The Epidemiological Study and Risk Factors of Drug-Resistant Tuberculosis In Samut Sakhon Province, Thailand
การศึกษาทางระบาดวิทยา และปัจจัยเสี่ยงต่อการเกิดวัณโรคดื้อยา ในจังหวัดสมุทรสาคร

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ABSTRACT

Objective: Study the epidemiology of pulmonary, extrapulmonary and disseminated tuberculosis, prevalence of drug resistant tuberculosis and its risk factors in Samut Sakhon Province.

Material and Methods: A descriptive, retrospective, cross-sectional, analytic review was conducted. Data from Tuberculosis Case Management Program (TBCM) registry were collected from October 1, 2016 to September 30, 2017. The incidence and treatment outcomes of pulmonary TB, disseminated TB and extrapulmonary TB (EPTB), and prevalence of drug-resistant pulmonary TB (DR-PTB) were described. Multivariate analysis with logistic regression for odds ratio was performed to determine possible risk factors for drug-resistant pulmonary tuberculosis.

Results: Of the total 581 cases of tuberculosis, mean age was 39.4 ± 13.7 years old. 375 were male (64.5%). There were 449 (77%), 98 (17%), and 34 (6%) cases of pulmonary, extrapulmonary, and disseminated tuberculosis respectively. Of all, 507 (87.3%) were new cases, 370 (63.7%) were Thais. Most of non-Thais were Myanmars (203 cases, 34.3%). 98 were HIV infected (16.9%). Of the tuberculosis with pulmonary involvement, the incidences of isolated isoniazid-resistant (HR-PTB) and rifampicin-resistant/multidrug-resistant pulmonary tuberculosis (RR/MDR-PTB) were 10.2% and 6.8% respectively. Prevalence of primary RR/MDR-PTB was 3.8%. Positive HIV status was a significant risk factor for developing any DR-PTB (OR 2.83, 95%CI 1.20-6.65, p 0.017). Mortality rate among any DR-PTB was higher than that of drug-susceptible pulmonary tuberculosis (OR 5.21, 95%CI 2.16- 12.54,

p < 0.001. The strongest predictor for disseminated tuberculosis was positive HIV status (OR 25.42, 95%CI 10.69-60.43). While non-Thai nationality was not a risk factor for DR-PTB, they had higher propensity to be transferred out to other public health facilities (OR 4.81, 95% CI 2.46 - 9.40, p < 0.001).

Conclusion: Prevalence of DR-PTB in Samut Sakhon Province was higher than an average of Thailand. Its risk factor was positive HIV status. Immigrants were not a risk factor for developing DR-PTB but they had a higher transfer-out rate than that of Thai people.

Keyword : drug-resistant tuberculosis, risk factor
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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาลักษณะทางระบาดวิทยาของวัณโรคปอด วัณโรคนอกปอดและวัณโรคแพร่กระจาย และศึกษาหาความชุกของวัณโรคดื้อยา และปัจจัยเสี่ยงที่เกี่ยวข้อง ในจังหวัดสมุทรสาคร

วิธีการศึกษา: ศึกษาเชิงบรรยายและวิเคราะห์ จากข้อมูลที่ได้รับการลงทะเบียนวัณโรคจากโปรแกรมลงทะเบียนวัณโรค TBCM ตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2559 ถึง 30 กันยายน พ.ศ. 2560 โดยศึกษาอุบัติการณ์และผลการรักษาวัณโรคปอด วัณโรคแพร่กระจาย และวัณโรคนอกปอด รวมถึงความชุกของวัณโรคดื้อยาในกลุ่มที่มีวัณโรคปอดร่วมด้วย และวิเคราะห์หาปัจจัยเสี่ยงที่อาจจะเกี่ยวข้องกับการเกิดวัณโรคดื้อยา โดยใช้วิธี multivariate analysis ด้วย logistic regression เพื่อหา odds ratio

ผลการศึกษา: มีผู้ป่วยวัณโรคทั้งหมด 581 คน อายุเฉลี่ย 39.4 ± 13.7 ปี ส่วนใหญ่เป็นเพศชาย 375 คน (ร้อยละ 64.5) เป็นวัณโรคปอด วัณโรคนอกปอด และวัณโรคแพร่กระจายทั้งหมด 449 คน (ร้อยละ 79), 98 คน (ร้อยละ 17) และ 34 คน (ร้อยละ 6) ตามลำดับ เป็นผู้ป่วยรายใหม่ 507 คน (ร้อยละ 87.3) เป็นชาวไทย 370 คน (ร้อยละ 63.7) ประชากรต่างชาติส่วนใหญ่เป็นชาวเมียนมาร์ 203 คน (ร้อยละ 34.3) จากจำนวนผู้ป่วยทั้งหมด ติดเชื้อเอชไอวี 98 คน (ร้อยละ 16.9) ในผู้ป่วยวัณโรคที่มีวัณโรคปอดร่วมด้วย มีผู้ป่วยที่มีการดื้อยา isoniazid ร้อยละ 10.2 และดื้อยา rifampicin หรือดื้อยาหลายขนาน ร้อยละ 6.8 ความชุกของวัณโรคดื้อยาหลายขนานแบบปฐมภูมิ ร้อยละ 3.8 การติดเชื้อเอชไอวีเพิ่มความเสี่ยงต่อการเกิดวัณโรคดื้อยา คิดเป็น 2.83 เท่า (95% CI 1.20-6.65, p 0.017) การเป็นวัณโรคดื้อยาเพิ่มความเสี่ยงต่อการเสียชีวิต คิดเป็น 5.21 เท่า (95%CI 2.16- 12.54, p < 0.001) โดยการติดเชื้อเอชไอวีจะเพิ่มความเสี่ยงต่อการเป็นวัณโรคแพร่กระจาย คิดเป็น 25.42 เท่า (95%CI 10.69-60.43) ประชากรต่างชาติไม่ใช่ปัจจัยเสี่ยงต่อการเกิดวัณโรคดื้อยา แต่จะมีอัตราการเคลื่อนย้ายไปยังสถานพยาบาลแห่งอื่นสูงกว่าประชากรไทย

สรุป: ความชุกของวัณโรคปอดดื้อยาในเขตจังหวัดสมุทรสาคร มีมากกว่าความชุกโดยเฉลี่ยของประเทศไทย ปัจจัยเสี่ยงที่สำคัญคือการติดเชื้อเอชไอวี ประชากรต่างชาติไม่ใช่ปัจจัยเสี่ยงต่อการเกิดวัณโรคดื้อยา แต่มีโอกาสเคลื่อนย้ายประชากรสูงกว่าประชากรไทย

คำสำคัญ: วัณโรคดื้อยา ปัจจัยเสี่ยง
วารสารแพทย์เขต 4-5 2562 ; 38(3) : 232-242.

Introduction

From the past, there were some impediments in the diagnosis of drug-resistant tuberculosis, especially in Thailand. Because of the lack of advanced laboratory to culture mycobacteria and the tests for drug susceptibility, and also abundant of time needed for mycobacteria culture, culture of mycobacteria had some limitations and previously was not routinely done. This led to lack of data for estimation of drug-resistant tuberculosis in Thailand. However, there are newer molecular technologies that can give the information of mycobacteria drug resistance panels worldwide, bring a more rapid and reliable result, making diagnosis of drug-resistant tuberculosis much easier, more rapid, and less labor intensive. Samut Sakhon Province, is one of the most crowded areas of foreign workers, non-registered population, and migrants, maybe a unique area that has a distinctive data about drug-resistant tuberculosis epidemiology. We aim to study the epidemiology of tuberculosis, diagnosed between October 1, 2016 to September 30, 2017, attending to pulmonary, extrapulmonary and disseminated tuberculosis, prevalence of drug-resistant tuberculosis and its possible risk factors, and treatment outcomes.

Objective

to study the epidemiology of pulmonary, extrapulmonary and disseminated tuberculosis, prevalence of drug resistant tuberculosis and its risk factors in Samut Sakhon Province.

Methods

A descriptive, retrospective, cross-sectional, analytic study. Data were retrospectively collected from October 1, 2016 to September 30, 2017 from the National Registry of Tuberculosis Case Management Program (TBCM), registered by Samut Sakhon Hospital tuberculosis clinic team. The researchers revised the demographic data, comorbidities, HIV status, diagnosis subtypes (pulmonary, extrapulmonary, or disseminated tuberculosis), evidence of tuberculosis diagnosis (e.g. sputum smear, culture, molecular testing), radiographic findings, drug-susceptibility panels, treatment regimens and results of treatment. For all the patients who have been registered as tuberculosis, but subsequently misdiagnosed, were excluded from the study. The data were then statistically analyzed. The study protocol was approved by the Ethics Committee on Human Experimentation of Samut Sakhon Hospital. Informed consent was not obtained as it was waived by the Ethics Committee on Human Experimentation of Samut Sakhon Hospital.

The patients were classified into three diagnosis subtypes based on clinical manifestation, radiological findings, and evidence of specimen collected. The first one was pulmonary tuberculosis (PTB), defined as tuberculosis with parenchymal lung involvement with or without tuberculous pleuritis. The second one was disseminated tuberculosis, defined as tuberculosis involved of 2 or more

organs with or without pulmonary involvement. And the third one was extrapulmonary tuberculosis (EPTB), defined as tuberculosis involvement of single organ other than the lungs parenchyma (e.g. pleura, lymph node, CNS etc.).

The demographic and clinical data (e.g. nationalities, co-morbidities, HIV status, prisoner status etc.) were collected from medical records and revised by the researchers. The radiographic findings were reviewed by the radiologists in pulmonary tuberculosis or disseminated tuberculosis with pulmonary involvement and subsequently categorized into 2 subgroups: cavitary and non-cavitary radiographic subgroups. The treatment results were classified into success, failure, died, and loss to follow up as defined by WHO definitions and reporting framework for tuberculosis[1]. If disseminated tuberculosis cases had pulmonary involvement and available drug susceptibility data, we brought them along with group 1 PTB to analyze the drug resistance pattern and its risk factors.

In PTB and disseminated TB with pulmonary involvement, all respiratory specimens with acid fast bacilli (AFB) smear positive were sent for further genotypic drug susceptibility testing (DST) for isoniazid and rifampicin-resistant gene, using either Line Probe Assay (2nd generation Hain MTBDR plus, Nehren, Germany), Nucleic acid amplification test (NAAT) either Anyplex™ MTB/NTM real-time Detection or Anyplex™ II MTB/MDR detection (Seegene, Songpa-gu, Seoul, Korea) or GeneXPert MTB/RIF (Capheid Inc., Sunnyvale, CA, USA). Phenotypic drug susceptibility testing for isoniazid and rifampicin resistance were using of standard solid culture on Löwenstein–Jensen (LJ) medium or liquid culture of drug susceptibility test (MGIT 960; Becton Dickinson, Franklin Lakes, NJ, USA) or multiple methods. Susceptibility was determined on the basis of the following drugs and concentrations: minimum inhibitory concentration (MIC) of isoniazid, 0.1 μg/mL, rifampicin, 1.0 μg/mL, respectively. In the case of clearly diagnosis of pulmonary tuberculosis by confirmed molecular testing and genotypic DST was done, not all respiratory specimens of the patients with smear positive was sent for phenotypic DST. Not all respiratory specimens with AFB smear negative were done molecular diagnosis of tuberculosis, if done so, respiratory specimens were processed using either NAAT, GeneXPert MTB/RIF or standard mycobacterial culture where available. In EPTB group, not all extrapulmonary specimens were tested for genotypic DST or phenotypic DST.

All data were analyzed using SPSS statistical software package, version 17.0 for Windows (SPSS, Chicago IL, USA). Incidence of tuberculosis (PTB, disseminated TB, and EPTB) was counted and shown in percentage. The prevalence of drug-resistant tuberculosis (both isoniazid resistant and rifampicin resistant/MDR-TB) was described. Categorical variables were compared with chi-square analyses or Fisher's exact test where appropriate. To determine possible risk factors for developing

drug-resistant tuberculosis, multivariate analysis with logistic regression was performed for odds ratio. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

There were all 611 tuberculosis cases had been diagnosed and registered from October 1, 2016 to September 30, 2017. Thirty cases were excluded from the study due to misdiagnosis (of other diagnosis such as nontuberculous pulmonary infection, bronchogenic cancer, congestive heart failure, normal chest radiography etc.). Of the total cases of 581, the demographic data of cases were shown in Table 1. Most of the cases were male (64.5%), new cases (87.3%), and Thai people (63.7%). Myanmar was a main population group in non-Thais, with 203 patients. The percentage of HIV positive was 16.9% and median CD4 count was 121±176 cell/mm^3

Table 1 Demographic data of the study subject

Demographic data	Number (%)
Age (years) (mean ± S.D.)	39.4 ± 13.7
Sex	
Male	375 (64.5)
Female	206 (35.5)
Prisoner	28 (4.8)
TB registry	
New case	507 (87.3)
Treatment after default	17 (2.9)
Recurrent	19 (3.3)
Treatment after failure	3 (0.5)
Transferred in	35 (6.0)
Nationality	
Thai	370 (63.7)
Non-Thai	211 (36.3)
Diabetes mellitus	39 (6.7)
Cirrhosis	16 (2.7)
COPD	10 (1.7)
HIV positive	98 (16.9)
Median CD4 count ± S.D.	121 ±176

Table 2 Proportion of organ involved in disseminated TB group

Organ involvement	Number of cases (%)
Pulmonary	27 (79)
Lymph node	18 (52)
Liver and spleen	14 (41)
Meninges	5 (14)
Colitis/ileitis	5 (14)
Pleura	3 (8)
Bone marrow	3 (8)
Genitourinary	2 (5)
Pericardium	2 (5)
Bloodstream	2 (5)

Table 3 Organ involvements in EPTB group

Organ involvement	Number of cases (%)
Lymph node	57 (58)
Pleura	22 (23)
Colitis/Ileitis	6 (6)
Bone/joint	5 (5)
CNS (meningitis or tuberculoma)	4 (4)
Miscellaneous	4 (4)
Total	**98 (100)**

Group 1 Pulmonary tuberculosis

There were 449 cases of PTB, in which 277 cases (61.8%) were AFB smear positive and 172 cases (38.3%) were AFB smear negative. Out of the smear positive PTB, there were missing both genotypic and phenotypic drug-resistance data by 46 cases, as they were excluded from analysis. The reasons of the missing data were lack of data in cases transferred from other regions of Thailand, positive sputum smears but there were no TB gene detection by genotypic methods and no mycobacteria growths in cultures. So, there were only 231 cases with positive AFB smears and had drug resistance data. In negative smear PTB and disseminated TB with pulmonary involvement, there were 13 and 21 cases with confirmed diagnosis of tuberculosis and available drug-resistance data, respectively. The prevalence of isolated isoniazid-resistant pulmonary TB

(HR-PTB) was 10.2% (27 out of 265 cases) and the prevalence of Rifampicin Resistant/MDR pulmonary tuberculosis (RR/MDR-PTB) was 6.7% (18 out of 265 cases), summarized in Table 4. The prevalence of primary RR/MDR-PTB (defined as RR/MDR-PTB in new case) and RR/MDR-PTB in previously treated TB were 3.8% (9 out of 238) and 33% (9 out of 27) respectively.

Among the patients with any DR-PTB (45 out of 265 cases, 17.0%), the possible risk factors were shown in Table 5.

Table 4 Drug resistance among pulmonary tuberculosis and disseminated tuberculosis with pulmonary involvement

	Number of cases	%
Total cases of pulmonary tuberculosis	449	
➢ Positive AFB smear pulmonary tuberculosis	277	
● With available drug resistance data	231	
○ Isolated isoniazid –resistant (HR-PTB)	24	
○ Rifampicin-resistant/MDR-PTB	11	
● Missing drug resistance data	46	
➢ Negative AFB smear pulmonary tuberculosis	172	
● With available drug resistance data	13	
○ Isolated isoniazid-resistant (HR-PTB)	1	
○ Rifampicin-resistant/MDR-PTB	2	
Total cases of disseminated TB with pulmonary involvement	27	
● With available drug resistance data	21	
○ Isolated isoniazid-resistant (HR-PTB)	2	
○ Rifampicin-resistant/MDR-PTB	5	
Total cases with available drug resistance data	265	100
● **Isolated isoniazid-resistant (HR-PTB)**	27	10.2
● **Rifampicin-resistant/MDR-PTB**	18	6.8

Table 5 Possible risk in DR-TB

Possible risk factors	Any DR-PTB n (%)	DS-PTB n (%)	Odd ratio (95% CI)	P-value
HIV status	43	214		
Negative	29 (67.4)	184 (86.0)	Reference	
Positive	14 (32.6)	30 (14.0)	2.83 (1.20-6.65)*	0.017*
Cavity on CXR	44	219		
No cavity	28 (63.6)	130 (59.4)	Reference	
Cavity	16 (36.4)	89 (40.6)	1.07 (0.50-2.30)	0.844
Prisoner patient	45	220		
Non-prisoner	42 (93.3)	205 (93.2)	Reference	
Prisoner	3 (6.7)	15 (6.8)	0.58 (0.12-2.79)	0.505†
Treatment category	45	220		
New case	36 (80.0)	202 (91.8)	Reference	
Prior TB treatment	9 (20.0)	18 (8.2)	2.44 (0.97-6.15)	0.058
Nationality	45	220		
Thai	33 (73.3)	143 (65.0)	Reference	
Non-Thai	12 (26.7)	77 (35.0)	0.91 (0.41-2.04)	0.837

*statistically significant, † Fisher's exact test

Treatment outcomes in pulmonary TB with available drug resistance data were success 79.5%, died of any cause 9.4%, transferred out 7.8%, ongoing treatment 2.5%, and loss to follow up 0.8%. A mortality rate among any DR-PTB was 31.4%, whereas that among drug-susceptible pulmonary tuberculosis (DS-PTB) was 8.1% (OR 5.21, 95%CI 2.16- 12.54, p < 0.001). Presence of isolated isoniazid resistance without rifampicin resistance (HR-PTB) did not demonstrate a significant increase in risk of death, compared to DS-PTB (12.0% vs 8.1%, OR 1.55, 95%CI 0.41-5.74, p 0.508).

Group 2 Disseminated tuberculosis

In the second group, there were 34 cases of disseminated TB. The organs involved in disseminated TB were shown in Table 2. Most of the cases had pulmonary and lymph node involvement. The risk factor for developing disseminated TB was HIV positive (OR 25.42, 95%CI 10.69-60.43). The 2 most common couple organs infection were pulmonary and lymph node (14 out of 34 cases, 41%) and pulmonary and hepatosplenomegaly (10 out of 34, 29%) respectively.

Of the 34 cases of disseminated TB, there were only 21 cases with available drug susceptibility test results. 7 of them (33.3%) had any drug-resistance and 5 of them (23.8%) were RR/MDR-TB. Treatment outcomes in this group were success 70.6%, ongoing treatment 8.8%, died of any causes 14.7%, and transferred out 5.9%.

Group 3 Extrapulmonary tuberculosis

In the third subgroup of cases, EPTB group, there were 98 cases out of total of all 581 cases of tuberculosis of any organs, classified by organ as illustrated in Table 3.

Of the cases with TB lymphadenitis (57 cases), the diagnosis was made based on lymph node pathology with caseating granulomatous inflammation, NAAT, direct AFB stain from specimens and culture for Mycobacteria with the numbers of 42 (73%), 22 (39%), 9 (16%), and 3 (5%) cases respectively. Of the cases with TB pleuritis (22 cases), the diagnosis was made based on pleural fluid ADA, NAAT, physician-directed and close pleural biopsy with the numbers of 18 (82%), 5 (22%), 5(22%), and 1 (4%) respectively. The mean pleural fluid ADA in the study was 58 ± 14 IU/ml. Treatment outcomes in EPTB group were relatively good with success rate of 89%, transferred out 6%, ongoing treatment 2%, and died of any causes 2%.

In overall outcome of three study group, there were only 4 (0.6%) cases of total 581 cases that loss to follow up. Non-Thai people had lower mortality rate than Thais (4.5% vs 9.6%, p = 0.041) but tended to have higher transfer-out rate (15.4% vs 3.6%, OR 4.81, 95% CI 2.46 - 9.40, p < 0.001).

Discussion

In the pulmonary tuberculosis group and disseminated tuberculosis with pulmonary involvement, The prevalence of HR-PTB in Samut Sakhon Province (10.2%) was slightly higher than the global average of isoniazid resistance (8.5%, estimated 7.4–9.7%) [2]. The prevalence of primary RR/MDR-PTB and RR/MDR-PTB in previously treated TB were 3.8% and 33% respectively, higher than the estimated Thailand tuberculosis profile data reported by WHO[2], 2.2% (estimated 1.5-2.9%) and 24% (estimated 16-32%) respectively. In order to determine the cause of such higher incidence of DR-PTB, we estimated its risk factors.

To determine the risk factors for developing any DR-TB, hypothesis that crowded area of migrants may affect the tuberculosis resistant pattern, as in some reports.[3,4] However, immigrant status was not a risk factor observed by our study data. HIV status was the only risk factor to demonstrate risk for developing any DR-TB. History of previously treated tuberculosis had a trend toward any DR-TB in our study (OR 2.44, 95% CI 0.97-6.15, p 0.058, NS) but did not show statistical significance. This was unlike other previous studies [3-16] that showed the strongest determinant for RR/MDR-TB were history of previously treated tuberculosis and positive HIV status in some studies[4]. The reason of distinct results in our study might be low number of cases with any DR-TB and RR/MDR-TB in our study. Longer period of study in order to recruit more patients is needed. Nonetheless, as a result from our study, although immigrant status was not a risk factor for DR-TB, they had higher incidence of transfer-out rate compared to Thais (15.4% vs 3.6%, p < 0.001).

About mortality rate of DR-PTB, in our study, the mortality rate among any DR-PTB was

higher than DS-PTB but when compare those of isolated HR-PTB to DS-PTB, isolated HR-PTB did not demonstrate a significant increase in risk of death. This may imply from our study that the major risk of death in any DR-PTB group might be contributed from the presence of RR/MDR-PTB, not HR-PTB but however, we cannot conclude from the study directly because of low number of RR/MDR-PTB cases.

Unsurprisingly, in disseminated TB group, the two most common involved organs were lungs and lymph nodes and its strongest predictors was positive HIV status, like other studies.[18, 19] This was because the lungs are the entry site organ of *Mycobacterium tuberculosis* and low immune status leads to dissemination of the disease.

In extrapulmonary TB group, the two most common involved organs were lymph nodes and pleurae, like previous study[17] in a regional part of Thailand. However, the true incidence of EPTB remains unclear, may be underdiagnosed due to lack of a gold standard test and its difficulty in diagnosis.

Conclusion

The prevalence of DR-PTB in Samut Sakhon Province was markedly higher than the average of Thailand and the presence of DR-PTB had higher mortality rate than those of DS-PTB. Positive HIV status was a major risk factor for developing DR-PTB. Immigrants were not risk factor for developing DR-PTB but they had a higher transfer-out rate than that of Thai people.

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