

Original paper

## Computerised tomography scan in multi-drug-resistant versus extensively drug-resistant tuberculosis

Payam Mehrian<sup>1A,D</sup>, Poopak Farnia<sup>2,3C</sup>, Dina Jalalvand<sup>2E</sup>, Mostafa Rezaei Chamani<sup>2B,F</sup>, Mahmood Bakhtiyari<sup>2C</sup>

<sup>1</sup>Telemedicine Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Mycobacteriology Research Centre (MRC), National Research Institute of Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>Department of Biotechnology, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

### Abstract

**Purpose:** Multi-drug-resistant tuberculosis (MDR-TB) is simultaneously resistant to isoniazid and rifampin. Of course, this germ may also be resistant to other anti-tuberculosis drugs. Patients with extensively drug-resistant tuberculosis (XDR-TB) are also resistant to all types of fluoroquinolone and at least one of the three injectable medications: amikacin, clarithromycin, or kanamycin, in addition to isoniazid and rifampin. Therefore, the main objective of the current study was to evaluate and compare the computed tomography (CT) scan findings of MDR-TB and XDR-TB patients.

**Material and methods:** In this comparative descriptive cross-sectional study 45 consecutive TB patients who referred to Masih Daneshvari Hospital, Tehran, Iran from 2013 to 2019 were enrolled. TB was diagnosed based on sputum smear and sensitive molecular and microbial tests. Patients were divided into two groups (MDR-TB and XDR-TB) based on two types of drug resistance. CT scan findings were compared for cavitory, parenchymal, and non-parenchymal disorders. The early diagnostic values of these factors were also calculated.

**Results:** Findings related to cavitory lesions including the pattern, number, size of the largest cavity, maximum thickness of the cavity, lung involvement, number of lobes involved, and the air-fluid levels in the two patient groups were similar ( $p > 0.05$ ). Parenchymal findings of the lung also included fewer and more nodules of 10 mm in the MDR-TB and XDR-TB groups, respectively. Tree-in-bud, ground-glass-opacity, bronchiectasis, cicatricial emphysema, and lobar atelectasis were similar in the two patient groups ( $p > 0.05$ ). Findings outside the parenchymal lung, including mediastinal lymphadenopathy and pericardial effusion, showed no statistically significant difference between the MDR-TB and XDR-TB groups ( $p > 0.05$ ). Parenchymal calcification was more common in the XDR group than in the MDR group (64.7% and 28.6%, respectively) with a significant difference ( $p = 0.01$ ).

**Conclusions:** CT scan findings in patients with XDR-TB are similar to those of patients with MDR-TB for cavitory, parenchymal, and non-parenchymal lung characteristics. However, patients with XDR-TB tend to have more parenchymal calcification and left-sided plural effusion. CT characteristics overlap between XDR-TB and those with MDR-TB. It can be concluded that CT scan features are not sensitive to the diagnosis.

**Key words:** tuberculosis, antimicrobial resistance, computerised tomography scan.

### Introduction

Tuberculosis (TB) is an ancient disease occurring worldwide with numerous early and late complications [1,2].

According to the World Health Organization (WHO) definition, multi-drug-resistant tuberculosis (MDR-TB) is resistant to both isoniazid and rifampin [3]. Of course, this germ may also be resistant to other anti-tuberculosis

### Correspondence address:

Dr. Dina Jalalvand, Shahid Beheshti University of Medical Sciences, 1068, block 5, Ekbatan town, Tehran, Iran, 1396843193, Tehran, Iran,  
e-mail: [Dinajalvand@gmail.com](mailto:Dinajalvand@gmail.com)

### Authors' contribution:

A Study design · B Data collection · C Statistical analysis · D Data interpretation · E Manuscript preparation · F Literature search · G Funds collection

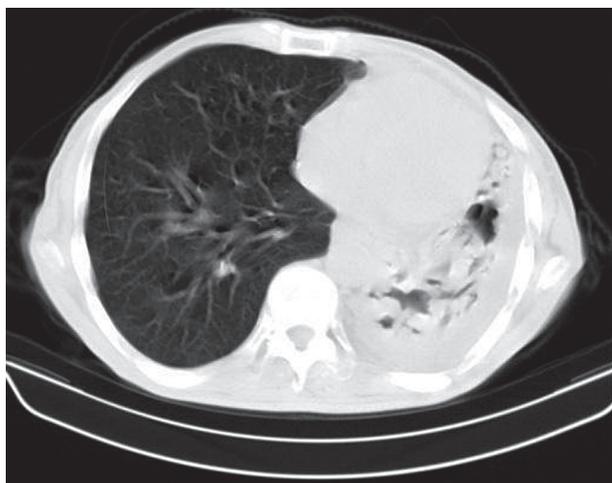
drugs [3]. Lack of compliance by patients and self-discontinuation are the main causes for drug resistance as well as single therapy and background diseases [3].

Patients with extensively drug-resistant tuberculosis (XDR-TB) are resistant to all types of fluoroquinolone and at least one of the three injectable medications (amikacin, clarithromycin, or kanamycin) in addition to isoniazid and rifampin [4]. In such cases, two years of continuous therapy is mandatory with direct observation by a physician [4]. In total, 3.2% of tuberculosis cases worldwide are drug resistant [4]. Usually MDR patients are younger and have multiple treatment sessions and cavitory involvement [5]. Despite multiple studies comparing the clinical findings of MDR and XDR cases [6-8], few studies have compared imaging findings and TB characteristics [7,9-16]. Therefore, the main objective of the current study was to evaluate and compare the CT scan findings of MDR-TB and XDR-TB patients.

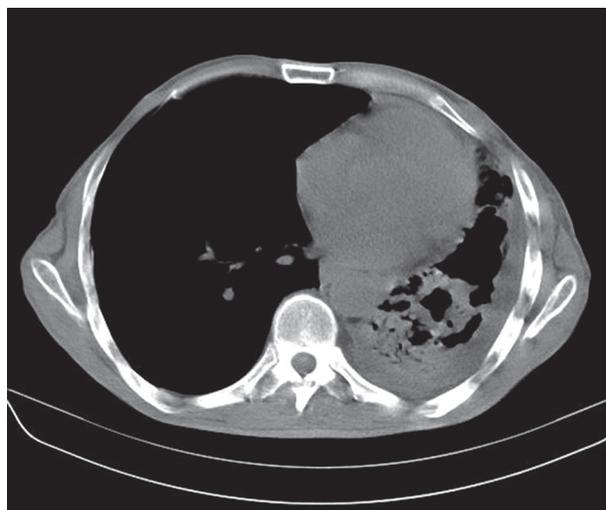
## Material and methods

In this comparative descriptive cross-sectional study, a total of 45 consecutive TB patients who referred to Masih Daneshvari Hospital, Tehran, Iran between 2013 and 2019 were enrolled. TB was diagnosed according to the WHO criteria by sputum smear and sensitive molecular and microbial tests. Additional inclusion criteria were age over 18 years, lacking chronic respiratory disease affecting the lung computed tomography (CT) scan findings, and the presence of CT scan results among existing medical documents. Patients were divided into two groups: MDR-TB and XDR-TB, based on two types of drug resistance.

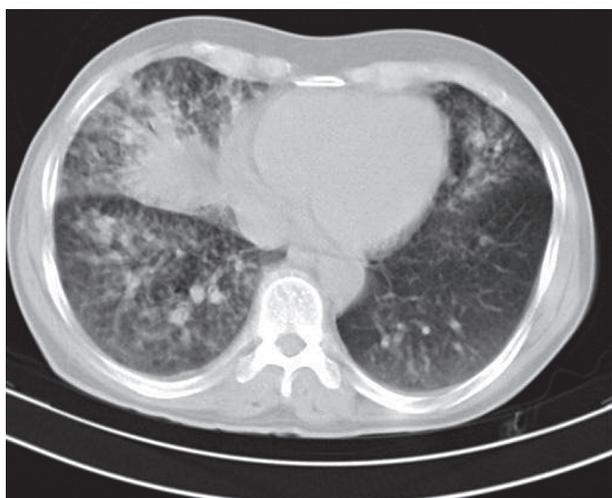
There were 17 eligible cases with XDR-TB and 28 appropriate patients with MDR-TB among 136 MDR cases and 34 patients with XDR. CT scans findings were compared for cavitory, parenchymal, and non-parenchymal



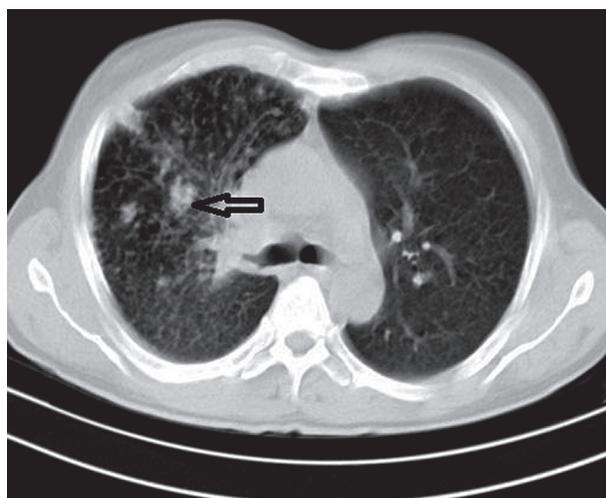
**Figure 1.** 66 year-old male with extensively drug-resistant tuberculosis. Axial computed tomography scan of the lung showing cavitory consolidation with airbronchogram in left lower lobe



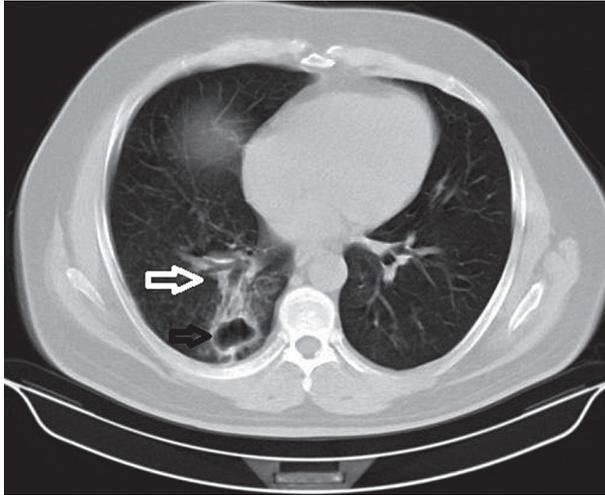
**Figure 2.** Mediastinal window computed tomography scan of the same patient as in Figure 1 showing left sided pleural effusion



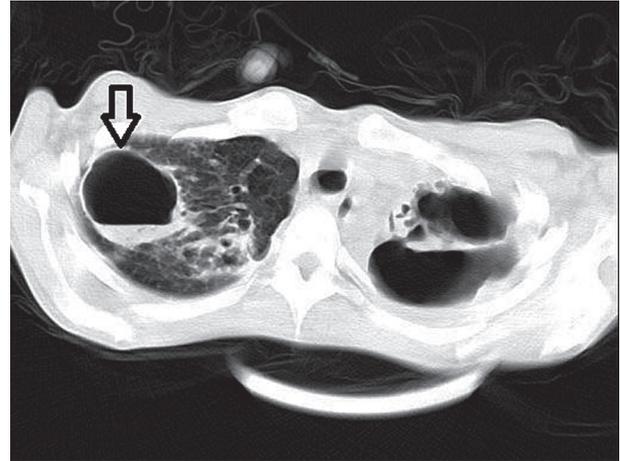
**Figure 3.** 51 year-old male with multi-drug-resistant tuberculosis. Axial computed tomography scan of the lung showing consolidation in right middle lobe with extensive nodular infiltration



**Figure 4.** The same patient as in Figure 3. Lung window computed tomography scan showing a macronodule (black arrow) measuring 12 mm in right upper lobe. Note also micronodular infiltration of the same side



**Figure 5.** 47 year-old male with extensively drug-resistant tuberculosis. Axial computed tomography scan of the lung showing bronchiectasis (white arrow) with cavity formation (black arrow) in right lower lobe



**Figure 6.** 21 year-old female with extensively drug-resistant tuberculosis. Lung window computed tomography scan showing a cavitory lesion with air-fluid level (black arrow) associated with bronchiectasis in right upper lobe. Note also the fibrocavitory lesion involving left upper lobe

disorders. The early diagnostic values of these factors were also calculated (Figures 1–6).

Data analysis was done by SPSS version 25.0 software. The categorical variables were shown as frequencies and percentages. The numerical variables were demonstrated as mean and standard deviation. The  $\chi^2$ , Kolmogorov-Smirnov, independent sample *t*-test, and Mann-Whitney *U* test were utilised. A *p*-value of less than 0.05 was considered statistically significant.

## Results

The mean patient age was  $43.1 \pm 15.2$  years ( $44.3 \pm 15.5$  and  $41.4 \pm 15.2$  in MDR and XDR cases, respectively;  $p > 0.05$ ). Among the 45 subjects, 26 were men (17 MDR and 9 XDR) and 19 were women (11 MDR and 8 XDR); the difference was not significant ( $p > 0.05$ ). Among the

MDR and XDR cases, 21.4% and 8.9% were smokers, respectively ( $p > 0.05$ ). Previous first-line anti-TB therapy was positive in 57.8% and 37.8% of cases in the MDR and XDR groups, respectively ( $p > 0.05$ ). The mean time intervals between CT scan and positive microbiology results were  $26.2 \pm 16$  and  $35.5 \pm 14.4$  days, respectively, which showed no significant difference ( $p > 0.05$ ). Diabetes and HIV were seen in seven and six cases, respectively; this difference was not statistically significant ( $p > 0.05$ ).

As shown in Table 1, the findings related to cavitory lesions including the pattern, number, size of the largest, maximum thickness of the cavity, lung involvement, number of involved lobes, and the air-fluid level in the two patient groups were similar ( $p > 0.05$ ). In cavitory lesions, unilateral cases were more common in both MDR and XDR findings.

**Table 1.** Cavitory lesions across the groups

Variable	MDR-TB	XDR-TB	<i>p</i> value
Cavitory	24 (85.7%)	13 (76.5%)	0.43
Pattern			
In nodule and mass	16 (57.1%)	12 (70.6%)	0.36
In consolidation	12 (42.9%)	6 (35.3%)	0.61
In nodule and mass plus consolidation	4 (4.13%)	5 (29.4%)	0.21
Total number	$1.5 \pm 1$	$2 \pm 2$	0.39
Size of largest cavitory lesion (mm)	$29 \pm 25$	$45 \pm 15$	0.44
Largest thickness (mm)	$5.5 \pm 2$	$6 \pm 2$	0.44
Laterality			
Unilateral	$29 \pm 25$	9 (62.9%)	0.12
Bilateral	$5.5 \pm 2$	4 (23.5%)	0.25
Number of lobes	$1.3 \pm 0.98$	$1.82 \pm 1.70$	0.20
Air-fluid level	7 (25.0%)	5 (29.4%)	0.74

**Table 2.** Parenchymal lesions across the groups

Variable	MDR-TB	XDR-TB	<i>p</i> value
Micronodule < 10 mm***	28 (100%)	17 (100%)	1.000
Number of lobes with micronodules*	3.96 ± 1.64	3.47 ± 1.74	0.35
Macronodule < 10 mm***	15 (53.6%)	8 (47.1%)	0.67
Number of lobes with macronodules*	1 (0-2)	0 (0-1)	0.58
TIB***	23 (82.1%)	15 (88.2)	0.58
Number of lobes with TIB*	2.71 ± 1.95	2 (1-2)	0.83
Ground glass opacity and consolidation***	18 (64.3%)	15 (88.2%)	0.07
Number of lobes with ground glass opacity and consolidation**	1 (0-2)	2 (1-2)	0.10
Bronchiectasis***	23 (82.1%)	15 (88.2%)	0.58
Number of lobes with bronchiectasis**	1 (0-2)	2 (1-3)	0.17
Cicatrical emphysema***	4 (14.3%)	2 (11.8%)	0.80
Number of lobes with cicatrical emphysema**	–	–	0.85
Parenchymal calcification***	8 (28.6%)	11 (64.7%)	0.01
Number of lobes with parenchymal calcification*	0.5 ± 0.18	0.76 ± 0.16	0.32
Lobar atelectasis***	4 (14.3%)	3 (17.6%)	0.76
Number of lobes with lobar atelectasis**	–	–	0.70

\*Mean ± SD tested by independent sample *t*-test\*\*Median and IQR tested by Mann-Whitney *U* test\*\*\* $\chi^2$  test**Table 3.** Extra-parenchymal lesions across the groups

Variable	MDR-TB	XDR-TB	<i>p</i> value
Mediastinal lymphadenopathy	17 (60.7%)	10 (58.8%)	0.90
Pericardial effusion	2 (7.1%)	3 (17.6%)	0.27
Hilar lymphadenopathy	12 (43%)	10 (58.8%)	0.29
Hilar lymphadenopathy laterality			
Unilateral	9 (32.1%)	9 (52.9%)	0.16
Bilateral	3 (10.7%)	1 (5.9%)	0.58
Not seen	16 (57.1%)	7 (41.2%)	0.29
Calcified lymphadenopathy	3 (10.7%)	5 (29.4%)	0.11
Pleural effusion	20 (71.7%)	16 (94.1%)	0.06
Pleural effusion laterality			
Unilateral	15 (53.6%)	14 (82.4%)	0.051
Bilateral	5 (17.9%)	2 (11.8%)	0.58
No effusion	8 (28.6%)	1 (5.9%)	0.06
Loculated pleural effusion	3 (10.7%)	3 (10.7%)	0.58

As shown in Table 2, the parenchymal findings of the lung also included fewer and more nodules of 10 mm in the MDR and XDR groups, respectively. Tree-in-bud, ground-glass-opacity (GGO), bronchiectasis, cicatrical emphysema, and lobar atelectasis were similar in the two patient groups ( $p > 0.05$ ). Parenchymal calcification was more common in the XDR group (64.7% vs. 28.6%), with a significant difference ( $p = 0.01$ ). Micronodules, TIB, GGO, and bronchiectasis were more common findings in

the XDR group, and micronodules, TIB, and bronchiectasis were more common findings in the MDR group.

As shown in Table 3, the findings outside of the parenchymal lung, including mediastinal lymphadenopathy and pericardial effusion, showed no statistically significant difference between the MDR-TB and XDR-TB groups ( $p > 0.05$ ). However, pleural effusion and mediastinal lymphadenopathy were most common findings in both the XDR and the MDR group.

## Discussion

Proper prescription of second-line anti-tuberculosis drugs must be ensured to thoroughly treat existing MDR-TB, reduce further transmission, and prevent the emergence of XDR-TB [17]. Interestingly, CT scanning may be used to monitor therapeutic responses after initial treatments for TB cases [18]. In the current study, the CT scan findings of MDR and XDR tuberculosis patients were compared. Only one significant difference that was related to parenchymal calcification with a significantly higher rate among XDR cases was found. Other common but non-significant findings in the XDR cases included greater cavity thickness, bilateral cavities, number of lobes, GGO, pleural effusion, calcified lymphadenopathy, and consolidation. Overall, this study demonstrated that imaging findings are not useful in distinguishing between MDR and XDR tuberculosis.

Contrary to the current results, Cha *et al.* [10] noted a significant age difference between MDR and XDR groups. A lack of matching with the group-to-group method may explain the differing results. Some differences may relate to the age at which anti-TB treatment was initiated. Bacilli are currently transmitted to younger patients. Other factors include decreased immune response and sedentary lifestyle. Lee *et al.* [11] reported that cavities are more common in patients with XDR with further lobe involvement than in MDR patients. Wang *et al.* [9] reported that multiple cavities with thick-walled status are the most promising imaging sign for diagnosing MDR-TB. This issue was found to be true for both MDR and XDR patients in the current study.

Yeom *et al.* [14] reported extensive lung involvement in XDR and MDR patients compared with non-resistant cases. This result may be explained by the transposition of microorganism-containing fluid to the bronchial tree and further parenchymal involvement. In the current study, the type of cavitory lesion did not differ between XDR and MDR cases. Cha *et al.* [10] reported that multiplex cavities are more common in both MDR and XDR cases than in treatment-responsive cases. Fishman *et al.* [15] showed no difference in cavitory pattern between MDR and XDR cases. Other studies have assessed the level of cavitory involvement in AIDS patients [10,12,13]. Cha *et al.* [10] reported lower cavitation in immunosuppressed patients with a positive HIV status compared with HIV-negative patients with greater immunity. Therefore, as seen in the current study, cavitory lesions are the main pulmonary finding for MDR or XDR without AIDS.

In the current study, the parenchymal findings were similar across the XDR and MDR groups, except for parenchymal calcification, which had a higher rate in XDR cases than in MDR patients. Furthermore, GGO and consolidation showed a borderline significance of 0.06. Additional studies with larger sample sizes would demonstrate definitively the relationship status. Cha *et al.* [10] showed that bronchial obstruction and large nodules are

more common in MDR and XDR cases versus non-resistant cases. Hence, the use of CT scanning to identify parenchymal lesions is recommended. The micronodules were also common in the current study, being found in all patients with either MDR or XDR. Yeom *et al.* [14] also showed a greater rate of parenchymal findings in patients compared with non-resistant cases.

Similarly, Lee *et al.* [11] showed that micronodules and bronchiectasis are more common in XDR than in MDR cases. This issue would help to disseminate caseous necrosis and granulomatous inflammation. This finding also showed the higher invasion rate of XDR compared with MDR cases. When tree-in-bud and consolidation are accompanied by such findings, the presence of antimicrobial resistance is suggested, and further microbiological assessments would be beneficial. However, as shown in the current study, there are no distinguishing CT scan differences between MDR and XDR cases. Some studies have compared MDR and XDR cases with non-resistant cases [9,13]. Further cases of macronodules and bronchial obstruction were reported in MDR and XDR patients than in non-resistant patients. This higher rate of parenchymal involvement was also reported by Yeom *et al.* [14]. These findings indicate that the psychopathological mechanism and course of development for MDR and XDR are the same [10].

The current study had some limitations: 1) existing medical data were used, which led to a small sample size from among those with CT scan results; 2) selection bias may be present because CT scans are usually ordered for patients with more severe symptoms with features of greater invasiveness; 3) the use of existing data led to decreased control on the imaging protocols; 4) the smaller sample size in the XDR group compared with the MDR group led to decreased potency of the presented analyses; and 5) previous studies [19,20] compared drug-resistant with drug-susceptible cases, whereas the current study could not include a control group among drug-sensitive cases. Enrolment of a control group would help emphasise the actual role of CT scanning in the treatment monitoring of TB patients.

## Conclusions

Overall, it may be concluded that CT scan findings in patients with XDR-TB are similar to those in patients with MDR-TB when considering cavitory, parenchymal, and non-parenchymal lung characteristics. However, XDR-TB patients tend to have more parenchymal calcification and left-sided plural effusion. CT characteristics overlap between patients with TB (XDR-TB) and those with MDR-TB (MDR-TB). It can be concluded that CT scan features are not sufficiently accurate to use in diagnosing grade of resistance.

## Conflict of interest

The authors report no conflict of interest.

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