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Clinical Characteristics And Radiological Features Of Multi-Drug-Resistant (MDR) Pulmonary TB Patients

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ABSTRACT
Tuberculosis is currently still a public health problem both in Indonesia and internationally, so it has become one of the goals of sustainable health development.WHO estimates that 10 million people suffer from pulmonary tuberculosis (TB) and it caused 1.4 million deaths in 2019. Multidrug Resistant Tuberculosis (MDR-TB) is a type of tuberculosis that is resistant to at least two first-line antibiotics. This study uses the Literature Review method with a Narrative Review design to identify and summarize previously published articles regarding the clinical characteristics and radiological features of mult-drug-resistant pulmonary TB patients. From the results it was found that there was a relationship between clinical characteristics and radiological features of mult-drug-resistant pulmonary TB patients, the emergence of MDR-TB did not only indicate that the treatment strategy had failed; MDR-TB itself can be a barrier to anti-tuberculosis treatment. So clinical-radiological characteristics should always be determined where appropriately administered drugs have not reached the levels necessary to treat all mycobacterial populations, in order to modify and strengthen national programs in a timely manner, and evaluate trends in drug resistance patterns

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INTRODUCTION

Tuberculosis is currently still a public health problem both in Indonesia and internationally, so it has become one of the goals of sustainable health development.1 The problems faced are related to disease, discovery, treatment, and also treatment failure. Tuberculosis is an infectious disease caused by the bacterium Mycobacterium tuberculosis .1There are several species of Mycobacterium, including: M. tuberculosis, M. bovis, M. africanum, M. Leprae and so on, which are also known as BTA (Acid-Fast Bacteria).

The source of transmission of infectious diseases is through the air (airborne disease). Mycobacterium tuberculosis bacteria can be transmitted to other humans through droplets when active pulmonary TB sufferers cough or sneeze. Mycobacterium tuberculosis will die quickly when exposed to direct sunlight, but can survive for several hours in dark and damp places,4 which mainly attacks the lungs. The organ systems most commonly affected

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include the respiratory system, gastrointestinal system, lymphoreticular system, skin, central nervous system, musculoskeletal system, reproductive system and liver.

WHO estimates that 10 million people suffer from pulmonary tuberculosis (TB) and caused 1.4 million deaths in 2019. Indonesia ranks second after India with 845,000 cases and 98,000 deaths, which is equivalent to 11 deaths/hour in 2020. Although there has been a decline New cases of pulmonary TB reached 9%, but not fast enough to reach the 2020 target. 6 However, this infectious disease still exists and is one of the main health problems in the world, especially in Asia and Africa. Right now, we are faced with a quite worrying phenomenon, namely the emergence of cases of anti-TB drug resistance (OAT). OAT resistance is a condition where administering OAT can no longer kill M. tuberculosis germs.

Multidrug Resistant Tuberculosis (MDR-TB) is a type of tuberculosis that is resistant to at least two first-line antibiotics, such as isoniazid (INH) and rifampicin (RMP) with or without resistance to other anti-tuberculosis drugs (OAT).8 Drug resistance occurs due to the use of OAT inappropriate dosage in patients who are still sensitive to the OAT regimen.

There are many factors that cause MDR TB, such as patient non-compliance in swallowing non-standard drugs (ISTC), lack of diagnostic services, drugs, transportation, logistics and costs of controlling the TB program, history of previous TB treatment, unavoidable side effects of drugs, high numbers therapy failure and even death. Globally in 2020, there were 157,903 cases of OAT resistance consisting of 132,222 cases of MDR-TB, and 25,681 cases of XDR-TB (Extensive Drug Resistant Tuberculosis). In Indonesia, data from the Indonesian Ministry of Health in 2021 shows that there are 8,268 MDR-TB patients.

Diagnosing MDR-TB is not easy, because the symptoms and clinical signs are not typical. Patients with MDR-TB based on their treatment history are divided into primary and secondary groups. Drug resistance in the treatment of TB, especially MDR-TB and TB with Extensive Drug-Resistance (XDR) or MDR-TB, is a significant health problem in various countries, and is an obstacle to global TB control programs. Most patients have more than one complaint for more than one month and the most common symptom is cough with phlegm followed by fever, weight loss, loss of appetite, shortness of breath and hemoptysis.

The problem that arises is the delay in predicting TB becoming drug resistant due to unavailability of sputum or unavailability of molecular rapid test (MRT) kits. X-ray examination plays an important role in this case, because it supports the diagnosis of TB, even though it is not the gold standard for TB diagnosis, namely microbiology/genomic examination. X-ray examination is more convenient because it is fast, practical, non-invasive and cheap to help diagnose and evaluate TB treatment.

Treatment for MDR TB patients will be more difficult, cost more and provide less satisfactory results. Until now, no new OAT has been found to treat MDR TB cases. Several clinical studies have shown that there are several antimicrobials that can be used as OAT, such as macrolides, quinolones and beta-lactams. However, only the quinolone group is considered to be effective as an anti-TB agent. Currently, it cannot be concluded from the clinical trials that are suitable for MDR TB therapy.

The DOTS program is a Tuberculosis treatment strategy recommended by the World

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Health Organization (WHO). This program includes four main pillars, namely microscopic diagnosis, directly observed treatment short course, high quality and adequate anti-Tuberculosis drugs, and an effective monitoring and management system.

METHOD

This research employs a Literature Review with a Narrative Review design to identify, review, evaluate, and interpret all available research. By utilizing this method, a systematic review and identification of journals can be conducted, following predetermined steps or protocols. The eligibility criteria encompass both inclusion and exclusion standards. The inclusion criteria specify that the literature must be in the form of scientific journals and/or proceedings, sourced from PubMed, Google Scholar, or ScienceDirect, with open access and full text availability. The literature should be published between 2020 and 2024 and written in either English or Indonesian. Conversely, the exclusion criteria represent the inverse of the inclusion criteria. To refine the research scope, the PICO method (Population/Problem, Intervention, Comparison, Outcomes) is applied. This structured approach ensures a comprehensive and focused review of the clinical characteristics and radiological features of multi-drug-resistant pulmonary TB patients, leading to more robust and actionable insights.

Table 1. PICO Summary

Component	Information
Population/problem	Clinical characteristics and radiological features
Intervention	TB patient
Comparison	MDR
Outcomes	Correlation

Quality assessment

Literature selection uses the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. The PRISMA Flow Diagram in this research is shown in Figure 1.

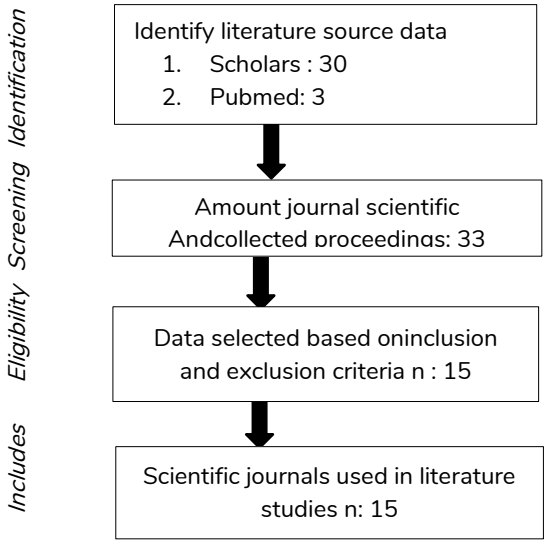

Figure 1. PRISMA Flow Diagram

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RESULTS AND DISCUSSION

Table 2. Literature Review Journal

No	Journal Name	Title	Method	Writer	Conclusion
1	Medicines	Chest X-ray Features in Drug-Resistant Tuberculosis Patients in Nigeria; a Retrospective Record Review	Retrospective analysis	Oladimeji, O., et al	A total of 2555 RO TB patients were studied, the majority (66.9%) were men, aged 29-38 years (36.8%), had previously been treated (77%), came from the Southwest treatment area (43.5%) , HIV negative (76.7%) and diagnosed bacteriologically (89%). X-ray findings were abnormal in 97% of participants, with cavitation being the most common (41.5%).
2.	Journal of Medicine and Health	Radiological Description of Chest Photo of Drug-Resistant Pulmonary TB Patients with and Without Type 2 DM at the Islamic Hospital Jakarta Sukapura	This research is a comparative descriptive study. This research uses a cross sectional research design.	Fachri, M., et al	In the results of a radiological chest x-ray examination, it was found that infiltrates are a picture that is often found in both DM and non-DM patients. In DM patients, the appearance of cavities and fibrosis tends to be found after the infiltrate. In non-DM patients, nodules tend to be found after the infiltrate. However, this is not yet statistically significant.
3.	Bioscientia Medicina: Journal of Biomedicine & Translational Research	Comparison of Chest X-Ray Assessment in Multi-Drug Resistance to Drug-Sensitive Tuberculosis Patients	Case-control design to compare the radiological characteristics of multiple drug resistance and drug sensitivity in Palembang during January-July 2020.	Rifani, SAM, et al	MDR tuberculosis has wider lesions, more dominant infiltrates and cavities compared to drug-sensitive tuberculosis.
4.	Journal of Respiration	Radiographic Features of Multidrug-Resistant Pulmonary	This research was conducted retrospectively	Sulaiman, SC, et al	The presence of lung lesions, ground glass opacities or consolidation with bilateral lung

No	Journal Name	Title	Method	Writer	Conclusion
		Tuberculosis: A Retrospective Study at Dr. Soetomo Surabaya	at the Department of Radiology, RSUD Dr. Soetomo Surabaya, Indonesia, using secondary data.		involvement, fibrosis, multiple cavities, interstitial opacities, pleural thickening, and mediastinal shift are the main features of MDR-TB.
5.	Journal of Public Health	Predictor Factors of Multi-Drug Resistance Tuberculosis on the Characteristics of Chest Radiographic Lesions	A cross-sectional research design	Majdawati, A., et al	The clinical symptom with the strongest predictor value was cough accompanied by shortness of breath (42.7%) followed by coughing up blood or coughing up phlegm (38.7%). Chest radiographic characteristics were as follows: lesion type: mass (OR: 2.631), consolidation (OR: 2.681), pleural thickening (OR: 2.314), and fibrosis as the strongest predictor (OR: 5.610).
6.	Forbes Journal of Medicine	Using Sociodemographic and Clinical Characteristics to Distinguish Between Drug-sensitive and Drug-resistant Tuberculosis	Retrospective analysis	Varol, Y., et al	There was a statistically significant difference in educational status between the two groups. Apart from that, work history was also statistically significantly different between the MDR-TB and DS-TB groups, radiology showed bilateral images
7.	Althea Medical Journal	Thoracic Radiography Findings of Multi-Drug Resistant Tuberculosis at Dr. Hasan Sadikin General Hospital Bandung	This was a cross-sectional retrospective descriptive study.	Kurnia, MT, et al	Large lesions, calcification, fibrosis, infiltration, consolidation, cavities, and clouding of the visor are the main characteristic radiographic findings in the majority of MDR-TB patients.

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No	Journal Name	Title	Method	Writer	Conclusion
8.	The Journal of the Association of Chest Physicians	Clinico-demographic characteristics of multidrug-resistant pulmonary tuberculosis presenting to tertiary care hospitals of India	Retrospective analysis	Rai, DK, et al	The most frequently occurring symptom in study patients was cough (100%) followed by fever, shortness of breath, anorexia, and hemoptysis in decreasing order. On radiological examination, 56.75% of patients had bilateral disease. Chest radiographs showed more advanced disease in 18.91% of patients, moderate disease in 67.56%, and 13.51% of patients had minimal disease. HIV test results were carried out on 58 patients, of which 2 patients showed positive results (3.4%). Sputum examination results for AFB were negative in 25 (34.72%) patients.
9.	Annals of International Medical and Dental Research	To Study Clinico-Radiological Profile of Multi-Drug Resistant Tuberculosis Patients	Prospective study	Phandi, N., et al	The most frequent symptom was cough with phlegm which was present in 94 (94%) patients. On radiology, unilateral disease was present in 48 (48%) patients, bilateral disease was present in 52 (52%) patients. Parenchymal infiltration was present in 79 (79%) patients. Cavitation was present in 23 (23%), fibrocavitary disease was present in 37 (37%) study subjects. Previous history of ATT has a significant relationship with the extent of the lesion on chest X-ray ($p < 0.05$)

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No	Journal Name	Title	Method	Writer	Conclusion
10.	International Journal of Infectious Diseases	Radiographic improvement and its predictors in patients with pulmonary tuberculosis	A prospective cohort study	Heo, EY, et al	The extent of radiographic lesions decreased from 22.8% at diagnosis to 10.5% after 6 months of treatment. Age, previous history of TB, presence of cavitary or fibrotic lesions, and multidrug-resistant TB were n associated with poor radiography.
11.	Halu Oleo University Faculty of Medicine	Characteristics of Multidrug Resistant Tuberculosis (MDR TB) Patients in Southeast Sulawesi 2014-2017	This research is a descriptive research	Aini, ZM, et al	Characteristics of MDR TB patients in Southeast Sulawesi in 2014-2017 dominated by age 15-55 years, male gender, self-employed work, cases of treatment dropout, chest x-ray examination in the form of infiltrates and cavities, BTA examination (+1), type of resistance Rifampicin, and is still on temporary treatment.
12.	Indonesian Respirology Journal	Characteristics of Multidrug Resistant Tuberculosis sufferers who took part in the Programmatic Management of Drug-Resistant Tuberculosis at the H. Adam Malik Central General Hospital, Medan	The research is descriptive in cross-sectional nature.	Sinaga, B, Y, M., et al	The dominant characteristics are 64.28% women, 42.86% aged 33-44 years, 50% high school seniors, 42.87% housewives, 64.29% married. All had a history of taking anti-tuberculosis drugs (OAT). The most common symptom is shortness of breath (57%). Chest radiographs showed infiltrates and nodules in 92.85% of patients, cavities in 42.85% of patients.

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No	Journal Name	Title	Method	Writer	Conclusion
13.	Korean Journal of Radiology	Radiological Findings of Extensively Drug-Resistant Pulmonary Tuberculosis in Non-AIDS Adults: Comparisons with Findings of Multidrug-Resistant and Drug-Sensitive Tuberculosis	The research is retrospective	Cha, J., et al	The research results showed that there were several cavities, nodules and bronchial dilatation as depicted on CT in young patients with positive BTA, so it could be suggested that there was MDR TB or XDR TB and not DS TB. There were no significant differences in imaging findings between XDR TB and MDR TB patients.
14.	International Journal of Health Sciences	Radiological evidence in clinical prevalence of hematological changes in multidrug resistant pulmonary tuberculosis	This prospective research was conducted during February 2018 to December 2020.	Thungathurthi, S., et al	Chest radiography depicts tracheal deviation, lung volume loss, pleural effusion, lobar collapse and manifestations of fibrosis. Defensive leukocytes, phagocytic neutrophils, nucleated platelet cells and platelet volume increased in severe lung grading ($p<0.0001$).
15.	Bioscientia Medicina: Journal of Biomedicine & Translational Research	Comparison of Chest X-Ray Findings between Primary and Secondary Multidrug Resistant Pulmonary Tuberculosis	This research is an analytical observational study with a retrospective design	Septafianty, R. et al	The most common chest x-ray findings in primary MDR pulmonary TB were consolidation (96.2%), which was mostly unilateral (52.0%), with cavities (71.2%), which were mostly multiple (83.8%) with a moderate severity category. The most common chest x-ray findings in secondary MDR pulmonary TB are consolidation (100%), most of which are bilateral (60.4%), accompanied by cavities (80.2%), most of which are multiple (90.1%) with severe severity category. Pleural thickening (47.5%) was also found

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Based on the literature search that had been carried out, literature was found that specifically discussed the clinical characteristics and radiological images of mult-drug-resistant pulmonary TB patients and several pieces of literature were found that discussed the clinical characteristics and radiological images of mult-drug-resistant pulmonary TB patients.

In the first journal by Oladimeji, O., et al (2022), a study was a retrospective analysis. In the research, the clinical characteristics were that the majority were men, aged 29-38 years, had previously been treated, came from the Southwest treatment area, were HIV negative and diagnosed bacteriologically. X-ray findings with cavitation being the most common. The second journal is by Fachri, M, et al (2021), with comparative descriptive research with a cross sectional research design. In the study, the clinical characteristics of the patient were male, age >=43 years, drug withdrawal cases, rifampicin resistance (TB-RR), diabetes mellitus, and chest x-ray radiology results showed infiltrates.

The third journal was conducted by Rifani, SA M, et al (2021), The research carried out was a case control study to compare the radiological characteristics of multiple drug resistance and sensitivity to drugs in Palembang during January-July 2020. The aim of this research was to determine the differences in chest X-ray results in patients with drug-sensitive pulmonary tuberculosis and drug-resistant tuberculosis in Palembang. In the study, it was found that the clinical characteristics of men, aged 40 - 49 years, suffering from diabetes mellitus, old cases of TB, sputum BTA +2 and on thorax photos, tuberculosis that was resistant to various types of drugs had wider lesions, more dominant infiltrates and cavities. compared with drug-sensitive tuberculosis.

The fourth journal conducted by Sulaiman, SC, et al (2018), this type of research is retrospective research. In the study, the clinical characteristics of men, aged 46 - 55 years, BMI with low body weight were found and the chest radiographs that were often found in MDR pulmonary TB were ground-glass opacity and consolidation with bilateral lung involvement, fibrosis, multiple cavities, interstitial opacities. , pleural thickening, and mediastinal shift.

The fifth journal conducted by Majdawati, A., et al (2023), the research design used was cross-sectional. In the study, clinical characteristics of cough with shortness of breath were found and chest radiographs showed consolidation, pleural thickening, fibrosis with locations on the medial right and inferior left. The sixth journal conducted by Varol, Y., et al (2022), this research is a retrospective study. In the study, the dominant clinical characteristics were cough and shortness of breath and the radiographic images were bilateral.

The seventh journal conducted by Kurnia, MT, et al (2022, this research is a retrospective descriptive study with a cross-sectional design. This research obtained radiological examination results of large lesions, calcification, fibrosis, infiltration, consolidation, cavities, and cloudiness in the eyes. The eighth journal conducted by Rai, DK, et al (2020), this research is a retrospective study of 85 MDR pulmonary tuberculosis patients who were diagnosed at the pulmonary medicine department of AIIMS Patna between January 1 2016 and December 31 2017. The study found the characteristics of the

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symptoms that appeared most frequently in the study patients was cough followed by fever, shortness of breath, anorexia, and hemoptysis and on radiological examination, 56.75% of patients had bilateral disease.

The ninth journal conducted by Pandhi, N., et al (2019), this type of research is a prospective study conducted at Chest and TB Hospital, Amritsar involving 100 patients diagnosed with Drug Resistant Tuberculosis. The study found that the most clinical characteristics of patients were in the 21-30 year age group, followed by the <20 year age group. The most common symptom is cough with phlegm. On radiology, unilateral disease was present in 48 (48%) patients, bilateral disease was present in 52 (52%) patients. Parenchymal infiltration was present in 79 (79%) patients. Cavitation was present in 23 (23%), fibrocavitary disease was present in 37 (37%) study subjects.

The tenth journal conducted by Heo, E. Y, et al (2009), this research is a prospective cohort study involving patients with culture-proven pulmonary TB. The study obtained clinical characteristics of patients which found that increasing age, previous history of TB, the presence of cavities or fibrotic lesions and multidrug-resistant TB were significantly associated with poor radiographic response.

The eleventh journal conducted by Aini, Z. M, et al (2019), this research is a descriptive study to determine the characteristics of MDR TB sufferers in Southeast Sulawesi Province in 2014-2017 through medical records as research data. The research obtained clinical characteristics, namely age 15-55 years, male gender, history of TB treatment in cases after stopping treatment (default), and dominant radiological examination with infiltrates and cavities.

The twelfth journal conducted by Sinaga, BY M (2013), this research is descriptive, cross-sectional. Data were obtained from patient medical records. This research is the first research since there was a PMDT program in Medan, namely at H. Adam Malik Hospital Medan. The research found clinical characteristics, namely age 35-44 years, female gender, clinical symptoms of shortness of breath, and on radiological examination the dominant appearance was cloudy spots (infiltrates)/nodular shadows. The thirteenth journal conducted by Cha, J., et al (2009), this research is a retrospective study. The research found clinical characteristics, namely male, average age 38 years and chest radiography examination showed the presence of nodules and reticulo-nodular opacities.

The fourteenth journal conducted by Thungathurthi, S., et al (2022), this research is a prospective study conducted during February 2018 to December 2020. Permission and protocol approval have been obtained from the Jayamukhi College of Pharmacy, Institutional Review Board. The research showed clinical characteristics, namely laboratory examination showed a decrease in the number of lymphocytes and average platelet size, and chest radiography showed tracheal deviation, loss of lung volume, pleural effusion, lobar collapse and manifestations of fibrosis.

The fifteenth journal conducted by Septafianty, R., et al (2021), this research is an analytical observational study with a retrospective design. The research obtained clinical characteristics, namely age 46-55 years, male and female gender, comorbid diabetes mellitus factors, status on treatment, clinical symptoms of shortness of breath, the most

common chest x-ray finding in primary MDR pulmonary TB is consolidation (96.2 %), most of which were unilateral (52.0%), accompanied by cavities (71.2%), most of which were multiple (83.8%) with a moderate severity category. The most common chest x-ray findings in secondary MDR pulmonary TB are consolidation (100%), most of which are bilateral (60.4%), accompanied by cavities (80.2%), most of which are multiple (90.1%) with severe severity category. Pleural thickening (47.5%) was also found.

CONCLUSION

Based on the literature that discusses the clinical characteristics and radiological features of mult-drug-resistant pulmonary TB patients, it can be concluded that there is a relationship between the clinical characteristics and radiological features of mult-drug-resistant pulmonary TB patients, MDR-TB is the main cause throughout the world . The emergence of MDR-TB does not simply signal that treatment strategies have failed; MDR-TB itself can be a barrier to anti-tuberculosis treatment. So clinical-radiological characteristics should always be determined where appropriately administered drugs have not reached the levels necessary to treat all mycobacterial populations, in order to modify and strengthen national programs in a timely manner, and evaluate trends in drug resistance patterns. Therefore, early detection of drug resistance among retreatment cases is necessary.

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