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REVIEW

Radiological imaging of pulmonary cavitations in adult multidrug-resistance and extensively drug-resistance tuberculosis patients

Justin Ginting[1], Katharina Ellen Dominika[2], Ardo Sanjaya[3], Julia Windi Gunadi[4*]

Abstract

Mycobacterium tuberculosis is a pathogen that causes the infectious disease tuberculosis. Based on its resistance, tuberculosis can be divided into Drug-susceptible Tuberculosis (DS-TB) and Drug-resistant Tuberculosis (DR-TB). MDR-TB is one type of DR-TB when *M. tuberculosis* complex strains unresponsive to rifampicin and isoniazid. Another type of DR-TB is XDR-TB, A strain of *M. tuberculosis* that was unresponsive to rifampicin, isoniazid, fluoroquinolones, and at least 1 drug from group A. Research on the comparison of lung cavities in DS-TB, MDR-TB, and XDR-TB is still limited, this literature review is intended to explore comparative studies of lung cavity radiography in adult MDR-TB and XDR-TB patients. This literature review uses secondary data from literature searches through PubMed and Google Scholar by searching for keywords such as "Pulmonary Cavity", "Multidrug Resistance Tuberculosis", "Extensively Drug Resistance". Articles were included in the inclusion criteria if published in national or international journals with topics that match the research objectives within the last ten years. We found 7 studies that compared the radiologic features of lung cavities in individuals who have been diagnosed with DS-TB, MDR-TB, and XDR-TB. The literature review results showed that the radiologic features of cavities from DR-TB appear to be more massive than those in DS-TB. Similarly, in XDR-TB, the radiological picture of cavities appears more massive than in MDR-TB. The conclusion that can be drawn is that cavitation can be seen in DS-TB and DR-TB, and more cavitation in XDR-TB than in MDR-TB and DS-TB.

Keywords: cavity, multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis

Introduction

Mycobacterium tuberculosis is a pathogen that causes the infectious disease tuberculosis. This disease often affects the lungs and can affect other tissues.[1] The incidence of TB cases continues to increase every year. An estimated 10.6 million people will be sick with TB by 2022.[2] The disease is preventable and curable. However, if handled inappropriately, the disease can become resistant. Based on its resistance, tuberculosis can be divided into Drug-susceptible Tuberculosis (DS-TB) and Drug-resistant Tuberculosis (DR-TB). Many TB strains are impervious to first- and second-line treatment. 12.711 patients with Multidrug-resistant Tuberculosis (MDR-TB) were included in a study of 64 across 22 countries. Of these, 9% were Extensively drug-resistant patients (XDR –TB**)**.[3] MDR-TB is one type of DR-TB when *M. tuberculosis* complex strains unresponsive to rifampicin and isoniazid. Another type of DR-TB is XDR-TB, a strain of *M. tuberculosis* that was unresponsive to isoniazid, rifampicin, fluoroquinolones, and a group A drug that led to the condition.

Affiliation
[1]Departement of Radiology, Faculty of Medicine, Universitas Kristen Maranatha, Bandung, Indonesia
[2]Faculty of Medicine, Universitas Kristen Maranatha, Bandung, Indonesia
[3]Department of Anatomy, Faculty of Medicine, Universitas Kristen Maranatha, Bandung, Indonesia
[4]Department of Physiology, Faculty of Medicine, Universitas Kristen Maranatha, Bandung, Indonesia

Correspondence
julia.windi@maranatha.ac.id

Lack of treatment and drug resistance are the underlying reasons for the formation of cavities. A cavity is a pathological air-filled cavity in the lung parenchyma caused by *M. tuberculosis* infection. With the formation of cavities, the basal membrane and alveolar are permanently damaged. So even if TB treatment is successful and the patient is cured, the cavities remain. Cavities can increase transmission, morbidity, and mortality. Since the interior of the cavities is rich in oxygen, it facilitates the replication and proliferation of bacteria. It is this mutation of bacterial replication that allows drug resistance to occur. The second possible cause of resistance is because the inside of the cavities has poor vascularization, so it will inhibit the drug penetration process. Due to cavities, treatment may not be effective and there is often a risk of drug resistance and relapse.[4]

Cavities can be seen and evaluated by X-ray or CT scan. Cavities give a round radiolucent appearance without pulmonary scars. With X-ray and CT scans, the size, shape, number, location, and thickness of the cavities can be measured. This can be related to the severity of the infection as well as the age of the patient. Although early-stage tuberculosis is diagnosed by microbiological testing, imaging studies may also be performed to aid in the diagnosis. Based on the literature, thick-walled cavities are considered as a radiographic sign for diagnosing pulmonary MDR-TB, especially when the number of cavities is more than 3.[5]

The propensity score may need to be considered before comparing cavities in MDR-TB and XDR-TB patients. Propensity score matching is a method used to analyze data to reduce bias that may occur due to differences between the groups being compared. Later, patients in each group can be matched in advance according to age, gender, smoking history, diabetes mellitus, and so on. Research on the comparison of lung cavities in DS-TB, MDR-TB, and XDR-TB is still limited. Therefore, the purpose of this literature review is to examine in more depth the comparative radiographic images of the lung cavity in adult MDR-TB and XDR-TB patients.

Discussion

Mycobacterium tuberculosis is a pathogen that causes the infectious disease tuberculosis. This disease often affects the lungs and can affect other tissues. Infection from tuberculosis itself can cause cavities to form. The journey of cavitation formation begins with the entry of *Mycobacterium tuberculosis* into the lungs which will later be phagocytes by alveolar macrophages. Infected alveolar macrophages will recruit an inflammatory response, namely monocyte cells. Necrotic toxins from *M. tuberculosis* can induce host cells to necrosis so that later a necrotic nucleus will form inside the granuloma.[4,13] Patients with a weakened immune system will experience an increased risk of cavitation formation due to the rupture of the granuloma wall. So that the necrotic nucleus will undergo liquefaction, and the remaining empty cavity will later be called a cavitation.

The disease is curable, but if the handling and treatment are not appropriate, drug resistance may occur. Besides past treatment experience, cavities are an important indicator of resistance. The oxygen pressure inside the cavities is higher than the oxygen pressure in the necrotic nodules. Thus, when necrotic nodules turn into cavities, the replication of *M. tuberculosis* will increase dramatically.[14] The difficulty in penetrating avascular cavities, and a multitude of mycobacteria are thought to be responsible for resistance.[15]

The methodology of this literature review is based on secondary data obtained from literature searches made in PubMed and Google Scholar by searching for keywords such as "Pulmonary Cavity", "Multidrug Resistance Tuberculosis", "Extensively Drug Resistance". Articles were included in the inclusion criteria if they were published in national or international journals with topics that were by the research objectives within the last ten years. The results of the literature search found 7 articles that qualify for analysis and discussion in this literature study. The results of data extraction from the seven articles can be seen in the table below.

The results of Yang et al., DS-TB and DR-TB can be distinguished based on radiological and clinical characteristics. The radiological image of the cavity in DR-TB usually appears more massive than in DS-TB.[6] MDR-TB is one type of DR-TB when *M. tuberculosis* complex strains unresponsive to rifampicin and isoniazid.[16] Based on the literature, thick-walled cavities are considered as a radiographic sign for diagnosing pulmonary MDR-TB, especially when the number of cavities is more than 3.[5]

Table 1. Research findings on comparison of radiologic features of lung cavities in MDR-TB and XDR-TB adults

Author (year)	Research subject	Relevant findings
Yang et al., 2022[6]	2237 patients	This study found a strong correlation between several cavities and DR-TB. This study also confirmed that the size and number of nodules and cyst were higher in DR-TB.
Butova et al., 2023[7]	168 patients	In MDR-TB, 45.5% of patients had more than 3 lung cavities while only 7.9% of patients in the DS-TB group. DS-TB patients had 74% of small cavities, while the MDR-TB group had only 35.2%.
Icksan et al., 2018[8]	366 patients	Among MDR-TB patients, 57.9% had cavity, compared to 6% in DS-TB patients. MDR-TB patients had multiple cavities in 68.3% of cases, while those with DS-TB had 14.2%.
Burhan et al., 2022[9]	447 patients	Patients who had been previously treated for MDR-TB had a higher incidence of cavities, around 70% and in DS-TB around 30%.
Chuchottaworn et al., 2015[10]	5059 patients	Findings from the study showed that multiple cavities (>3 cavities) were associated with MDR-TB.
Cheon, 2017[11]	97 patients	In this study, it was found that the mean cavity thickness in the MDR-TB group was 8.3 mm and the XDR-TB group was 11.5 mm. The average cavity size in the MDR-TB group was 21 mm while in the XDR-TB group it was 36 mm, making XDR-TB appear more aggressive than MDR-TB.
Mehrian et al., 2020[12]	45 patients	From the results of the study, the findings related to cavities in both the MDR-TB and XDR-TB groups were similar to the CT scan results.

In this study, all cases of pulmonary TB confirmed in culture were collected and analyzed by Butova et al., using the cohort study method. The data were used from all patients treated for one year at Kharkiv TB Pharmacy No. 1 in Kharkiv, Ukraine. 168 patients with pulmonary TB were divided into 2 groups: 1. Pulmonary TB-MDR patients, 2. Pulmonary DS-TB. More than 3 pulmonary cavities were found in 45.5% of group 1 patients while in group 2 patients only about 7.9%. Smaller cavities were found in 74% of group 2 patients, while in group 1 patients, around 35.2%.[7]

A cross-sectional method was used by Icksan et al., to compare the findings of thoracic cardiography in both groups, with 183 patients in each DS-TB or MDR-TB group. The prevalence of cavities in patients with MDR-TB was 57.9%, while those with DS-TB had 6%. 68.3% of MDR-TB and 14.2% of DS-TB patients had multiple cavities.[8]

Between February 2017 and November 2018, Burhan et al., utilized the cross-sectional analysis method of a prospective cohort study and recruited participants from 7 DR-TB referral hospitals in 7 cities across Indonesia (Dr. Wahidin Sudirohusodo, Makassar; Persahabatan H. Adam Malik, Medan; Dr. Kariadi, Semarang; Dr. Sardjito, Yogyakarta; Sanglah, Denpasar; and Dr. Soetomo, Surabaya). Patients who had been previously treated for MDR-TB had a higher incidence of cavities around 70%, and in DS-TB around 30%.[9]

Another study was conducted by Sulaiman et al., retrospectively at RSUD Dr. Soetomo Surabaya's Department of Radiology in Indonesia using secondary data obtained from patients' medical records from September 2015 to March 2018. 167 individuals were enrolled in the study due to MDR-TB. On thoracic radiographs, cavities were found in 131 patients (78%) with 87% of them having multiple cavities.[15]

Another study was conducted by Wang et al., on January 29, 2018, using a literature search approach in PubMed. The combination of search terms was " ((multidrug-resistant tuberculosis) OR (extensive* drug-resistant tuberculosis)) AND (CT or computed tomography or X-ray or radiograph or imaging)". The results of a literature comparison found that cavity lesions in MDR-TB occurred in around 70% of patients, and in DS-TB around 30%. Cavities in MDR-TB are likely to be more numerous and larger. Greater and more numerous cavities are found in MDR-TB.[5] Chuchottaworn et al., findings suggest that cavity characteristics associated with MDR-TB include having a maximum diameter of ≥30 mm, ≥3 cavities, and cavities in ≥2 lung zones.[10]

Another type of DR-TB is XDR-TB, A strain of *M. tuberculosis* that was unresponsive to isoniazid, rifampicin, fluoroquinolones, and a group A drug that led to the condition.

Based on a retrospective study by Cheon et al., there were 50 MDR-TB patients and 25 XDR-TB patients after propensity score matching, there were differences from significant radiological findings in the thickness and size of the cavitary. In the MDR-TB group, the cavity was 8.3 mm thick while in those of the XDR-TB, it was 11.5 mm. The MDR-TB group had a cavitary size of 21 mm, while the XDR-TB group had 36 mm, making XDR-TB appear more aggressive than MDR-TB.[11] Possibly because XDR-TB has a much

higher difficulty and failure rate in treatment compared to MDR-TB patients (WHO in 2013 stated that 48% of MDR-TB patients were cured, while in XDR-TB only 20% were cured and 44% died)[17], so later more massive cavities can form.

A further comparative descriptive cross-sectional study was conducted by Mehrian et al., from 2013 to 2019, involving 45 TB patients referred to Masih Daneshvari Hospital, Tehran, Iran. They classified patients as either MDR-TB or XDR-TB. From the results of the study, it was found that the findings related to cavities with CT scans in the MDR-TB and XDR-TB groups were similar. From this study, it was concluded that CT scan images to distinguish MDR-TB and XDR-TB were not sensitive.[12]

However, in Cheon et al.'s examination which used propensity score matching, a 2:1 matching of the MDR-TB group and the XDR-TB group was performed, which initially consisted of 72 MDR-TB patients and 25 XDR-TB patients. Before and after propensity score matching, the CT results were compared. According to this examination, the cavity thickness for MDR-TB was on average 80 mm, while for XDR-TB it was about 115 mm. The MDR-TB group had a cavitary size of 21 mm, while the XDR-TB group had 36 mm.[11]

In Mehrian et al.'s study, there may be a potential explanation for why CT images of MDR-TB were not significantly different from XDR-TB. This is because propensity score matching was not previously performed.[12] Propensity score matching itself is used to minimize biased research results, by matching patients from each group based on age, gender, habit history, and disease history. Hopefully, after propensity score matching is carried out, there will be an increase in the effectiveness of research data.

Conclusion and Recommendation

Cavities are found in Drug-susceptible Tuberculosis (DS-TB) and Drug-Resistant Tuberculosis (DR-TB). Unlike DS-TB, MDR-TB patients have a greater number of cavities, which are more numerous in terms of size and thickness. In comparison to MDR-TB, XDR-TB appears to be more severe with greater wall thickness and cavity size than MDR-TB. However, due to limited sources of existing research, future studies can further examine the differences between cavity imaging in patients with DS-TB, MDR-TB, and XDR-TB and compare them at the same time.

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