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Comparison of Chest X-Ray Assessment in Multi-Drug Resistance to Drug-Sensitive Tuberculosis Patients

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A B S T R A C T

Background. Indonesia ranks third in tuberculosis cases, with 23,000 new dual drug-resistant tuberculosis patients. The delay in predicting tuberculosis resistance occurs because sputum tools are not yet available. This study aimed to determine the differences in chest x-rays for drug-sensitive multiple drug-resistant tuberculosis in Palembang. **Method.** A case-control design to compare the radiological characteristics of multiple drug resistance with drug-sensitive at Palembang during January-July 2020. One hundred thirty-eight patients consisted of cases of drug-sensitive tuberculosis and multidrug-resistant tuberculosis based on the rapid molecular test that met the inclusion criteria, analyzed for posteroanterior chest X-rays by a radiologist without knowing the diagnosis—comparative chi-square using SPSS 22. **Result.** Multidrug resistance tuberculosis had more extensive or moderate lesions than drug-sensitive tuberculosis 89.8% vs 72.4%. The multidrug-resistant group has more infiltrate detected, namely 84.1% vs 69.6% and cavity 37.6% vs 30.4%. Atelectasis and pleural effusion are common in drug-resistant tuberculosis. Bivariate analysis showed that multidrug-resistant tuberculosis lesion infiltrates compared to drug-sensitive tuberculosis with p = 0.025; OR 2,6 (CI 95% 1,1-6,0) sensitivity 85.5%, specificity 30.4%. Multivariate analysis showed the presence of infiltrates p = 0.028; OR 2.58 (CI 95% 1.1-6.003). Consolidation, nodules, cavities, fibrosis, atelectasis, pleural effusion were not significant differences in the two groups. **Conclusion.** Multidrug-resistant tuberculosis has a more expansive lesion, the presence of infiltrates and cavities that is more dominant than drug-sensitive tuberculosis.

1. Introduction

Indonesia is in the third rank for drug-sensitive TB (DS-TB) with an estimated 842.000 new cases and dual drug-resistant TB (MDR-TB) with an estimated 23.000 new cases. Dr Moh. Hoesin general hospital Palembang is a diagnostic and treatment referral centre for multidrug-resistant TB in South Sumatra Province, since starting service in 2014 it has found 532 cases of dual drug-resistant TB and has provided treatment to 229 patients.[1-3]

The problem that arises is the delay in predicting TB to become drug-resistant due to the unavailable sputum or the missing molecular rapid test (MRT) equipment. X-ray examination plays a vital role in this, because it supports the diagnosis of TB, although it is not the gold standard for TB diagnosis, namely microbiological/genomic examinations. X-rays are more comfortable to do because they are fast, practical, not invasive and inexpensive in helping to diagnose and evaluate TB treatment.[4-7]

Bernard F. Laya et al. (2015), there are differences in the picture pattern of patients infected with multiple drug-resistant TB, the dominant radiographic pattern is consolidation without a cavity, pleural effusion, and lymphadenopathy, similar to the primary form of TB.[4]

Kim et al., 2004 reported findings in both disease groups indicating that cavities were more common in multiple drug-resistant TB patients than in sensitive TB patients.[8] Icksan et al., 2018 at Persahabatan Hospital Jakarta, have analyzed the differences in radiological findings in sensitive and drug-resistant TB There are reported significant differences in lesion area and morphology, making it essential to assist in the diagnosis of MDR-TB[9]. The purpose of this study was to determine the differences in the chest X-ray image of drug-sensitive TB and multiple drug-resistant TB in Palembang.

2. Methods

A diagnostic test with a case-control design was carried out to analyze the comparison of the radiological characteristics of the chest X-rays of MDR TB with DS-TB and to assess the accuracy of the variation in radiological findings that could predict MDR TB in the internal disease ward of RSMH Palembang during January-July 2020. Subjects were patients who had diagnosed with multiple drugs resistant pulmonary tuberculosis and drug-sensitive who underwent treatment at RSMH Palembang and met the inclusion criteria. This study consisted of 138 research subjects divided into 69 cases of DS-TB and 69 cases of MDR TB. The dependent variables were MDR-TB and DS-TB; the independent variables were infiltrated, consolidation, cavity, nodule, fibrosis, calcification, atelectasis, pleural effusion and lesion area. The lesion area was determined according to the American Thoracic Society (ATS) category; namely, the lesions were minimal, moderate and extensive. Each group took data from medical records to obtain identity data including name, age, gender, education, occupation, place of residence, new cases or old cases, history of DM, BMI, sputum AFB and traced the PA chest X-ray results according to the date listed in the medical record when the patient was first diagnosed with TB or MDR-TB at RSMH. A chest X-ray was read and interpreted by a chest radiologist from RSMH consultant to determine the extent and morphology of the lesion. The radiologist does not know the patient's diagnosis to be interpreted. Then the data were collected and analyzed using SPSS version 22.

3. Results

One hundred thirty-eight study subjects were divided into two groups, namely MDR-TB and DS-TB, each totalling 69. The mean age of MDR-TB patients was 45.1 ± 14.8 years, and sensitive TB 48.6 ± 17.0 years, there was no difference in the age of the two groups. The gender distribution was mostly male, both at MDR-TB (62.3%) and DS-TB (73.9%). Most of the education of the two groups in high school. The distribution of jobs to patients includes labour, private / state employees, farmers, traders, homemakers, students and unemployed. *Body Mass Index* (BMI) of the majority of the two groups is normal weight. The distribution of age, sex, education and BMI did not have significant differences between MDR-TB patients and DS-TB patients.

Based on comorbid *diabetes mellitus* (DM), there were 5 MDR patients and 4 DS-TB patients who had DM disease. HIV was found in 3 patients with DS-TB, while HIV disease was not found in MDR-TB. All MDR-TB patients were old TB cases, but no new cases were found. Meanwhile, in DS-TB, there were 25 new cases and 44 old cases.

From the microscopic results of the sputum smear, the MDR data showed that all MDR patients were examined for AFB with the most favourable results (29 patients). While the BTA results in DS-TB patients with the most results were negative (10 people). For the molecular rapid test results, MDR patients obtained the most results, namely Mtb detected medium, namely 37 patients. DS-TB was also mostly in the medium, namely 34 patients. The results of patient characteristics data can be seen in **table 1.**

In this study, the MDR-TB group had a larger detectable area of lesions, namely 62 (89.8%) samples, while the sensitive TB group was 50 (72.4%). The infiltrate also showed that the MDR-TB patient group was more detected by 58 (84.1%) while in the sensitive TB group, it was 48 (69.6%). Both MDR-TB and

sensitive TB groups had the same number of samples in the detected consolidation of 18 (26.1%). Fibrosis was detected more sensitive in TB patients by 11 (15.9%) while there was MDR-TB of 7 (10.1%). More nodules were detected in sensitive TB patients by 4 (5.8%) while only 1 (1.4%) sample was in the MDR-TB patient group. The cavity was detected more in MDR-TB patients by 26 (37.6%) while in the sensitive TB group by 21 (30.4%). Calcification was not detected in either group. Atelectasis and pleural effusions were mostly found in sensitive TB patients by 10 (14.4%), whereas in MDR-TB patients there were 8 (11.6%) atelectasis and 5 (7.2%) pleural effusions. The distribution of radiological characteristics can be seen in **table 2.**

Comparative analysis with chi-square, the radiological infiltrates of the two groups had a significant difference p = 0.023; OR 2.6 (95% CI; 1.1 - 6.0). The presence of infiltrates in the MDR group was 58 patients (84.1%) while in SO-TB there were 48 patients (69.6%) with a sensitivity value of 85.5%, a specificity of 30.4%. The lesion area also had a significant value p = 0.009; OR 3.36 (95% CI 1.3-8.6). The lesion area of MDR-TB was wide/medium as many as 62 patients, of which a minimum of 7 patients and in large/medium TB-SO 50 patients, of which at least 19 patients, obtained a sensitivity of 89.9%, a specificity of 27.54%. Fibrosis, nodules, cavities, calcification, fibrosis, atelectasis and pleural effusion did not have a significant difference between MDR-TB and DS-TB.

The distribution of the lesions based on the location of the area in the lungs which is divided into the upper right lung, middle right, lower right, upper left, middle left and lower left shows that most of the lesions on MDR and DS-TB have a location distribution that does not differ significantly between MDR and DS-TB only the infiltrates lesion on the left-centre which had a significant difference.

Table 1. General characteristics of MDR-TB and drug-sensitive TB patients

Characteristics	MDR TB (%) n = 69	DS-TB (%) n = 69	P*
Age			
Mean ± SD	45.1 ± 14.8	48.6 ± 17.0	0.146
< 30	7	12	
30 – 39	19	10	
40 – 49	22	12	
50 – 59	9	13	
≥ 60	12	22	
Gender			
Male	43 (62.3)	51 (73.9)	0.144
Female	26 (37.7)	18 (26.1)	
Education			
Primary	9 (13)	11 (15.9)	0.861
Junior high	20 (29)	15 (21.7)	
Senior high	36 (52.5)	36 (52.5)	
Collage	4 (5.8)	7 (10.1)	
Employment			
Housewife	19 (27.5)	7 (10.1)	
Labor	12 (17.4)	20 (29)	
Farmer	19 (27.5)	8 (11.6)	
Traders	4 (5.8)	3 (4.3)	
Civil servants/private	19 (27.5)	19 (27.5)	
Student	1 (1.4)	5 (7.2)	
Doesn't work	5 (7.2)	7 (10.1)	
Body mass index (BMI)			0.593
Underweight	25 (36.2)	24 (34.8)	
Normoweight	37 (53.6)	41 (59.4)	
Overweight	7 (10.1)	4 (5.8)	
Mean + SD	18.9 ± 2.9	18.9 ± 2.5	

Comorbidity			
DM.	5 (7.3)	4 (5.7)	0.765
HIV	1 (1.4)	3 (4.3)	0.075
TB status			
Old Case	68 (98.6)	43 (63.2)	0.000
New Case	1 (1.4)	25 (93)	
BTA Sputum			
Negative	3 (4.9)	10 (76.9)	
Positive 1	13 (21.3)	0	
Positive 2	29 (47.5)	2 (15.4)	
Positive 3	16 (16.2)	1 (17.6)	
MRT result			
High	19 (27.5)	3 (4.3)	0.000
Medium	37 (53.6)	34 (49.3)	
Low	13 (18.8)	22 (31.9)	
Very low	0	10 (14.5)	

**chi-square* test

Table 2. Distribution of MDR-TB and DS-TB radiological characteristics

Characteristic	Category	TB		P value	OR 95 % CI
		MDR n (%)	DS n (%)		
Lesion Area	Medium /	62 (89.8)	50 (72.4)	**0.009**	3.36
	Minimum Size	7 (10.1)	19 (27.5)		(1.3 - 8.6)
Infiltrates	yes	58 (84.1)	48 (69.6)	**0.025**	2.6
	no	11 (15.9	21 (30.4)		(1.1 – 6.0)
Consolidation	Yes	18 (26.1)	18 (26.1)	1.00	1
	No	51 (73.9)	51 (73.9)		(0.47-2.1)
Fibrosis	Yes	7 (10.1	11 (15.9)	0.437	0.66
	no	62 (89.9)	58 (84.1)		(0.24-1.86)
Nodules	Yes	1 (1.4)	4 (5.8)	0.172	0.23
	no	68 (98.6)	65 (94.2)		(0.02-2.1)
Cavity	Yes	26 (37.6)	21 (30.4) 48	0.369	1.3
	no	43 (62.4)	(69.6)		(0.68-2.8)
Calcification	Yes	0 (0)	0 (0)	-	-
	no	69 (100)	69 (100)		
Atelectasis	Yes	8 (11.6)	10 (14.4)	0.613	0.774
	no	61 (88.4)	59 (85.6)		(0.28-2.09)
Pleural effusion	Yes	5 (7.2)	10 (14.4)	0.171	0.46
	no	64 (92.7)	59 (85.6)		(0.15-1.4)

*Chi-square test

Table 3. Multivariate Analysis of Lesion Morphology

		B	SE.	Sig	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Step 8[a]	Presence of infiltrates	.948	. 431	.028	2.581	1.110	6.003
	Constant	-.206	.194	.288	.814		

Table 4. Distribution of radiological characteristics based on lung location in MDR-TB and DS-TB

Characteristic	Category	MDR TB n (%)	DS-TB n (%)	P*
Lesion Area	Minimum	7 (10.1)	19 (27.5)	
	Moderate	22 (31.9)	23 (33.3)	
	Large	40 (58)	27 (39.1)	
Infiltrates	Top right	29 (33)	22 (31.9)	0.189
	Middle right	26 (29.5)	17 (24.6)	0.139
	Bottom right	17 (19.3)	11 (15.9)	0.204
	Top left	24 (27.3)	26 (37.7)	0.475
	Middle left	30 (34.1)	19 (27.5)	0.05
	Bottom left	8 (9.1)	4(5.8)	0.227
Consolidation	Top right	5 (7.2)	7 (10.1)	0.54

	Middle right	8 (11.6)	8 (11.6)	1
	Bottom right	5 (7.2)	4 (5.8)	0.7
	Top left	4 (5.8)	2 (2.9)	0.4
	Middle left	3 (4.3)	3 (4.3)	1
	Bottom left	3 (4.3)	1 (1.4)	0.31
Cavity	Top right	7 (10.1)	2 (2.9)	0.085
	Middle right	8 (11.6)	14	0.163
	Bottom right	1 (1.4)	3 (4.3	0.310
	Top left	12 (17.4)	2 (2.9)	0.03
	Middle left	7 (10.1)	5 (7.2)	0.546
	Bottom left	1 (1.4)	0	0.316
Calcification	Top right	0	0	0
	Middle right	0	0	0
	Bottom right	0	0	0
	Top left	0	0	0
	Middle left	0	0	0
	Bottom left	0	0	0
Fibrosis	Top right	0	0	0
	Middle right	2 (2.9)	3 (4.3)	0.649
	Bottom right	3 (4.3)	4 (5.8)	0.698
	Top left	0	1 (1.4)	0.316
	Middle left	0	2 (2.9)	0.154
	Bottom left	2 (2.9)	3 (4.3)	0.649
Nodules	Top right	0	1 (1.4)	0.316
	Middle right	0	3 (4.3)	0.08
	Bottom right	0	1 (1.4)	0.316
	Top left	1 (1.4)	1 (1.4)	1
	Middle left	0	2 (2.9)	0.154
	Bottom left	0	1 (1.4)	0.316
Atelectasis	Top right	3 (4.3)	4 (5.8)	0.698
	Middle right	2 (2.9)	3 (4.3)	0.649
	Bottom right	1 (1.4)	2 (2.9)	0.559
	Top left	2 (2.9)	5 (7.2)	0.245
	Middle left	1 (1.4)	5 (7.2)	0.095
	Bottom left	2 (2.9)	3 (4.3)	0.649
Pleural effusion	Top right	0	1 (1.4)	
	Middle right	0	1 (1.4)	
	Bottom right	2 (2.9)	7 (10.1)	0.085
	Top left	0	0	
	Middle left	0	0	0.466
	Bottom left	3 (4.3)	5 (7.2)	

*Chi-square test

4. Discussion

The study sample consisted of 138 patients consisting of 69 MDR-TB patients and 69 DS-TB patients. The mean age of the two MDR groups was 45.1 ± 14.8 years. The increasing age, the higher the likelihood of TB disease, this is due to TB reactivation and the longer duration of TB exposure. Besides, TB also often occurs in the productive age group, because the influence of active activity and mobilization causes a high possibility of exposure to tuberculosis. In terms of gender characteristics, it was found that there were more males than females in both the MDR-TB group of 62.3% and the DS-TB group of 73.9%. This is under the WHO report (2018) which shows the prevalence of pulmonary TB is more prevalent in men as much as 57%, women as much as 32% and the remaining 11% are children. Liu et al. (2017) reported that most MDR-TB patients were male (71.4%) and female (28.6%) with a ratio of 2.5:1. Pasaribu R (2019) reported that there were 57.75% male MDR-TB patient at RSMH Palembang and 42.25% female. According to WHO 2018, 90% of tuberculosis in adults is more in men than women with a ratio of 2: 1. This is because men are more exposed to risk factors for tuberculosis through social interactions such as smoking and lack of medication adherence.[1,10-11]

In terms of education, the distribution was not different in the two groups; most of the patients had a high school education. This is in line with various previous studies in Palembang, namely Syafriani et al., 60% of MDR-TB patients are mostly high school graduates.[12] The distribution of jobs obtained in the MDR-TB research sample is mostly civil servants or private, followed by farmers. People who work in closed environments with poorly ventilated systems and have direct contact with large numbers of people who may also be active pulmonary TB patients are at more risk than workers who are not in direct contact with large crowds. The physical work fatigue factor can cause decreased immunity and susceptible to infection.[13]

Based on the *body mass index* (BMI), the majority of MDR-TB patients were normal weight. This is the same as Suliyanti's (2013) study regarding the nutritional status and level of protein-energy consumption in pulmonary tuberculosis patients in Medan, namely 51.7% of patients with normal nutritional status probably because most of the pulmonary tuberculosis patients at RSMH have received treatment using anti-tuberculosis drugs for more than two months (advanced phase). The nutritional status of tuberculosis patients usually improves.[14]

Significant effects of comorbidities on tuberculosis include diabetes mellitus and HIV. DM increases the risk of TB to 1.5 to 7.8 times compared to people without DM Pulmonary TB patients with DM also have the risk of becoming MDR-TB as much as 2.1 - 8.8 times compared to TB patients without D.M.15 In this condition, there is a decrease in immunity due to phagocytic activity, neutrophil bactericides, T lymphocyte cellular immunity, and decreased cytokine levels. In this study, MDR-TB patients with DM were found in 5 patients, and four patients in DS-TB. There were no significant differences between MDR-TB and DS-TB in this study.

HIV positive people have a 30 times greater risk of getting TB than HIV negative people. HIV infection will speed up the latent TB process to become active. TB is the second most common opportunistic infection in HIV patients after candidiasis. Also, it is estimated that 3.3% of TB patients are also infected with HIV.5 In HIV positive TB patients, chest X-ray results vary widely depending on the level of immunity of HIV patients. In this study, HIV was only present in 1 MDR-TB patient and 3 DS-TB patients; there was no significant difference in distribution between the two groups.

In the microbiological examination of sputum AFB, more of the sputum AFB on MDR-TB was detected positive. However, in DS-TB, the data on the AFB results were only 13 samples because, in RSMH, it was sufficient to enforce TB from the MRT results.

Lesion area is in the broad or moderate category, was mostly found in both TB groups. The more extensive the lesions found, the higher the progression and duration of tuberculosis infection. This also indicates that tuberculosis patients who go to RSMH are TB patients who have a heavier TB severity because RSMH is a type A referral hospital that has more complete health facilities.

In this study, either MDR-TB or drug-sensitive infiltrates lesions were the most common, and these lesions were a sign of active tuberculosis. These results are consistent with the study of Zahirifard S (2003) assessing the radiological characteristics of MDR-TB in 35 patients, obtained infiltrates in 89% of patients.[16] Cavities in this study were found as many as 26 MDR-TB patients and 21 DS-TB patients. The majority of patients present a classic cavitary appearance with a smooth inner wall surrounded by infiltrates. The presence of the cavity was a significant predictor of resistance in addition to previous treatment history. Kim et al. in 2004 stated that cavities were found in 66% of patients with MDR pulmonary TB.[17]

Histologically, cavitating granulomas are characterized by progressive tissue inflammation, weak activation of cell-mediated immunity (CMI) and adaptive, and accumulation of B cells. Granuloma structure correlates with disease progression and control of the extent of the infection, causing damage to lung parenchymal tissue. In post-primary

tuberculosis, the body's defence is dominated by the formation of necrotic elements which is more significant than cases of primary infection.[18-20]

Consolidation in both groups was found to be the same number, namely 18 patients (26.1%). Consolidation is also an active lesion of TB, and several studies showed a significant number of MDR-TB. However, in this study, the number of consolidations was not different; this was due to the possibility that DS-TB who went to RSMH had a more severe disease course. Nodules and fibrosis in both groups were not expected, namely less than 10%, and calcification was not found in both groups. These lesions were inactive TB lesions; possibly not many lesions were found in the two groups because the study patients were still active TB patients and the x-rays that were read were X-rays taken at a time not much different from when the patient was examined for sputum. Nodules, fibrosis and atelectasis were more common in cases of SO TB than MDR TB. This shows the ability of tissue damage response in delayed-type hypersensitivity (DTH), which is large to inactivate germs in cases of DS-TB which have a longer duration. Pleural involvement in the form of pleural effusion was found in 5 MDR patients and 10 DS-TB patients. Pleural effusion is also a sign that TB bacteria are still active and is more common in DS-TB.

The lesion area determined by the *American Thoracic Society* (ATS) had a significant difference between MDR TB and DS-TB. Moderate/extensive lesion area had a 3.36 times tendency for MDR-TB. This result is following the research of Icksan et al. (2018) which compared the radiological findings of MDR-TB and DS-TB at the Persahabatan Hospital Jakarta; there was also a significant difference in the degree of lesions in the two groups, namely 69% vs 27%.9 This difference was due to the progression of the damaged tissue and long duration of pulmonary damage due to TB occurs in MDR.

Infiltrates lesions had a higher tendency to appear in MDR-TB by 2.6 times compared to DS-TB. Different things found in cavitary lesions in this study were not significantly different in both MDR-TB and DS-TB ($p = 0.369$). This is under the research obtained by Cha et al. (2009) who also found that cavity prevalence did not differ between MDR and DS-TB, but in terms of the number and size of the cavity, it had a significant difference.[18]

From the comparison of the two groups, all the presence of lesions other than infiltrates did not have a significant difference between MDR-TB and DS-TB. This study is consistent with Fishman et al., In 1998 for the first time conducting a study of the radiological features of sensitive TB compared to drug-resistant TB, and concluded that the radiological findings and patterns of the two disease groups were similar, not significantly different.[19]

In a condition where the number of TB germs is high, the possibility of resistance will also increase, either primary resistance or secondary resistance that occurs due to exposure to TB drugs that have been previously consumed. Secondary resistance is the most common condition. Many bacterial colonies are characterized by active TB lesions, including infiltrates, consolidations and cavities.

Cavities form when the central part of the granuloma epitheloid cells undergoes caseous necrosis and is extruded through the associated regional bronchi. Difficulty penetrating the avascular cavity containing large numbers of mycobacteria is believed to be the cause of resistance.

This study has research limitations, among others, in comparing the two groups, matching should be done. This study also uses secondary data through medical and retrospective records, so that in terms of determining risk factors, it is highly dependent on the completeness of existing data. Only one radiologist carried out this radiological assessment. Also, the comparative assessment of lesion morphology would be better if more sophisticated modalities such as CT scan of the chest were used.

5. Conclusion

Radiologically, MDR-TB has a more expansive

lesion, the presence of infiltrates and cavities that is more dominant than DS-TB. The finding of these lesions may raise the suspicion of tuberculosis resistance. Further research is needed to analyze in detail the morphology of TB lesions that can differentiate MDR TB and DS-TB.

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