An Analysis of the Relationship between Factors Causing Multi-Drug Resistant Tuberculosis (Mdr-Tb) in the Minahasa Regency Area

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ABSTRACT

The World Health Organization (WHO) estimates that only 8.5% of multidrug-resistant tuberculosis (MDR-TB) is successfully treated. This study analyzes the factors contributing to Multi-Drug Tuberculosis Resistance in Minahasa Regency. This research uses mixed methods that combine quantitative and qualitative methods. Quantitative data uses a cross-sectional study approach, while qualitative in-depth interview data is the basis for strengthening quantitative data. The research was conducted from April to May 2024 in three districts in Minahasa: Tompaso, Kawangkoan, and Langowan. This study involved 111 respondents (94 people with pulmonary TB and 17 people with MDR-TB) and six key informants (4 from the patient's family and two health workers). The results showed that the incidence of MDR-TB in TB sufferers was significantly related to age ≤40 years (p=0.016), marital status (p=0.011), and adherence to taking medication (p=0.000). Multivariate analysis showed a significant relationship simultaneously between age, marital status, and medication adherence and the incidence of MDR-TB, with a p-value of 0.000 (OR 5.529). These results were strengthened by key informants who explained that sufferers experienced difficulties in complying with treatment due to complaints of OAT side effects and the large variety of drugs. In conclusion, there is a significant relationship between age, marital status, adherence to taking medication, and the incidence of MDR TB in Minahasa Regency.

Keywords: Multi-drug resistant Tuberculosi, Minahasa

1. BACKGROUND

Tuberculosis (TB) as an infectious disease is still a problem in public health because it can be a contributing factor to morbidity and even death. According to WHO, approximately 10.6 million individuals were diagnosed with tuberculosis globally in 2021, marking an increase of around 600,000 cases compared to the estimated 10 million cases in 2020. Meanwhile, Indonesia is known to be 1 of the 5 countries that have the heaviest incidence of TB besides India, China, the Philippines, and Pakistan (WHO, 2021).

TB in Indonesia ranks third after India and China, with 824,000 cases and 93,000 deaths per year, equivalent to 11 deaths per hour. According to the Global TB Report in 2022 (WHO, 2022), the highest number of TB cases was found in the age group of 25 to 34 years. In Indonesia, most TB cases are in the productive age group, especially at the age of 45 to 54 years.

The efforts made globally and by the Indonesian government do not always go well. In some cases, the treatment even stops or what is known as Multi Drag TB. This causes the success of TB treatment not to be achieved due

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to incomplete and inadequate patient treatment. Irregularity and non-compliance with regimens, doses, improper use of drugs, interruptions in OAT availability, and poor drug quality are factors in treatment failure.

Multidrug resistant tuberculosis (MDR-TB) occurs when TB germs are resistant to multiple OAT. WHO estimates the prevalence of MDR-TB to be around 440,000 cases annually worldwide with a mortality rate of around 150,000 and around 8.5% that have been found and treated. In Indonesia, which is categorized as the High Burden Countries with the highest TB prevalence in the world, there are 8,900 TB cases. 2% of MDR-TB cases are estimated to come from new TB cases and 14.7% from re-treated TB cases (WHO, 2016). In 2021, the number of MDR TB patients in Indonesia is 28,000 cases.

The (WHO, 2017) reported that 3 indicators for high burden countries (HBC) were divided into TB, MDR-TB, and TB/HIV. 48 countries are listed under one, two, or all three indicators. There are 13 high burden countries (HBC), including Indonesia. The World Health Organization in 2019 set a treatment success standard of 85%. The treatment success rate for MDR-TB was 56% in 2018. The success rate of TB treatment in Indonesia in 2018 (data as of January 31, 2019) was 80.12% with a total of 431,876 cases. Cure coverage was 153,598 cases and complete treatment was 192,426 cases (WHO, 2019).

In 2021 in North Sulawesi, the coverage of the final results of MDR-TB treatment where those who recovered were 35.13%, complete treatment was 59%, Lost to follow up 47.3% and died 10.81%. This is still far from the indicator of cured treatment, which is 80% (DINKES North Sulawesi, 2021). In Minahasa district in 2021, the total number of patients treated was 616 patients and those declared cured were 137 patients or 22.24%, and patients with Lost to follow up status were 31 patients or 5.03%.

MDR-T cases in Minahasa Regency, North Sulawesi, recorded the number of patients in 2021 totaling 31 out of the total number treated The Case Detection Rate (CDR) was 44% CDR coverage in 2022. It still has not reached the target set of 70%. The high rate of new case finding indicates that TB prevention has not been effective and risks a continuous increase in transmission.

Based on the findings of the Health Research and Development Agency of the Republic of Indonesia, one of the factors causing MDR-TB in Indonesia is non-compliance in TB treatment, so that some patients choose to stop taking anti-tuberculosis drugs because they feel uncomfortable with the side effects that arise after taking Anti Tuberculosis Drugs (Alveryna et al., 2020).

According to the Ministry of Health of the Republic of Indonesia 2018, TB patients experience side effects from the use of anti-tuberculosis drugs. Side effects caused by OAT include loss of appetite, nausea, vomiting, abdominal pain, headache, itchy skin, joint pain, tingling sensation, visual disturbances, hearing loss, and redness of urine (Abbas, 2017). The severity of OAT side effects often experienced by TB patients will also have an impact on patient compliance in taking medication so that it can cause patients to drop out and make patients not recover from TB disease (Sari et al., 2017).

Therefore, the researcher is interested in identifying the factors that cause multidrug-resistant tuberculosis (MDR-TB) in Minahasa Regency by analyzing the relationship between these causative factors. This study aims to analyze the relationship between the factors causing MDR-TB in Minahasa Regency.

2. RESEARCH METHODOLOGY

This study uses a mixed-method approach that combines quantitative and qualitative methods. The researcher will analyze the factors causing a particular disease in the study sample and then integrate the quantitative analysis results with the qualitative findings to obtain more valid analysis results. The design of this study uses an Explanatory Sequential Design, which involves planning an explanatory mixed method. Initially, the research will collect quantitative data with a cross-sectional approach, meaning data collection is done only at a specified time. The data obtained will include factors related to and

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causing MDR-TB. Subsequently, qualitative data will be collected to help explain and strengthen the quantitative analysis results. The study will be conducted in the working area of Minahasa Regency, specifically in three districts: Tompaso, Kawangkoan, and Langowan, from April to May 2024. In conducting this research, the researcher adheres to the ethical guidelines obtained from the Ethics Committee of Prof. Dr. R. D. Kandou General Hospital in Manado, with the ethical approval number No.121/EC/KEPK-KANDOU/VI/2024.

The population in this study consists of all pulmonary tuberculosis patients, including those experiencing multi-drug-resistant tuberculosis, totaling 94 pulmonary tuberculosis patients and 17 MDR-TB patients. Due to insufficient research samples, the researcher decided to include the entire population as the study sample (total sampling) to understand what causes patients to be affected by MDR-TB thoroughly. Total sampling is used as the sampling technique in this study, with the entire population being taken as the research sample, totaling 111.

For qualitative analysis, the researcher uses six main informants, adhering to the standard sample for qualitative research, and adds one representative informant who is an MDR-TB patient to provide in-depth information related to MDR-TB incidence. The researcher identifies four informants as family members of the patients or as Treatment Supervisors (PMO) for MDR-TB patients. The main informants in this study represent all MDR-TB and pulmonary TB patients at the community health centers in Minahasa Regency.

Additionally, the researcher selects two key informants: one healthcare worker (nurse/doctor) handling MDR-TB patients and one healthcare worker (nurse/doctor) handling pulmonary TB patients. The main informants in this study aim to provide qualitative data sources regarding patient adherence. In contrast, the key informants are intended to provide information about the care and treatment of MDR-TB and pulmonary TB patients.

2.1 Technique of Collecting Data

Validated and reliable by (Octaviani & Kusuma, 2018) with a Cronbach's alpha greater than 0.6). Respondents filled these out, and secondary data comprised the number of patients from Tompaso, Langowan, and Kawangkoan Health Centers. Additionally, qualitative data sources came from in-depth interviews between the researcher and patients diagnosed with MDR-TB, as well as document reviews of the factors leading to an MDR-TB diagnosis and medication records of MDR-TB and pulmonary TB patients at the health centers in Minahasa Regency. In-depth interviews collected data until no new information emerged from MDR-TB patients, at which point the data were considered saturated. The interview and question topics followed the technical guidelines for managing latent tuberculosis infection (ILTB) from the Ministry of Health of the Republic of Indonesia, 2020.

There are two variables in this study, namely the independent variable and the dependent variable. The independent variables consisted of age, gender, latest education, occupation, income, marital status, and medication adherence. Furthermore, the dependent variable is MDR-TB patients as a positive group and Pulmonary TB patients as sensitive patients.

2.2 Technique of Analyzing Data

Quantitative data will be processed through editing, coding, data entry into SPSS data analysis software, and cleaning. Once the researcher completes data entry into SPSS, the data analysis stages include univariate, bivariate, and multivariate analyses. Bivariate analysis uses the Chi-Square test with the assumption that if the p-value is < 0.05, it can be concluded that the two tested variables are related. Multivariate analysis employs logistic regression testing, where a significance value < 0.05 indicates a partial (individual) relationship between the independent and dependent variables.

Transcribing interview data, coding, organizing data, data reduction, triangulation, presentation, and concluding will process qualitative data.

3. RESULT AND DISCUSSION

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The results of the research from the results of univariate analysis are from the characteristics of age, gender, latest education, occupation, income, marital status, and compliance with taking medication are as follows; the largest number of respondents were at the age of ≤41 years with a total of 89 (80.2%), and the few respondents were aged 42-56 years with a total of 22 (19.8%). Then the characteristics of gender, the largest number of respondents were male as many as 84 (76%) and the number of respondents were female as many as 27 (24%). Furthermore, the characteristics of education, namely the largest number of respondents with education ≤ SMA there are 96 people (86.5%) and the few with undergraduate education 15 (13.5%). From the characteristics of salary / income, it turns out that respondents with income <UMP are 33 (29.7%), and respondents with income ≥UMP are 78 (70.3%). Then seen from the marital status, the number of respondents with married status was 75 (67%), and respondents with unmarried status were 36 (32.4%). And the last characteristic is the Respondent's Medication Compliance, it was noted that the number of respondents who were not compliant with taking medication was 17 (38.7%), and respondents with compliant status were 94 (61.3%).

Table 1. Characteristics of MDR-TB sufferers

Characteristics	n	%
Age		
≤41 Years Old	89	80,2
42-56 Years Old	22	19,8
Sex		
Male	84	76
Female	27	24
Education		
≤Senior High School	96	86,5
Bachelor Degree	15	13,5
Work		
Work	91	82
Doesn't Work	20	18
Income		
<UMP	33	29,7
≥UMP	78	70,3
Marital status		
Marry	75	67,6
Not married yet	36	32,4
Medication Adherence		
Not obey		
Obedient	17	38,7
	94	61,3

In the second stage of bivariate analysis, the researcher tested two variables simultaneously using the Chi-Square test to assess their relationship. The independent variables include age, gender, highest education level, occupation, income, marital status, and medication adherence. The dependent variable consists of MDR-TB patients as the positive group and pulmonary TB patients as the sensitive group.

The cross-tabulation or Chi-Square test results obtained a P-value of 0.001 (<0.05), indicating a significant relationship between age and MDR-TB occurrence. Additionally, the cross-tabulation or Chi-Square test showed a significant relationship between marital status and MDR-TB occurrence with a P-value of 0.011 (<0.05). Furthermore, medication adherence and MDR-TB occurrence were also found to have a significant relationship with a P-value of 0.000 (<0.05).

On the other hand, several variables showed no significant relationship: gender with MDR-TB occurrence had a P-Value of 0.486 (>0.05), education with MDR-TB occurrence had a P-Value of 0.819 (>0.05), occupation with MDR-TB occurrence had a P-Value of 0.157 (>0.05), and income with MDR-TB occurrence had a P-Value of 0.262 (>0.05).

Table 2. Bivariate Analysis

No	Variable	P-value
1	Age	0,016
2	Gender	0,486
3	Highest Education	0,819
4	Occupation	0,157
5	Income	0,262
6	Marital Status	0,011
7	Medication Adherence	0,000

The incidence of MDR-TB is high in the productive age group, particularly in the 25-34 year age range. Age groups associated with increased MDR-TB risk include those aged 18-25 years and those aged 26-45 years. Individuals in younger age groups or the productive age range are more likely to contract MDR-TB due to being more active in their jobs and facing difficulties in adhering to medication schedules because of their busy work schedules. This non-compliance in treatment leads to

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higher susceptibility to MDR-TB. Similarly, in Amhara, individuals younger than or equal to 25 years old are more vulnerable to MDR-TB. (Soesanti & Husen, 2022).

MDR-TB is often found more frequently in males compared to females. Men also often have more contacts outside the home, given that they can be the primary breadwinners in a family. The lifestyle of men, such as smoking, contributes to a higher risk of developing pulmonary tuberculosis because smoking damages the lung's defense mechanisms (Al Qarni Bayan, 2022). Research by (Absor et al., 2020) found that the highest level of education associated with the highest level of treatment adherence in pulmonary tuberculosis patients is education below the college level. According to this study, individuals with higher education levels better understand their disease, which impacts their motivation to recover.

All respondents, 82% of whom worked and conducted activities outside their homes. Additionally, 16 patients with Multi-Drug Tuberculosis Resistance were employed. According to research by (Qoyyima et al., 2020) respondents who work tend to undergo pulmonary tuberculosis treatment for more than six months because individuals who work often cannot adhere to medication guidelines due to reasons such as forgetting amidst their busy schedules outside the home, reluctance to take medication due to side effects impacting work performance, or personal reasons of each patient.

The income characteristics of the study respondents showed that 78 (70.3%) respondents had incomes ≥ Minimum Wage, and 33 (29.7%) had incomes < Minimum Wage. According to a systematic literature review, socioeconomic status in terms of low income is strongly associated with the incidence of pulmonary tuberculosis.

The cross-tabulation resulted in a p-value of 0.011, concluding that there is a significant relationship between marital status and the occurrence of Multi-Drug Tuberculosis Resistance in Minahasa Regency. This finding is supported by (Ratnasari, 2020), who stated that the interaction and proximity of respondents meeting their partners or core family members in the same household can trigger bacterial transmission, potentially leading to the infection of the respondents' partners with pulmonary tuberculosis.

In The relationship between Medication Adherence and the occurrence of Multi-Drug Tuberculosis Resistance in Minahasa Regency, The research results indicate a significant relationship between medication adherence and the occurrence of Multi-Drug Tuberculosis Resistance in Minahasa Regency, with a p-value of 0.000 < 0.05. This is because when someone is non-adherent to anti-tuberculosis medication, they are more likely to be diagnosed with Multi-Drug Tuberculosis Resistance compared to those who adhere to their medication.

In addition, the three variables that had an association with MDRT, namely age, marital status, and medication adherence, were analyzed again using multivariate analysis.

Table 3. Multivariate Analysis

Variable	B	P-value	OR
Age, Marital status, Medication adherence	1,710	0,000	5,529

The results of the analysis related to the incidence of Multi-Drug Tuberculosis Resistence in the Minahasa Regency area found 17 patients with Multi-Drug Tuberculosis Resistence. A total of 7 independent variables were examined as factors associated with the incidence of Multi-Drug Tuberculosis Resistence in the Minahasa Regency area and 3 variables were stated to have an association with the incidence of Multi-Drug Tuberculosis Resistence in the Minahasa Regency area, namely age, marital status, and drug compliance. In the logistic regression test results, it was found that the OR value of 5.529 in the three variables including age, marital status, and drug compliance had a risk of 5.529 causing the incidence of Multi-Drug Tuberculosis Resistance. Misuse of anti-tuberculosis drugs, non-compliance in taking medication can increase the chance of drug resistance so that the drugs consumed will no longer be effective in killing tuberculosis

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bacteria that already exist in the body and can result in a longer treatment period (Yobeanto & Setiawan, 2022).

The results of research conducted by (Sutrisna & Rahmadani, 2022) said that people with an age of <45 years are more at risk of being diagnosed with Multi-Drug Tuberculosis Resistance due to their productive age and have many activities outside the home. This is in line with the results of this study because it was found that the age of <42 years diagnosed with Multi-Drug Tuberculosis Resistance was 10 respondents. The high mobility that occurs at a young age allows for greater exposure to tuberculosis germs. Also, the productive age group that has many activities outside the home often passes the time of taking medicine which results in the medicine not being taken according to the doctor's recommendation. The statement that respondents often forgot to take medicine was stated by informant 1 as the PMO of respondents with Multi-Drug Tuberculosis Resistance. informant 1 said that informant 1 often reminded respondents to take medicine but respondents ignored the attention of informant 1 and consequently forgot to take medicine.

It can be seen in the results of the study that as many as 17 respondents diagnosed with Multi-Drug Tuberculosis Resistence were classified into the category of non-adherent in taking medication. If people with pulmonary tuberculosis do not undergo therapy or treatment regularly, it is possible that people with pulmonary tuberculosis will be resistant to treatment and aggravate the disease because the bacteria will live longer in the body so that it can infect the body more severely and refer to the re-treatment of people with pulmonary tuberculosis and this allows people with pulmonary tuberculosis to be categorized as Multi-Drug Tuberculosis Resistence (Amalia et al., 2022).

Therefore, successful treatment of pulmonary tuberculosis is needed so that the quality of life of pulmonary tuberculosis patients can be improved and optimal recovery can be achieved. Several reasons were expressed by each informant in the results of interviews with informants that the side effects of taking anti-tuberculosis drugs were the cause of respondents' non-compliance with taking anti-tuberculosis drugs. In a study conducted by (Priyaputranti et al., 2023), they found two cases of drug side effects associated with the use of anti-tuberculosis drugs, including the appearance of nausea and aches throughout the body. Compliance in the treatment of tuberculosis is very important to achieve recovery and anticipate the emergence of drug resistance or commonly referred to as Multi-Drug Tuberculosis Resistance. Regular intake of medication in accordance with the recommendations of the health worker handling the patient is the right step for the recovery of people with pulmonary tuberculosis. The side effects felt after taking OAT resulted in many respondents who were not compliant in taking medication. This is due to the lack of information about the side effects of OAT regularly (Depo & Pademme, 2022).

The results of interviews with informant 1 and informant 2 concluded that the side effects felt by respondents were in the form of lack of appetite, difficulty sleeping, easy fatigue, and lack of energy so that respondents with Multi-Drug Tuberculosis Resistance immediately stopped their treatment. Respondents often did not take their medication because the medicine did not taste good, there were too many variations of medicine, they forgot, and they underestimated the treatment because they thought the disease was a common cough that could heal quickly. Even though this has been explained repeatedly by the health worker handling the respondent and also the respondent's PMO. Meanwhile, other respondents would always take medication despite the side effects and this was stated by informant 3 that even though the respondent felt side effects such as difficulty eating, feeling nauseous, and cold sweats after taking medication, the respondent would still force herself to continue taking anti-tuberculosis drugs and this was also due to the encouragement of the PMO who continuously reminded and tried to explain to the respondent to take anti-tuberculosis drugs. The statements from each informant concluded that the importance of PMO support with respondents' compliance in taking anti-tuberculosis drugs. In line with research conducted by (Depo & Pademme, 2022) which states that there is a

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relationship between support from PMOs and patient compliance in undergoing pulmonary tuberculosis treatment. The results of this study are in line with the results of research conducted by (Papeo et al., 2021) that when people with pulmonary tuberculosis are obedient in taking anti-tuberculosis drugs, the quality of life of people with pulmonary tuberculosis will improve and can produce positive treatment in this case the recovery of people with pulmonary tuberculosis. Likewise, with the results of research conducted by (Amalia et al., 2022), there is a very strong relationship between patient compliance in taking anti-tuberculosis drugs and their quality of life which can lead to the recovery of people with tuberculosis.

CONCLUSION

Based on the results obtained, it can be concluded that there is a significant relationship between age, marital status, and medication adherence of 5.529 times for the occurrence of multidrug tuberculosis resistance in Minahasa Regency with a p-value of 0.000.

SUGGESTION

The Health Office is expected to increase intensive socialization about MDR-TB in the cities and districts of Minahasa Regency, so that case finding and handling of MDR-TB in the regions will be better. Health centers are expected to educate the community about the importance of maintaining the quality of the home environment, both in terms of lighting, ventilation, reducing the density of the number of occupants, as well as the cleanliness of the house and the environment to reduce the risk of developing TB disease. It is recommended for future researchers to conduct further research involving qualitative research methods, so as to explore information in more depth, especially about factors of adherence to treatment, treatment history, and also other factors.

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