ORIGINAL ARTICLE

Characteristics of Multidrug-Resistant Tuberculosis and Smear-Positive Pulmonary Tuberculosis: A Case–Referent Study

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ABSTRACT

Introduction: Multidrug-resistant tuberculosis (MDR-TB) remains a global health concern; however, data about characteristics of multidrug resistance are limited. This investigation aimed to compare features of MDR-TB and smear-positive pulmonary TB without multidrug resistance in Indonesia. **Methods:** A case–referent study was undertaken among patients with smear-positive pulmonary TB who were under treatment in 2017 in three cities (Bandung, Tasikmalaya, and Cilacap) to examine the factors associated with MDR-TB among patients with smear-positive pulmonary TB. There were 57 patients with MDR-TB (case group) and 161 patients with smear-positive pulmonary TB (referent group). Chi-square tests were used to measure differences between the groups, and the odds ratio (OR) was calculated to estimate the risk factors. **Results:** Univariate analysis determined the following correlated factors for MDR-TB: age, lived in an urban area, health insurance, visited other countries, had chronic obstructive pulmonary disease, vomiting, headache, burning sensation, jaundice, treatment failure, stopped taking, and non-compliance during the continuation phase. **Conclusion:** These factors related to MDR-TB among smear-positive pulmonary TB patients can guide healthcare providers to plan interventions to control the development of MDR-TB in the future.

Keywords: Case–control, MDR-TB, Risk factors

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a global health concern, with limited treatment choices, prolonged treatment, and drug toxicity. Rifampicin drug resistance has been found among 61% of people with bacteriologically confirmed TB (1). The MDR-TB treatment success rate in 2019 was 57%, and treatment success of MDR-TB remains below the target of more than 90% globally (1). Therefore excellent TB care is essential to prevent morbidity and mortality from TB and to reduce transmission.

Indonesia is a country with a high burden of MDR-TB; 2.4% of incident TB cases and 14% of relapse TB cases were assessed by the national MDR-TB body (1). Nevertheless, 46% of MDR-TB patients in Indonesia were effectively cured in 2014 (2). Recognising the risk factors may contribute to the development of essential services and practical MDR-TB control approaches.

Various risk factors have been connected to MDR-TB. The most frequent determinant was previous treatment (3). Other factors were younger age (3), gender (4), education (3), occupation (3), human immunodeficiency virus (5), type 2 diabetes (3), smoking (3), alcohol abuse (6), living in an urban area (7), and socioeconomic status (8). However, the risk factors of MDR-TB in Indonesia may be different, and further understanding of this area is necessary.

Therefore, this study used demographic and treatment data identified in prior studies and TB-related data in Indonesia to compare the characteristics of MDR-TB and smear-positive pulmonary TB without multidrug resistance in Indonesia and determine risk factors that may contribute to MDR-TB. The study results may enhance patient management by enabling prevention of these factors and guiding patient treatment, thereby facilitating the successful outcome of treatment and reduction of the overall burden of the disease.

MATERIALS AND METHODS

Study design

A case–referent study was performed with TB patients in three cities in Indonesia.

Sample and Setting

Patients with MDR-TB were included in the group of cases, where sputum cultures showed *Mycobacterium tuberculosis*, and drug susceptibility testing (DST) showed resistance to both isoniazid (INH) and rifampicin

(RMP). In addition, positive smear-positive pulmonary TB patients were included in the referent group, with at least two positive initial sputum smear tests for acid-fast bacilli (AFB+). This study was conducted in Bandung, Tasikmalaya, and Cilacap between June and October 2017. Smear-positive pulmonary TB and pulmonary MDR-TB in hospitals and community health centres were diagnosed by physical examination, chest x-ray, and sputum smear or sputum culture. The study included 218 smear-positive pulmonary TB patients, including 57 patients with MDR-TB and 161 patients without MDR-TB.

Variables

Demographic, illness-related, and treatment-related characteristics were collected in this study. First, demographic characteristics consisted of binary variables: age categorized into 15-35 years and more than 355 years, gender divided into male and female, a residential area for urban and rural, marital status composed of married and not married, religion consisted of Islam and Christian, ethnicity for Sunda and non-Sunda, work, education level, health insurance, and visits to other countries with yes or no response formats. Second, illness-related characteristics included the history of TB, frequency of TB, comorbidities, contact with MDR-TB cases, Directly Observed Treatment, Short-course (DOTS) supporter, alcohol and smoking, and TB signs had questions structured to yes/no format. Finally, treatment-related characteristics included treatment categories were divided into relapse, failure, relapse after failure, and dichotomous questions for history of stopping taking medication and treatment compliance.

Data sources/measurement

This study followed the Standards for the Reporting of Observational Studies in Epidemiology (STROBE) guideline. To obtain demographic and illness-related characteristics, we interviewed the patients who visited community health centres/ hospital TB clinics for medication routine control. In addition, we retrieved secondary data from patient records for treatment-related characteristics in this study.

Data analysis

All data analyses were performed on a computer. Frequency and percentage were used to describe the data, and the chi-square test was used to compare the two groups. In addition, the odds ratio (OR) was applied to examine potential factors that could be related to MDR-TB. All tests of significance were double-sided, and $p < 0.05$ was considered statistically significant.

Ethical clearance

The institutional review board approved this study, with ethics committee approval number 770/UN6.KEP/EC/2018. The eligible patients were asked to participate in this study, and they signed informed consent if they agreed to participate in this study. We interviewed and retrieved patients' data after patients signed the consent.

RESULTS

MDR-TB patients (case group) were significantly older than smear-positive pulmonary TB patients without multidrug resistance (referent group) (mean ± SD; 45.14 ± 14.69 vs. 37.86 ± 15.01; $p < 0.01$). The number of patients who lived in urban areas was significantly greater for TB patients with than without MDR-TB [55/57 (96.5%) vs. 121/161 (75.2%); $p \leq 0.01$]. The proportion of patients who had no work was significantly lower for TB patients with MDR-TB than for TB patients without MDR-TB [3/57 (0.05%) vs. 311/161 (19.3%); $p \leq 0.05$]. The ratio of patients who had health insurance was notably greater for TB patients with than without MDR-TB [54/57 (94.7%) vs. 129/161 (80.1%); $p \leq 0.05$] (Table I).

Of 57 MDR-TB patients, 44 (77.2%) had a history of pulmonary TB, and of 161 smear-positive pulmonary TB patients, 105 (65.2%) had a history of pulmonary TB; the difference was not significant. The percentage of patients who had suffered TB once was greater for TB patients with than without MDR-TB [47/57 (82.5%) vs. 108/161 (67.1%); $p \leq 0.01$]. The proportion of patients who had COPD was significantly greater for MDR-TB patients than for those without drug resistance [11/57 (19.3%) vs. 10/161 (6.2%); $p \leq 0.01$]. The proportions of patients who ingested alcohol and who smoked were considerably greater for the MDR-TB group than for the smear-positive pulmonary TB patients without drug resistance ($p \leq 0.05$ and $p \leq 0.01$, respectively). The percentage of patients who received DOTS was significantly lower for MDR-TB patients than TB patients without resistance [39/57 (68.4%) vs. 152/161 (94.4%); $p \leq 0.01$]. The percentages of patients who experienced vomiting, headache, and burning sensation were significantly greater for MDR-TB patients than smear-positive pulmonary TB patients ($p \leq 0.01$). The proportion of patients who exhibited jaundice was considerably greater for TB patients with than without MDR-TB [20/57 (35.1%) vs. 34/161 (21.1%); $p \leq 0.05$] (Table I).

The percentages of patients who had failed treatment [33/57 (57.9%) vs. 4/161 (2.5%)], who had ever stopped taking anti-TB medication [24/57 (42.1%) vs. 31/161 (19.3%)], and who had non-compliance during the continuation phase [16/57 (28.1%) vs. 11/161 (6.8%)] were significantly greater for TB patients with MDR-TB than without MDR-TB (all $p \leq 0.01$) (Table I).

DISCUSSION

Risk factors of MDR-TB can be classified into demographic, illness-related, and treatment-related characteristics. In the present study, the significant

Table I: Demographic characteristics, illness-related characteristics and treatment-related characteristics of 57 patients with MDR-TB and 161 patients with smear-positive pulmonary TB

Variable	Case		Referent		COR	95% CI	*p*-value
	n	%	*n*	%			
Demographic characteristics							
Age					0.43	0.23–0.82	0.01
15–35 years	17	29.8	80	49.7			
>35 years	40	70.2	81	50.3			
Gender				5	1.57	0.84–2.94	0.15
Male	37	64.9	87	4.0			
Female	20	35.1	74	46.0			
Residential area					9.09	2.12–38.97	0.003
Urban	55	96.5	121	75.2			
Rural	2	3.5	40	24.8			
Marital status					2.6	0.31–21.15	0.37
Married	56	98.2	154	94.7			
Not married	1	1.8	7	4.3			
Religion					0.61	0.31–1.20	0.15
Islam	40	70.2	128	79.5			
Christian	17	29.8	33	20.5			
Ethnic					1.38	0.75–2.53	0.30
Sunda	29	50.9	69	42.9			
Non-Sunda	28	49.2	92	57.1			
Work					0.23	0.07–0.80	0.01
No work	3	0.05	31	19.3			
Work	54	99.95	130	80.7			
Education level					0.35	0.48–2.52	0.27
Low	55	96.5	159	98.8			
High	2	13.5	2	1.2			
Health Insurance					4.47	1.31–15.21	0.01
Yes	54	94.7	129	80.1			
No	3	5.3	32	19.9			
Living with					0.68	0.32–1.43	0.31
Family	11	19.3	42	26.1			
Alone	46	80.7	119	73.9			
Ever visited other countries	45	78.9	37	23.0	12.56	6.22 –26.21	0.00
Illness-related characteristics							
History of TB					1.81	0.90–3.63	0.10
Yes	44	77.2	105	65.2			
No	13	22.8	56	34.8			
Frequency of TB					0.43	0.20–0.93	0.03
1 time	10	17.5	53	32.9			
More than once	47	82.5	108	67.1			
COPD	11	19.3	10	6.2	3.61	1.44–9.04	0.00
DM	4	7.0	6	3.7	1.95	0.53–7.18	0.31
Cancer	13	22.8	24	14.9	1.69	0.80–3.59	0.17
Contact with MDR-TB	30	52.6	83	51.6	1.04	0.57–1.91	0.90
HIV status					2.17	0.25–18.41	0.47
HIV (-)	56	98.2	155	96.3			
HIV (+)	1	1.8	6	3.7			
DOTS supporter	39	68.4	152	94.4	0.13	0.05–0.31	0.00
Alcohol consumption	30	52.6	56	34.8	2.08	1.12–3.85	0.02
Smoking	32	56.1	58	36.0	2.27	1.23–4.20	0.00
TB signs							
Fever	55	96.5	142	88.2	3.68	0.83–16.33	0.07
Cough	46	80.7	127	78.9	1.12	0.52–2.39	0.77
Night sweats	49	86	139	86.3	0.97	0.41–2.32	0.94
Nausea	50	87.7	129	80.1	1.77	0.74–4.27	0.20
Vomiting	46	80.7	10	6.2	63.15	25.22–158.10	0.00
Skin rash	45	78.9	116	72.0	1.45	0.71–3.00	0.31
Headache	38	66.7	29	18.0	9.10	4.60–18.00	0.00
Burning sensation	29	50.9	10	6.2	16.64	6.86–35.66	0.00
Jaundice	20	35.1	34	21.1	2.08	1.07–4.03	0.03
Treatment-related characteristics							
TB treatment category							
Relapse	28	49.1	91	56.5	0.74	0.41–1.36	0.33
Failure	33	57.9	4	2.5	53.97	17.55–169.92	0.00
Treatment after failure	4	1.1	4	2.5	2.96	0.72–12.26	0.12
Ever stopped taking anti-TB	24	42.1	31	19.3	3.05	1.58–5.88	0.00
Noncompliance in intensive phase	19	33.3	36	22.4	1.74	0.89–3.37	0.10
Noncompliance in continuation phase	16	28.1	11	6.8	5.32	2.29–12.35	0.00

Note: MDR-TB = multidrug-resistant tuberculosis; COR = crude odds ratio; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HIV = human immunodeficiency virus.

factors related to MDR-TB were age, place of residence, health insurance ownership, and visiting other countries. Young age (15–35 years) had an OR of <1 at 0.43, which agreed with a past study with ORs of 0.8 for those aged <25 and 0.45 for those aged 26–45 years (9). However, another study showed that those aged <40 years were 2.56 times more likely to have MDR-TB (10). This may be because younger people are economically productive and work outside and meet many people. People who lived in urban areas were nine times more likely to have MDR-TB. This supported a prior study in India that found a higher proportion of MDR-TB patients lived in urban (51%) than rural (2%) areas (11). Those who had health insurance had a higher percentage of MDR-TB. This is expected as 83.94% of the population in Indonesia is registered under the National Health Insurance and Healthy Indonesia Card (12). However, this result contrasts with a review that found that lacking health insurance was a risk factor of MDR-TB (13). Patients who had visited other countries were more likely to have MDR-TB. Similarly, international travel had a higher prevalence of emerging TB in Sri Lanka (14). Other demographic characteristics have been related to MDR-TB in a past study, such as gender and employment status. Males were 1.38 times more likely to have MDR-TB in Europe (15), and unemployment increased the possibility of MDR-TB (13).

Certain illness-related characteristics were significantly related to MDR-TB, namely, COPD comorbidity, vomiting, headache, burning sensation, and jaundice. The most frequent MDR-TB comorbidities in Georgia were liver disease, DM, HIV, psychiatric diseases, and others (16). Those who had COPD were 3.61 more likely to suffer from MDR-TB in the present study. A comparable result was found in China, where the MDR-TB percentage was more significant among COPD patients (17), and COPD has been found to adversely affect treatment outcomes in MDR-TB (18). The treatment for MDR-TB may have adverse effects; vomiting may occur with ethionamide, and jaundice may be caused by efavirenz, nevirapine, pyrazinamide, ethionamide cause or other drugs (19). Zidovudine or efavirenz may trigger headache and burning sensations. In addition, vomiting may present as a gastrointestinal side effect of MDR-TB (20).

Treatment failure, discontinue of medication, and non-compliance during the continuation phase were correlated with MDR-TB. Similarly, the past study found that MDR-TB may develop because of problems in previous TB treatment (21). Treatment failure had an OR of 53.97, higher than that of a past study of 3.82 (10). Patients with non-compliance with treatment were 1.74 times more likely to develop MDR-TB. This result was consistent with a prior study with an OR of 3.38 (22). History of TB treatment has been found to be the most important factor in MDR-TB (21), but the present research found that history of TB was not a risk factor of MDR-TB. Further research of MDR-TB is essential to investigate health behaviours and intervention development as these parameters have been studied in non-MDR-TB (23, 24). The family could contribute to overcoming MDR-TB issues with the expanded capacity of families to help MDR-TB patients during treatment (25). In addition, community members could be involved in the intervention using positive deviance, as MDR-TB is one of the recognizable health problems in the community (26).

This study has identified associated historical factors of MDR-TB; however, the sequential development between the elements and the disease is difficult to determine. Therefore, further investigations are essential, considering the potential for recall bias.

CONCLUSION

Several factors were found to be associated with the development of MDR-TB in this study. These can be classified into demographic, disease-related and treatment-related characteristics. Older age, vomiting and TB treatment failure had the highest ORs for each category characteristic, respectively. A prevention program for MDR-TB needs to consider these factors, and healthcare providers could control these factors in advance among TB patients to prevent MDR-TB cases.

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