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Factors Associated with Multidrug-Resistant Tuberculosis Patients in the Upper Northeast Thailand

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Abstract: A matched case-control study was conducted to identify the factors associated with MDR in the Upper Northeast Thailand. The ratio of MDR per non-MDR was 1:2 and medical records were retrospectively reviewed. To identify the factors associated with MDR by conditional logistic regression analysis and were presented by adjusted matched Odds Ratio (mOR_{adj}) and 95% confidence interval (95% CI). In total 273 cases were included, divided into 91 MDR and 182 non-MDR. The factors associated with MDR; irregular TB follow up in the past was 264.6 times higher risk (95% CI: 23.1-3036.4) to have MDR. DOT by self administrative was 36.0 times higher risk (95% CI: 2.3-576.2) as compared with DOT by health care providers. Co-morbidity diseases were 5.8 times higher risk to have MDR (95% CI: 1.5-21.9). Strengthening DOTs strategy for shorting the delay of diagnosis and treatment, decreasing irregular TB follow up that aimed to increase success rate and prevent MDR. Should be developed TB/DM collaborative strategies and guidelines for preventing the transmission of *M. tuberculosis* in DM patients.

Key words: Risk factors, MDR, TB, patients, Thailand

INTRODUCTION

Multidrug-Resistant tuberculosis (MDR) still has been a major problem of public health in worldwide also in Thailand. MDR can only be treated with second-line drug regimens which are much more expensive, about 100 times high costly as compared with Tuberculosis (TB) patients have to be used for a longer duration of drug taking, higher side effects and more likely to cause adverse drug reactions and much poorer outcomes as compared with standard first-line drugs. Inadequate treatment of MDR can lead to worse patient outcomes while increasing the risk of extensive Drug-Resistant tuberculosis (XDR) (Johnston *et al*., 2009).

In Thailand, based on a national drug resistance survey conducted from 2000-2006, the MDR rate was reported of 0.9 and 20.4% among new and previous TB treated cases, respectively and the third national drug resistance survey conducted in 2006 revealed levels of MDR in new and previous TB treated cases were 1.7 and 34.5%, respectively (Bureau of Tuberculosis, 2008). Although, drug resistance rates in new cases are lower than hotspot (3.0%) but the overall burden of MDR should be considered in both of new and previous TB treated cases. Moreover, a drug resistance survey conducted among prisoners with newly detected TB revealed a higher prevalence of MDR was 5.9% that higher than hotspot (WHO, 2009). Various risk factors associated with MDR have been shown in the previous studies but most of them were done in other countries. A few studies were conducted in Thailand; almost all studies were conducted based on referral tertiary hospital. The reported factors associated with MDR were being HIV positive, previous imprisonment, a history of prior TB treatment and advanced radiological abnormalities.

However, different geographical, demographical and treatment strategies may provide different an explanation. Therefore, risk factors for MDR may be different in each country and setting. Also, in Thailand still have some controversy regarding HIV positive, one study that was performed in the Northern region where presents high HIV prevalence had confirmed that HIV positive as a risk factor for MDR (Yoshiyama *et al*., 2001) while other studies have not mentioned (Hongthiamthong *et al*., 1994; Maranetra, 1996; Tansuphasiri *et al*., 2003). However, much less is known about the other risk factors and few studies have specifically assessed factors associated with MDR in Thailand. A limited of information and controversy about the determine risk factors of MDR in Thailand have not been systematically investigated.

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Therefore, matched case-control study was conducted to identify the factors associated with MDR among tuberculosis patients in the Upper Northeast Thailand.

MATERIALS AND METHODS

This matched case-control study was conducted to identify the factors associated with MDR among tuberculosis patients in the Upper Northeast Thailand. The ratio of MDR case per non-MDR matched controls was 1:2, MDR cases were TB patients who were diagnosed or treated by second-line drugs (CAT4). Controls were non-MDR patients who had the same gender and age with cases. MDR and non-MDR cases were registered at TB clinic in 7 provincial hospitals and the TB Demonstrated Center of the Office of Disease Prevention and Control 6th, Khon Kaen province (DPC6) during October 2008 and September 2010. Medical records were retrospectively reviewed for socio-demographics, clinical characteristics; TB treatment history, co-morbidities, sputum cultures, Drug Susceptibility Test (DST). The sample size was calculated to detect risk factors associated with MDR that interested independent variable was previous TB treated, the estimated proportion of previous TB treatment in control group is 0.09 and detect a six fold increased risk of MDR (Sharma *et al*., 2003) using the approach of sample size calculation for pair-matched case-control studies in case-control studies: design, conduct and analysis (Schlesselman, 1982) and adjusted the relationship of the variances by $n_p = n_1/(1 - \rho^2_{1,2,3...,p})$ (Hsiehl *et al*., 1998). Therefore, the required minimum subjects in MDR cases was 90 matched pairs making the number of 270 subjects, divided into 90 MDR cases and 180 non-MDR matched controls.

The study had enrolled all MDR cases that met all inclusion criteria, totally there were 91 MDR cases and 182 non-MDR matched controls. Data analysis was performed using STATA programme Version 10.0. The descriptive statistics were performed to explain socio-demographic and clinical characteristics. Multivariable conditional logistic regression by backward method was used to identify the factors associated with MDR, selected independent variables for inclusion based on plausibility, a priori evidence, completeness of data or had a p-value of Wald test ≤0.25 (Hosmer and Lemeshow, 2000) in univariate analysis were entered into a initial model, no multicollinearity was reported in the STATA results. This study was approved by the ethical committee of Faculty of Medicine, Khon Kaen University (approval number: HE542002).

RESULTS AND DISCUSSION

Socio-demographic characteristics: During the study period, 91 MDR cases were diagnosed or treated by second-line drugs (CAT4) and 182 non-MDR cases were matched controls. Among 273 cases, two hundred and one cases were male (73.6%), the mean age was 46.5 years (SD = 12.5) and 46.3 years (SD = 12.3), respectively. Marital status was married 72.5% in MDR cases and 76.9% in non-MDR cases. Most of the MDR cases were live in rural (67.0%) and almost all non-MDR cases were live in urban (84.6%). The majority of MDR were farmer (49.4%) and 41.8% were labor in non-MDR (Table 1).

Table 1: Socio-demographic and clinical characteristics

Characteristics	MDR $n_1 = 91$ (%)	Non-MDR $n_2 = 182$ (%)
Gender		
Male	67 (73.6)	134 (73.6)
Female	24 (26.4)	48 (26.4)
Age of TB initiation (year)		
<35	14 (16.1)	36 (19.8)
35-44	22 (25.3)	44 (24.2)
45-54	28 (32.2)	57 (31.3)
55-64	17 (19.5)	32 (17.6)
>65	6 (6.9)	13 (7.1)
Mean (SD)	46.5 (12.5)	46.3 (12.3)
Marital status		
Married	66 (72.5)	140 (76.9)
Single	17 (18.7)	33 (18.1)
Divorced/Separated	5 (5.5)	9 (5.0)
Monk	3 (3.3)	-
Residence area		
Rural	61 (67.0)	28 (15.4)
Urban	30 (33.0)	154 (84.6)
Occupation		
Farmer	45 (49.5)	53 (29.1)
Labor	25 (27.5)	76 (41.8)
Government officer	5 (5.5)	11 (6.0)
Trader/Merchant	4 (4.4)	10 (5.5)
Unemployed	3 (3.3)	17 (9.3)
Others	9 (9.8)	15 (8.3)
Co-morbidity diseases		
No	53 (58.2)	122 (67.1)
Yes	38 (41.8)	60 (32.9)
Types of co-morbidity disease ($n_1 = 38$, $n_2 = 60$)		
Diabetes Mellitus (DM)	26 (68.4)	32 (53.3)
Hypertension (HT)	12 (31.6)	8 (13.3)
Others	15 (39.5)	27 (45.0)
Patient's delay (day) ($n_1 = 45$, $n_2 = 108$)		
≤28	4 (8.9)	31 (28.7)
>28	41 (91.1)	77 (71.3)
Median day (IQR: Q_3 - Q_1)	40.0 (61.0-31.0)	33.0 (61.5-28.0)
A number of TB treatments (time) ($n_1 = 86$)		
Never treated	1 (1.2)	0
1	22 (25.6)	180 (98.9)
2	43 (50.0)	2 (1.1)
3	16 (18.5)	0
4	3 (3.5)	0
7	1 (1.2)	0
Median (IQR: Q3-Q1)	2.0 (2.0-1.0)	1.0 (1.0-1.0)
HIV results		
Positive	5 (5.5)	14 (7.7)
Negative	61 (67.0)	146 (80.2)
Not examined	16 (17.6)	21 (11.6)
Unknown	9 (9.9)	1 (0.5)

Clinical characteristics: In total of 273 cases who had at least 1 co-morbidity (MDR cases 41.8% and non-MDR 32.9%), type 2 Diabetes Mellitus (DM) was the most common in both MDR cases (68.4%) and non-MDR (53.3%) followed by Hypertension (HT) which was 31.6 and 13.3%, respectively. Patient's delay were classified as the time between onset of first symptoms and first utilization of a health care provider not >4 weeks (28 days), 91.1% [median 40.0 days (IQR = 51.0-31.0)] and 71.3% [median 33.0 days (IQR = 61.5-28.0)] were delay >28 days in MDR cases and non-MDR, respectively. For a number of TB treatments (times), in non-MDR, the majority of subjects had one time of TB treatment (98.9%). In MDR cases, only one (1.1%) case had never treated TB before, 74.0% had at least 2 times of TB treatment (min = 1 and max = 7). From HIV results, MDR cases were HIV positive for 5.5% and non-MDR were 7.7%, almost all both groups were HIV negative (67.0 and 80.2%, respectively). However, some subjects still had not examined HIV testing; although, TB/HIV integrates has settled (Table 1).

Factors associated with MDR: Multivariable conditional logistic regression was used to identify the factors associated with MDR. Univariate analysis for alcohol consumption was associated with MDR (mOR_{crude} = 5.1; 95% CI: 1.1-24.9). Co-morbidity diseases was not associated with MDR (mOR_{crude} = 1.6; 95% CI: 0.9-2.8) but was p-value of Wald test <0.25 and had a priori evidence associated with MDR. TB drugs administration was categorized into 4 groups, DOT by health care providers was reference, TB drugs administration by self administrative was associated with MDR (mOR_{crude} = 8.1; 95% CI: 1.4-47.2). Irregular TB follow up, a number of previous TB treatments also were significantly associated with MDR (Table 2).

The final of multivariable conditional logistic Regression Model included the independent variables that associated with MDR after adjusted the other variables. TB patients who had irregular TB follow up in the history was 264.6 times higher risk (95% CI: 23.1-3036.4) to have MDR as compared with patients who had regular TB follow up. TB drugs administration; reference group was DOT by health care providers, the results showed that DOT by family was associate with MDR, adjusted mOR was 11.2 times (95% CI: 1.1-112.8) and drugs intake by self administrative was also associate with MDR, adjusted mOR was 36.0 times (95% CI: 2.3-576.2). The last independent variable in the final model was co-morbidity diseases; TB patients who had co-morbidity diseases were 5.8 times higher risk to have MDR as compared with patients who had no co-morbidity diseases (95% CI: 1.5-21.9) (Table 3).

Table 2: Factors associated with MDR by univariate analysis of conditional logistic regression analysis

Variables	MDR (n_1 = 91) (%)	Non-MDR (n_2 = 182) (%)	Univariate analysis mOR_{crude} (95% CI)	p-value
Smoking	53.9	36.9	2.7 (0.7-10.6)	0.145
Alcohol consumption	60.0	34.9	5.1 (1.1-24.9)	0.044*
Irregular TB follow up	73.4	7.1	101.6 (14.0-734.5)	<0.001*
Adverse TB	9.2	1.7	13.9 (1.72-113.8)	0.014*
TB drugs administration	5.4	10.0	1.00	-
DOT by village health volunteer	4.1	8.3	1.1 (0.1-10.4)	0.967
DOT by couple/relatives	55.4	60.0	3.7 (0.7-19.1)	0.121
Intake by self administrative	35.1	21.7	8.1 (1.4-47.2)	0.019*
Co-morbidity diseases	41.8	32.9	1.6 (0.9-2.8)	0.119
Diabetes mellitus	27.5	17.6	1.9 (1.01-3.7)	0.047*
Hypertension	15.4	4.4	5.6 (1.8-17.4)	0.003*
Previous treated ≥2 times	75.6	1.1	128.5 (17.8-926.2)	<0.001*

Table 3: Factors associated with MDR by multivariable conditional logistic regression analysis

Variables	MDR (n_1 = 91) (%)	Non-MDR (n_2 = 182) (%)	Multivariable analysis mOR_{adj} (95% CI)	p-value
Irregular TB follow up				
No	26.6	92.9	1.00	<0.001*
Yes	73.4	7.1	264.6 (23.1-3036.4)	-
TB drugs administration				
DOT by health providers	5.4	10.0	1.00	0.863
DOT by village health volunteer	4.1	8.3	0.7 (0.01-70.8)	0.041*
DOT by family	55.4	60.0	11.2 (1.1-112.8)	0.011*
Intake by self administrative	35.1	19.4	36.0 (2.3-576.2)	-
Co-morbidity diseases				
No	58.2	67.1	1.00	0.010*
Yes	41.8	32.9	5.8 (1.5-21.9)	-

Among 91 MDR cases, most of cases were male (73.6%), (the ratio of male to female 2.8:1.0). This ratio of male to female was similar to the previous studies that mentioned the ratio of male more than female among MDR (Tesana *et al*., 2003). Most of the MDR lived in rural (67.0%) and were a farmer (49.4%), this result meant that most of the MDR had low socioeconomics and needed much more money and also time to go to the hospital to get MDR treatment for 18-24 months and this result was similar to the previous study in the Lower Northern of Thailand (Pimnumyen and Siripornpibul, 2010).

The median duration of symptoms before TB treated (patient's delay) of MDR was 40 days (IQR = 61.0-31.0), that lower than the study in the Srinagarind Hospital (Reechaipichitkul, 2002) shown the patient's delay of MDR was 3.8 months (range: 3 days to 2 years). The main cause of the difference might be the different of study timing, in present, TB management has coordinated in all of public health sections and the patients have easier to reach the health services that might be getting the shorter duration of patient's delay. However, patient's delay were classified as the time between onset of first symptoms and first utilization of a health provider not >4 weeks (28 days) (Aoki and Mori, 1985; Asch *et al*., 1998), 91.1% [median 40.0 (IQR = 61.0-31.0)] and 71.3% [median 33.0 (IQR = 61.5-28.0)] were delay >28 days in MDR and non-MDR, respectively this result showed the problem of patient's awareness of theirs health but it was not associated with MDR.

The commonest co-morbidity disease of MDR was type 2 diabetes mellitus (88.4%) followed by hypertension (31.6%), this result was different from the other studies (Akkasilp *et al*., 2009; Reechaipichitkul, 2002) have shown the commonest co-morbidity were HIV infection for 35.0 and 37.0%, respectively. In the current study, 66 cases had been through a counseling HIV testing and just only 5 cases (5.5%) were HIV infection, this reported quite small proportion of HIV infection because many of MDR had no counseling HIV testing (not examined = 17.6%, unknown = 9.9%). The previous studied (Flament-Saillour *et al*., 1999; Kliiman and Altraja, 2009) reported HIV infection is the commonest co-morbidity of MDR but HIV infection was not significant associate with MDR. In Thailand, Yoshiyama *et al*. (2001) reported HIV infection was a risk factor of MDR while other studies did not mentioned (Akkasilp *et al*., 2009; Boonsarngsuk *et al*., 2009; Hongthiamthong *et al*., 1994).

A matched case-control study was conducted to identify the risk factors associated with MDR. Data analysis by the conditional logistic regression, this approach is the appropriate method for analysis (Kleinbaum, 2002). The factors associated with MDR were irregular TB follow up, TB drugs administration and co-morbidity disease.

Irregular TB follow up in the past, in MDR cases were 73.4% higher than non-MDR cases were 7.1%, this study showed irregular TB follow up was significantly associate with MDR both of univariate and multivariable conditional logistic regression analysis; mOR_{adj} 264.6 times (95% CI: 23.1-3036.4). Similarly with the studies by Law *et al*. (2008) reported that the patients who had the history of frequent travel are higher risk factor for MDR and Sharma and Mohan (2004) found that poor compliance for TB treatment was significant risk factor with MDR. Both frequent travel and poor compliance have made irregular TB follow up that why TB cases had developed to have MDR. The best way to manage MDR is prevent TB cases to have MDR by implementing good NTP and effectively addressing all the risk factors that associated.

TB drugs administration in the study was categorized in 4 groups, DOT by health care providers was reference; TB drugs intake by self administrative was significantly associated with MDR (mOR_{adj} = 36.0; 95% CI: 2.3-576.2) and DOT by family also was significantly associated with MDR (mOR_{adj} = 11.2; 95% CI: 1.1-112.8). The result is inconsistent with the previous study (Granich *et al*., 2005) reported type of TB drug therapy divided into 3 groups; self-administered only, directly observed and both self-administered and directly observed was not associate with MDR.

Reversely, the result similar to the study by Law *et al*. (2008) reported that DOT in the previous treatment was associated with MDR. Poor case managements such as permitting patients to self administer or tailor their own regimens may also induce drug resistance (Spradling and Ridzon, 2003). However, treatment with properly implemented DOTs has a success rate exceeding 95% and prevents the emergence of further multidrug-resistant strains of tuberculosis.

Among total of 273 cases had at least 1 co-morbidity diseases (MDR cases 41.8% and non-MDR cases 32.9%), type 2 diabetes was the most common in both of MDR and non-MDR (68.4 and 53.3%) followed by hypertension 31.6 and 13.3%, respectively. Co-morbidity diseases was significant associate with MDR both of univariate and multivariable; mOR_{adj} 5.8 times (95% CI: 1.5-21.9). The result inconsistent with the study by Shen *et al*. (2009) and Suarez-Garcia *et al*. (2009) that reported DM was not associated with MDR.

As the results, strengthening NTP with DOTs strategy for shorting the delay of diagnosis and treatment, increasing compliance or decreasing irregular TB follow up that aimed to increase success rate of TB treatment,

particularly increasing case detection rate that is the best way to prevent MDR and The commonest co-morbidity disease is DM should be developed TB/DM collaborative strategies and guidelines for preventing the transmission of *M. tuberculosis* in DM patients.

CONCLUSION

This study was observational study that matched case-control, retrospectively reviewed the routinely medical records of MDR and non-MDR. Hence, data was uncompleted in term of education, Body Mass Index (BMI), contact history of MDR, alcohol abuse, smoking, the history of imprisonments, health insurance, injecting drugs use, contact history of TB. From this reasons, this study was unable to determine the exact association of these factors. Further study should be considered the difference study design for completing all risk factors that have shown the association with MDR. As the multivariable conditional logistic regression analysis, 95% CI mOR_{adj} of irregular TB follow up and TB drugs administration variables are not precise although sample size was calculated, a possible discussion for the results might be that the interesting of independent variable for sample size calculation is previous TB treatment so has an effect on inadequate sample size to explain the other variables.

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