IJTID. Volume 13 No 2 May-August 2025 e-ISSN: 2356-0991; p-ISSN:2085-1103
Sinta 2 (Decree No: 105/E/KPT/2022) Available online at https://e-journal.unair.ac.id/IJTID

Original Article

IJTID
(INDONESIAN JOURNAL OF TROPICAL AND INFECTIOUS DISEASE)
Scientific Journal of Tropical and Infectious Disease

Resistance Pattern of Anti-TB Drugs in Drug-Resistant TB of Pulmonary Tuberculosis Patients in Dr. Soetomo Academic Hospital, Surabaya, Indonesia

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OPEN ACCESS

ARTICLE INFO

Received: December 08, 2024
Accepted: December 13, 2024
Published: August 31, 2025
Available online: August 31, 2025

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Keywords:
Pulmonary Tuberculosis
Drug-Resistant TB
Resistance Pattern
Anti-TB Drugs

Abstract

Pulmonary tuberculosis is an infectious disease that can be transmitted through the air due to infection with *Mycobacterium tuberculosis* bacteria. According to the WHO, TB is the second-highest cause of death in infectious diseases in the world. This study aims to determine patterns of anti-TB drug resistance in drug-resistant TB patients in Dr. Soetomo Academic Hospital from January 2022 to December 2023. This was a descriptive retrospective using patient medical record data in Dr. Soetomo Academic Hospital for the period January 2022 - December 2023. This study included 261 drug-resistant pulmonary TB patients, the majority of whom were new TB patients (61.3%). Anti-TB drug resistance was most prevalent in RR-TB (43.7%), with the highest number of new cases (28.4%). Drug susceptibility test showed High-dose Isoniazid (INH^{HD}) had a high resistance rate (56%). Isoniazid (H) had a high resistance rate (66%). Pyrazinamide (Z) showed high sensitivity (66%). Levofloxacin (Lfx) showed high sensitivity (89%). High-dose Moxifloxacin (Mfx^{HD}) high sensitivity level (94%). Moxifloxacin (Mfx) high sensitivity level (92%). Bedaquiline (Bdq) high sensitivity level (98%). Linezolid (Lzd) high sensitivity level (99%). Clofazimine (Cfz) high sensitivity level (97%). Amikacin (Amk) high sensitivity level (100%). Drug-resistant pulmonary TB patients recently show a high drug sensitivity pattern to the second-line anti-TB drugs. MTB has become resistant to Isoniazid. However, it is still sensitive to Pyrazinamide by 66% and Levofloxacin by 89%. Moxifloxacin, Bedaquilin, Linezolid, Clofazimine, and Amikacin have high sensitivity >90%.

Cite this as: Maritsa, O.M., Mertaniasih, N.M., Permatasari, A., Kusmiati, T. (2025). Resistance Pattern of Anti-TB Drugs in Drug-Resistant TB of Pulmonary Tuberculosis Patients in Dr.Soetomo Academic Hospital Surabaya Indonesia. *Indonesian Journal of Tropical and Infectious Disease*, 13(2) : 143-154. https://doi.org/10.20473/ijtid.v13i2.66525

INTRODUCTION

Pulmonary tuberculosis (TB) is an airborne infectious disease caused by infection with *Mycobacterium tuberculosis* bacteria.[1] According to the World Health Organization (WHO), TB is still a global public health problem today.[2] TB is the second-highest cause of death in infectious diseases in the world.[3] The estimated number of people diagnosed with TB worldwide is 10.6 million cases. Up from the previous 2021 of 10.3 million people.[4] Based on the latest data from the WHO Tuberculosis Report 2023, Indonesia currently ranks second with the highest TB caseload after India, with 724 thousand cases and an increase in 2023 of 820 thousand cases.[2,5] Globally in 2022, it is estimated that 410,000 people will experience drug resistance. In Indonesia in 2022, the number of deaths reached 93 thousand, and as many as 12 thousand people were recorded with drug-resistant TB cases. The success rate of drug-sensitive TB treatment is 85% and drug-resistant TB treatment is 55%. This figure has not yet reached the target, indicating that the urgency of commitment needs to be increased and the national TB elimination strategy to achieve the 90% target strengthened by 2024.[6]

Resistance of *Mycobacterium tuberculosis* to anti-TB drugs is a condition where the bacteria cannot be destroyed with anti-TB drugs.[7] Anti-TB drug resistance can be caused by gene mutation or selective pressure. The mechanism of drug resistance is influenced by several factors, including non-compliance of TB patients in taking drugs regularly or not completing the treatment program. [8] The cause of anti-TB drug resistance is due to inadequate use of drugs, which occurs when the treatment given is not in the right way in terms of drug dosage, treatment duration, and is not suitable for the patient's condition. Also, inappropriate treatment regimens can lead to treatment failure of TB patients.[9] Gene mutation is the main mechanism that causes drug resistance to MTB, mutations in certain genes can change the target of drug action, reduce effectiveness, and the bacteria can still survive in extreme conditions.[10] Selective pressure on MTB causes phenotypes to become more favorable in certain environments due to bacterial resistance to antibiotics.[11] Resistance in new patients is patients who have never received treatment before or received anti-TB drugs for less than 1 month. This patient is infected from a previously treated patient.[12] Differences in the characteristics of TB patients mean that drug-resistant TB transmission is more often transmitted from patients who are not on treatment or whose treatment is ineffective. Effective treatment and patient management are important in reducing the transmission of resistant strains to other individuals.[13] TB patients infected by drug-resistant patients have worse clinical outcomes and longer cure times, especially if infected with untreated patients.[14] DR-TB pulmonary TB patients reported include RR-TB, MDR-TB, Pre-XDR-TB, and XDR-TB.[15] RR-TB is determined from the results of the Xpert MTB/RIF examination, in RR-TB patients, followed by MGIT 960 culture examination. The MGIT 960 system is an efficient and rapid TB diagnosis method used for anti-TB drug susceptibility testing.[16] This test records and reports the sensitivity of first-line and second-line anti-TB drugs such as fluoroquinolones (Levofloxacin, Moxifloxacin, and Ofloxacin), aminoglycosides (Amikacin, Kanamycin, and Capreomycin), and Bedaquilin, Linezolid, and Clofazimine.[17,18] The purpose of this study was to determine the pattern of anti-TB drug resistance among DR-TB pulmonary TB patients in Dr.

Soetomo Academic Hospital, Surabaya, from January 2022 to December 2023.

MATERIALS AND METHODS

Materials

The data used in this research were secondary data, obtained from medical records of drug-resistant pulmonary TB patients in new and re-treatment cases, and adult age criteria of 18-65 years. The variables in this study were drug-resistant pulmonary TB patients, age, gender, drug-resistance TB classification, culture MGIT, and Drug-Susceptibility Testing (DST). The sample size was 261 patients who met the inclusion criteria.

Methods

This study used a retrospective descriptive observational design. DR-TB data on RR-TB using Xpert® MTB/RIF and anti-TB drugs sensitivity using BACTEC™ MGIT™ 960 system obtained from sputum of pulmonary TB patients and reported drugs Isoniazid, Pyrazinamide, Levofloxacin, Moxifloxacin, Bedaquilin, Linezolid, Clofazimine, and Amikacin were obtained from pulmonary TB patients' medical records at the Dr. Soetomo Academic Hospital for the period January 1, 2022, to December 31, 2023.

RESULTS AND DISCUSSION

Patient Demographics

Drug-resistant pulmonary TB patients recorded in medical record data at the Dr. Soetomo Academic Hospital from January 1, 2022, to December 31, 2023, totaled 261 patients (Table 1). Demographic characteristics of patients based on gender: 149 patients (57.1%) were male, while 112 patients (42.9%) were female. This is related to the level of physical activity and greater workload in men. Frequent social activities that involve interaction with many people, as well as unhealthy lifestyles such as smoking and drinking alcohol, lead to decreased immunity and increased risk of TB. Men, therefore, tend to be more susceptible to TB infection.[19,20]

Age distribution was grouped based on the age range of 18-24 years as many as 27 patients (10.3%), age 25-34 years as many as 38 patients (14.6%), age 35-44 years as many as 52 patients (19.9%), age 45-54 years as many as 89 patients (34.1%), and age 55-65 years as many as 55 patients (21.1%). Old age is thought to increase the risk of TB disease. This may be due to factors such as the causative agent, individual conditions in the level of immunity, and an unhealthy home environment.[7] Mature age is related to productive working age, and activities related to many people are risk factors for increased transmission from surrounding TB patients.[19,20]

Table 1. Demographics of Drug-Resistant Pulmonary TB Patients with TB Treatment History in Dr. Soetomo Academic Hospital, January 2022 - December 2023

Patient Demographics	TB Treatment History				Total n=261
	New Cases	Relapse	Loss to follow up	Treatment Failure	
Gender					
Male	90 34.5%	37 14.2%	8 3.2%	14 5.3%	149 57.1%
Female	70 26.8%	21 8%	7 2.7%	14 5.3%	112 42.9%
Age					
18-24	24 9.2%	2 0.8%	0 0%	1 0.4%	27 10.3%
25-34	20 7.7%	10 3.9%	4 1.5%	4 1.5%	38 14.6%
35-44	28 10.7%	11 4.2%	5 2%	8 3%	52 19.9%
45-54	58 22.2%	18 6.9%	2 0.8%	11 4.2%	89 34.1%
55-65	30 11.5%	17 6.5%	4 1.5%	4 1.5%	55 21.1%

Drug Susceptibility Test Examination

Sensitivity of anti-TB drugs in patients with drug-resistant pulmonary TB (Table 2) showed that High-dose Isoniazid (INH^{HD}) had a high level of resistance in 135/239 patients (56%). Isoniazid (H) showed high resistance in 100/151 patients (66%). Pyrazinamide (Z) showed sensitivity in 86/131 patients (66%). Levofloxacin (Lfx) showed sensitivity in 213/238 patients (89%). Moxifloxacin (Mfx) showed sensitivity in 11/12 patients (92%). High-dose Moxifloxacin (Mfx^{HD}) showed sensitivity in 215/228 patients (94%). Bedaquilin (Bdq) showed sensitivity in 235/239 patients (98%). Linezolid (Lzd) showed sensitivity in 237/239 patients (99%). Clofazimine (Cfz) showed sensitivity in 232/239 patients (97%). Amikacin (Amk) showed sensitivity in 86/86 patients (100%).

This study revealed that most patients were resistant to Isoniazid of 66%. Isoniazid is the first-line anti-TB drug given to patients diagnosed with TB, is often resistant; and unsupervised and incomplete treatment can increase drug resistance.[21] In addition, they are still sensitive to pyrazinamide (66%). Pyrazinamide has a different mechanism of action from other TB drugs; bacteria are less prone to resistance to Pyrazinamide than Isoniazid and Rifampicin, and Pyrazinamide regimens generally do not require frequent dosing, reducing the potential for resistance.[22] The high sensitivity rates of Levofloxacin, Moxifloxacin, Bedaquilin, Linezolid, Clofazimine, and Amikacin are likely due to the fact that these drugs are used with appropriate indications and are not drugs that are freely used in the community. This requires further research. Levofloxacin and Moxifloxacin are fluoroquinolone class drugs commonly used for drug-resistant TB patients, the sensitivity rate is still high especially in strains that do not have gyrA or gyrB gene mutations, a high level of sensitivity due to the use of the right dose and combination.[23] Second-line anti-TB drugs such as Levofloxacin, Moxifloxacin, Bedaquilin, Linezolid, Clofazimine, and Amikacin have high sensitivity because they have different and more specific mechanisms of action compared to the first-line anti-TB drugs.[24]

The WHO recommends individualized DR-TB treatment based on DST results for first-line and second-line drugs. Nearly a quarter of cases are resistant to at least one first-line drug, so second-line drugs are more widely used in TB treatment, with more side effects and higher costs.[25] DST plays a role in TB management and control, especially in the context of increasing drug resistance. DST enables rapid identification of MTB strains that are resistant to drugs such as isoniazid and rifampicin as first-line drugs, and is important in preventing the spread of DR-TB, thereby facilitating the provision of effective treatment therapy based on specific resistance profiles. First-line anti-TB drugs have a high incidence of drug resistance, possibly because first-line anti-TB drugs are the main TB treatment given to patients who are first diagnosed with TB. The causative factor of this resistance is due to treatment non-compliance and is related to the long duration of treatment, so that the chance of resistance increases. Meanwhile, second-line anti-TB drugs are currently still sensitive and effective as a treatment for TB patients. Factors determining the effectiveness of TB drugs are the ability of bactericidal or bacteriostatic activity that can kill and inhibit the development of bacteria, the ability of drugs to reach the concentration of infection sites, side effects, the ability to overcome drug resistance, and the duration of treatment.[26] TB patients should receive the correct dose. The standard dose for

drugs is Rifampicin 10 mg/kg, maximum 600 mg; Isoniazid 5 mg/kg, maximum 300 mg; Ethambutol 15 mg/kg, and Pyrazinamide 25 mg/kg. Levofloxacin 750-1000mg, Moxifloxacin 400-800mg, Linezolid 600 mg, Bedaquiline 400mg once daily for 2 weeks, followed by 200mg 3 times a week for 24 weeks, Clofazimine the first 2 months 200-300mg then reduced to 100mg, and Amikacin 12-15mg/kg.[27] An indicator of successful TB treatment is if the TB patient completes therapy with symptoms resolved or cured as measured by a negative BTA at the end of treatment and at least one follow-up examination.[28]

Table 2 Drug-Resistant Pulmonary TB based on the Treatment History with Drug Susceptibility Testing (DST) in Dr. Soetomo Academic Hospital, January 2022 - December 2023

TB Treatment History	**Drug Susceptibility Test Results**										
	Sensitivity Pattern	INH HD	H	Lfx	Mfx HD	Mfx	Bdq	Lzd	Cfz	Z	Amk
New Cases	S	67	34	128	131	6	145	143	143	49	49
	R	78	62	16	9	0	0	2	2	30	0
	Total	145	96	144	140	6	145	145	145	79	49
Relapse	S	21	10	48	47	3	53	53	53	22	22
	R	32	21	5	3	0	0	0	0	11	0
	Total	53	31	53	50	3	53	53	53	33	22
Loss to follow up	S	6	3	13	13	1	14	15	13	7	7
	R	9	4	2	1	0	1	0	2	1	0
	Total	15	7	15	14	1	15	15	15	8	7
Treatment Failure	S	10	4	24	24	1	23	26	23	8	8
	R	16	13	2	0	1	3	0	3	3	0
	Total	26	17	26	24	2	26	26	26	11	8
Total	S	104 44%	51 34%	213 89%	215 94%	11 92%	235 98%	237 99%	232 97%	86 66%	86 100%
	R	135 56%	100 66%	25 11%	13 6%	1 8%	4 2%	2 1%	7 3%	45 34%	0 0%

Note : S = Sensitive; R = Resistant; N = Amount

Research conducted in India revealed that, as a country with the highest MDR-TB rate in the world, DR-TB is one of the main obstacles to progress towards TB elimination.[29] In another study in India, many patients were found to have high resistance to fluoroquinolone class drugs at 72.8% and resistance to Second-Line Injectable Drugs (SLID) at 15.7%. Resistance to fluoroquinolones with SLID was 11.5%. Selection of appropriate treatment regimens is needed as a substitute for fluoroquinolones.[30] Research conducted in China, as the country with the third highest number of TB cases after India and Indonesia. Drug-resistant TB strains, especially MDR-TB and XDR-TB, are increasing the dependence on second-line TB drugs. Analysis of all TB drugs showed resistance of 56.8%, requiring increased targeted interventions for drug-resistant TB in China. The country accounts for a quarter of global MDR-TB cases.[31] Research conducted in the Philippines, as the fourth highest TB country, found that patients had SLID resistance of 56%, Fluoroquinolone resistance of 30.7%, MDR-TB patients were found to be 5.3% and XDR-TB as much as 8%. In his study, the addition of the drug Bedaquiline in the treatment regimen against DR-TB assessed its effectiveness, safety, and tolerability. The results of regimens

containing Bedaquiline in MDR/XDR-TB patients were highly effective with good safety and treatment outcomes.[32] Previous research conducted in Dr. Soetomo Hospital, Surabaya, Indonesia, said that the use of the drug Bedaquiline can improve recovery and reduce the risk of death of MDR-TB patients, as well as in patients who cannot be followed up and use in combination with drugs Levofloxacin, Clofazimin, and Linezolid increases the efficacy of therapy.[33] DR-TB in different countries can be influenced by health policy factors and TB treatment; the implementation of the DOTS (Directly Observed Treatment Short-course) program is effective in reducing TB drug resistance.[34]

Classification of Drug-Resistance Patterns

The results of the data analysis of this study showed that the number of drug-resistant TB patients with positive MTB culture (Table 3) results came from new cases as many as 160 patients (61.3%), relapse cases as many as 58 patients (22.2%), loss to follow up cases as many as 15 patients (5.7%), and failed cases as many as 28 patients (10.8%). There is a difference with that revealed by the Ministry of Health of the Republic of Indonesia (2020), that cases of DR-TB are usually more prevalent in TB with re-treatment cases.[35] New cases of drug-resistant TB patients may contain MTB strains in newly diagnosed TB patients who have never received TB drugs or a history of anti-TB drugs for less than one month. These patients are infected with MTB that is resistant to TB drugs, which is called primary resistance. New TB patients who develop resistance can occur due to close contact with DR-TB patients.[36]

This study revealed that drug-resistant pulmonary TB patients in new cases were more numerous, possibly due to social and psychological factors. Patients undergoing re-treatment may not visit the referral hospital, and comorbid conditions could also contribute. Dr. Soetomo's a referral hospital may not cover all drug-resistant TB patients in East Java, Indonesia. This highlights the need for an informative communication approach, intersectoral cooperation, and further research.

Table 3 Classification of Drug Resistance with Pulmonary TB Treatment History in Dr. Soetomo Academic Hospital, January 2022 - December 2023

Drugres istance	Treatment History				Total
	New Cases	Relapse	Loss to follow up	Treatment Failure	
RR	74 28.4%	25 9.5%	5 1.9%	10 3.8%	114 43.7%
MDR	66 25.3%	28 10.7%	6 2.3%	13 5%	113 43.3%
Pre-XDR	16 6.1%	5 1.9%	2 0.7%	2 0.7%	25 9.6%
XDR	4 1.5%	0 0%	2 0.7%	3 1.5%	9 3.4%
Total	160 61.3%	58 22.2%	15 5.7%	28 10.8%	261 100%

Note : RR = Rifampicin Resistant; MDR = Multidrug Resistant; Pre-XDR = Pre-Extensively Drug Resistant; XDR = Extensively Drug Resistant

The results of this study are in line with research at Margono Soekarjo Hospital, Indonesia, showing the majority of new TB patients are 7,3 times more likely to develop resistance. Contact transmission of drug-resistant TB causes new TB cases to experience primary resistance, which causes an increase in drug-resistant cases. Furthermore, relapsed TB patients have a 3.7 times higher risk of developing drug resistance than those who have never received previous treatment.[36]

Diagnosis of TB using the GeneXpert MTB/RIF test to detect drug resistance to rifampicin based on the drug sensitization test. Patients with RR-TB were new cases (43.7%), relapsed cases (9.5%), loss to follow-up cases (1.9%), and

failed cases (3.8%). MDR-TB in new cases (43.3%), relapse cases (10.7%), loss to follow-up cases (2.3%), and failed cases (5%). Pre-XDR-TB in new cases (6.1%), relapse cases (1.9%), loss to follow-up cases and failed cases (0.7%). XDR-TB in new cases (1.5%), loss to follow-up cases (0.7%), and failed cases (1.5%). The highest number of patients with RR-TB was found in the new TB cases group, totaling 74 people (28.4%).

In this study, it was found that the highest number of new cases of pulmonary TB patients experienced RR-TB at the Dr. Soetomo Academic Hospital in 2022-2023. New TB cases are patients who have never received previous treatment or received anti-TB drugs for less than 1 month (<28 doses). RR-TB is rifampicin resistance, without resistance to other anti-TB drugs.[15] The causes of drug-resistant TB are patient non-compliance with treatment regimens, non-completion of treatment, gene mutations, resistant strains transmitted from TB-infected people, and poor immunity.[37] Contact transmission of drug-resistant TB causes new case patients to develop primary resistance, leading to an increase in RR-TB cases.

This study is in line with Wahidah *et al*. (2024), it was found that the majority of anti-TB drug-resistant categories were in RR-TB as many as 85 patients (53.8%). MDR-TB was 59 patients (37.3%), Pre-XDR-TB was 11 patients (7%), and XDR-TB was 3 patients (1.9%). The drugs Rifampicin and Isoniazid are experiencing significant resistance in patients because these drugs are used as first-line anti-TB drugs and are the most effective in eliminating TB.[29] Research conducted at Dr. Mohammad Hoesim Palembang General Hospital found that 52 subjects (56.5%) had RR-TB, 33 subjects (35.8%) had MDR-TB, 6 subjects (6.5%) had Pre-XDR-TB, and 1 subject (1.2%) had XDR-TB.[38]

All countries must be committed to ending TB globally with the End TB Strategy and SDGs, promptly diagnose TB, record and report TB incidence, and DR-TB cases.[39] In addition, implementation is important to intensify education on patient adherence to complete treatment.[40] Long-term research services are needed to continue to determine anti-TB drug resistance patterns, to determine trends, and diagnostic capabilities.

STRENGTH AND LIMITATION

The strength of this study lies in the use of Drug Susceptibility Testing (DST) for anti-TB drug sensitivity. However, the limitation of this study was that the data were collected over a limited period of time, so it did not include long-term changes in the variables studied and unmeasured variables that might affect the results of the study, such as close contact with DR-TB and comorbidities.

CONCLUSIONS

This study showed that drug-resistant pulmonary TB patients recently show a high drug sensitivity pattern to the second-line anti-TB drugs. MTB has become resistant to Isoniazid. However, it is still sensitive to Pyrazinamide by 66% and Levofloxacin by 89%. Moxifloxacin, Bedaquilin, Linezolid, Clofazimine, and Amikacin have high sensitivity >90%.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to all participants who participated in this study and to all staff at Dr. Soetomo Academic Hospital, Surabaya, Indonesia.

ETHICAL CLEARANCE

All the protocols and the use of medical records for the data on this research are approved by Dr. Soetomo Surabaya General Hospital ethics committee (Ref. No.1477/LOE/301.4.2/X/2023).

FUNDING

This study did not receive any funding.

CONFLICT OF INTEREST

All of the authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Every author has equally contributed to this research, from the design, data analysis, and interpretation, critically revising it, and giving their final approval of the article.

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