient to become resistant to first-line anti-TB drugs.

Theme II: Risk Factors of TB MDR

A. Primary TB

The respondent said that this was the first time he had been sick with MDR TB. The patient previously had no history of similar illness and inadequate TB treatment. He did not have a medical history of coughing for a long time since his childhood until he got the illness.

This was the first time Patient 5 had TB, the doctor checked for sputum and drug resistance and the results were positive, the patient was directly being put in the MDR TB treatment program for 2 years.

Just like patient 5, patient 6 also had no previous history of TB disease. The patient immediately suffered from drug-resistant TB for the first time. But the patient had a history of a long cough that was not diagnosed by the doctor when the patient was young.

Patient 7 said that there was a neighbor who had lingering cough, it was possible that the patient was exposed to TB but did not realize that he was infected and then did not take any medicine, or he was infected MDR TB from his neighbor



B. Relapsed Patients

The next respondent told that he had a previous medical history of TB (Category 1), then he experienced the same symptoms and was diagnosed with TB again but this time it is MRD TB.

According to patient 8, there was no repeated sputum test and the patient had been confirmed cured by the doctor and did not need any further treatment.

In contrast to patient 8, patient 9 had completely recovered, which was confirmed by laboratory results but later she is reinfected.

C. Inadequate Medical History

Patient 10 has a history of TB disease but he had an inadequate treatment. The patient dropped out of treatment because he had difficulty to pay for the transportation, and the patient did not have a companion to assist him during treatment.

Patient 11 had been sick with TB before (10 years ago) but he experienced disturbing side effects every time he took the medicine, so that the patient felt unable to continue the treatment, and stopped it by himself without telling or consulting with the doctor.

D. Failed treatment

Patient 12 was diagnosed with a category 1 TB patient, but at the end of the treatment, there was no improvement in the sputum test result, then the patient was referred and tested for drug resistance and the result was positive.

Theme III: Patient knowledge of TB treatment

A. Patients know that if they drop out, they have to start over

The following informant tells about what he knows about TB treatment

Patient 13 knew that treatment must be repeated from the beginning if he missed taking the

medicine. He knew this because his doctor had provided him with good education/knowledge about TB.

B. Patients do not know that if they stop taking the drug/medication, they have to start the treatment from the beginning

The following respondent differs from the previous respondent regarding what he knew about TB treatment.

Patient 14 did not know that if a patient stops taking the drug before completing the treatment program, he must start again from the beginning. The patient did not remember the doctor ever inform/educate him about this.

Patient 15 said he didn't know if he dropped out of treatment he had to start from the beginning. This happened due to the lack of information from the doctor.

C. Patients know that TB treatment must be complete and should not be interrupted

This respondent said that he knew the treatment of TB. This treatment must be completed and patients should not stop the treatment by themselves without consulting with the doctor.

Patient 16 knew that TB treatment must be carried out according to the specified time, cannot be discontinued, which is 6 months for category 1 and 2 years for MDR TB

D. Patients do not know that TB treatment must be complete and should not be discontinued

The following respondent tells about his experience of dropping out of medicine before the due date.

Due to a lack of education from the doctor, patient 17 did not know that TB treatment must be completed for 6 months, which caused the patient to stop taking medicine once the medicine from the doctor ran out.

At the beginning of the treatment, patient 18 was actually given education by the doctor,



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but the patient admitted that he did not really understand that TB treatment must be done completely.

Theme IV: Medication Adherence

A. Patients medication adherence is good

The next respondent told how he took his medicine correctly and regularly

Patient 19 said that he had never missed taking TB drugs or missed going to the *puskesmas* (Community Health Center) during his illness

b. Patients do not comply taking medication

The following respondents told the reasons why they were not obedient in taking medicine

Patient 20 said that he had forgotten to take his medicine so it caused the patient missing one schedule

Patient 21 said that he had missed taking medicine once because he had not had time to take medicine at the *puskesmas* (Community Health Center), but then he continued to take medicine accordingly.

Patient 22 said that due to financial problem, he could not afford to go to the *puskesmas* (Community Health Center) to take the medicine.

Theme V: Patients' compliance with repeated sputum tests

A. patient knows the need for re-examination of sputum

The next respondent said that he did not know about the need for a repeat sputum examination/test

Patient 23 did not know the need for a sputum examination for treatment evaluation. The doctor did not suggest him to do it.

B. patient does not know the need for re-examination of sputum

Unlike the previous respondent, the following respondent E always checks sputum regularly.

Patient 24 received good information/education to check sputum for evaluation of the treatment

DISCUSSION

The results of this study indicate that most of the subjects in this study were male (67.2%), the majority aged 41-50 years (26.9%), and the majority lived in Pekanbaru (65.7%). One study that showed relatively identical results was a study conducted by Huda (2017) at RSUD (Regional Public Hospital) Dr. H. Abdul Moeloek Lampung Province. This descriptive study involving 246 people aims to determine the description of patients with Multi Drug-Resistant Tuberculosis (MDR TB) in RSUD dr. H. Abdul Moeloek Lampung Province period January-December 2015. The result of this study showed that patients who experienced rifampicin resistance based on the age of MDR TB patients were the group 26-45 years with 15 patients (51.72%), group 12-25 years with 9 patients (31.03%), group 46-65 years with 5 patients (17.24%), and the lowest > 66 years 0 patients (0%). Based on sex, most MDR TB patients were female which were 15 patients (51.72%), while male 14 patients (48.27%) (Huda, Safitri, & Marhamah, 2018)

Productive age is an age group that is a risk factor for MDR TB. This age group is the group that is more easily exposed and infected by MDR TB because they interact more with other people and have high mobility. Male are more at risk of developing MDR TB than female. This is presumably because women are more easily worried about being ostracized by their family and environment if they are proven to have a contagious disease such as TB. In addition, the male is generally the breadwinner of the family and is more active outside the home, so it is easy to be exposed and infected with MDR TB from other people (Nunkaidah, Lestari, & Afa, 2017)



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However, different results were obtained in Fadlilah's (2021) study, which showed that the majority of MDR TB patients were aged 26-33 years old. In terms of age characteristics, it can be seen that the results of the research conducted by the researcher are in line with (Fadlilah, 2021) study, in which was the majority of MDR TB patients were male.

Smoking habit is more common in male patients. Smoking makes a person more susceptible to tuberculosis, and the death rate from TB is higher in smokers compared to nonsmokers. Smoking habits can also damage the lung defense mechanism called mucociliary clearance. In addition, cigarette smoke increases airway resistance and causes easy leakage of blood vessels in the lungs will also damage macrophages which are cells that can eat nuisance bacteria. The increasing number of TB patients can create a new problem: the increasing number of patients with MDR-TB. Several other studies have found that children who are exposed to cigarette smoke (passive smoker) are also more likely to get TB later. It was also found that TB in smokers is more contagious than TB patients who do not smoke. Smoking habit is also a factor in the progression of pulmonary tuberculosis and the occurrence of fibrosis (Suyastri, Ermayanti, & Russilawati, 2019). In this study, MDR TB patients who smoke are 9 out of 15 male patients (60%).

The Identical results were also obtained in a study conducted by Hendra (2017) at the Haji Adam Malik General Hospital in Medan. This descriptive study with a cross-sectional design involving 178 people was aimed at knowing the characteristics of MDR-TB patients with comorbid DM. The results of this study showed that resistance to rifampin was found in all TBMDR patients with DM (Hendra, 2017).

This study showed that there were only 24 patients (35.8%) who underwent HIV testing. The study subjects who underwent HIV test, the majority showed negative results, there was only 1 person (4%) who showed a positive result. Globally, there were 10.4 million TB cases in 2016, and 10% of them were co-infected HIV. In individuals with HIV, the risk of developing TB is up to 26 times higher than in the general population, even in HIV patients who have relatively high CD4 cells (Tornheim & Dooley, 2018). TB-HIV coinfection occurs through several mechanisms, namely HIV-1 inhibition of the development of T cells that are reactive to *M. tuberculosis*, inhibition of phagocytosis and autophagy in macrophages, macrophage death and tissue necrosis in HIV-1 coinfection, and hypersensitivity reactions known as TB immune reconstitution inflammatory response syndrome (TB-IRIS) (Bell & Noursadeghi, 2018)

Furthermore, based on in-depth interviews conducted to 27 patients, it was found that 12 patients had a history of category 1 TB, which then relapsed, 9 patients had a history of drug withdrawal, 3 patients had a failed treatment and 3 patient were primary cases. In 12 patients who relapsed, mostly due to there was no follow-up after the completion of treatment, it is impossible to know the treatment results for 6 months, whether it works or not. The doctor who treated the patient did not recommend re-examination and stated that the patient had finished treatment after 6 months. There is a possibility that the patient has not recovered and is not continuing treatment. Then the patient was reinfected and became a case of MDR TB.

However, a few patients have been confirmed cured by repeated examinations, but then they were reinfected. Drug resistance is related to previous treatment history. In patients with a history of previous treatment, developing resistance is 4 times higher, while the occurrence



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of MDR is 10 times or more compared to patients who have never been treated (Nofizar, Nawas, & Burhan, 2010).

According to many studies the strongest risk factor for MDR TB is the history of previous treatment with Anti Tuberculosis drugs. One of the studies that prove a very strong relationship between risk factors of previous TB treatment and MDR TB is a study conducted (Balaji, 2010). In 9 patients who had a history of dropping out of treatment, there were patients who were not informed/educated by doctors about TB treatment, patients with poor economic conditions and patients who could not handle the side effects of the medicine that caused inadequate treatment and the patients became resistant to anti-TB drugs.

TB patients with inadequate previous treatment and experiencing higher anti-TB drugs resistance (96.2%) than TB patients who recovered (23.1%). Statistical test results obtained p value = 0.001 and OR = 40.0 (95% CI: 4.66 - 343.14), meaning that the previous treatment was inadequate as a cause of anti-TB drugs resistance. TB patients with inadequate previous treatment were at risk of developing resistance 40 times higher compared to TB patients with adequate treatment (analytical journal).

Sri Melati's research (2010) showed that the results of treatment carried out on MDR-TB patients at the pulmonary polyclinic were 32 (34.5%) MDR-TB dropouts, 26 (27.9%) failed MDR-TB, and 16 (17.2%) patients are still on MDR-TB treatment. Patients with complete treatment of MDR-TB 11 patients (11.8%), MDR-TB patients who were considered completed MDR-TB treatment 6 (6.0%) and MDR-TB patients who recovered were 2 (2.1%). It can be concluded that patients with a history of dropping out of treatment are the most common risk factors for MDR TB (Munir, 2010).

Inadequate management of TB as a cause of resistance can be viewed from the side of the service provider/health worker due to incorrect diagnosis, the treatment that does not use the right combination of dose, type, and inadequate amount of medication, duration, and counseling to the patients. Most of the respondents who suffered from MDR TB had an accurate diagnosis status in the previous TB treatment. Only 7 respondents were not right in carrying out the initial diagnosis of TB treatment (only used chest X-rays photo without carrying out the bacteriological examination.)

In research subjects who showed positive results on microscopic examination, there were 2 people (3%) positive 1, 5 people positive 2 (7.5%), and 1 person (1.5%) positive 3. A positive result 1 means that 10-99 Acid Fast Bacilli (AFB) is obtained in 100 fields of view, a positive result 2 means that 1-10 AFB is obtained per field of view, and a positive result 3 means that more than 10 AFB is obtained per field of view (Bakti, Mertaniasih, Ernawati, Soebadi, & Hadi, 2018). Uniquely, all patients who were the subjects of this study were MDR TB patients, so microscopic examination should have shown positive results. However, this result is reasonable, similar to the results found in the Rasool (2019) study in Pakistan. The study found that 34.52% of culture-positive TB patients showed negative results on AFB examination (Rasool, Khan, Mohy-Ud-Din, & Riaz, 2019). This result may be due to inadequate sputum samples used as examination material so that the results of the smear examination cannot describe the actual conditions in the lungs.

Several previous studies have shown different results from the research that researchers have done. One study that showed different results was obtained in a study in Southeast Sulawesi. This descriptive study involving 40 people aims to explain the characteristics of MDR TB patients in Southeast Sulawesi in 2014-2017.



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The results of the study showed that the majority of MDR TB patients in Southeast Sulawesi in 2014-2017 showed positive microscopic examination 1 (Aini & Rufia, 2019)

This study shows the result from mapping the MDR TB patient in RSUD Arifin Achmad and shows the characteristic of the patients, also shows an in-depth interview to find the risk factors of MDR TB. However, since there's no limitation to when the patients diagnosed with TB, the interview relied on the patients' memory. It would be better if there is a future study with longer period of time and has patients with ongoing treatment as subjects.

CONCLUSION

Most of the MDR-TB patients at the Arifin Achmad Hospital, Riau Province, were male (67.2%), aged 41-50 years (26.9%), and lived in Pekanbaru City (65.7%). There were 30 patients (44.8%) who underwent microscopic examination; the majority (73.3%) showed negative results. Twenty-five patients (37.3%) underwent culture examination; the majority (76%) showed negative results. Most MDR-TB patients in Arifin Achmad Hospital, Riau Province (80.6%) had rifampin resistance results based on TCM examination. 7 patients (10.4%) underwent LPA Line II examination. All patients showed positive results. There were 24 patients (35.8%) who underwent HIV testing. In patients who underwent HIV testing, the majority (96%) showed negative results. There were 12 patients (44.4%) who had a previous history of TB disease who had been declared finished taking medication by a doctor. 9 patients (33.3%) with a history of inadequate TB treatment. 3 patients (11.1%) were declared treatment failure. 3 patients (11.1%) were primary TB and confirmed the laboratory examination results for resistance to OAT. Smoking and DM are not very influential as risk factors for MDR TB. Nine MDR TB patients smoke (33.3%) and 2 DM patients (7.4%).

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