ORIGINAL ARTICLE

An analysis of risk factors for Multidrug Resistant Tuberculosis (MDR-TB): a hospital-based study

Sri Wahyuningsih[1*], Andi Zulkifli[2], A. Arsunan Arsin[2], Ansariadi[2], Sudirman Nasir[3], Masyita Muis[4], Andi Agus Mumang[5]

[1]Master Program in Epidemiology, Faculty of Public Health, Hasanuddin University, Indonesia
[2]Department of Epidemiology, Faculty of Public Health, Hasanuddin University, Indonesia
[3]Department of Health Promotion, Faculty of Public Health, Hasanuddin University, Indonesia
[4]Department of Occupational Health and Safety, Faculty of Public Health, Hasanuddin University, Indonesia
[5]Postgraduate school, Hasanuddin University, Indonesia

Corresponding Author: Sri Wahyuningsih **Email:** sriwahyuningsh@gmail.com

Received: 25 October 2022 **Revised:** 24 January 2023 **Accepted:** 12 February 2023 **Available online:** May 2023
DOI: 10.55131/jphd/2023/210208

ABSTRACT

Multidrug Resistant Tuberculosis (MDR-TB) is the world's most serious problem and one of the leading causes of death. Because of its difficult diagnosis, high rates of treatment failure, and death, MDR-TB is a new challenge in TB control programs. The study aims to identify and analyze the risk factors of Multidrug Resistant Tuberculosis (MDR-TB). The study used a case control study design and was conducted at the Labuang Baji Hospital in Makassar City, Indonesia. The sample was 140 people consisting of 70 in the case group and 70 in the control group. Purposive sampling was used to collect the data. Data were analyzed using STATA program with Multiple Logistic Regression. Significant risk factors of Multidrug Resistant Tuberculosis (MDR-TB) were duration of treatment (OR= 5.655 [Cl 95%: 2.507-12.999]; p<0.001), previous treatment history (OR= 4.833 [Cl 95%: 2.092-11.525]; p<0.001), PMO factor (OR= 3.106 [Cl 95%: 1.227-8.338]; p=0.008), compliance with drugs (OR= 10.961 [Cl 95%: 4.640-26.40]; p<0.001), drug side effects (OR=2.521 [Cl 95%: 1.070-6.126]; p=0.020) and protective factor is the complexity of drug regimen (OR= 0.329 [Cl 95%: 0.136-0.768]; p=0.005). It can be concluded that compliance with drugs is a dominant risk factor for MDR-TB. Improved TB control programs by monitoring the treatment of patients who experienced treatment failure (dropout) probably will increase treatment adherence and cut off MDR-TB transmission.

Key words:
Multidrug Resistant Tuberculosis (MDR-TB); risk factors; Labuang Baji Hospital

Citation:
Sri Wahyuningsih, A. Zulkifli, A. Arsunan Arsin, Ansariadi, Sudirman Nasir, Masyita Muis, Andi Agus Mumang. An analysis of risk factors for Multidrug Resistant Tuberculosis (MDR-TB): a hospital-based study. J Public Hlth Dev. 2023;21(1):91-101 (https://doi.org/10.55131/jphd/2023/210208)

INTRODUCTION

The final TB strategy of the World Health Organization (WHO) aims to reduce death from tuberculosis (TB) to less than 5% in 2035. However, deaths from tuberculosis that are resistant to drugs (Multidrug Resistant Tuberculosis or MDR-TB) are very high.[1] In 2020, it was also reported that 56% of people with world pulmonary TB were in five countries, namely India, Indonesia, China, the Philippines and Pakistan.[2]

Apart from WHO efforts to expand access to TB treatment, tuberculosis resistance to various drugs (MDR-TB), such as Isoniazid and Rifampicin remain a major threat to public health. A total of 484,000 MDR-TB cases were reported in 2018 worldwide, contributing to 44.21% of TB-related deaths. In 2019, 465,000 MDR-TB cases were reported, an increase of 3.9% from 2018. Among these cases, more than half (or 62%) were not treated.[3] MDR-TB has become a new challenge in the TB control program due to the difficulty of diagnosis enforcement, the high number of failures in therapy and death. Many factors contribute to drug resistance in developing countries including Indonesia.[4] Some of the factors include unequal TB treatment service facilities in 34 provinces, MDR-TB referral hospitals and satellite hospitals that provide referral services for MDR-TB, and not all hospitals have a good Directly Observed Treatment Short-Course (DOTS) program.[5]

Generally, there are four factors of drug-resistance risk in MDR TB patients: patient, doctor, drug, and health service.[6] Based on the Indonesian health profile in 2021, to assess the progress or success of TB control, there are two main national indicators: Case Detection Rate (CDR) and Success Rate (SR). At the provincial level, CDR was high in three provinces, namely 122.2% in DKI Jakarta Province, 84% in South Sulawesi Province and 78.5% in Papua Province.

Previous studies reported that the incidence of MDR pulmonary TB infection is caused by the length of previous treatment. Treatment with OAT (antituberculosis drugs) for ≥6 months is 12 times more likely to result in pulmonary MDR-TB than patients who receive therapy <6 months.[7] Research conducted in India concludes previous treatment failures, contact with resistant TB, and comorbid disease as significant risk factors for the development of TB that is resistant to drugs.[8] Furthermore, research in China explains that comorbidity (i.e., complexity of the drug regimen) is significantly a risk factor associated with MDR-TB, including rifampicin and streptomycin resistance.[9] Studies conducted in Brazil reported that lung cavitation and previous treatment for tuberculosis are associated with MDR-TB and another study also reported that the risk factor is noncompliance of patients during the treatment.[10,11]

The Sulawesi-Selatan Provincial Health Office records the fluctuating incidence and prevalence of MDR-TB from 2019-2021. In 2019, there were 201 and 18,863 cases, and this decreased in 2020 to 127 and 12,271 cases. Meanwhile, it increased again to 147 and 14,778 cases in 2021. The discovery of MDR-TB cases in 2021 shows that Makassar City ranked the highest in the number of cases and the lowest rank was recorded for North Toraja and Toraja Regencies.

Labuang Baji Regional General Hospital (RSUD) is the one of MDR-TB referral hospital in South Sulawesi. This hospital receives patients from various public health centers (puskesmas) and hospitals in South Sulawesi. Based on the medical records from MDR-TB poly, MDR-TB patients were still high from 2019-2021. This study aims to determine the risk factors increasing the MDR-TB incidence at Labuang Baji Hospital

Makassar City. Further, this study focuses to investigate the risk factors from the aspect of treatments. Previous studies investigated one or two factors and not only about treatment aspect. However, to our best knowledge, our study is one of the studies that try to figure out more factors that may be associated with MDR-TB incidence, particularly in the treatment aspect. In Indonesia, the success of the TB treatment program is not yet adequate. Our study can contribute to adding information about significant factors associated with MDR-TB incidence from the aspect of treatment. We also investigated the dominant factors contributing to the incidence.

METHODS

Study design and participants

This study used a case–control study design conducted in Labuang Baji Hospital, Makassar city, Indonesia. Case group comprised patients diagnosed with multidrug resistant tuberculosis (MDR-TB) and control group included patients diagnosed with non-multidrug resistant tuberculosis (non-MDR-TB). A total of 85 MDR-TB cases were recorded in 2021. Lemeshow's formula was applied to determine the sample size as follows:

$$n = \frac{Z^2_{1-\alpha/2} \cdot P\,(1-P)N}{d^2(N-1) + Z^2_{1-\alpha/2} \cdot P\,(1-P)}$$

Information:

P = Proportion of prevalence (50% = 0.5)

n = Number of samples

N = Total population

d^2 = Absolute precision 5% (0.05)

Z^2_1-$\alpha/2$ = Z value at the upper limit for the confidence level 95% (1.96)

The case group sample obtained by the formula was 70 patients. For the control group, we used a 1:1 ratio for case and control. Therefore, the control group also obtained 70 patients and the total samples collected were 140 participants. The sample technique used purposive sampling. Purposive sampling refers to a group of non-probability sampling techniques in which units are selected because they have characteristics that we need in our sample. The inclusion criteria of the case group were those individuals diagnosed with MDR-TB, no coinfection with HIV/AIDS, and having outpatient status. For the control group, the inclusion criteria included non-MDR TB patients who had undergone treatment for less than six months. The exclusion criteria for both groups were having inpatient status and not being domiciled in Makassar during the study.

Instrument and Procedures

Medical procedures and subsequent interviews were conducted in Labuang Baji hospital in Makassar, involving multidrug resistant tuberculosis (MDR-TB) outpatients as the case group and non-MDR-TB outpatients as the control group who regularly visit the hospital's Pulmonary TB Poly (regular patients) or were first/new patients.

Researcher took about 5–10 minutes to conduct a face-to-face interview with each participant. The interview questionnaire collected information about socio demographic factors (age, sex, occupation, educational background (highest educational level completed), and marital status). Research variables consist of duration of treatment, previous treatment history, drug side effects, drug supervisor (PMO) factors, and compliance with drugs. For the four variables modified questionnaire from Wulan's research[7] was used, while compliance with drugs used the MARS-5 questionnaire. The same questionnaire was given to the control group. All independent variables were then

categorized into low risk and high risk. Low risk means all variables have positive results, while high risk implies having negative results.

All research work was performed after obtaining written informed consent from each participant. This study was approved by the Ethics Committee of Health Research, Hasanuddin University (approval letter number: 8588/UN4.14.1/TP.01.02/2022 to Faculty of Public Health, Hasanuddin University and Labuang Baji Hospital).

Data analysis

Data analysis was performed using STATA program software. Univariate analysis was applied for sociodemographic characteristics. Multivariate analysis with multiple linear regression models using the stratified forward method was applied to analyze the significant and dominant risk factor for the incidence of MDR-TB. Statistical tests were two-sided with a 95% confidence interval (CI; α=0.05).

RESULTS

Most of the respondents were male (95 respondents or 67.9%). Male respondents suffering from MDR-TB were 44 respondents (62.9%) compared to females (26 respondents or 37.1%). The highest respondents' age is in the range of 25-32 years (32 respondents or 22.9%), with 16 respondents or 22.9% having MDR-TB. Among the MDR-TB patients, those who completed high school were 58.6%, 52.4% were unemployed, and 77.1% were married. The characteristic of the control group (non-MDR-TB) also can be seen in Table 1.

Table 1. Characteristics of Respondents

Characteristics of Respondents	Incidence MDR-TB				Total	
	Case		Control			
	n	%	n	%	n	%
Sex						
Male	44	62.9	51	72.9	95	67.9
Female	26	37.1	19	27.1	45	32.1
Age (year)						
17-24	12	17.1	7	10.0	19	13.6
25-32	16	22.9	16	22.9	32	22.9
33-40	11	15.7	10	14.3	21	15.0
41-47	10	14.3	8	11.4	18	12.9
48-55	7	10.0	7	10.0	14	10.0
56-63	11	15.7	10	14.3	21	15.0
64-71	2	2.9	9	12.9	11	7.9
72-79	1	1.4	1	1.4	2	1.4
>80	0	0	2	2.9	2	1.4
Education						
No School	0	0	5	7.1	5	3.6
Elementary	4	5.7	14	20.0	18	12.9
Junior High School	15	21.4	3	4.3	18	12.9
High School	41	58.6	33	47.1	74	52.9
College Graduate	10	14.3	15	21.4	25	17.9

Characteristics of Respondents	Incidence MDR-TB				Total	
	Case		Control			
	n	%	n	%	n	%
Occupation						
No Jobs	36	51.4	42	60.0	78	55.7
PNS/TNI/POLRI	0	0	5	7.1	5	3.6
Private employees	8	11.4	7	10.0	15	10.7
Self-employed	19	27.1	16	22.9	35	25.0
Farmers/Fishermen/Labourers	6	8.6	0	0	6	4.3
Retired	1	1.4	0	0	1	0.7
Marital Status						
Married	54	77.1	49	70.0	103	73.6
Divorce	2	2.9	0	0	2	1.4
Not Married yet	14	20.0	21	30.0	35	25.0

Most respondents who were suffering from MDR-TB had a high risk related to the duration of treatment (58.6%), previous treatment history with treatment> 6 months (82.9%), PMO factor (31.4%), compliance with drugs (71.4%), and drug side effects (34.3%). Meanwhile, the complexity of drug regimen had low risk (Table 2).

Table 2. Research of Variables

Research Variable	Incidence MDR-TB				Total	
	Case		Control			
	n	%	n	%	n	%
Treatment Duration						
Low	29	41.4	56	80.0	85	60.7
High	41	58.6	14	20.0	55	39.3
Previous Treatment History						
Low	12	17.1	35	50.0	47	33.6
High	58	82.9	35	50.0	93	66.4
Complexity Of The Drug Regimen						
Low	58	82.9	43	61.4	101	72.1
High	12	17.1	27	38.6	39	27.9
PMO Factor						
Low	48	68.6	61	87.1	109	77.9
High	22	31.4	9	12.9	31	22.1
Compliance with Drugs						
Low	20	28.6	57	81.4	77	55.0
High	50	71.4	13	18.6	63	45.0
Drug Side Effects						
Low	46	65.7	58	82.9	104	74.3
High	24	34.3	12	17.1	36	25.7

Significant risk factors of Multidrug Resistant Tuberculosis (MDR-TB) were duration of treatment (OR= 5.655 [Cl 95%: 2.507-12.999]; p<0.001),

previous treatment history (OR= 4.833 [Cl 95%: 2.092-11.525]; p<0.001), PMO factor (OR= 3.106 [Cl 95%: 1.227-8.338]; p=0.008), compliance with drugs (OR= 10.961 [Cl 95%: 4.640-26.40]; p<0.001), drug side effects (OR=2.521 [Cl 95%: 1.070-6.126]; p=0.020) and protective factor is the complexity of drug regimen (OR= 0.329 [Cl 95%: 0.136-0.768]; p=0.005; Table 3).

Table 3. The Risk of Research Variables on the Incidence of MDR-TB

Research Variable	Incidence MDR-TB				Total		
	Case		Control				
	n	%	n	%	p	OR	Cl 95%
Treatment Duration							
Low	29	41.4	56	80.0	<0.001	5.655	2.507-12.999
High	41	58.6	14	20.0			
Previous Treatment History							
Low	12	17.1	35	50.0	<0.001	4.833	2.092-11.525
High	58	82.9	35	50.0			
The Complexity Of The Drug Regimen							
Low	58	82.9	43	61.4	0.005	0.329	0.136 -0.768
High	12	17.1	27	38.6			
PMO Factor							
Low	48	68.6	61	87.1	0.008	3.106	1.227-8.338
High	22	31.4	9	12.9			
Compliance with Drugs							
Low	20	28.6	57	81.4	<0.001	10.961	4.640-26.407
High	50	71.4	13	18.6			
Drug Side Effects							
Low	46	65.7	58	82.9	0.020	2.521	1.070-6.126
High	24	34.3	12	17.1			

Multiple logistics regression obtained by the duration of treatment, previous treatment history, complexity of drug regimen, PMO factors, drug compliance, and drug side effects had significant OR, so these factors can be included in multivariate analysis. Model 1 involved all factors. The complexity of the drug regimen (OR= 0.652 [Cl 95%: 0.241-1.760]; p=0.399) and drug side effects (OR= 2.124 [Cl 95%: 0.755-5.978]; p=0.153) were not statistically significant, therefore were excluded. Models 2 and 3 showed that three factors had significant results, in which compliance with drugs was the most dominant risk factor (OR= 9.068 [Cl 95%: 3.951-20.811]; p<0.001; Table 4).

Table 4. Results of Multivariate Analysis of Risk Factors for MDR-TB

Research Variable	Model 1		Model 2		Model 3	
	p	OR (Cl 95%)	*p*	OR (Cl 95%)	*p*	OR (Cl 95%)
Treatment duration	0.006	3.682 (1.465-9.256)	0.003	3.667 (1.540-8.729)	0.001	4.244 (1.810-9.949)
Previous treatment history	0.048	2.603 (1.007-6.723)	0.037	2.657 (1.058-6.673)		
The complexity of the drug regimen	0.399	0.652 (0.241-1.760)				
PMO factor	0.075	2.707 (0.902-8.119)				
Compliance with Drugs	<0.001	6.058 (2.519-14.567)	<0.001	7.734 (3.315-18.042)	<0.001	9.068 (3.951-20.811)
Drug side effects	0.153	2.124 (0.755-5.978)				

DISCUSSION

The characteristics of respondents in this study were mostly male which is in line with previous research.[12] The risk of MDR/RR TB increased for men with a risk ratio of 1.16 compared to the women.[13] The respondents with MDR-TB in the case group had the highest percentage for no job. Studies in Ethiopia show that one of the risk factors for MDR-TB is unemployment or not having a job.[14] Marriage status is more commonly found in MDR-TB sufferers.[15] People who are married and unemployed have a 1.5 times higher risk for MDR-TB compared to those who are married and working.[16]

This study found that respondents under the high risk category for treatment duration could increase the risk of MDR-TB incidence by 5.655 times compared to the low-risk category. This is in line with research conducted in China that showed the duration of treatment for >8 months can increase the incidence of MDR-TB by 2.72 times compared to treatment lasting for <6 months.[17] Meanwhile, several respondents said that the duration of treatment for more than six months is due to the gram positive bacilli (BTA) test remaining still positive, which can cause TB resistance.

Previous treatment history is mostly found under high risk category with high proportions in the case group compared to the control group. This study found that respondents with a previous treatment history under the high-risk category can have a 4.833 times increase in the risk for MDR-TB compared to the low-risk category. Research conducted in Brazil shows that patients who have a history of previous TB treatment have an increase in the risk for multidrug resistant tuberculosis by 13.86 times compared to patients who do not have a history of previous treatment.[18] This finding is in accordance with research conducted in Uganda that found the MDR-TB patients with a previous history of treatment were 3.46 times more likely to be absent from treatment.[19] Our study was also in line with research in Ethiopia, which found that the previous history of failure of treatment is a risk factor that caused 4.0 times more resistance to TB treatment.[20] Previous treatment history has also increased the risk of developing MDR-TB

by 2.6 times in the Burundi population.[4]

The complexity of the drug regimen in the case group is dominantly in the low-risk category compared to the control group. This study found that respondents in the low-risk category of drug regimen complexity can reduce the risk for MDR-TB incidence by 0.329 times compared to the high-risk category. Several respondents have a history of hypertension and diabetes mellitus which requires them to consume drugs every day combined with tuberculosis drugs. Increased vulnerability to TB disease can be caused by immunosenescence and an increase in comorbidities as a consequence of getting older.[21] The comorbidity is significantly associated with multidrug resistance [OR: 1.96 95% CI 1.17-3.27] compared to patients who are susceptible to disease.[9] Research conducted in India found that previous treatment failures, contact with resistant TB, and comorbid diseases are significant risk factors for MDR-TB.[8] Several respondents may have other disease treatment histories, such as hypertension and diabetes mellitus drugs that can cause non-compliance with treatment. However, in the current research, most respondents have a low-risk proportion of complexity of drug regimen, therefore can be a protective factor against MDR-TB incidence.

This study found that respondents in the high-risk category for PMO factors have an increased risk of MDR-TB (5.655 times) compared to the low-risk category. The majority of PMOs are health workers in the hospital and family. The family is one of the importance support agents for MDR-TB patient undergoing treatment. Low family support obtained by patients can be a risk factor for MDR TB. Family support can increase the expectations and quality of life of respondents. Respondents with family support are able to stabilize themselves psychologically, socially and physically.[5] The role of PMO is very important in assisting patients to achieve optimal treatment results.[22]

Respondents of the high-risk category for medication adherence have an increased risk of MDR-TB incidence, which is 10.961 times compared to the low-risk category. MDR-TB patients receive treatment for 18-24 months. One of the critical success factors is compliance. A study conducted in Thailand found that respondents who do not adhere to medication have a 16 times risk of developing MDR TB compared to respondents who regularly take medication.[23] Similar studies in Africa found that patients' adherence to drugs is the risk factor for MDR-TB incidence.[1] Research in Brazil also found a negative association between treatment adherence and MDR-TB occurrence.[24] One of the most important things in TB treatment is medication adherence. TB is an infectious disease that can be treated by taking antibiotics showing an effect on the incidence of MDR-TB in Bhutan.[25]

A similar study conducted in Uganda found that 55% of patients were non-adherent to TB treatment. This is due to the adverse effects of the drugs consumed.[26] Adherence to this treatment is not yet optimal globally with more than a third of patients not adhering to MDR-TB treatment therapy.[27] Adherence to treatment is important to avoid the occurrence of MDR-TB and treatment failure.[28]

Drug side effects were mostly high risk in the case group (34.3%) and low risk in the control group (82.9%). This study found that respondents with a high risk of experiencing drug side effects have an increased risk of MDR-TB (2.521 times) compared to the low-risk category. Studies conducted in Africa, France, Janssen, Amenia and Georgia also found that 91.1% of patients experienced >1 adverse event, and 11.2% experienced serious side effects.[29]

Treatment of MDR TB requires

monitoring of OAT side effects. The drugs' side effects generally appear in the first 2-4 months of treatment and should be treated immediately. The side effects that many respondents suffer include mild symptoms such as vomiting or dizziness. In addition, some respondents experience severe side effects such as hearing loss. Research conducted in South Africa also found similar results, indicating that 60% of patients experience hearing loss which is high among patients who are >50 years.[30]

In conclusion, treatment duration, previous treatment history, PMO factor, compliance with drugs, and drug side effects are significant risk factors for MDR-TB. However, the complexity of the drug regimen is a protective factor against the incidence of MDR-TB. The dominant risk of MDR-TB incidence is compliance with drug medication.

RECOMMENDATION

It needs to further enhance the TB control program by monitoring the treatment of patients who experience treatment failure (dropout), probably by increasing treatment adherence and cutting off MDR-TB transmission.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Workicho A, Kassahun W, Alemseged F. Risk factors for multidrug-resistant tuberculosis among tuberculosis patients: a case-control study. Infect Drug Resist. 2017;10:91-6. doi: 10.2147/IDR.S126274.
2. World Health Organization. Global tuberculosis: Perspectives, prospects, and priorities. [Internet]. [Cited 2022 May 17]. Availlable from: https://www. https://www.who.int/publications/digital/global-tuberculosis-report-2021
3. Iradukunda A, Ndayishimiye GP, Sinarinzi D, Odjidja EN, Ntakaburimvo N, Nshimirimana I, et al. Key factors influencing multidrug-resistant tuberculosis in patients under anti-tuberculosis treatment in two centres in Burundi: a mixed effect modelling study. BMC Public Health. 2021;21(1):2142. doi: 10.1186/s12889-021-12233-2.
4. Guglielmetti L, Veziris N, Aubry A, Brossier F, Bernard C, Sougakoff W, et al. Risk factors for extensive drug resistance in multidrug-resistant tuberculosis cases: A case-case study. Int J Tuberc Lung Dis. 2018;22(1):54–9. doi: 10.5588/ijtld.17.0387.
5. Sriwahyuni E, Lubis R, Aguslina Siregar F. The Effect Of Income, History Of Smoking, Side Effects And Medication Adherence To Drug Resistant Tuberculosis In Haji Adam Malik General Hospital Medan 2018. IJPHCS. 2021;8:2.
6. Dwi Cahyani T, Ratna Rahayu S, Jazilatun F, Nur Ayu Merzistya A. Multi-Drug Resistant Tuberculosis in Semarang City. Public Heal Perspect J. 2021;6(2):148–58. doi: 10.1183/13993003.00626-2020
7. Wulan Febriyanti R, Sri Lestari E, Hadi P, Rizke Ciptaningtyas V. Tuberkulosis Paru dengan Risiko Multi Drug Resistant di RS Rujukan Tertier di Jawa Tengah. Herb-Medicine Journal. 2021; 4:2
8. Kumar V, Jorwal P, Soneja M, Sinha S, Nischal N, Sethi P, et al. Evaluation of rapid diagnostic tests and assessment of risk factors in drug-resistant pulmonary tuberculosis. J Family Med Prim Care.

2020;9(2):1028-34. doi: 10.4103/jfmpc.jfmpc_883_19.
9. Tao NN, Li YF, Song WM, Liu JY, Zhang QY, Xu TT, et al. Risk factors for drug-resistant tuberculosis, the association between comorbidity status and drug-resistant patterns: a retrospective study of previously treated pulmonary tuberculosis in Shandong, China, during 2004-2019. BMJ Open. 2021;11(6):e044349. doi: 10.1136/bmjopen-2020-044349.
10. Nurdin N. Analisis faktor-faktor determinan Individu terhadap Tuberculosis Multidrug Resistant (TB MDR) di Provinsi Sumatera Selatan. J Kesehat Komunitas. 2020;6(1):63–7.
11. Soares VM, Almeida IN, Figueredo LJA, Haddad JPA, Oliveira CSF, Carvalho WDS, et al. Factors associated with tuberculosis and multidrug-resistant tuberculosis in patients treated at a tertiary referral hospital in the state of Minas Gerais, Brazil. J Bras Pneumol. 2020;46(2): e20180386. doi: 10.36416/1806-3756/e20180386.
12. Hamid M, Brooks MB, Madhani F, Ali H, Naseer MJ, Becerra M, et al. Risk factors for unsuccessful tuberculosis treatment outcomes in children. PLOS ONE. 2019;14(9):e0222776. doi: 10.1371/journal.pone.0222776.
13. McQuaid CF, Horton KC, Dean AS, Knight GM, White RG. The risk of multidrug- or rifampicin-resistance in males versus females with tuberculosis. Eur Respir J. 2020;56(3). doi: 10.1183/13993003.00626-2020.
14. Desissa F, Workineh T, Beyene T. Risk factors for the occurrence of multidrug-resistant tuberculosis among patients undergoing multidrug-resistant tuberculosis treatment in East Shoa, Ethiopia. BMC Public Health. 2018; 18(1):422. doi: 10.1186/s12889-018-5371-3.
15. Ratnasari NY. Faktor Resiko Kejadian Multi Drug Resistant Tuberculosis (MDR TB) di Surakarta, Jawa Tengah. SUARA FORIKES Journal Heal Res. 2020;11(1):67–72.
16. Gizachew Beza M, Hunegnaw E, Tiruneh M. Prevalence and Associated Factors of Tuberculosis in Prisons Settings of East Gojjam Zone, Northwest Ethiopia. Int J Bacteriol. 2017;2017:3826980. doi: 10.1155/2017/3826980.
17. Yao S, Yan J, Li L, Ma D, Liu J, Wang Q, et al. Determining Mycobacterium tuberculosis Drug Resistance and Risk Factors for Multidrug-Resistant Tuberculosis in Sputum Smear-Positive Tuberculosis Outpatients in Anhui Province, China, 2015-2016. Infect Drug Resist. 2020;13:1023-32. doi: 10.2147/IDR.S244482.
18. Arroyo LH, Yamamura M, Ramos ACV, Campoy LT, Crispim JA, Berra TZ, et al. Determinants of multidrug-resistant tuberculosis in São Paulo-Brazil: a multilevel Bayesian analysis of factors associated with individual, community and access to health services. Trop Med Int Health. 2020;25(7):839-49. doi: 10.1111/tmi.13409.
19. Batte C, Namusobya MS, Kirabo R, Mukisa J, Adakun S, Katamba A. Prevalence and factors associated with non-adherence to multi-drug resistant tuberculosis (MDR-TB) treatment at Mulago National Referral Hospital, Kampala, Uganda. Afr Health Sci. 2021;21(1):238-47. doi: 10.4314/ahs.v21i1.31.
20. Bade AB, Mega TA, Negera GZ. Malnutrition is Associated with Delayed Sputum Culture Conversion Among Patients Treated for MDR-TB. Infect Drug Resist. 2021;14:1659-67. doi: 10.2147/IDR.S293461.
21. Alateah SM, Othman MW, Ahmed M, Al Amro MS, Al Sherbini N, Ajlan HH. A retrospective study of tuberculosis prevalence amongst patients attending a tertiary hospital in Riyadh, Saudi

Arabia. J Clin Tuberc Other Mycobact Dis. 2020;21:100185. doi: 10.1016/j.jctube.2020.100185.
22. Amala A, Cahyati WH. Drop Out Pengobatan Pada Tuberkulosis Multidrug Resistant (Tb Mdr) Di Kota Semarang: Drop Out of Multidrug Resistant Tuberculosis (Mdr Tb) Treatment in Semarang City. Quality : Jurnal Kesehatan. 2021;15(1):24-36. doi: https://doi.org/10.36082/qjk.v15i1.161
23. Kamolwat P, Nateniyom S, Chaiprasert A, Disratthakit A, Mahasirimongkol S, Yamada N, et al. Prevalence and associated risk factors of drug-resistant tuberculosis in Thailand: results from the fifth national anti-tuberculosis drug resistance survey. Trop Med Int Health. 2021;26(1):45-53. doi: 10.1111/tmi.13502.
24. Fregona G, Cosme LB, Moreira CMM, Bussular JL, Dettoni VDV, Dalcolmo MP, et al. Risk factors associated with multidrug-resistant tuberculosis in Espírito Santo, Brazil. Rev Saude Publica. 2017;51(0):41. doi: 10.1590/S1518-8787.2017051006688.
25. Tenzin C, Chansatitporn N, Dendup T, Dorji T, Lhazeen K, Tshering D, et al. Factors associated with multidrug-resistant tuberculosis (MDR-TB) in Bhutan: A nationwide case-control study. PLOS ONE. 2020;15(7): e0236250. doi: 10.1371/journal.pone.0236250.
26. Kizito E, Musaazi J, Mutesasira K, Twinomugisha F, Namwanje H, Kiyemba T, et al. Risk factors for mortality among patients diagnosed with multi-drug resistant tuberculosis in Uganda- a case-control study. BMC Infect Dis. 2021;21(1):292. doi: 10.1186/s12879-021-05967-2.
27. Kibret KT, Moges Y, Memiah P, Biadgilign S. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies. Infect Dis Poverty. 2017;6(1):7. doi: 10.1186/s40249-016-0214-x.
28. Aristiana CD, Wartono M. Faktor-faktor yang mempengaruhi terjadinya Multi Drug Resistance Tuberkulosis (MDR-TB). J Biomedika dan Kesehat. 2018;1(1). doi: https://doi.org/10.18051/JBiomedKes.2018.v1.65-74
29. Mbuagbaw L, Guglielmetti L, Hewison C, Bakare N, Bastard M, Caumes E, et al. Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant Tuberculosis. Emerg Infect Dis. 2019;25(5):936-43. doi: 10.3201/eid2505.181823.
30. Hong H, Dowdy DW, Dooley KE, Francis HW, Budhathoki C, Han HR, et al. Prevalence of Pre-Existing Hearing Loss Among Patients With Drug-Resistant Tuberculosis in South Africa. Am J Audiol. 2020;29(2):199-205. doi: 10.1044/2020_AJA-19-00103.