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Predictors of multidrug resistance among pulmonary tuberculosis patients in a tertiary hospital in North Sumatera, Indonesia

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ABSTRACT

Background: Previous tuberculosis treatment for tuberculosis is known to confer a higher risk of multidrug-resistant tuberculosis (MDR-TB). Indonesia is ranked eighth among the 27 "high-burden" MDR-TB countries.

Objectives: This study aimed to determine the predictors of multi-drug resistance among patients with pulmonary tuberculosis in Indonesia.

Methods: This retrospective study was conducted in a tertiary referral teaching hospital in Medan, North Sumatera Province, Indonesia. Laboratory data and medical histories of all pulmonary tuberculosis patients attending the hospital were reviewed. Patients with culture positive for *Mycobacterium tuberculosis* and processed for drug-susceptibility testing (DST) to first-line anti-tuberculosis drugs between January 2010 and December 2013 were included. Logistic regression was used to determine significant predictors of MDR-TB based on odds ratios (OR) and 95% confidence intervals (CI).

Results: Of 6,174 patients with suspected pulmonary tuberculosis, 842 were confirmed positive by culture, of which DST results were reported for 765. Of these, 115 (15%) had diabetes mellitus, 73 (9.5%) were HIV-infected, and 98 (12.8%) were MDR-TB. Multivariate analysis indicated that patients with a history of previous tuberculosis treatment (OR = 3.75; 95% C.I. = 2.40 - 5.86 and aged 25 to 45 years (OR = 2.37; 95% C.I. = 1.07 - 5.27) were significant predictors of MDR-TB.

Conclusions: Previous tuberculosis treatment and age 25-45 were significant predictors of MDR-TB. Treating patients with previous tuberculosis treatment based on DST results should be considered.

Keywords: MDR-TB; predictors; previous tuberculosis treatment; Indonesia

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as a strain of *Mycobacterium tuberculosis* with resistance to at least the two major drugs used as first-line anti-tuberculosis drugs, namely rifampicin and isoniazid. The emergence of MDR-TB is a rapidly growing worldwide problem, and it has become a crucial threat to tuberculosis (TB) control as well as the most important public health concern in many countries.[1] MDR-TB causes socio-economic consequences to both individuals and society.[2] MDR-TB treatment has become more complicated, more toxic, more expensive, and less effective than the medication of patients infected by susceptible strains.

Indonesia, with an estimated population of 254 million in 2014, is listed as a high TB burden, high HIV burden and high MDR-TB burden country by the World Health Organization (WHO). In 2014 Indonesia was ranked as eighth among 27 "high burden" countries with MDR-TB cases worldwide, with an estimated 6,800 cases. In Indonesia, the prevalence of MDR-TB was 2% among new TB cases, and 12% of previously treated cases.[3] North Sumatera is a province of Indonesia with a population of about 13.5 million in 2014. It is subdivided into 25 districts and 8 autonomous cities. It is one of 10 provinces with the highest TB burden in Indonesia, with an estimated case notification rate of 111 cases per 100,000 population in 2014.[4] MDR-TB occurs when multidrug-resistant *M. tuberculosis* strains infect new patients or through the selection pressure of single-drug-resistant strains induced by prior treatment. MDR-TB decreases response to first-line anti-TB drugs leading to treatment failure and higher mortality rates as well as promoting disease transmission.[5] Epidemiological surveillance of drug resistant and MDR-TB is an essential tool for planning activities related to TB control.[6] A better understanding of the predictors related to MDR-TB may help to guide public health interventions by providing information on specific populations that can be targeted.[7] Continuous surveillance of MDR-TB based on a routine drug susceptibility testing (DST) of TB patients along with systematic data collection and analysis appears to be the most effective method to observe the drug resistance patterns. Despite the large proportion of MDR-TB in Indonesia, only limited data have evaluated the predictors of MDR-TB and have elaborated multidrug resistance

and the other drug resistances separately. The aim of the current study was to assess the predictors of multidrug resistance among patients with pulmonary tuberculosis diagnosed between January 2010 and December 2013 in a tertiary hospital in North Sumatera, Indonesia. A secondary aim was to identify resistance patterns of commonly used anti-TB drugs among patients with MDR-TB.

MATERIALS AND METHODS

Study design and settings

A retrospective study was conducted at the TB Provincial Reference Laboratory, which is based at the Department of Microbiology, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik Hospital, and a tertiary health care facility in Medan, North Sumatera Province, Indonesia. All pulmonary TB specimens received between January 2010 and December 2013 were routinely cultured, and for every culture-positive specimen, phenotypic DST was obtained. This laboratory runs all culture and culture-based phenotypic DST for the province of North Sumatera and is involved in national external and internal quality assurance programs. We selected all patients with culture-proven pulmonary TB and performed susceptibility tests to first-line anti-TB drugs.

Data Collection

The data was obtained from the TB laboratory of patients with pulmonary TB. We also collected information in the TB registry regarding patient's age, gender, education, occupation, history of TB treatment, HIV status, diabetes mellitus, cavity, sputum smear examination results, and DST pattern.

Drug susceptibility testing

Mycobacteria were cultured on a selective solid medium (Lowenstein–Jensen), and incubation was maintained at 37°C for up to eight weeks. *Mycobacterium tuberculosis* (MTB) was recognized using the p-nitrobenzoic acid and niacin tests. Patients with species other than MTB were excluded from the analysis. Positive MTB cultures had DST to first-line anti-TB drugs. The anti-microbial DST was performed using the WHO standard conventional proportional method.[8] The preferable first-line drugs were isoniazid (H) 0.2 µg/ml, rifampicin (R) 40 µg/ml, ethambutol (E) 2 µg/ml, and streptomycin (S) 4 µg/ml on slants with the H37Rv strain of MTB as the positive control.

Statistical analysis

All analyses were performed using R version 3.0.3. Data are presented descriptively using the mean and standard deviation (sd) for continuous variables and frequency and percentage for categorical variables. Bivariate comparison of factors between MDR and non-MDR positive cases was made using Student's t-test or Pearson's chi-square test as appropriate. Multivariate logistic regression was used to identify independent predictors for MDR-TB. The strength of the association was presented by odds ratios (OR) and 95% confidence intervals (CI). The level of statistical significance was set at a p-value <0.05 based on the likelihood ratio test.

Ethical issues

This study was approved by the Health Research Ethical Committee of North Sumatera, Medical School, Universitas Sumatera Utara, Medan and the Institute Ethics Committee of Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand.

RESULTS

Characteristics of patients

Of the 6,174 TB suspects, samples from 842 (13.6%) were culture-positive, 5,332 (86.4%) were culture-negative and 161 (2.6%) were contaminated. Of the 842 culture-positive isolates, 28 were not available for DST due to insufficient growth. Of the remaining 814 culture-positive isolates, 765 (94%) were identified as *Mycobacterium tuberculosis* complex, and 49 (6%) were classified as nontuberculous mycobacteria. Among 765 identified as *M. tuberculosis* complex, 115 (15.0%) had diabetes mellitus, 73 (9.5%) were HIV-infected, and 98 (12.8%) were MDR-TB. Table 1 shows the resistance patterns to first-line anti-TB drugs among the 765 *M. tuberculosis* complex. The proportion of MDR-TB among the new and previously treated cases was 7.2% and 22.8%, respectively (P < 0.01).

Multidrug-resistant tuberculosis

Among the 98 patients with MDR-TB, 71 (72.4%) were males, and the mean (sd) age was 44.5 (15.5) years. Sputum smear was positive in 80 (81.6%) of MDR-TB patients. A comparison of other characteristics is shown in Table 2. The only significant variables were a history of previous treatment and age group.

After adjusting for other variables, the final multivariable logistic regression model indicated that patients with a previous history of TB treatment (OR = 3.75; 95% C.I. = 2.40 - 5.86; *P* < 0.001) and age group 25 - 45 years (OR = 2.37; 95% C.I. = 1.07 - 5.27; *P* = 0.034) compared to age group <25 years were significant predictors of MDR-TB (Table 3).

Table 1 **Resistance patterns to the first-line anti-TB drugs of *M. tuberculosis* isolates from patients with pulmonary tuberculosis in North Sumatera, Indonesia, January 2010 to December 2013**

Type of resistance	New patients *n* (%)	Previously treated patients *n* (%)	Total patients *n* (%)
Total strains tested	489	276	765
Any resistance to H	60 (12.3)	96 (34.8)	156 (20.4)
Any resistance to R	89 (18.2)	96 (34.8)	185 (24.2)
Any resistance to E	85 (17.4)	96 (34.8)	181 (23.7)
Any resistance to S	114 (23.3)	93(33.7)	207 (27.1)
Resistance to H only	10 (2.0)	11 (4.0)	21 (2.7)
Resistance to R only	23 (4.7)	13 (4.7)	36 (4.7)
Resistance to E only	22 (4.5)	15 (5.4)	37 (4.8)
Resistance to S only	51 (10.4)	15 (5.4)	66 (8.6)
Total mono-resistance	106 (21.7)	54 (19.6)	160 (20.9)
H+R	10 (2.0)	12 (4.3)	22 (2.9)
H+R+E	5 (1.0)	9 (3.3)	14 (1.8)
H+R+S	2 (0.4)	7 (2.5)	9 (1.2)
H+R+E+S	18 (3.7)	35 (12.7)	53 (6.9)
Total MDR	35 (7.1)	63 (22.8)	98 (12.8)
H+E	5 (1.0)	4 (1.4)	9 (1.2)
H+S	8 (1.6)	7 (2.5)	15 (2.0)
H+E+S	2 (0.4)	11(4.0)	13 (1.7)
R+E	11 (2.2)	9 (3.3)	20 (2.6)
R+S	11(2.2)	5 (1.8)	16 (2.1)
R+E+S	9 (1.8)	6 (2.2)	15 (2.0)
E+S	13 (2.7)	7 (2.5)	20 (2.6)
Total poly-resistance other than MDR	59 (12.1)	49 (17.7)	108 (14.1)
Susceptible to all four drugs	289 (59.1)	110 (39.8)	399 (52.2)

MDR-TB: Multidrug-resistant tuberculosis, H: Isoniazid, R: Rifampicin, E: Ethambutol, S: Streptomycin

Table 2 **Characteristics of positive culture tuberculosis population and comparison of MDR and non-MDR pulmonary TB patients, January 2010-December 2013**

Characteristic	Total (*n*=765)	MDR-TB (*n*=98)	Non-MDR-TB (*n*=667)	P-value
Age, mean (sd)	42.5 (16.2)	44.4 (15.5)	42.2 (16.3)	0.21
Age-group (years)				0.04
<25	119 (15.6)	8 (8.2)	111 (16.6)	
25-45	292 (38.2)	46 (46.9)	246 (36.9)	
>45	354 (46.3)	44 (44.9)	310 (46.5)	
Gender				0.99
Male	562 (73.5)	71 (72.4)	491 (73.6)	
Female	203 (26.5)	27 (27.6)	176 (26.4)	
Education				0.26
None/informal	6 (1.0)	2 (2.0)	4 (0.6)	
Less than high school	323(42.0)	38 (38.8)	285 (42.7)	
High school and above	436(57.0)	58 (59.2)	378 (56.7)	

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Table 2 *Continues*

Characteristic	Total (*n*=765)	MDR-TB (*n*=98)	Non-MDR-TB (*n*=667)	P-value
Occupation				0.10
Unemployed	222 (29.0)	21 (21.4)	201 (30.1)	
Employed	543 (71.0)	77 (78.6)	466 (69.9)	
History of tuberculosis treatment				<0.001
Yes	276 (36.1)	63 (64.3)	213 (34.6)	
No	489 (63.9)	35 (35.7)	454 (68.1)	
Diabetes mellitus				0.59
Yes	115 (15.0)	17 (17.3)	98 (14.7)	
No	650 (85.0)	81 (82.7)	569 (85.3)	
HIV infection				0.07
Yes	73 (9.5)	17 (17.3)	98 (14.7)	
No	692 (90.5)	94 (95.9)	598 (89.7)	
Cavity				0.97
Yes	114 (14.9)	14 (14.3)	100 (15.0)	
No	651 (85.1)	84 (85.7)	567 (85.0)	
AFB smear				0.22
Positive	569 (74.4)	80 (81.6)	489 (73.3)	
Negative	196 (25.6)	18 (18.4)	178 (26.7)	

Numbers are frequency (%) unless stated otherwise.
MDR-TB: multidrug-resistant tuberculosis, HIV: human immunodeficiency virus, AFB: acid-fast bacilli

Table 3 **Significant predictors of MDR-TB**

Predictor	Adjusted OR (95% CI)	P-value
History of tuberculosis treatment: ref = New patient		< 0.001
Previous treatment	3.75 (2.40-5.86)	
Age-group (years): ref = < 25		0.034
25-45	2.37 (1.07-5.27)	
>45	1.92 (0.87-4.27)	

MDR-TB: multidrug-resistant tuberculosis, OR: odds ratio, CI: confidence interval

DISCUSSION

In this study, we determined potential predictors for MDR-TB in a tertiary hospital in North Sumatera, Indonesia. This is the first survey on predictors of anti-TB drugs resistance conducted in a government TB diagnostic and treatment centre in North Sumatera Province, Indonesia.

Twenty-two (22.4%) patients had resistance to isoniazid (H) and rifampicin (R) only, while 14 (14.3%), 9 (9.2%) and 53 (54.1%) had resistance to H, R and ethambutol (E), H, R and streptomycin (S) and all four drugs, respectively. The resistance against anti-TB drugs may result from the history of previous treatment of tuberculosis. Similar findings were found in other studies reported in the literature.[9,10]

Our results showed that the history of previous TB treatment and the age group were the only factors associated with MDR-TB. Those aged 25-45 years had a higher odds of MDR-TB compared to those aged less than 25 years. Mohammad et al. also found a higher odds of MDR-TB among those in the 25-44 year age group.[11] Consistent findings were found by Merza et al. who reported that age less than 45 years was independently associated with MDR-TB.[12-14] These contrast with the previous study in Pakistan which found that the age group between 10-25 years old had a higher risk of MDR strains infection.[15] However, the difference in these studies may be resulting from the difference in the cut-off points of the age groups. Moreover, it was suggested that the variation of the daily activities of each age groups contribute to the risk of MDR infection.[16] Young people tend to be more susceptible to MDR-TB because of the higher mobility and activities which were contributing to the lesser compliance to treatment.[17] Thus, this increased their susceptibility to MDR-TB infection.

The history of previous TB treatment was associated with the MDR-TB infection. This study confirmed that most MDR-TB patients (64.3%) had a history of previous tuberculosis treatment. This result supported the findings from the other studies.[12,15,18-23] Moreover, The WHO Global TB Report in 2014 stated that the prevalence of acquired

resistance was higher than the initial resistance in Indonesia.[3] Therefore, these suggested that there is a need for further assessment of the TB treatment program to prevent MDR-TB infection.[24]

In this study, males constituted 72% of the sample, a result which coincided with studies by Sagwa et al.[25] and Rifat et al.[26] which demonstrated that 66% and 67% of MDR-TB cases were male, respectively. These suggested that male is more likely to have a MDR-TB infection. However, Gender was not associated with the MDR-TB infection.[26] It is possible that females were more complied with the treatment than males.[5] Hence, males as predictors of the MDR-TB infection may be confounded by other variables.

The Fisher-Hoch et al. and Ibrahim et al. reported that diabetes was found to be the most common comorbidity associated with MDR-TB.[27,28] Moreover, a study in Taiwan demonstrated that among previously treated patients, diabetes was significantly related to isoniazid resistance but not with MDR-TB.[9] However, our study found no significant association between diabetes and MDR-TB infection. A Similar result was also found by Sobhy et al.[29] Furthermore, the significant association found was between diabetes and new TB cases, which were excluding MDR-TB.[30] Thus, the difference in the study population and design might be contributed to these findings variation.

Skrahina et al. and G. Mulisa et al. Reported that there was an association between TB-HIV co-infection and MDR-TB.[31,32] However, Our study did not find any evidence of this association. Moreover, there were several studies conducted in other countries supported our findings.[7,16,33-35] A systematic review and meta-analysis in Sub-Saharan Africa contended that the MDR-TB infection was not influenced by the HIV prevalence rates in the region.[36] Hence, although the co-infection of TB and HIV might suggest an increased risk of MDR-TB infection, there were significant evidence showing no association between those variables.

There are some limitations to this study which should be acknowledged. First, this was a retrospective analysis of routinely reported data; hence, it was not possible to explore other potential confounders such as smoking or alcohol use. Second, the data was taken from one government treatment centre and conducted in a hospital-based setting. Therefore we cannot generalize the findings to other settings or in other parts of Indonesia. Regardless of these limitations, our findings are consistent with the current literature and allowed us to predict and examine the profile of MDR-TB drug susceptibility. Moreover, the study provides a baseline for future studies to further evaluate the effectiveness of these predictors as screening tools to identify individuals at high risk of acquiring the MDR-TB infection. Furthermore, this information is useful for health centres which lack diagnostic tools and treatment facilities for MDR-TB. We encourage clinicians to identify these clinical predictors of MDR-TB to assist in risk stratification to deliver early detection, effective treatment, and transmission control.

CONCLUSION

The most common pattern of MDR-TB resistance was acquired resistance to all four drugs. The significant predictors for MDR-TB were previous TB treatment and age 25 to 45 years. It is essential to detect individuals who are at risk for MDR-TB infection to provide effective community-based MDR-TB control programs and proper treatment based on DST results.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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