CLINICAL ANALYSIS OF FOREIGN-BORN PATIENTS WITH TUBERCULOSIS FOUND IN MALAYSIA

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Abstract. In this retrospective study, we investigated 263 foreign patients who were diagnosed as having tuberculosis at the National Tuberculosis Center (NTBC) from January 2001 to December 2002. The age range was 14-72 years, with a mean of 33.3 ± 9.95 years. The study subjects were predominantly males (60%) and females comprised 40%, where the greater impact of tuberculosis was observed in the young and active ones (up to 34 years of age), than middle-age (up to 54). A significantly higher percentage of these patients were from the Southeast Asian countries (87%) and particularly occurred in single male (47.5%) and married female (71.4%) patients ($p<0.05$). We also found that tuberculosis was significantly higher in female (50.5%) and male (64%) with smoking laborers ($p<0.05$). Fever (70%), cough (90.5%) and BCG vaccination status showed a significantly higher percentage in male patients ($p<0.05$), whereas lymphadenopathy (22%) was found in a significantly higher percentage in females ($p<0.05$). Overall, pulmonary disease (94.3%) occurred more commonly in males and the pleura (3.2%) was the most common site of disseminated tuberculosis. By contrast, the lymph node (11.4%) and miliary (4.8%) forms were the more common extrapulmonary tuberculosis in females. More males had higher percentage of treatment completed at ≥ 6 (38%) and ≥ 9 (13.3%) months in pulmonary tuberculosis, whilst, more females showed higher percentage of treatment completed (8.7%) in extrapulmonary tuberculosis. Surprisingly, more women showed non-compliance to the anti-tubercular therapy than their counterpart in this study.

INTRODUCTION

WHO estimates that one-third of the world population is infected with *Mycobacterium tuberculosis* (MTB) (CDC, 2000). Prevalence of infection varies with country of origin and is as high as 50% in some groups, such as refugees (WHO, 1998). The global resurgence of TB has been accompanied by an increased frequency of multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB) (Schaberg *et al*, 1995; Pablos-Mendez, 1998). In Malaysia, tuberculosis is considered among the top 5 communicable diseases reported where the influx of immigrants was at its peak in the early and mid 1990s. The incidence rate of TB among immigrants in 1993 was 136.8/100,000 but decrease to 79.6/100,000 per immigrant population in 1999. TB cases among immigrants contributed 11% of the total TB cases in Malaysia for 1993 and decrease to 8.8% in 1999 (Ministry of Health Malaysia, 1999). Similar trend was observed in the developed countries such as USA, where the overall foreign-born population has increased from 5% in 1970 to 10% in 2000 (US Census Bureau, 2000). Tuberculosis remains to be a disease of great impact in Malaysia with no comprehensive epidemiological studies among foreign-born persons. We, therefore, conduct this study in order to demonstrate sex differences in tuberculosis in foreign-born patients in term of clinical manifestations, laboratories, diagnosis, the role of treatment and most importantly its outcome. This definitely helps us in better understanding and management of this re-emergence disease among these patients.

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MATERIALS AND METHODS

Patients

Two hundred sixty three foreign patients were registered for tuberculosis treatment from

1 January 2001 to 31 December 2002 with the National Tuberculosis Center (NTBC), Kuala Lumpur, Malaysia, where 80 to 90% of all notified cases of TB in Malaysia each year are treated, were studied. Data were collected from each patient's medical record. The following information: socio-demographic profiles, clinical presentations and investigation results, treatment medications and duration, patient compliance with therapy, and outcome of therapy response were also enlisted in the standardized data collection sheet. Among 263 patients, 251 (95.4%) of them were diagnosed as non-HIV with tuberculosis patients, whereas, 12 (4.6%) were diagnosed as AIDS (conformed anti-HIV antibody by the Western blot assay) according to CDC criteria 1993. Foreigners who were registered in this center were permanent residents 33 (12.6%), nonimmigrant visitors 230 (87.5%), while no illegal immigrants had been reported at the time of this study. Of 263 eligible participants, we were able to collect the data from their medical records; only 115 of these subjects which showed the duration of staying in Malaysia until the first entry to this center was from 1 to 336 with a median of 60 months. Their countries of origin were mainly from the Asian countries such as Indonesia, Myanmar, Bangladesh, Philippines, Korea, Palestine, and the remaining were from other regions. Majority of them were job-seekers or laborers 153 (58%) and most probably the reason for coming here is due largely to economic differences which this country can give a better and higher standard of living. The others were non-laborers 19 (7%) and unemployed such as housewife and student 91 (34.6%).

Definitions

Disease categories. The following definitions were recommended by the World Health Organization (WHO, 2002):

Case of tuberculosis: a patient in whom tuberculosis has been bacteriologically confirmed, or has been diagnosed by a clinician.

Pulmonary tuberculosis, sputum smear positive (PTB+)

Two or more initial sputum smear examinations positive for acid-fast bacilli (AFB) or one sputum smear examination positive for AFB plus radiological abnormalities consistent with active pulmonary tuberculosis as determined by a clinician, or one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis.*

Pulmonary tuberculosis, sputum smear negative (PTB-)

Case of pulmonary tuberculosis which does not meet the above definition for smear positive TB. In keeping with good clinical and public health practices, diagnostic criteria should include: at least three sputum specimens negative for AFB, and radiographic abnormalities consistent with active pulmonary tuberculosis, and no response to a course of broad spectrum antibiotics, and decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

Categories of patients for registration on diagnosis

New: patient who has never had treatment for TB or took anti-tuberculosis drugs for less than one month.

Relapse: patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

Failure: patient who, while on treatment, is sputum smear positive at 5 month or later during the course of treatment.

Return after default: patient who returns to treatment with positive bacteriology, following interruption of treatment for two months or more.

Transfer in: patient who has been transferred from another tuberculosis register to continue treatment.

Treatment outcome

Cure: patient who is sputum smear negative in the last month of treatment and on at least one previous occasion.

Treatment completed: patient who has completed treatment but who does not meet the criteria to be classified as cured or failure.

Treatment failure: patient who is sputum smear positive at five months or later during treatment.

Died: patients who dies for any reason during the course of treatment.

Defaulter: patient whose treatment was interrupted for 2 consecutive months or more.

Transfer out: patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

Treatment success: sum of patients cured and those who completed treatment.

Multi-drugs resistance to tuberculosis (MDR-TB) defined as resistance to at least 1 and/or 2 important drugs, isoniazid (INH) and/or rifampicin (RF), is a potential to tuberculosis control. The criteria for the monitoring the response to treatment were improvement of clinical symptoms and signs, x-ray or related laboratory findings when compare to baseline one with compliance to the therapy for at least 6 months duration.

Statistical analysis

The data was analyzed by using the statistical software, SPSS version 10 (SPSS Inc, Chicago, III, USA). The data with quantitative variables were expressed by range and mean while the qualitative variables were estimated by frequency and percentage. Statistical analysis was performed using either chi-square test or Fisher's exact test as appropriate. A p-value of <0.05 was regarded as statistically significant.

RESULTS

Table 1 demonstrated the socio-demographic characteristics of the study subjects at the time of diagnosis. The aged range was 14-72 years with a mean of 33.3 ± 9.95 years and the ratio of male to female was 1.5:1. The study subjects were predominant males 158 (60%) and females 105 (40%) where the greater impact of tuberculosis was observed in the young and active ones (up to 34), than middle age (up to 54). Our data showed that a higher percentage of tuberculosis infection in females than their counterpart particularly in their reproductive period from 15 to 44 years. However, no statistical significance was found ($p>0.05$). The significantly higher percentage of these patients were from the Southeast Asian countries (87%) and particularly occurred in single males (47.5%) and married female (71.4%) patients ($p<0.05$). We also found that tuberculosis was more significantly higher in male (64%) and female (50.5%) laborers ($p<0.05$). Moreover, male TB patients were found to be more strongly associated with smoking (44%) as one of the main risk behaviors ($p< 0.05$); from this study, 96% of them had first episode of tuberculosis. Males had higher percentage of history of previous tuberculosis (5%), whereas, females had higher percentage of history of contact with TB patients (15%).

At the time of diagnosis, the four main common presenting symptoms such as fever, cough, loss of appetite and/or weight and sputum production. We further investigated that fever (70%) and cough (90.5%) was shown significantly higher percentage in male than female patients ($p<0.05$). Lymphadenopathy (22%) was found significantly higher in females ($p<0.05$), whereas, the significantly higher percentage of BCG vaccination status (17%) was shown in male patients ($p<0.05$). The radiograph findings was the most useful tool that still routinely available for confirmation of pulmonary tuberculosis and opacity (60% *vs* 58%) was the most frequent abnormal appearance, which showed signs of consistent with tuberculosis in both sexes. Positive for sputum smear and culture for *M. tuberculosis* were shown similar results in this study as illustrated in Table 2.

Overall, pulmonary disease was more commonly occurred in males 149(94%) and the pleura were the most common disseminated form 5 (3.2%) in these patients. Whereas, lymph node 12 (11.4%) and miliary 5 (4.8%) forms were the more common extrapulmonary tuberculosis occurred in females. Interestingly, all 19 patients were in their reproductive years from 14-38 years. Moreover, extrapulmonary tuberculosis was not attributable to HIV infection; being 25 (9.5%) in non-HIV and 3 (1.1%) in HIV-infected patients as presented in Fig 1.

Table 3 further showed the role of treatment and outcome of these patients. 2EHRZ+4RH was the most common anti-tubercular regimen used (90%) in the standard recommended duration of treatment in this study. More males had treatment completed at ≥ 6 and 9 months duration with pulmonary tuberculosis, contrarily; more females had treatment completed at ≥ 6 and 9 months duration with extra-pulmonary tubercu-

Table 1
The socio-demographic characteristics of 263 foreign patients.

Variables	Male (158) No. (%)	Female (105) No. (%)	p-value
Range of age (14 -72 years)	15-70 years	14-72 years	
Mean ± SD	34.1 ± 10.24	32.2 ± 9.42	0.122
Sex ratio (M:F) = 1.5:1			
Age group			0.745
15-24	29 (18.4)	20 (19.1)	
25-34	59 (37.3)	47 (44.8)	
35-44	49 (31.0)	28 (26.7)	
45-54	15 (9.5)	7 (6.7)	
≥55	6 (3.8)	3 (2.9)	
Country of origins			
Asian origin			0.001
Southeast Asia (Indonesia, Myanmar, Philippines, etc)	126 (74)	103 (98.1)	
South Asia (Bangladesh, India, Nepal, etc)	24 (14)	1 (1)	
North Asia (Korea, Japan, etc)	2 (1.2)	-	
Middle-East Asia (Palestine)	-	1 (1)	
Other regions			
South African origin (Ghana, Nigeria, etc)	5 (3)	-	
Caucasian origin (Russia, or European countries)	1 (0.6)	-	
Marital status			0.002
Single	75 (47.5)	30 (28.8)	
Married	83 (52.5)	75 (71.4)	
Address			0.397
Kuala Lumpur	100 (63.3)	61 (58)	
Outsider	58 (36.7)	44 (42)	
Occupation			0.001
Labourer	101 (64)	53 (50.5)	
Non-labourer	15 (9.5)	3 (2.9)	
Unemployed	42 (26.6)	49 (46.7)	
Determining factors			
Smoking			0.001
Yes	70 (44.3)	5 (4.8)	
No	88 (55.7)	100 (95.2)	
Alcohol			0.156
Yes	3 (2)	-	
No	155 (98)	105 (100)	
Smoking and alcohol			0.066
Yes	5 (3.2)	-	
No	153 (96.8)	105 (100)	
Concomitant illness			
Diabetes mellitus			0.554
Yes	12 (7.6)	6 (5.7)	
No	146 (92.4)	99 (93.3)	
HIV-infected status			0.466
Yes	6 (3.8)	6 (5.7)	
No	152 (96.2)	99 (94.3)	
HIV risk factors			0.331
Intravenous drug uses	1 (0.6)	1 (1)	
Homosexual	1 (0.6)		
Heterosexual	4 (2.5)	7 (6.7)	
Not recorded	152 (96.2)	97 (92.4)	
Case category			
New case	150 (95)	103 (98.1)	0.19
History of previous tuberculosis			
Relapse	5 (3.2)	1 (1)	
Return after default	3 (2)	1 (1)	
History of contact with TB patients			0.551
Yes	20 (12.7)	16 (15.2)	
No	138 (87.3)	89 (84.8)	

Table 2
The clinical presentations and investigation results at the first entry.

Clinical presentations	Male (158) No. (%)	Female (105) No. (%)
Symptoms		
Cough[a]	143 (90.5)	86 (82)
Loss of appetite and/or weight	123 (77.8)	75 (71.4)
Fever[a]	111 (70.3)	60 (57.1)
Sputum	95 (60.1)	53 (50.5)
Hemoptysis	58 (36.7)	30 (28.6)
Dyspneoa	20 (12.7)	17 (16.2)
Pain (chest, loin, knee, hip, flank, etc)	17 (10.8)	7 (6.7)
Signs		
BCG vaccination status[a]		
Yes	27 (17.1)	11 (10.5)
No	84 (53.2)	73 (69.5)
Not recorded	47 (30)	21 (20)
Tuberculin skin test (Mantoux test)		
≥10 mm	54 (34.2)	42 (40)
< 10 mm	27 (17.1)	14 (13.3)
Not recorded	77 (48.7)	49 (46.7)
Lymphadenopathy[a]		
Cervical	9 (5.7)	21 (20)
Supraclavicular	2 (1.3)	1 (1)
Mixed (at least 2 sites)	1 (0.6)	-
Lesion or swelling (abscess or lump)	3 (2)	1 (1)
Hoarseness of voice	1 (0.6)	-
ESR		
≥ 10 mm at the first hour	133 (84.2)	97 (92.4)
< 10 mm at the first hour	16 (10.1)	2 (2)
Not recorded	9 (5.7)	3 (3)
X-ray findings		
Not available	1 (0.6)	-
Normal finding	6 (3.8)	14 (13.3)
Abnormalities		
Opacity (one = 61; ≥ 2 lobes = 95)	95 (60.1)	61 (58)
Cavity (one = 19; ≥ 2 lobes = 3)	18 (11.4)	4 (3.8)
Pleural effusion (uni = 14; bilateral = 2)	13 (8.2)	3 (3)
Consolidation	11 (7)	6 (5.7)
Fibrotic changes	5 (3.2)	1 (1)
Calcification	1 (0.6)	-
Pneumothorax	1 (0.6)	-
Miliary	2 (1.2)	5 (4.8)
Others	1 (0.6)	-
Other results (CT scan, MRI, ultra-sound, echocardiogram, PCR and opthalmoscopic examination)	6 (3.8)	2 (2)
Sputum smear positive for AFB		
Positive	74 (46.8)	36 (34.3)
Negative	81 (51.3)	65 (62)
Not done	3 (1.8)	4 (3.8)
Sputum culture positive for *M. tuberculosis*		
Positive	98 (62)	52 (49.5)
Negative	55 (34.8)	46 (43.8)
Not done	5 (3.2)	7 (6.7)
Fluid analysis (smear, culture and biochemical analysis)		
Positive	1 (0.6)	-
Not done	157 (99.4)	105 (100)
Tissue biopsy		
Positive		
Lymph node	6 (3.8)	10 (9.5)
Pleura	4 (2.5)	-
Synovial	1 (0.6)	-
Peritoneum	-	1 (1)
Appendix	-	1 (1)
Not done	148 (93.7)	93 (88.6)

[a]$p<0.05$ for differences between male and female groups by χ^2 test

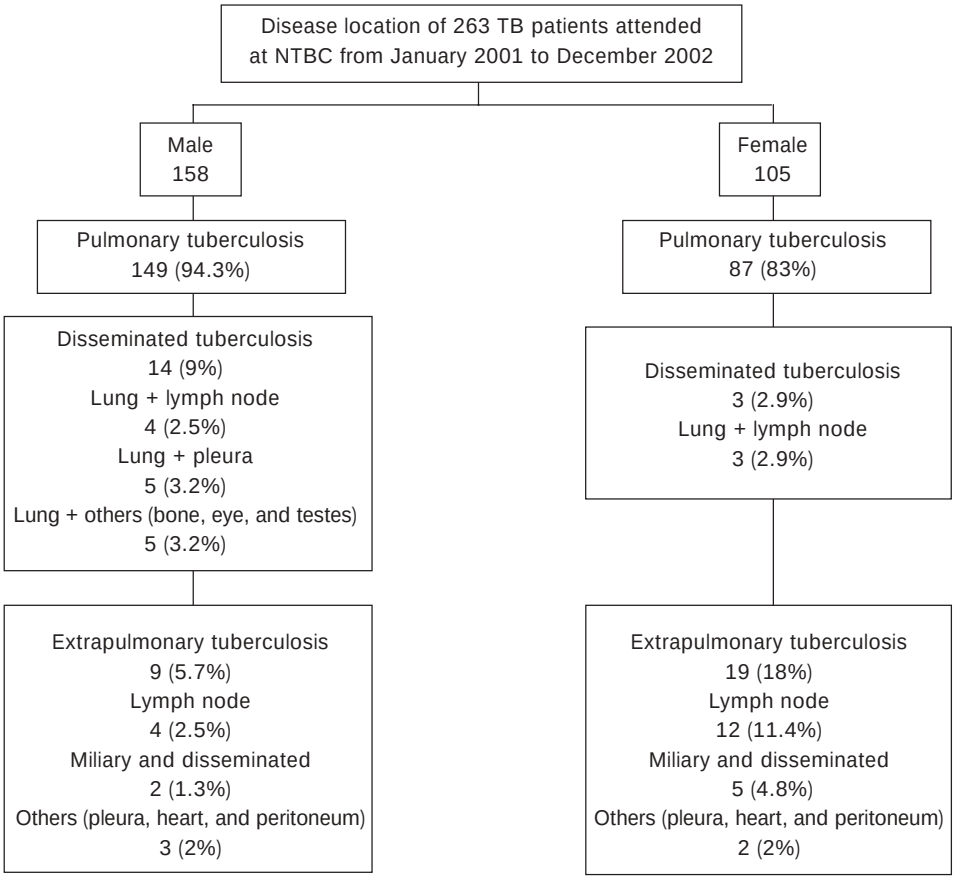

Fig 1–Diagram of disease location among 263 patients.

Table 3
The anti-tubercular therapy and outcome of these patients.

Duration	Male (158)		Female (105)		Total (263) No. (%)
	PTB/disseminated No (%)	EPT No (%)	PTB/ disseminated No (%)	EPT No (%)	
At least 6 months					
≥ 6 months	60 (38)	1 (0.6)	27 (25.7)	2 (2)	90 (34.2)
≥ 9 months	21 (13.3)	1 (0.6)	8 (7.6)	6 (5.7)	36 (13.7)
≥ 12 months	8 (5.1)	4 (2.5)	8 (7.6)	1 (1)	21 (8)
Total	89 (56.3)	5 (3.2)	43 (41)	10 (9.5)	147
Less than 6 months					
Continuing	2 (1.3)	-	1 (1)	-	3 (1.1)
Transfer out	17 (10.8)	2 (1.2)	16 (15.2)	2 (2)	37 (14.1)
Defaulted	41 (26)	2 (0.6)	26 (24.8)	7 (6.7)	76 (29)
Total	60 (38)	4 (2.5)	43 (41)	9 (8.6)	116

Anti-tubercular regimen: 2EHRZ+4RH: 236(89.7%); 2HRZ+4RH: 12(4.6%); 2SHRZ+4RH: 8(3%) and others 7(2.7%) Anti-tubercular drugs' adverse reaction occurred in 7(2.7%) patients; 6 in new cases and 1 in patient with previous history of TB. 6 cases had rifampicin and/or isoniazid, while, 1 case had ethambuthol. No MDR-TB was notified during the time of this study.

losis. Surprisingly, our data showed that more females were non-compliance to their treatment particularly in extra-pulmonary tuberculosis. Anti-tubercular drugs' adverse reaction occurred in 7 patients in which 6 cases had rifampicin and/or isoniazid while 1 case had ethambutol toxicity. No MDR-TB case was notified during the time of this study.

DISCUSSION

We comparatively look at socio-demographic profiles between sexes of these patients. The greater impact of tuberculosis was observed in the young and active ones (up to 34), than middle age (up to 54). The explanations for these are the possibility that immune ability to tuberculosis might be weakened in young generations by some factor(s) such as environmental pollution (Nagayama, 2001) or involving with persistent smoking (Koffi *et al*, 1997; Gajalakshmi *et al*, 2003). The higher percentage of tuberculosis was found in males during the period of 35 to ≥55 years than female patients. Not surprisingly, we observed that male patients had higher percentage of concurrent risk factors such as smoking, diabetes mellitus or a previous history of tuberculosis which predispose to the incidence of tuberculosis. Whereas, our data showed that a higher percentage of tuberculosis infection in females than their counterpart particularly in their reproductive period from 15 to 44 years. Tuberculosis is the leading cause of preventable suffering and death in women of reproductive age, moreover, the possibility that cases of tuberculosis are being under-reporting particularly in developing countries (Connolly and Nunn, 1996; Holmes *et al*, 1998). Other social backgrounds in both sexes were similar in term of race, marital status, present residence, and occupation. Tuberculosis is still highly prevalent among foreign patients, moreover, the coexisting factors play very much important roles in aggravating the course of this disease. Therefore, we propose health personnels should prompt in early diagnosis and strict measures also need to be taken. In addition, providing health education may help to prevent misconceptions and limited knowledge about this contagious disease.

Our study revealed that pulmonary was the main location occurred in both sexes but more common in male than female patients. This finding is consistent with those reported earlier (Wartski, 1993; Chemtob *et al*, 2002) and other investigators who rectified the feasible explanations of the lower incidence of tuberculosis in females (Prince *et al*, 1985; Daniel *et al*, 2003; Tollerud *et al*, 1989; Maini *et al*, 1996; Whitacre *et al*, 1999). This indicates that all pulmonary tuberculosis cases, therefore, respiratory features predominate which included chronic cough, loss of weight and/or appetite, sputum production, and fever should be promptly suspected of the disease with further specific investigations before any anti-tubercular therapy will be given. Whilst, lymphadenopathy was the most common sign and shown much more higher percentage among Asian female than male patients. This coexists with the fact that lymph node is the most common among disseminated or extrapulmonary tuberculosis in younger age group as encountered in this study and also well documented in others (Kok-Jensen and Viskum, 1994; Cowie and Sharpe, 1997; 1998; Kempainen *et al*, 2001). Our experience showed that extrapulmonary tuberculosis was not attributable to HIV infection which is in supported by previous reported studies (Kok-Jensen and Viskum, 1994; Ozbay and Uzun, 2002; Noertjojo *et al*, 2002) Hence, clinicians should be aware of the various forms of extrapulmonary tuberculosis (Alrajhi and Al-Barrak, 2002) and take serious action when patient presents with unusual features of tuberculosis. As investigation is concerned, we also found patients with positive tuberculin skin test (≥10 mm) were shown higher percentage in females. Therefore, it is still feasible to use this parameter as one of the indicators assessing the risk for *M. tuberculosis* infection in women which can have serious repercussions for families and households (Hudelson, 1996). Since majority are PTB patients, x-ray finding is absolutely considered to be one of the most important tool for the early confirmation but it needs accurate interpretation. Our study showed the opacity appearance and mainly involved in the upper lobe of lung in the chest x-ray finding was the most frequently found in both sexes. This supports the idea of screening for tuberculosis that is adopted as a policy

particularly among foreign-born population who enter this country for the purpose of working or study. These guidelines ultimately lead to early diagnosis and preventive therapy among these patients.

Our data also showed that a higher percentage of overall cure or treatment success in males and particularly at the standard 6 months regimen seen in patients with pulmonary tuberculosis. From this study, it indicates good implication for foreign workers whom are majority, including their organizations aware of the importance of this disease in term of the perception and knowledge about tuberculosis and tuberculosis services. Whereas, females showed a higher percentage of cure or treatment success at ≥ 9 months in mainly lymph node and miliary/ disseminated as extrapulmonary tuberculosis. This could be explained either extrapulmonary tuberculosis needs a longer treatment due the matter of fact to its complicated pathogenicity. Moreover, as women's health has an impact on both their families and the economy, the incorporation of sex difference in TB control programs could yield more beneficial outcomes (Uplekar *et al*, 2001). Surprisingly, a higher percentage of females defaulted treatment in extrapulmonary tuberculosis and contrarily in pulmonary tuberculosis than male patients. The main reasons are; half of these patients (38/76) were returning back to their home countries for further treatment which considers quite a common situation that we encountered in this study, poor compliance due in particular to its side effects of ATT, which were detected among 7 patients, 1 patient was transferred to other hospital, 1 patient was absconded during hospitalization and the remaining were shown unspecific reasons. Even though we take all these explanations in to account, however, the foreigner's data must be taken in the national tuberculosis surveillance system and control activities for foreigners need to be strengthened (Yoshiyama *et al*, 1999). The result of patients who developed MDR-TB had not been notified in this study, however, there were various reports of MDR-TB by other investigators (Kallich, 1991; Schaberg *et al*, 1996; Kobashi *et al*, 1998; Weis *et al*, 2001). Resistance of *Mycobacterium tuberculosis* (MTB) strains is an increasing problem worldwide (Schaberg *et al*, 1996). Moreover, MDR-TB had contributed to result in more frequent and longer hospitalizations (Weis *et al*, 1999). Therefore, we suggest that directly observed therapy should be strictly enrolled with close monitoring to all patients with defaulted treatment or with result of anti-tubercular drug' adverse reactions whom are at high risk in developing drug resistance.

In conclusion, our data showed there are sex differences in various aspects of tuberculosis in Malaysia where a country with the intermediate level of tuberculosis and adequate infrastructures. However, the attention should be highlighted particularly in the foreign-born population whom may pose the significant increasing the incidence of tuberculosis in the host countries and the potential impact on national tuberculosis control program.

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