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# Multidrug resistant tuberculosis risk factors in Makassar, Indonesia

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**ABSTRACT**

Multidrug resistant tuberculosis (MDR-TB) is a significant public health concern in Indonesia, resulting in substantial morbidity and mortality rates. This study aimed to quantify the impact of risk factors of MDR-TB. A case-control study was conducted at Makassar Community Lung Health Center (BBKPM) in Makassar City. A total of 132 respondents, 66 cases, and 66 controls have participated in the study. Data was analyzed using the Stata version 14 tool, odds ratio (OR), and multiple logistic regression. Multiple logistic regression analysis identified significant risk factors for the occurrence of MDR-TB include previous TB treatment (OR=8.46, 95% CI: 3.278-21.858), positive acid-fast bacilli (AFB) sputum (OR=6.40, 95% CI: 2.525-16.260), and adverse drug event (OR=3.45, 95% CI: 1.008-11.867). The probability of developing MDR-TB is 95.9% if there is previous TB treatment with cases of relapse/loss to follow-up/failed treatment, positive AFB sputum, and adverse drug event. The most dominant risk factor for the occurrence of MDR-TB is a previous TB treatment. We suggest that an efficient directly observed treatment shortcourse (DOTS) strategy, particularly in the management of adverse drug event, overseeing and supporting patients who have recovered from MDR-TB, involves the collaboration of MDR-TB healthcare professionals and patient supporters in the Yamali TB community, moving synergistically as an effort to MDR-TB control and prevention.



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## 1. INTRODUCTION

Multidrug resistant tuberculosis (MDR-TB) remains a significant challenge in TB management and is a major public health issue in numerous countries worldwide. MDR-TB refers to a strain of *Mycobacterium tuberculosis* resistant to first-line anti-TB medications, specifically rifampicin (R) and isoniazid (H), which are highly effective against *Mycobacterium tuberculosis* bacteria. MDR-TB poses a new challenge in TB control initiatives due to its challenging diagnosis and high rates of therapeutic failure and mortality [1]. The World Health Organization (WHO) data from 2015-2020 indicates that the global estimate of MDR-TB cases remained consistent. In 2021, the predicted proportion of MDR-TB patients is 3.6%, which amounts to 450,000 cases. The current figure has risen compared to 2020, which stood at 3.1% (437,000 cases). This is believed to be connected to the coronavirus disease 2019 (COVID-19) epidemic,

which has hindered the early detection of TB. The anticipated global proportion of individuals suffering from MDR-TB in 2021 is 3.6%. Among these, 3.6% of individuals with MDR-TB were new cases, while 18% had a history of TB treatment. In Southeast Asia in 2020, there were 164,000 cases of MDR-TB, and in 2021, there was a rise to 172,000 cases. Ten countries, including China, Democratic Republic of Congo, India, Indonesia, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, and Vietnam, represent almost 70% of the expected global MDR-TB cases in 2021 [2].

Indonesia is ranked fifth among the 30 nations with the highest burden of MDR-TB in the world in 2021 [2]. In 2020, it is anticipated that 2.4% of new TB patients and 13% of previously treated TB patients would have MDR-TB, totaling approximately 24,000 cases (8.8 per 100,000 population) [1]. In 2021, there will be an increase of 28,000 cases (10 per 100,000 population) of MDR-TB, which is attributed to the influence of the COVID-19 pandemic on the detection of TB [2]. The notification rate for all tuberculosis cases in South Sulawesi Province is escalating annually. In 2021, Ministry of Health of the Republic of Indonesia, reported 165 cases per 100,000 population, rise to 267 cases per 100,000 population in 2022 [3]. In 2020, the South Sulawesi Provincial Health Office reported 28.7% of TB cases in Makassar is the highest percentage among all cities and districts in South Sulawesi Province [4].

In Sudan, research found that patients who had been in contact with MDR-TB patients were five times more likely to get MDR-TB than patients who had not been in contact with MDR-TB patients [5]. Research in Pakistan indicates that cavities shown on X-ray exams are a risk factor for MDR-TB. Patients with lung cavities are 30 times more likely to develop MDR-TB than patients without lung cavities on X-ray [6]. A study conducted in Mali indicates that the presence of 3+ acid-fast bacilli (AFB) sputum significantly affects the occurrence of MDR-TB. Patients with 3+ AFB sputum results have a twofold increased chance of acquiring MDR-TB [7]. Patients with previous TB treatment are five times more likely to develop MDR-TB than patients without such a history [8]. A correlation exists between adverse drug event and the prevalence of MDR-TB [9]. MDR-TB patients with comorbid diabetes mellitus are four times as likely to develop MDR-TB than MDR-TB patients non-comorbid [10]. A correlation exists between dietary status and the prevalence of MDR-TB. Patients with body mass index (BMI) <18.5 kg/m2 have a 1.57 times higher risk of MDR-TB compared to those with a BMI ≥18.5 kg/m2 [11]. Extensive studies have been carried out on risk factors for MDR-TB. Further exploration of clinical factor research is still required. The prevalence of MDR-TB remains high. It is crucial to address the risk factors associated with MDR-TB to reduce its occurrence. Researchers are interested in investigating factors that may elevate the occurrence of MDR-TB at BBKPM in Makassar City.

## 2. METHOD

This quantitative analytical research is conducted through a case-control study design. MDR-TB patients as cases and non-MDR-TB patients as controls. The study was conducted from October to December 2023 at BBKPM in Makassar City. The ethical clearance of research has been approved by the Hasanuddin University Research Ethics Commission under the number 5619/UN4.14.1/TP.01.02/2023.

The study's population consists of all TB patients who have received and are presently receiving treatment at BBKPM in 2022. The sampling method used in this study was total sampling, a 1:1 ratio between cases and controls. The sample size was 132 samples, with 66 cases and 66 controls. The control sampling method employed was purposive sampling based on certain criteria, i) this study included TB patients receiving outpatient treatment at the BBKPM Makassar City in 2022, ii) excluded from the study were TB patients with human immunodeficiency virus (HIV), TB patients aged 1-14 years, and TB patients with incomplete data in the medical records BBKPM Makassar City in 2022.

The study gathered data from the SITB and medical records of the BBKPM Makassar City in 2022. The data was examined using Stata version 14. Data was analyzed using univariate, bivariate, and multivariate analysis. The odds ratio (OR) test assessed the relationship and magnitude of risk factors between the dependent and independent variables. The methodology employed is multivariate and involves multiple logistic regression. This study's limitations include a discrepancy between TB patient data from the SITB and medical records, resulting in the exclusion of one respondent due to data being solely documented in the SITB without corresponding medical records. Additionally, comorbidity factors in the study were restricted to hypertension and diabetes mellitus. At the same time, comorbid HIV was removed as a study factor due to the absence of patients with comorbid HIV in the case group. Patients with comorbid HIV were considered exclusion criteria in the control group.

## 3. RESULTS AND DISCUSSION

Table 1 indicates that a higher percentage of participants were male in both the case and control groups. The case group had the largest number of males at 60.61%, while the control group had 57.09%. Physiological and behavioral factors determine the disparity in the occurrence of MDR-TB between men and women. The X chromosome contains several immune-related genes that increase susceptibility to TB. The X chromosome consists of almost 1,100 genes, most of which have immunomodulatory properties, in contrast to the 100 genes found on the Y chromosome. Additionally, women exhibit a stronger immune response to antigenic reactions, such as vaccination or infection, than men [12].

Table 1. Frequency distribution of respondent characteristics at BBKPM Makassar 2022

| Characteristics of respondents | MDR-TB | | | | Total | |
|---|---|---|---|---|---|---|
| | Cases | | Controls | | | |
| | n=66 | % | n=66 | % | n=132 | % |
| Gender | | | | | | |
| Male | 40 | 60.61 | 38 | 57.58 | 78 | 59.09 |
| Female | 26 | 39.39 | 28 | 42.42 | 54 | 40.91 |
| Age | | | | | | |
| 15-24 | 11 | 16.67 | 10 | 15.15 | 21 | 15.91 |
| 25-34 | 13 | 19.70 | 8 | 12.12 | 21 | 15.91 |
| 35-44 | 14 | 21.21 | 11 | 16.67 | 25 | 18.94 |
| 45-54 | 13 | 19.70 | 15 | 22.73 | 28 | 21.21 |
| 55-64 | 10 | 15.15 | 16 | 24.24 | 26 | 19.70 |
| 65-74 | 4 | 6.06 | 5 | 7.58 | 9 | 6.82 |
| ≥75 | 1 | 1.52 | 1 | 1.52 | 2 | 1.52 |
| Education level | | | | | | |
| No Education | 4 | 6.06 | 0 | 0 | 4 | 3.03 |
| Primary school | 7 | 10.61 | 3 | 4.55 | 10 | 7.58 |
| Middle secondary | 15 | 22.73 | 6 | 9.09 | 21 | 15.91 |
| Higher secondary | 23 | 34.85 | 31 | 46.97 | 54 | 40.91 |
| Degree and above | 17 | 25.76 | 26 | 39.39 | 43 | 32.58 |
| Employment status | | | | | | |
| Unemployed | 32 | 48.48 | 19 | 28.79 | 51 | 38.64 |
| Government employee | 5 | 7.58 | 12 | 18.18 | 17 | 12.88 |
| Private empleyee | 6 | 9.09 | 7 | 10.61 | 13 | 9.85 |
| Self-employed | 4 | 6.06 | 9 | 13.64 | 13 | 9.85 |
| Farmer/fisherman/labor | 9 | 13.64 | 6 | 9.09 | 15 | 11.36 |
| Retired | 1 | 1.52 | 4 | 6.06 | 5 | 3.79 |
| Student | 2 | 3.03 | 9 | 13.64 | 11 | 8.33 |
| Others | 7 | 10.61 | 0 | 0 | 7 | 5.30 |
| Marital status | | | | | | |
| Married | 41 | 62.12 | 47 | 71.21 | 88 | 66.67 |
| Divorced/separated | 5 | 7.58 | 3 | 4.55 | 8 | 6.06 |
| Single | 20 | 30.30 | 16 | 24.24 | 36 | 27.27 |

Most participants in the case group were aged between 35 and 44 years, accounting for 21.21%, whereas in the control group, 24.24% fell within the 55-64 year age range. Individuals in the pre-elderly category are more prone to infectious diseases due to a decline in the immune system's capacity to combat infections as they age [13]. The majority of respondents have completed higher secondary school. The percentage of higher secondary schools was 34.85% in the case group and 46.97% in the control group. In the case group (48.48%) and the control group (28.79%), most respondents did not work. There were more married in the cases and control groups. 62.12% of respondents in the case group were married, compared to 71.21% in the control group.

Table 2 indicates that AFB sputum exhibited predominantly high risk in the case group (71.21%) and low risk in the control group (59.09%). Similarly, in terms of the lung cavity, the majority of participants in the case group (59.09%) were classified as high risk, whereas in the control group, the majority (54.55%) were classified as low risk. In the case group, the previous treatment history was predominantly associated with high risk (59.09%), while in the control group, it was largely associated with low risk (78.79%).

Regarding adverse drug event, a higher percentage of respondents in the control group (92.42%) were classified as low risk compared to the case group (75.76%). Similarly, the majority of respondents in both the case group (72.73%) and the control group (65.15%) had a low-risk level for the comorbidity. The majority of respondents in the case group (56.06%) were classified as being at high risk in terms of BMI patients, while the majority of respondents in the control group (57.58%) were classified as being at low risk.

AFB sputum is associated with an increased risk of MDR-TB, OR=3.57 (confidence interval (CI) 95%: 1.632-7.882). Cavity is not statistically significant as a risk factor for MDR-TB (p-value>0.05).

Previous TB treatment is a significant risk factor for MDR-TB, OR=5.36 (CI 95%: 2.341-12.513). Adverse drug event increase the incidence of MDR-TB, OR=3.90 (95% CI: 1.242-14.451). Comorbidity variables and BMI are not significantly associated with MDR-TB (p-value>0.05).

Table 2. Bivariate analysis MDR-TB risk factors at BBKPM Makassar 2022

| Variables | MDR-TB | | | | Total | | |
|---|---|---|---|---|---|---|---|
| | Cases | | Controls | | | | |
| | n=66 | % | n=66 | % | P value | Odds ratio | CI 95% |
| AFB sputum | | | | | | | |
| Positive | 47 | 71.21 | 27 | 40.91 | 0.000 | 3.57 | 1.632-7.882* |
| Negative | 19 | 28.79 | 39 | 59.09 | | | |
| Cavity | | | | | | | |
| Yes | 39 | 59.09 | 30 | 45.45 | 0.116 | 1.73 | 0.822-3.662 |
| No | 27 | 40.91 | 36 | 54.55 | | | |
| Previous TB treatment | | | | | | | |
| Relapse/loss to follow up (LTFU)/failure | 39 | 59.09 | 14 | 21.21 | 0.000 | 5.36 | 2.341-12.513* |
| New | 27 | 40.91 | 52 | 78.79 | | | |
| Adverse drug event | | | | | | | |
| High risk | 16 | 24.24 | 5 | 7.58 | 0.008 | 3.90 | 1.242-14.451* |
| Low risk | 50 | 75.76 | 61 | 92.42 | | | |
| Comorbidity | | | | | | | |
| High risk | 18 | 27.27 | 23 | 34.85 | 0.347 | 0.70 | 0.311-1.568 |
| Low risk | 48 | 72.73 | 43 | 65.15 | | | |
| BMI | | | | | | | |
| <18.5 kg/m$^2$ | 37 | 56.06 | 28 | 42.42 | 0.117 | 1.73 | 0.822-3.655 |
| ≥18.5 kg/m$^2$ | 29 | 43.94 | 38 | 57.58 | | | |

* = Statistically significant

Table 3 displays the variables considered in the logistic regression test based on their statistical significance with a p-value<0.25 from the bivariate test. The variables included AFB sputum, cavity, previous TB treatment, adverse drug event, and BMI. The final results of the multivariate analysis using logistic regression indicate that previous TB treatment, AFB sputum, and adverse drug event are risk factors of MDR-TB.

Table 3. Multivariate analysis MDR-TB risk factors at BBKPM Makassar 2022

| Research variables | Coef. | p-value | Adjusted odds ratio | CI 95% (*LL-UL*) |
|---|---|---|---|---|
| Previous TB treatment | 1.858 | 0.000 | 8.46 | 3.278-21.858 |
| AFB sputum | 2.136 | 0.000 | 6.40 | 2.525-16.260 |
| Adverse drug event | 1.240 | 0.049 | 3.45 | 1.008-11.867 |

Among these three variables, previous TB treatment has the highest impact as a risk factor, AOR=8.64 (95% CI=3.278-21.858). The logistic regression equation is displayed in (1) and the probability of MDR-TB for high-risk respondents is indicated in (2).

$$\begin{aligned} y &= conts + coef_{(AFBSputum)} + coef_{(PreviousTBTreatment)} + coef_{(AdverseDrugEvent)} \\ y &= -2.064 + 1.858 + 2.136 + 1.240 \\ y &= 3.17 \end{aligned} \quad (1)$$

After obtaining the value of *y*, the probability of the subject is calculated using (2):

$$\begin{aligned} P &= \frac{1}{(1 + exp^{(-y)})} \\ P &= \frac{1}{(1 + exp^{(-3.17)})} \\ P &= 95.9\% \end{aligned} \quad (2)$$

The multivariate analysis results indicated that respondents with positive AFB sputum, previous TB treatment (relapse/ loss to follow up (LTFU)/treatment failure), and adverse drug event at high risk had a 95.9% probability of developing MDR-TB.

### 3.1. AFB sputum

AFB sputum is a risk factor for MDR-TB. Respondents with positive AFB sputum were 3.57 times more likely to develop MDR-TB than those with negative AFB sputum. This study aligns with previous research conducted in Mali, indicating that those with sputum BTA (3+) have a 1.98 times higher risk of MDR-TB compared to those with sputum BTA (<3+) [7]. The findings from a study conducted in China indicated that the presence of positive AFB sputum in new patients undergoing a long-term regimen was linked to the development of MDR-TB [14]. Positive AFB sputum has a fourfold higher risk of poor treatment outcomes for MDR-TB compared to negative AFB sputum [15]. A study in West Java found that sputum smear results were a significant factor in predicting the outcome of MDR-TB treatment [16]. Most cases showed the presence of positive AFB sputum. Respondents having positive sputum results for acid-fast bacilli are very contagious and can spread pulmonary TB illness to others. Increased positivity in sputum results correlates with a higher risk of transmission to others [15]. Positive sputum results for acid-fast bacilli contribute to the transmission of TB and MDR-TB, potentially leading to drug resistance.

### 3.2. Cavity

Cavity is not a significant risk factor for MDR-TB. This study aligns [16] indicating that cavities represent a negligible risk factor. In China, it was found that cavities in newly diagnosed patients are not a risk factor for MDR-TB [14]. A study conducted in China found that cavities were not linked to negative treatment results in individuals with MDR-TB [15]. Contrary to the study, there is a connection between X-ray and the occurrence of MDR-TB [17]. Patients with cavities on X-ray have a 30.1 times higher risk of getting MDR-TB compared to patients without cavities [6].

### 3.3. Previous TB treatment

Previous TB treatment increases the likelihood of developing MDR-TB. Respondents with a history of previous TB treatment (relapse/LTFU/failure) had a 5.36 times higher probability of MDR-TB compared to those in the new diagnosis. This study aligns with earlier studies indicating that patients with previous TB treatment are 2.8 times more likely to develop MDR-TB compared to newly diagnosed patients [18]. This study aligns with research conducted in Mali, indicating that previous TB treatment is a risk factor for the development of MDR-TB. Patients with a history of two previous treatments are 3.25 times more likely to develop MDR-TB compared to patients with more than two previous treatments. Many patients with MDR-TB are respondents receiving initial TB therapy who fail to adhere to proper drug administration (dosage, schedule, and preventive strategies) [7]. These findings align [6], [8], [19] that patients in Pakistan, Bhutan, and Zimbabwe who had received therapy before were at a significantly higher risk of 19.2 times, 5.9 times, and 3.53 times developing MDR-TB compared to participants diagnosed with a new therapy. Unlike a study conducted in Pakistan, previous TB treatment was not linked to death and treatment failure in MDR-TB patients [20]. A study conducted in Eritrea, East Africa, found no correlation between previous TB treatment and the failure of MDR-TB treatment [21]. MDR-TB develops due to the patient's noncompliance with therapy, leading to bacterial mutation and resistance to the prescribed drugs. Inadequate supervision during treatment and limited access to health services are closely linked to the emergence of MDR-TB [18].

### 3.4. Adverse drug event

Adverse drug event increases the likelihood of developing MDR-TB. Respondents with high-risk adverse drug event were 3.9 times more likely to have MDR-TB occurrences than those with low-risk adverse drug event. This study aligns indicating a correlation between adverse drug event and the prevalence of MDR-TB [9]. Patients who undergo 24 months of treatment are 1.4 times more likely to develop MDR-TB compared to patients who undergo short-term treatment [22]. Nilamsari *et al.* [23] found that 70% of patients undergoing anti-TB therapy suffered from at least one unfavorable condition as a result of adverse drug event. The study identified five significant negative effects: hyperuricemia (52.5%), gastrointestinal disorders (40%), ototoxicity (37.5%), hypokalemia (27.5%), and arthralgia (12.5%). Kamara *et al.* [24] indicated that patients with long-term regimens were more prone to encountering negative side effects than those on short-term regimens. Research shows that 16 respondents having adverse drug event are classified as high risk, 62.5% of them being on long-term regimens.

Adverse drug event suffered by respondents were mild symptoms such as reduced appetite, stomach ache, joint pain (pyrazinamide (Z), Lfz), arthritis (Z, Lfz, ethionamide (Eto), H, bedaquiline (Bdq)), mild nausea and vomiting, weakness, shortness of breath (linezolid (Lzd)), headaches (cycloserine (Cs)), sleep disturbances (Lfz, Cs) and changes in skin color (clofazimine (Cfz)) that respondents feel when consuming anti-TB therapy can still be minimized by respondents by getting enough rest, improving their diet and taking medication for complaints and vitamin B6 which has been given by health workers while patients who experience high risk adverse drug event such as optic neuritis/vision disorders (ethambutol (E), Lzd), chest pain (levofloxacin (Lfx),

Cfz, delamanid (Dlm)), depression/hallucinations (H, Lfz, Eto, Cs), gastrointestinal disorders/nausea, vomiting (Eto, Cfz, H, E, Z, Lfz, Lzd, Bdq) which is severe enough that the respondent requires hospitalization, reddish spots on the skin with itching or mild symptoms that the respondent feels but requires hospitalization due to pain that never stops such as peripheral neuropathy (H, Eto, Lzd) results in pain with burning or tingling. This can disrupt the treatment regimen for TB patients, leading to mistrust in TB therapy, resulting in patients discontinuing their prescriptions and increasing the risk of developing MDR-TB.

### 3.5. Comorbidity

Comorbidity is not a significant risk factor for MDR-TB. The study included 41 individuals with comorbidities. Among them, 19.51% had a history of hypertension, 58.54% had a history of diabetes mellitus, and 21.95% had a history of both hypertension and diabetes mellitus. Only a tiny percentage of responders have comorbidities (hypertension and/or diabetes mellitus), indicating no correlation between comorbid variables and the occurrence of MDR-TB. This study aligns with a study conducted in Ethiopia [25], which found no correlation between hypertension and the occurrence of MDR-TB. Studies conducted [5] in Sudan and [25] found no correlation between Diabetes Mellitus and the prevalence of MDR-TB. This study aligns by finding no correlation between hypertension or diabetes mellitus in adult TB patients at Sirindhorn Hospital, Bangkok [26]. Different from the research in China has found that individuals who have a history of diabetes mellitus are associated with poor treatment of MDR-TB [15].

### 3.6. BMI

BMI does not pose a risk for MDR-TB. This study aligns that patients with a BMI <18.5 kg/m2 do not correlate with the occurrence of MDR-TB in primary resistant patients [27]. This study aligns with previous research conducted in Ethiopia, indicating that diabetic patients with a BMI <18.5 or >25 kg/m2 do not have a significant association with the occurrence of MDR-TB [28]. This study aligns with research conducted in Ethiopia, patients with BMI <18.5 kg/m2 do not have a correlation with the occurrence of MDR-TB in primary resistance patients [27]. BBKPM Makassar offers supplementary assistance to TB sufferers in the form of "Proten" milk. This milk is provided by the government as a subsidy to enhance the nutritional status of TB sufferers. A study conducted in China found that being overweight or obese has a reduced risk of TB compared to individuals with normal weight [29]. Obesity in persons with TB is associated with higher levels of CD4+ T cells and the hormone leptin, which enhances immunological defense and lowers the chances of developing active TB [30].

## 4. CONCLUSION

TB patients can enhance their medication adherence. The institutional focus includes an efficient directly observed treatment short course (DOTS) strategy, particularly in the management of adverse drug event, overseeing and supporting patients who have recovered from MDR-TB, involves the collaboration of MDR-TB healthcare professionals and patient supporters in the Yamali TB community, moving synergistically with an innovative health system, a digital TB service network system in health service facilities, both government and private, to improve access to quality TB services. This aims to control MDR-TB and reduce economic burden, morbidity, and mortality in the future. Future researchers are expected to deepen the research topic for further clinical risk factors, such as additional laboratory tests and HIV comorbidities, to determine the extent of risk associated with MDR-TB and identify potential strategies in the future for MDR-TB control and prevention.

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