Socio-Demography and Clinical Factors Related with Pulmonary Tuberculosis Severity among Children and Adolescents in Kelantan from 2012 to 2015

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ABSTRACT: An escalating trend of severe pulmonary tuberculosis among children and adolescents would substantially contribute to mortality among these groups. This study aimed to determine the association of socio-demography and clinical factors with pulmonary tuberculosis severity among children and adolescents in Kelantan from 2012 to 2015. This study was a comparative cross-sectional study between mild pulmonary tuberculosis and severe pulmonary tuberculosis patients according to chest radiograph among children and adolescents using Tuberculosis Information System as a source population. All notified cases that fulfilled the inclusion and exclusion criteria were included in the study. Descriptive statistics, simple and multiple logistic regressions were used for data analysis. Out of 456 tuberculosis cases among children and adolescents, 85.1% were pulmonary tuberculosis cases. The mean age for children and adolescents with severe pulmonary tuberculosis was 15.79 and majority of them were female (55.1%), Malay (89.8%), literate (90.8%) and resided in rural area (80.6%). In terms of clinical factors, none was Human Immunodeficiency Virus (HIV) positive, 23.5% smokers, 19.4% had no Bacillus Calmette-Guerin (BCG) scar and 72.4% had positive sputum smear. After adjusting the confounders by multiple logistic regression, cigarette smoking [AOR 1.43; 95% CI: 1.21, 3.61; *p*-value = 0.03], positive sputum Acid-Fast Bacilli (AFB) smear [AOR 2.32; 95% CI: 1.29, 4.13; *p*-value = 0.004] and absence of BCG scar [AOR 1.24; 95% CI: 1.12, 8.04; *p*-value = 0.002] were significantly associated with severe pulmonary tuberculosis infection among children and adolescents. The study provides important criteria of children and adolescents to be prioritized for tuberculosis screening and early diagnosis in the tuberculosis control program.

Keywords: pulmonary tuberculosis, severity, children, adolescents.

Introduction

Tuberculosis is an airborne bacterial disease and remains a menace to the nation and society globally. In 2015, there were approximately 10.4 million new incidences of tuberculosis cases worldwide, of which 5.9 million were men, 3.5 million were women and 1 million were children according to World Health Organization (WHO). According to Malaysia Child Act (2001), children are defined as persons below the age of eighteen. Meanwhile, WHO defined adolescents as young people between the age of 10 and 19 years old (WHO, 2017a). In Malaysia, recent report from Ministry of Health (MOH) depicted that the proportion of tuberculosis cases among children and adolescents in Malaysia range between 17% and 20% out of total tuberculosis cases with an increasing trend from year 2010 to 2015 (MOH, 2016). Meanwhile, exclusively for the state of Kelantan, the proportion of tuberculosis cases among children and adolescents range from 1% to 3.01% out of total cases from year 2000 to 2015, also with an increasing trend (Kelantan State Health Department, 2016).

There are very few studies regarding the prevalence of severe pulmonary tuberculosis among children and adolescents based on chest radiograph in Malaysia and worldwide. A cross-sectional study in tertiary care hospital in Karachi found that out of 325 children under 5 year old with tuberculosis, 40 (12.3%) cases had severe pulmonary tuberculosis according to chest radiograph (Zafar, 2014). Meanwhile, a cohort study on 87 adolescents aged 12 to 18 years old with tuberculosis in Worcester, South Africa found that 8 (9%) cases had severe pulmonary tuberculosis with abnormal changes on chest radiograph (Mahomed *et al.*, 2013).

This study aimed to determine the association of socio-demography and clinical factors with pulmonary tuberculosis severity among children and adolescents in Kelantan from 2012 to 2015. Among the known socio-demographic factors contributing to severe pulmonary tuberculosis infection among children and adolescents are older children (Du Rant *et al.*, 1999; Moyo *et al.*, 2010), female gender (Karim *et al.*, 2007), low literacy or education level (Hoa *et al.*, 2003;

Maingi *et al.*, 2014) and resident of rural area (Cheng *et al.*, 2005). Whereas the known clinical factors associated with severe pulmonary tuberculosis infection include cigarette smoking (Altet-Gomez *et al.*, 2005; Leung *et al.*, 2004), positive HIV status (Burman *et al.*, 2007), absence of BCG scar (Tidjani *et al.*, 1986) and positive sputum AFB smear (Ralph *et al.*, 2010).

Chest radiography is a rapid imaging technique that allows lung abnormalities to be identified. Chest radiograph is used to diagnose conditions of the thoracic cavity, including the airways, ribs, lungs, heart and diaphragm. Chest radiograph has historically been one of the primary tools for detecting tuberculosis, especially pulmonary tuberculosis. Chest radiograph has high sensitivity for pulmonary tuberculosis and thus it is a valuable tool to identify tuberculosis as a differential diagnosis for patients, especially when the radiograph is read to identify any abnormality that is consistent with tuberculosis. Moreover, chest radiograph is useful in diagnosing pulmonary and extrapulmonary tuberculosis in children in combination with history, evidence of tuberculosis infection and microbiological testing (WHO, 2016).

The capability of chest radiograph to sensitively and specifically detect severe pulmonary tuberculosis cases depends on the intensity of the disease presentation, which in turn is influenced by a range of other factors (Van Cleeff *et al.*, 2005). One of the major factors is the immune status of the patient. In mild immunocompromised tuberculosis patients, the appearance of chest radiograph is often classical with cavitation and upper lobe infiltrates, while in severely immunocompromised tuberculosis patients, the appearance is often atypical. Other factors contributing to the severity of the disease on chest radiograph are delay in diagnosis and the gender of the patient (Harries *et al.*, 2004).

Materials and Methods

This study applied a cross-sectional study design based on retrospective record review and was conducted within three months period starting from January to March 2017 in Tuberculosis and Leprosy Control Unit, Kelantan State Health Department.

The reference populations were all children and tuberculosis patients in Kelantan and the study samples were children and adolescent pulmonary tuberculosis patients in Kelantan registered in Tuberculosis Information System (TBIS) from 2012 to 2015 who fulfilled study inclusion and exclusion criteria. In this study, the inclusion criteria were confirmed cases of tuberculosis who were notified to respective District Health Offices in Kelantan and registered in TBIS from 1st January 2012 to 31st December 2015, diagnosed as pulmonary tuberculosis and aged of 1 year old to 19 years old. All extrapulmonary tuberculosis cases without concomitant pulmonary tuberculosis were excluded.

The sample size was calculated for each variable of associated factors for severity of pulmonary tuberculosis infection among children and adolescent using Power and Sample Size calculation software as well to compare two independent proportions. The largest estimated sample for each group was 144 using the proportion of mild or non-severe pulmonary tuberculosis children and adolescents in HIV positive patient 0.17 (Giri *et al.*, 2013). The estimated proportion of 0.06, 5% type 1 error, 80% power and additional 10% missing data were applied in the data analyses.

Data were collected from Kelantan TBIS. TBIS is an online registry set up by the Ministry of Health for surveillance purpose of tuberculosis disease in Malaysia. The retrieved information includes socio-demography, co-morbidities, presence of BCG scar, sputum AFB smear result, HIV status, and chest radiograph findings.

Operational definitions

In this study, pulmonary tuberculosis severity is classified based on chest radiograph finding. The severity is divided into two groups which were mild (chest radiograph with no lesion or minimal lesion) and severe (chest radiograph with moderate and far advanced lesions).

No lesion is defined as chest radiograph with no lesion or cavity on any lung field. Minimal lesion is defined as chest radiograph with slight lesions with no cavity in which the lesion is confined to small parts of one or both lungs but the total extent does not exceed the upper zone. Moderate advanced lesion is defined as chest radiograph with involvement of one or both lungs

and far advanced lesion is defined as more extensive chest radiograph lesion than the moderate advanced lesion (MOH, 2012).

Pulmonary tuberculosis for this study includes smear positive and negative pulmonary tuberculosis as well as extrapulmonary tuberculosis with concomitant pulmonary tuberculosis (MOH, 2012).

Statistical analysis

Statistical Package for Social Science (SPSS) version 22.0 statistical software was used for data entry and analysis. Descriptive statistics with mean and standard deviation (SD), frequency and percentages were calculated. Simple and multiple logistic regression analyses were used to determine factors associated with tuberculosis infection among children and adolescents. A *p*-value of less than 0.05 was considered statistically significant.

Results

Out of 456 total tuberculosis cases among children and adolescents registered in TBIS, 356 (78.0%) cases were pulmonary tuberculosis, 68 (14.9%) cases were extrapulmonary tuberculosis and another 32 (7.1%) cases were pulmonary tuberculosis with concomitant extrapulmonary tuberculosis. Based on the inclusion criteria, only pulmonary tuberculosis and pulmonary tuberculosis with concomitant extrapulmonary tuberculosis cases were included in this study and hence, the total samples regarded as pulmonary tuberculosis were 388 cases.

The severity of pulmonary tuberculosis was based on chest radiograph results done prior to the diagnosis of tuberculosis. Out of the 388 samples, majority of chest radiographs had minimal lesion (69.8%) followed by moderate advanced lesion (23.5%), no lesion (4.9%) and lastly, far advanced lesion (1.8%). Those with no lesion and minimal lesion on chest radiographs were grouped as mild pulmonary tuberculosis infection (290 cases; 74.7%), whereas moderate and far advanced lesion were categorized as severe pulmonary tuberculosis infection (98 cases; 25.3%).

From the total 388 samples with pulmonary tuberculosis, a total of 242 samples were included in this study in which 144 samples obtained via simple random sampling for mild tuberculosis and only 98 samples available for severe tuberculosis. Majority of children and adolescents with severe pulmonary tuberculosis were female, Malay, literate and rural residents. Details regarding socio-demographic characteristic are shown in Table 1.

Table 1: Socio-demographic characteristics of pulmonary tuberculosis cases among children and adolescent (n=242)

Factors	**Pulmonary tuberculosis severity, frequency (%)**	
	Mild (n=144)	**Severe (n=98)**
Age*	16.19 (3.11)	15.79 (4.24)
Gender		
Male	65 (45.1)	44 (44.9)
Female	79 (54.9)	54 (55.1)
Ethnicity		
Others	11 (7.6)	10 (10.2)
Malay	133 (92.4)	88 (89.8)
Literacy		
Literate	133 (92.4)	89 (90.8)
Illiterate	11 (7.6)	9 (9.2)
Location		
Non-urban	119 (82.6)	79 (80.6)
Urban	25 (17.4)	19 (19.4)

*Mean (SD)

Majority of children and adolescents with severe pulmonary tuberculosis were non-smoker, HIV negative, presence with BCG scar, and positive pre-treatment sputum smear. Details regarding clinical characteristic are shown in Table 2.

Table 2: Clinical characteristics of pulmonary tuberculosis cases among children and adolescents (n=242)

Factors	Pulmonary tuberculosis severity, frequency (%)	
	Mild (n=144)	**Severe (n=98)**
Smoking		
No	122 (84.7)	75 (76.5)
Yes	22 (15.3)	23 (23.5)
HIV infection		
No	140 (97.2)	98 (100.0)
Yes	4 (2.8)	0 (0.0)
BCG Scar		
Present	136 (94.4)	79 (80.6)
Absent	8 (5.6)	19 (19.4)
Sputum smear		
Negative	68 (47.2)	27 (27.6)
Positive	76 (52.8)	71 (72.4)

In the simple logistic regression analysis, there was no significant association between socio-demographic factors with severe pulmonary tuberculosis among children and adolescents. For clinical characteristics, cigarette smoking, absence of BCG scar and positive sputum smear results showed statistically significant association with severe pulmonary tuberculosis. Details regarding factors associated with severe pulmonary tuberculosis among children and adolescents by simple logistic regression are shown in Table 3.

Table 3: Factors associated with severe pulmonary tuberculosis among children and adolescents in Kelantan 2012-2015 by simple logistic regression (n=242)

Factors	Crude OR (95% CI)	Wald statistics (df)	*p*-value
Age	0.97 (0.90,1.04)	0.75 (1)	0.388
Gender			
Male	1.00		
Female	1.01 (0.60,1.69)	0.001 (1)	0.971
Ethnicity			
Others	1.00		
Malay	0.73 (0.29,1.79)	0.48 (1)	0.488
Literacy			
Literate	1.00		
Illiterate	1.22 (0.49,3.07)	0.18 (1)	0.669
Location			
Urban	1.00		
Rural	1.15 (0.59,2.22)	0.16 (1)	0.688
HIV infection			
No	1.00		
Yes	0.00 (0.00,0.00)	0.00 (1)	0.999
BCG Scar			
Present	1.00		
Absent	1.76 (1.27,4.97)	10.03 (1)	0.002
Sputum smear			
Negative	1.00		
Positive	2.35 (1.36,4.08)	9.27 (1)	0.002

Multiple logistic regression was used to determine the significant associated factors. All significant variables with p-value of less than 0.25 from univariable analysis and clinically important variables were chosen for multiple logistic regression analysis. Details regarding factors associated with severe pulmonary tuberculosis among children and adolescents by multiple logistic regression were shown in Table 4.

Table 4: Factors associated with severe pulmonary tuberculosis among children and adolescents in Kelantan 2012-2015 by multiple logistic regression (n=242)

Factors	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Wald statistics[b] (df)	*p*-value[b]
Smoking				
No	1.00	1.00		
Yes	1.70 (1.19,3.26)	1.43 (1.21,3.61)	2.61 (1)	0.03
Sputum smear				
Negative	1.00	1.00		
Positive	2.35 (1.36,4.08)	2.32 (1.29,4.13)	8.09 (1)	0.004
BCG scar				
Present	1.00	1.00		
Absent	1.76 (1.27,4.97)	1.24 (1.12,8.04)	9.84 (1)	0.002

[a]Simple logistic regression, [b]Multiple logistic regression
Forward LR method was applied
No multicollinearity and no interaction were found
Hosmer Lemeshow test, p-value=0.533
Classification table 74% correctly classified
Area under Receiver Operating Characteristics (ROC) curve was 66.1%

Discussions

This is a baseline study to determine the association between socio-demographic and clinical factors with severe pulmonary tuberculosis infection among children and adolescents in Kelantan.

The result of this study showed that children and adolescents who were smokers were 1.43 times more likely to develop severe pulmonary tuberculosis infection, compared to non-smoking group, after other confounders were controlled in multivariable analysis. Leung *et al.* (2004) reported similar finding through a study in Hong Kong in which smoking patients were 1.2 times more likely to have moderate or extensive tuberculosis lesion on chest radiographs which indicated severe pulmonary tuberculosis infection. Findings of this study are also in line with another study conducted in Spain which reported that smoking patients were 1.9 times more

likely to developed severe pulmonary tuberculosis (Altet-Gomez *et al.*, 2005). Smoking increases the risk of rapid disease progression and severity through a few mechanisms. One of the mechanisms states that smoking reduces the defence on the surface of the respiratory apparatus, alters the mucociliary apparatus through cell destruction and dysfunction, exerts cilio-static and cilio-toxic effects and reduces lysozyme A activity. As a result, germs and toxic substances reach the alveolar tissue in greater numbers. Furthermore, smoking also produces alterations in both natural and acquired cell immunity, affecting macrophages and leukocytes. The effect of oxidative stress is particularly important, as it induces apoptosis in both activated and non-activated macrophages, favouring the multiplication of the bacilli, in a chronic process (Altet-Gomez *et al.*, 2005; Sopori, 2002; Stämpfli and Anderson, 2009).

This study found that children and adolescents without BCG scars were 1.24 times more likely to develop severe pulmonary tuberculosis, compared with those with BCG scars, after other confounders were controlled in multivariable analysis. Findings of this study are in line with an unmatched case-control hospital-based study in India among Indian children (Kumar *et al.*, 2005). They reported that children without BCG scar have almost two times higher risk of getting severe tuberculosis as compared to those children with BCG scar (AOR 1.98; 95%CI 1.09,3.57; p=0.023). It is reported that the BCG efficacy in preventing severe tuberculosis such as TB meningitis ranges from 52%-84% (Thilothammal *et al.*, 1996). As the immune response against *Mycobacterium tuberculosis* is less effective among children and adolescents, dedicated vaccination against tuberculosis using BCG in neonates has led to a reduction in incidence of severe childhood tuberculosis and deaths including miliary tuberculosis and tuberculous meningitis (Waako *et al.*, 2013). Moreover, recent studies have suggested that BCG vaccination may have a non-specific beneficial effect on infant survival and that a BCG scar may be associated with lower child mortality (Roth *et al.*, 2005; Tidjani *et al.*, 1986). Therefore, absence of BCG scar could be related to weakened immunity defense against tuberculosis. However, a study in India found that the absence of BCG scar may not be an indicative of the absent immune response to BCG or indicative of not receiving BCG. The study showed no difference in leukocyte migration levels in young BCG vaccinated children between those who developed BCG scar and those who did not (Mahomed *et al.*, 2013).

We also found significant association between pre-treatment AFB sputum smear results with severe pulmonary tuberculosis infection. Children and adolescents with positive pre-treatment AFB sputum smear were 2.32 times more likely to develop severe pulmonary tuberculosis, as compared to those with negative pre-treatment AFB sputum smear, after controlling for other confounders in multivariable analysis. Koh *et al.* (2006) reported that patients with AFB smear positive sputum were significantly associated with extensive lesion on chest radiographs, indicating severe pulmonary tuberculosis. A study in Papua, Indonesia was done to see the association between sputum AFB smear status and chest radiograph changes as a predictor for severity of tuberculosis. They reported that cavitary disease on chest radiograph at diagnosis was significantly associated with a higher baseline AFB density in sputum (p=0.007) (Ralph *et al.*, 2010).

Sputum positive patients are capable of transmitting infection and those whose sputum is positive on direct microscopy are the most likely to infect their contacts. The number of bacilli depends on the extent of the lesion or the presence of cavitation of lungs in case of pulmonary form of tuberculosis. The larger the cavity or lesion, the larger the amount of bacilli present. There is smaller number of bacilli in an extrapulmonary lesion. Thus, the grading of a positive smear reflects the extent of lesion in a particular patient or size of cavitation as well as being directly proportional to the infectiousness of the case (Rajpal *et al.*, 2002).

Conclusions

As a conclusion, this study had demonstrated that the significant associated factors for severe pulmonary tuberculosis were tobacco smoking, absence of BCG scar and positive pre-treatment AFB sputum smear. By delineating these possible significant risk factors for tuberculosis infection and its severity can assist and guide health authorities to design a better and comprehensive plan for the national tuberculosis control programme, focusing more attention towards children and adolescents group without marginalizing them. Inadvertently, dynamic transmission of tuberculosis in our community could be mitigated.

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