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Comparison of pediatric pulmonary and extra-pulmonary tuberculosis in Singapore

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COMPARISON OF PEDIATRIC PULMONARY AND EXTRA-PULMONARY TUBERCULOSIS IN SINGAPORE

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ABSTRACT

Background: Tuberculosis (TB) is a major cause of mortality and morbidity in the world. Each case represents on-going transmission and has a significant public health burden. We aim to (i) examine the clinical profile of paediatric TB and (ii) compare pulmonary TB (PTB) with extra-pulmonary TB (EPTB).

Methods: Retrospective study of patients admitted to KK Women's and Children's Hospital, Singapore, from January 2008 to September 2017 for active TB disease. We compared clinical characteristics and outcomes of patients with PTB and EPTB. Outcome of interest was recovery rate.

Results: Seventy-five patients were diagnosed as active TB; 65% PTB and 35% EPTB. Patients with EPTB were more likely to be younger [Median age 5.1 (interquartile range (IQR) 1.2, 10.2) vs 10.1 (IQR 3.5, 13.5) years], immunodeficient (34.6% vs 6.1%), have lower haemoglobin count [11.5 (IQR 10.2, 11.9) vs 12.0 (IQR 10.5, 13.9) g/dL] and lower recovery rate (26.9% vs 57.1%). Using positive TB culture as the gold standard, T-Spot had higher sensitivity and specificity than tuberculin skin test (TST) and combined T-Spot and TST. Overall mortality rate was 8.0%; CNS TB alone higher than PTB (28.6% vs 4.1%).

Conclusion: Extra-pulmonary TB is more common in the younger age group and is associated with higher mortality and sequelae rates.

INTRODUCTION

Tuberculosis (TB) remains a major cause of morbidity and mortality in the world. Following the introduction of Singapore Tuberculosis Elimination Programme in 1997; the incidence of TB declined from 57 per 100,000 residents in the 1990s to a low of 35 per 100,000 residents in 2007. In 2016, the age-standardized incidence rate of TB was 38.7 per 100,000 residents in Singapore; children below 19 years old contributed only 2.1% of the total TB population. The majority (83.5%) of cases had pulmonary TB (PTB) with or without extra-pulmonary involvement, while the remainder (16.5%) had exclusively extra-pulmonary TB (EPTB) (1).

The presentation of TB in children can range from non-specific symptoms to severe clinical presentation; which makes diagnosis challenging. Although PTB is the most common involvement, all other organs can be involved as well (2, 3). Globally in 2014, almost 10 million people developed TB, of which EPTB represented almost 15% of the overall TB (4). In adults, proportion of EPTB to PTB has increased due to a decrease in PTB rates (5). However, little is known of the global impact of pediatric EPTB due to difficulties in pediatric TB case detection and low notification rates (6). The last published review of pediatric TB in Singapore was by Freda M. Paul in 1967, which focused on the fatality of tuberculous meningitis. With the changing demographics in Singapore, a new review of pediatric TB is needed (7, 8). The aims of this study were to (i) examine the clinical profile and treatment outcomes of pediatric TB and (ii) compare PTB with EPTB.

METHODS

Setting

Kandang Kerbau (KK) Women's and Children's Hospital (KKH) is the largest tertiary pediatric hospital in Singapore with approximately 350 pediatric beds. We collected data of all patients who were admitted for TB work-up in KKH from January 2008 to September 2017. Approval was obtained from the centralized institution review board of Singhealth Research.

Patient identification and data collection

A patient list with the code tuberculosis was generated using International Classification of Disease [ICD9CM or ICD10AM (from 2012 onwards)]. Patients who were treated for active TB were included, latent TB cases were excluded. Data pertaining to demographic profile, clinical presentation, investigations and treatment of selected cases were collected from case notes, electronic records and the infectious disease database.

Case definitions

Both microbiologically proven cases and non- microbiologically proven cases were included. Microbiologically proven cases were defined as those with positive TB culture and/or TB polymerase chain reaction (PCR). Non-microbiologically proven cases were defined as those with negative TB culture or PCR but positive TB smear, tuberculin skin test, interferon gamma release assay (IGRA) in the presence of clinical diagnosis of TB or positive CXR. EPTB was defined as any active TB case involving organs other than lungs and pleural. Multi-organ TB was defined as active TB involving 2 or more organs and was considered EPTB.

Close contact was defined as living in the same household or in frequent contact with smear

positive pulmonary TB case. Immunodeficiency was either primary immune disorders or secondary to an underlying disease or immunosuppressive drugs. Definitions of symptoms were adapted from the South African Guidelines 2013 (9);

- Significant cough was defined as cough duration of ≥ 14 days
- Significant fever was defined as temperature ≥ 38°C for ≥ 14 days
- Significant weight loss was defined as ≥ 1kg for ≥ 1 month
- Fatigue: Patient's or parents' complaint of reduced playfulness or lethargy

In our center, T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom) is the preferred type of IGRA used for children ≥ 2 years old because of the lower rate of indeterminate results compared to QuantiFERON-TB Gold and QuantiFERON-TB In-tube (10). Tuberculin skin test (TST) might be performed when T-spot was not available (i.e. out of office hours). Positive TST was defined as reading of ≥ 10mm at 48 hours. All patients had CXR performed and reported by in-house radiologists. All our patients had microbiological investigations. Consecutive fluid specimens were sent for acid-fast bacilli (AFB) smear and culture.

The TB culture method was by the automated MGIT960 system for liquid growth and Lowenstein Jensen slants for solid growth (10, 11).

Statistical analysis

Analysis was carried out using SPSS version 19 (IBM, Armonk, New York, USA). For categorical data, we performed chi-square tests or Fisher's exact test when cell sizes were less than 5 for univariate analysis. For continuous data, we performed Student T test for parametric data or Mann-Whitney U test for non-parametric data. A P value of <0.05 was statistically significant.

RESULTS

Seventy-five patients were included; 49 (65.3%) had PTB and 26 (34.7%) had EPTB. Further breakdown of EPTB: 5 (6.7%) lymphatic; 7 (9.3%) central nervous system (CNS); 1 (1.3%) pericardial, 2 (2.7%) gastro-intestinal; 1 (1.3%) eye, 2 (2.7%) musculoskeletal and 8 (10.7%) multi-organ TB involving ≥2 systems. Of the multi-organ TB: 2 (2.7%) had involvement of pulmonary and CNS, 1 patient (1.3%) each had involvement of CNS and lymphatics; GIT and MSK; pulmonary and GIT; pulmonary and lymphatics; GIT, lymphatics and MSK; GIT and pulmonary. The majority had no known TB contact (n=47, 62.7%) whereas 26 (34.7%) had household contact and 2 (2.7%) school contact. Table 1 describes baseline characteristics of all patients. Significant fever, cough and weight loss were the most common clinical presentation of TB. However, only 20 (26.7%) patients presented with ≥ 2 significant symptoms. Twelve (16.0%) patients were immunodeficient: 4 human immunodeficiency virus infection, 2 severe combined immunodeficiency, 2 malignancies (1 patient had medulloblastoma and 1 had neuroblastoma) on chemotherapy, 1 Ebstein Barr Virus-related haemophagocytic lymphohistiocytosis, 1 mendelian susceptibility to mycobacterial disease, 1 juvenile idiopathic arthritis on biologics and 1 Crohn's disease on immunosuppressant.

Abnormal CXR was found in 51 patients (68.0%) with the following changes: pulmonary infiltrates (n=24,32.0%), hilar adenopathy (n=7,9.3%), military (n=4,5.3%), lobar collapse (n=3, 4.0%), pleural changes (n=2, 2.7%), cavitation (n=2, 2.7%), widened mediastinum (n=1,1.3%) and combination of findings (n=8,10.7%). Patients with PTB were more likely to have abnormal CXR compared to those with EPTB ($p<0.01$). The majority of patients (n=45, 60.0%) had

microbiologically proven TB. Twenty (26.7%) had at least one positive AFB smear and 39 (52%) had at least one positive TB culture. TB PCR was sent in 55 patients (73.3%); 26 (47.3%) were positive and 29 (52.7%) were negative.

Comparing EPTB with PTB (Table 2), patients with EPTB were younger [Median age 5.05 years (interquartile range (IQR) 1.23, 10.23) vs 10.10 years (IQR 3.47, 13.45), p=0.03], more likely to be immunodeficient (p<0.01) and had lower hemoglobin (Hb) level [Median Hb level 11.15 g/dL (IQR 10.23, 11.90) vs 12.00 g/dL (IQR 10.50, 13.85), p=0.01]. BCG vaccination rate was lower in the EPTB group compared to the PTB group (76.0% vs 89.3%, p=0.14). All patients received isoniazid and rifampicin with pyrazinamide and/or ethambutol. Patients with extra-pulmonary TB needed longer duration of treatment compared to those with pulmonary TB [Median 12 (IQR 9, 12) vs 6 (IQR 6, 9) months, p<0.01]. Patients who were immunodeficient were also treated for a longer period compared to immunocompetent patients [Median 12 (IQR 9.8, 12.0) vs 6 (IQR 6, 9) months, p<0.01].

Overall mortality rate was 8.0% with higher mortality rate of CNS TB than pulmonary TB (28.6% vs 4.1%, p=0.02). Mortality rate for EPTB was 15.4%. PTB patients were more likely to fully recover compared to EPTB (57.1% vs 26.9%, p=0.01). Sequelae were found in 9 PTB (18.4%, bronchiectasis 3, restrictive lung disease 2, bronchus compression 3 and complications from underlying conditions 2), 9 EPTB (34.6%, intestinal perforation 1, kyphosis 1, CNS infarct 1, seizures 2, developmental delay 2, complications from underlying conditions 2) and 4 CNS TB (57.1%, seizures 2, developmental delay 2).

T-Spot was performed in 41 (54.7%) patients: 32 (78.0%) positive, 6 (14.6%) negative and 3 (7.3%) indeterminate. TST was performed in 31 patients (41.3%): 26 (83.9%) positive and the

median reading was 14.5 mm (IQR 11, 20). Thirteen (17.3%) patients had both positive T-Spot and TST. Table 3 describes the sensitivity and specificity of AFB smear, TB PCR, IGRA and TST in predicting active TB infection using positive TB culture as the reference standard for active TB disease. The sensitivity and specificity of T-Spot for active TB disease were higher than that of TST but similar to combined T-Spot and TST.

DISCUSSION

Our study compares the demographics, clinical spectrum and investigation results of PTB and EPTB.

The median age of patients with EPTB was significantly younger than PTB [Median age 5.05 vs 10.10 years, p=0.03], similar to another paediatric TB study (12). EPTB had lower recovery rate, high mortality, relapse and sequelae rates compared to PTB. Similar to other studies, this implied that younger children had higher risk of serious TB (13, 14). Mortality rate for CNS TB was significantly higher than pulmonary TB (28.6% vs 4.1%, p=0.02). The mortality of TB meningitis from our review had decreased drastically from a peak of 60% in 1955 (7, 8). Mass BCG vaccination campaign, implemented in 1957, was one of the key interventions that led to a marked decrease in TB mortality rates, especially EPTB and for children < 5 years old (15, 16). Similar to a retrospective pediatric study in China, more patients had no BCG vaccination in the EPTB group (76.0% vs 89.1%) even though the difference was not significant (12). This finding suggests that children who received BCG vaccination might have less chance of contracting EPTB. Clinical trials are needed to further ascertain the protectiveness of the vaccination towards EPTB.

Children with TB rarely present with classical symptoms as seen in a survey from a high burden community (17). This is similar to our study in which only 26.7% of patients presented with ≥ 2 out of 5 significant symptoms stated by South African Society for Pediatric Infectious Diseases (9). Marais et al stated that the index of suspicion should be increased when symptoms such as

prolonged cough of more than 2 weeks, significant weight loss and fatigue exist together with positive TB contact (18). Four (5.3%) of our patients with TB had ≥ 2 significant symptoms and positive contact history. Nevertheless, available scoring systems should not be used for predicting pediatric TB infection as they lack sensitivity and specificity (19).

Sixty-eight percent of patients had abnormal CXR, which was higher than a large-scale multicenter center study conducted in India (20). This can be explained by significant variation between radiologists when interpreting pediatric CXR (21). Moreover, CXR had a high sensitivity but low specificity for detecting active TB as many radiological changes seen in TB could be present in other infections (22).

A positive microbiological culture remains the gold standard for diagnosis of active TB but is often limited by the prolonged turnover time. In this study, the percentage of patients with eventual positive TB culture (49.0% and 57.5%) was more than those with ≥1 positive AFB smear (26.5% and 28.0%) in both the PTB and EPTB group, which could lead to a delay in identification and treatment of active TB disease. Our higher TB culture rates compared to 15.7% in China and 34% in USA could be due to more aggressive sampling methods or different culture methods (12, 23).

Immunological investigations such as TST and IGRA can aid in the diagnosis of TB but each has its own limitations. In children < 4 years old, T-Spot is preferred as it has lower rate of indeterminate results compared to QuantiFERON-TB test (24). While IGRA and TST are good predictors of latent TB infection, their sensitivity for active TB infection are much more limited (25, 26). However, if we considered positive TB culture as the reference standard for diagnosis of active TB, T-spot had the highest sensitivity followed by TB PCR and TST in this study

(85.7%, 74.1% and 73.3% respectively). These findings were similar to a meta-analysis that consisted of predominantly adult populations (27). In contrast to our findings, a retrospective study of active TB cases in 6 large pediatric centers in United Kingdom found out that IGRA was no more sensitive than a TST of >15mm in predicting active TB infection (28). This could be due to increased threshold for specificity by increasing the cut-off for TST from 10mm to 15mm. In the same study, a combination of both TST and IGRA correctly predicted more than 90% of culture positive cases, which was similar to our findings (28). Regardless of TST or IGRA results, treatment for TB should not be delayed if factors are strongly suggestive of TB (contact history, radiologic and microbiologic) (29).

The limitations of this study were the small sample size and its retrospective nature. It was not powered to correlate the effect of age, gender, and symptoms to laboratory results. This study only included patients who received inpatient treatment for TB in KKH, potentially missing the less severe group who received outpatient therapy.

CONCLUSION

EPTB is more common in the younger age group and is associated with higher mortality and sequelae rates. As TB culture has a long turnover time, treatment for TB should not be delayed if other factors are strongly suggestive of TB. Clinicians should have a high index of suspicion for EPTB and should pay special attention to the younger age group.

What is already known on this topic

Diagnosis of pediatric TB can be challenging as presentation ranges from non-specific symptoms to severe clinical presentation. The proportion of EPTB has increased in the adult population. However, little is known about the global impact of pediatric EPTB.

What this study adds

Locally, this study aims to re-examine the clinical profile and treatment outcomes of pediatric TB in Singapore. Globally, this study aims to add new information to the differences between pediatric PTB and EPTB.

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Table 1. Characteristics of Pediatric Patients with TB (n=75)

Characteristics	Results (%)
Median Age (years)	8.8 (IQR 2.6, 13.1)
Age group	
0 - 1.9 years	15 (20.0)
2.0 - 4.9 years	12 (16.0)
≥ 5 years	48 (64.0)
Gender	
Male	39 (52.0)
Female	36 (48.0)
Nationality	
Singapore residents	53 (70.7)
Non-Singapore residents	22 (29.3)
BCG vaccination (missing 4)	
Received	60 (80.0)
Not received	11 (14.7)
TB Sites	
Pulmonary	49 (65.3)
Extra-pulmonary	26 (34.7)
Comorbidities (missing 1)	
Immune-deficient	12 (16.2)
Not immune-deficient	62 (83.3)
Contact history	
Positive contact	28 (37.3)
No contact history	47 (62.7)
Symptoms	
Significant fever	20 (26.7)
Significant cough	25 (33.3)
Significant weight loss	24 (32.0)
Fatigue	4 (5.3)
Lymphadenopathy	10 (13.3)
≥ 2 symptoms stated above	20 (26.7)
No symptom stated above	33 (44.0)
Microbiological	
Microbiologically proven	45 (60.0)
Not microbiologically proven	30 (40.0)
Microbiological results	
≥ 1 site/sample positive AFB smear	20 (26.7)
≥ 1 site/ sample positive TB culture	39 (52.0)
≥ 1 site/sample positive TB PCR	26 (34.7)
Treatment outcome	
Recovered	35 (46.3)
Death	6 (8.0)
Relapsed	2 (2.7)
Sequelae	19 (25.3)

Lost to follow up	11 (14.6)
Still completing treatment	2 (2.7)

Table 2. Comparison of Pulmonary and Extra-pulmonary TB

	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)	P value
Median age (years)	10.1 (IQR 3.5, 13,5)	5.1 (IQR 1.2, 10.2)	0.03
Gender			
Males	25 (51.0)	14 (53.8)	0.82
Females	24 (49.0)	12 (46.2)	
Nationality			
Singapore residents	37 (75.5)	16 (61.5)	0.21
Non-Singapore residents	12 (24.5)	10 (38.5)	
Received BCG vaccine	41 (89.1)	19 (76.0)	0.14
Comorbidities			
Immune-deficient	3 (6.1)	9 (34.6)	<0.01
Not immune-deficient	46 (93.9)	17 (65.4)	
Contact history			
Positive contact	22 (44.9)	6 (23.1)	0.06
No contact history	27 (55.1)	20 (76.9)	
Symptoms			
Significant fever	9 (19.1)	11 (47.8)	0.01
Significant cough	22 (51.2)	3 (13.6)	<0.01
Significant weight loss	18 (39.1)	6 (27.3)	0.34
Fatigue	2 (4.2)	2 (8.3)	0.60
Lymphadenopathy	2 (4.1)	8 (30.8)	<0.01
≥ 2 symptoms stated above	14 (28.6)	5 (23.1)	0.61
No symptom stated above	22 (44.9)	11 (42.3)	0.83
Hematological results			
Median hemoglobin (g/dL)	12.0 (IQR 10.5, 13.9)	11.2 (IQR 10.2, 11.9)	0.03
Median white blood cells ($x10^9$/L)	11.2 (IQR 7.5 15.6)	10.2 (IQR 7.6, 12.0)	0.15
Median Platelet ($x10^9$/L)	376.5 (IQR 281.5, 451.0)	377.0 (IQR 339.5, 507.0)	0.38
Median ESR (mm/hr)	40.0 (IQR 15.0, 85.0)	34.0 (IQR 19.0, 54.5)	0.61
Median CRP (mg/L)	36.0 (IQR 16.5, 84.4)	32.4 (IQR 8.6, 69.3)	0.43
Immunological results			
Positive TST	20 (40.8)	6 (23.1)	0.10
Positive IGRA	20 (40.8)	12 (46.2)	0.80
Microbiological			
Microbiologically proven	26 (53.1)	19 (73.1)	0.10
Not microbiologically proven	23 (46.9)	7 (26.9)	
Microbiological results			
≥ 1 site/sample positive AFB smear	13 (26.5)	7 (28.0)	0.89
≥ 1 site/sample positive AFB culture	24 (49.0)	15 (57.7)	0.47
≥ 1 site/sample positive TB PCR	14 (40.0)	12 (60.0)	0.15
Abnormal CXR	41 (83.7)	10 (38.5)	<0.01
Treatment outcome			
Recovered	28 (57.1)	7 (26.9)	0.01

Death	2 (4.1)	4 (15.4)	0.17
Relapsed	1 (2.0)	1 (3.8)	-
Sequelae	10 (20.4)	9 (34.6)	0.18
Lost to follow up	8 (16.3)	3 (11.5)	0.73
Still completing treatment	0 (0.0)	2 (7.7)	-
Median duration of treatment (months)	6.0 (IQR 6.0, 9.0)	12.0 (IQR 9.0, 12.0)	<0.01

Table 3. Sensitivity and specificity of investigations

	≥1 TB Culture		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
	Positive	Negative				
≥1 AFB Smear (n=74, missing 1)						
Positive	14	6	35.9 (21.2- 52.8)	82.9 (66.4-93.4)	70.0 (50.2-84.4)	53.7 (46.7-60.5)
Negative	25	29				
≥1 TB PCR (n=55)						
Positive	20	6	74.1 (53.7-88.9)	78.6 (59.1-91.7)	76.9 (61.3-87.5)	75.9 (61.8-85.9)
Negative	7	22				
T-Spot (n=41)						
Positive	18	14	85.7 (63.7-97.0)	30.0 (11.9-54.3)	56.3 (47.9-64.3)	66.7 (36.6-87.4)
Negative	3	6				
TST (n=31)						
Positive	11	15	73.3 (49.9-92.2)	6.3 (0.2-30.2)	42.3 (34.5-50.5)	20.0 (3.0-66.6)
Negative	4	1				
Combining TST and T-Spot (n=59)						
1 or both positive	25	25	86.2 (68.3-96.1)	16.7 (5.6-34.7)	50.0 (44.6-55.4)	55.6 (27.1-80.8)
Both negative	4	5				

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PAEDIATRIC TUBERCULOSIS IN SINGAPORE – A RETROSPECTIVE REVIEW

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Conflicts of interest: None

ABSTRACT

Background: Tuberculosis (TB) is a major cause of mortality and morbidity in the world. Each case represents on-going transmission and has a significant public health burden. We aim to (i) examine the clinical profile of paediatric TB and (ii) compare pulmonary TB (PTB) with extra-pulmonary TB (EPTB) in Singapore.

Methods: Retrospective study of patients admitted to KK Women's and Children's Hospital, Singapore, from January 2008 to September 2017 for active TB disease. We compared clinical characteristics and outcomes of patients with PTB and EPTB.

Results: Seventy-five patients were diagnosed as active TB; 65% PTB and 35% EPTB. Patients with EPTB were more likely to be younger [Median age 5.1 (interquartile range (IQR) 1.2, 10.2) vs 10.1 (IQR 3.5, 13.5) years], immunodeficient (35% vs 6%), had lower haemoglobin count [Median 11.5 (IQR 10.2, 11.9) vs 12.0 (IQR 10.5, 13.9) g/dL], lower recovery rate (27% vs 57%) and required longer duration of treatment [Median 12 (IQR 9, 12) vs 6 (IQR 6,9) months]. BCG vaccination rate was lower in the EPTB group compared to the PTB group (76% vs 89%). Overall mortality rate was 8.0%; Central nervous system (CNS) TB alone higher than PTB (29% vs 4%).

Conclusion: Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate, higher rates of sequelae and mortality.

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INTRODUCTION

Tuberculosis (TB) remains a major cause of morbidity and mortality in the world. Following the introduction of Singapore Tuberculosis Elimination Programme in 1997; the incidence of TB declined from 57 per 100,000 residents in the 1990s to a low of 35 per 100,000 residents in 2007. In 2016, the incidence rate of TB was 38.7 per 100,000 residents in Singapore; children below 19 years old contributed only 2.1% of the total TB population. The majority (84%) of cases had pulmonary TB (PTB) with or without extra-pulmonary involvement, while the remainder (17%) had exclusively extra-pulmonary TB (EPTB) (1).

The presentation of TB in children can range from non-specific symptoms to severe clinical presentation; which makes diagnosis challenging. Although PTB is the most common involvement, all other organs can be involved as well (2, 3). Globally in 2014, almost 10 million people developed TB, of which EPTB represented almost 15% of the overall TB (4). In adults, proportion of EPTB to PTB has increased due to a decrease in PTB rates (5). However, little is known of the global impact of pediatric EPTB due to difficulties in pediatric TB case detection and low notification rates (6). The last published review of pediatric TB in Singapore was by Freda M. Paul in 1967, which focused on the fatality of tuberculous meningitis. With the changing demographics in Singapore, a new review of pediatric TB is needed (7, 8). The aims of this study were to (i) examine the clinical profile and treatment outcomes of pediatric TB and (ii) compare PTB with EPTB.

METHODS

Setting

Kandang Kerbau (KK) Women's and Children's Hospital (KKH) is the largest tertiary pediatric hospital in Singapore with approximately 350 pediatric beds, and accounts for 54% of pediatric admissions nationally (based on market trends, Corporate communications, KKH). We collected data of all patients who were admitted for TB work-up in KKH from January 2008 to September 2017. Approval was obtained from the centralized institution review board of Singhealth Research.

Patient identification and data collection

A patient list with the code tuberculosis was generated using International Classification of Disease [ICD9CM or ICD10AM (from 2012 onwards)]. Patients who were treated for active TB were included, latent TB cases were excluded. Data pertaining to demographic profile, clinical presentation, investigations and treatment of selected cases were collected from case notes, electronic records and the infectious disease database.

Case definitions

Both microbiologically proven cases and non- microbiologically proven cases were included. Microbiologically proven cases were defined as those with positive TB culture and/or TB polymerase chain reaction (PCR). Non-microbiologically proven cases were defined as those with negative TB culture or PCR but positive TB smear, tuberculin skin test, interferon gamma release assay (IGRA) in the presence of clinical diagnosis of TB or suggestive chest X-ray (CXR). EPTB was defined as any active TB case involving organs other than lungs and pleural.

Multi-organ TB was defined as active TB involving 2 or more organs and was considered EPTB. CNS TB (subset of EPTB) was defined as TB meningitis or meningoencephalitis.

Close contact was defined as living in the same household or in frequent contact with smear positive pulmonary TB case. Immunodeficiency was either primary immune disorders or secondary to an underlying disease or immunosuppressive drugs. Definitions of symptoms were adapted from the South African Guidelines 2013 (9);

- Significant cough was defined as cough duration of ≥ 14 days
- Significant fever was defined as temperature ≥ 38°C for ≥ 14 days
- Significant weight loss was defined as ≥ 1kg for ≥ 1 month. Weight loss was further expressed as a percentage of body weight at diagnosis.
- Fatigue: Patient's or parents' complaint of reduced playfulness or lethargy

In our center, T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom) is the preferred type of IGRA used for children ≥ 2 years old because of the lower rate of indeterminate results compared to QuantiFERON-TB Gold and QuantiFERON-TB In-tube (10). Tuberculin skin test (TST) might be performed when T-spot was not available (i.e. out of office hours). Positive TST was defined as reading of ≥ 10mm at 48 hours. All patients had CXR performed and reported by in-house radiologists. All our patients had microbiological investigations. Consecutive fluid specimens were sent for acid-fast bacilli (AFB) smear and culture. The TB culture method was by the automated MGIT960 system for liquid growth and Lowenstein Jensen slants for solid growth (10, 11). Multi-drug-resistant TB (MDR-TB) was defined as resistance to both rifampicin and isoniazid.

Statistical analysis

Analysis was carried out using SPSS version 19 (IBM, Armonk, New York, USA). Categorical data were expressed as counts and percentages whereas continuous data were expressed as median and interquartile ranges (IQR). Differences between categorical data were analysed by chi-square tests or Fisher's exact test when cell sizes were less than 5. Differences between continuous data were analysed by Mann-Whitney test. All statistical tests were 2-tailed and a P value of <0.05 was statistically significant.

RESULTS

Seventy-five patients were included; 49 (65%) had PTB and 26 (35%) had EPTB. Further breakdown of EPTB: 5 lymphatic; 7 central nervous system (CNS); 1 pericardial, 2 gastro-intestinal; 1 eye, 2 musculoskeletal and 8 multi-organ TB. Of the multi-organ TB: 2 had involvement of pulmonary and CNS, 1 patient each had involvement of CNS and lymphatics; GIT and MSK; pulmonary and GIT; pulmonary and lymphatics; GIT, lymphatics and MSK; GIT and pulmonary.

Table 1 describes the differences between PTB and EPTB. Patients with EPTB were younger [Median age 5.05 years (IQR 1.23, 10.23) vs 10.10 years (IQR 3.47, 13.45), p=0.03], more likely to be immunodeficient (35% vs 6%, p<0.01) and had lower hemoglobin (Hb) level [Median Hb level 11.15 g/dL (IQR 10.23, 11.90) vs 12.00 g/dL (IQR 10.50, 13.85), p=0.01]. BCG vaccination rate was lower in the EPTB group compared to the PTB group (76% vs 89%, p=0.14). Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). However, only 20 (27%) of our patients presented with ≥ 2 significant symptoms. Patients with PTB were more likely to have significant cough whereas those with EPTB were more likely to present with significant fever and/or lymphadenopathy (Table 1). Twenty-eight patients (37%) had positive TB contact; 26 household contacts and 2 school contacts. Only 4 (5%) patients had ≥ 2 significant symptoms and positive contact history.

Abnormal CXR was found in 51 patients (68%) with the following changes: pulmonary infiltrates (n=24, 32%), hilar adenopathy (n=7, 9%), military (n=4, 5%), lobar collapse (n=3, 4%), pleural changes (n=2, 3%), cavitation (n=2, 3%), widened mediastinum (n=1, 1%) and combination of findings (n=8, 11%). Patients with PTB were more likely to have abnormal CXR

compared to those with EPTB (84% vs 39%, p<0.01).

More than half of PTB and EPTB had microbiologically proven disease (53% and 73% respectively). T-Spot was performed in 41 (55%) patients: 32 (78%) positive, 6 (15%) negative and 3 (7%) indeterminate. TST was performed in 31 patients (41%): 26 (84%) positive with median reading was 14.5 mm (IQR 11.0, 20.0). However, there were no significant differences in the percentage of positive smear, culture, PCR, TST or T-Spot disease between PTB and EPTB. There were no cases of MDR-TB in our cohort.

All patients received isoniazid and rifampicin with pyrazinamide and/or ethambutol. Patients with EPTB needed longer duration of treatment compared to those with PTB [Median 12 (IQR 9, 12) vs 6 (IQR 6, 9) months, p<0.01]. Twelve (16.0%) patients were immunodeficient; Table 2 describes the types of immunodeficiences in both PTB and EPTB patients Patients who were immunodeficient were also treated for a longer period compared to immunocompetent patients [Median 12 (IQR 10, 12) vs 6 (IQR 6, 9) months, p<0.01].

Overall mortality rate was 8.0%. Mortality rate of PTB and EPTB was 4% vs 15% (p=0.17). Event-free survival in PTB patients compared to EPTB was 57% vs 27% (p=0.01). For CNS TB alone, the mortality rate was higher than that of PTB (29% vs 4%, p=0.02). Event-free survival in CNS TB was only 71%. CNS TB accounted for almost all mortality and sequelae in EPTB. Table 3 describes the details of sequelae, mortality and relapse cases of PTB and EPTB.

DISCUSSION

Our study compares the demographics, clinical spectrum, investigation results and outcomes of PTB and EPTB.

The median age of patients with EPTB was significantly younger than PTB [Median age 5.05 vs 10.10 years, p=0.03], similar to another paediatric TB study (12). EPTB had lower recovery rate, high mortality, relapse and sequelae rates compared to PTB. Similar to other studies, this implied that younger children had higher risk of serious TB (13, 14). Mortality rate for CNS TB was significantly higher than PTB (29% vs 4%, p=0.02). The mortality of TB meningitis from our review had decreased drastically from a peak of 60% in 1955 (7, 8). Mass BCG vaccination campaign, implemented in 1957, was one of the key interventions that led to a marked decrease in TB mortality rates, especially EPTB and for children < 5 years old (15, 16). A retrospective pediatric study in China showed that EPTB was more prevalent in the BCG unvaccinated group (59% vs 41%, p=0.05); our study showed similar results that more patients had no BCG vaccination in the EPTB group compared to PTB group (76% vs 89%) even though the difference was not significant (12). This finding suggests that children who received BCG vaccination have less chance of contracting EPTB.

Children with TB rarely present with classical symptoms as seen in a survey from a high burden community (17). This is similar to our study in which only 27% of patients presented with ≥ 2 out of 5 significant symptoms stated by South African Society for Pediatric Infectious Diseases (9). Marais et al stated that the index of suspicion should be increased when symptoms such as prolonged cough of more than 2 weeks, significant weight loss and fatigue exist together with positive TB contact (18). Four (5%) of our patients with TB had ≥ 2 significant symptoms and

positive contact history. Nevertheless, available scoring systems should not be used for predicting pediatric TB infection as they lack sensitivity and specificity (19).

Sixty-eight percent of patients had abnormal CXR, which was higher than a large-scale multicenter center study conducted in India (20). This can be explained by significant variation between radiologists when interpreting pediatric CXR (21). Moreover, CXR had a high sensitivity but low specificity for detecting active TB as many radiological changes seen in TB could be present in other infections (22).

A positive microbiological culture remains the gold standard for diagnosis of active TB but is often limited by the prolonged turnover time. In this study, the percentage of patients with eventual positive TB culture (49.0% and 57.5%) was more than those with ≥1 positive AFB smear (26.5% and 28.0%) in both the PTB and EPTB group, which could lead to a delay in identification and treatment of active TB disease. Our higher TB culture rates compared to 15.7% in China and 34% in USA could be due to more aggressive sampling methods or different culture methods (12, 23).

Immunological investigations such as TST and IGRA can aid in the diagnosis of TB but each has its own limitations. In children < 4 years old, T-Spot is preferred as it has lower rate of indeterminate results compared to QuantiFERON-TB test (24). While IGRA and TST are good predictors of latent TB infection, their sensitivity for active TB infection are much more limited (25, 26). Regardless of TST or IGRA results, treatment for TB should not be delayed if factors are strongly suggestive of TB (contact history, radiologic and microbiologic) (27).

The limitations of this study were the small sample size and its retrospective nature. It was not powered to correlate the effect of age, gender, and symptoms to laboratory results. This study

only included patients who received inpatient treatment for TB in KKH, potentially missing the less severe group who received outpatient therapy.

CONCLUSION

Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate, higher rates of sequelae and mortality. As TB culture has a long turnover time, treatment for TB should not be delayed if other factors are strongly suggestive of TB. Clinicians should have a high index of suspicion for EPTB and should pay special attention to the younger age group.

What is already known on this topic

Diagnosis of pediatric TB can be challenging as presentation ranges from non-specific symptoms to severe clinical presentation. The proportion of EPTB has increased in the adult population. However, little is known about the global impact of pediatric EPTB.

What this study adds

Locally, this study aims to re-examine the clinical profile and treatment outcomes of pediatric TB in Singapore. Globally, this study aims to add new information to the differences between pediatric PTB and EPTB. Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate, higher rates of sequelae and mortality

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Table 1. Comparison of Pulmonary and Extra-pulmonary TB

	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)	P value
Median age (years)	10.1 (IQR 3.5, 13,5)	5.1 (IQR 1.2, 10.2)	0.03
Gender			
Males	25 (51)	14 (54)	0.82
Females	24 (49)	12 (46)	
Nationality			
Singapore residents	37 (76)	16 (62)	0.21
Non-Singapore residents	12 (24)	10 (38)	
Received BCG vaccine	41 (89)	19 (76)	0.14
Comorbidities			
Immunodeficient	3 (6)	9 (35)	<0.01
Not immunodeficient	46 (94)	17 (65)	
Contact history			
Positive contact	22 (45)	6 (23)	0.06
No contact history	27 (55)	20 (77)	
Symptoms			
Significant fever	9 (19)	11 (48)	0.01
Significant cough	22 (51)	3 (14)	<0.01
Significant weight loss	18 (39)	6 (27)	0.34
Median weight loss (%body weight)	10.6 (IQR 5.8, 20.0)	16.3 (IQR 13.6, 40.6)	0.29
Fatigue	2 (4)	2 (8)	0.60
Lymphadenopathy	2 (4)	8 (31)	<0.01
≥ 2 symptoms stated above	14 (29)	5 (23)	0.61
No symptom stated above	22 (45)	11 (42)	0.83
Hematological results			
Median hemoglobin (g/dL)	12.0 (IQR 10.5, 13.9)	11.2 (IQR 10.2, 11.9)	0.03
Median white blood cells ($x10^9$/L)	11.2 (IQR 7.5 15.6)	10.2 (IQR 7.6, 12.0)	0.15
Median Platelet ($x10^9$/L)	376.5 (IQR 281.5, 451.0)	377.0 (IQR 339.5, 507.0)	0.38
Median ESR (mm/hr)	40.0 (IQR 15.0, 85.0)	34.0 (IQR 19.0, 54.5)	0.61
Median CRP (mg/L)	36.0 (IQR 16.5, 84.4)	32.4 (IQR 8.6, 69.3)	0.43
Immunological results			
Positive TST	20 (41)	6 (23)	0.10
Positive IGRA	20 (41)	12 (46)	0.80
Microbiological			
Microbiologically proven	26 (53)	19 (73)	0.10
Not microbiologically proven	23 (47)	7 (27)	
Microbiological results			
≥ 1 site/sample positive AFB smear	13 (27)	7 (28)	0.89
≥ 1 site/sample positive AFB culture	24 (49)	15 (58)	0.47
≥ 1 site/sample positive TB PCR	14 (40)	12 (60)	0.15
Abnormal CXR	41 (84)	10 (39)	<0.01
Treatment outcome			
Recovered	28 (57)	7 (27)	0.01
Death	2 (4)	4 (15)	0.17
Relapsed	1 (2)	1 (4)	-
Sequelae	10 (20)	9 (35)	0.18
Lost to follow up	8 (16)	3 (12)	0.73
Still completing treatment	0 (0)	2 (8)	-
Median duration of treatment (months)	6.0 (IQR 6.0, 9.0)	12.0 (IQR 9.0, 12.0)	<0.01

Table 2. Types of immunodefiencies in Pulmonary and Extra-pulmonary TB

Types of immunodeficiencies	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)
HIV	2 (4)	2 (8)
Malignancy	0 (0)	2 [b] (8)
Immunodeficiency	0 (0)	2 [c] (8)
Others	1 [a] (2)	3 [d] (12)

[a] Ebstein Barr Virus-related haemophagocytic lymphohistiocytosis

[b] 1 Medulloblastoma on chemotherapy, 1 Neuroblastoma on chemotherapy

[c] Severe combined immunodeficiency

[d] 1 Crohn's disease on immunosuppressant, 1 Juvenile idiopathic arthritis on biologics, 1 Mendelian susceptibility to mycobacterial disease

Table 3. Outcomes of Pulmonary and Extra-pulmonary TB

	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)
Types of sequelae 10 PTB (20%) 9 EPTB (35%)	3 (6) Bronchus compression 3 (6) Bronchiectasis 2 (4) Restrictive lung diseases 2 (4) Complications from underlying condition	1 (4) Intestinal perforation 1 (4) Kyphosis 1 (4) CNS infarct 2 (8) Seizures 2 (8) Developmental delay 2 (8) Complications from underlying condition
Reasons for mortality 2 PTB (4%) 4 EPTB (15%)	1 (2) Septic shock 1 (2) Pulmonary haemorrhage	2 (8) Septic shock 1 (4) Severe cerebral edema 1 (4) Underlying malignancy
Reasons for relapse 1 PTB (2%) 1 EPTB (4%)	1 (2) Reactivation of pulmonary TB with TB pericarditis (cause unknown)	1 (4) Recurrent TB lymphadenitis (cause unknown)

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Conflicts of interest: None

ABSTRACT

Background: Tuberculosis (TB) is a major cause of mortality and morbidity in the world. Each case represents on-going transmission and has a significant public health burden. We aim to (i) examine the clinical profile of paediatric TB and (ii) compare pulmonary TB (PTB) with extra-pulmonary TB (EPTB) in Singapore.

Methods: Retrospective study of patients admitted to KK Women's and Children's Hospital, Singapore, from January 2008 to September 2017 for active TB disease. We compared clinical characteristics and outcomes of patients with PTB and EPTB.

Results: Seventy-five patients were diagnosed as active TB; 65% PTB and 35% EPTB. Patients with EPTB were more likely to be younger [Median age 5.1 (interquartile range (IQR) 1.2, 10.2) vs 10.1 (IQR 3.5, 13.5) years], immunodeficient (35% vs 6%), had lower haemoglobin count [Median 11.5 (IQR 10.2, 11.9) vs 12.0 (IQR 10.5, 13.9) g/dL], lower recovery rate (27% vs 57%) and required longer duration of treatment [Median 12 (IQR 9, 12) vs 6 (IQR 6,9) months]. Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). Overall mortality was 8% with septic shock responsible for 3 of the 6 deaths.

Conclusion: Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate and higher sequelae rate.

INTRODUCTION

Tuberculosis (TB) remains a major cause of morbidity and mortality in the world. Following the introduction of Singapore Tuberculosis Elimination Programme in 1997; the incidence of TB declined from 57 per 100,000 residents in the 1990s to a low of 35 per 100,000 residents in 2007. In 2016, the incidence rate of TB was 38.7 per 100,000 residents in Singapore; children below 19 years old contributed only 2.1% of the total TB population. The majority (84%) of cases had pulmonary TB (PTB) with or without extra-pulmonary involvement, while the remainder (17%) had exclusively extra-pulmonary TB (EPTB) (1).

The presentation of TB in children can range from non-specific symptoms to severe clinical presentation; which makes diagnosis challenging. Although PTB is the most common involvement, all other organs can be involved as well (2, 3). Globally in 2014, almost 10 million people developed TB, of which EPTB represented almost 15% of the overall TB (4). In adults, proportion of EPTB to PTB has increased due to a decrease in PTB rates (5). However, little is known of the global impact of pediatric EPTB due to difficulties in pediatric TB case detection and low notification rates (6). The last published review of pediatric TB in Singapore was by Freda M. Paul in 1967, which focused on the fatality of tuberculous meningitis. With the changing demographics in Singapore, a new review of pediatric TB is needed (7, 8). The aims of this study were to (i) examine the clinical profile and treatment outcomes of pediatric TB and (ii) compare PTB with EPTB.

METHODS

Setting

Kandang Kerbau (KK) Women's and Children's Hospital (KKH) is the largest tertiary pediatric hospital in Singapore with approximately 350 pediatric beds, and accounts for 54% of pediatric admissions nationally (based on market trends, Corporate communications, KKH). We collected data of all patients who were admitted for TB work-up in KKH from January 2008 to September 2017. Approval was obtained from the centralized institution review board of Singhealth Research.

Patient identification and data collection

A patient list with the code tuberculosis was generated using International Classification of Disease [ICD9CM or ICD10AM (from 2012 onwards)]. Patients who were treated for active TB were included, latent TB cases were excluded. Data pertaining to demographic profile, clinical presentation, investigations and treatment of selected cases were collected from case notes, electronic records and the infectious disease database.

Case definitions

Both microbiologically proven cases and non- microbiologically proven cases were included. Microbiologically proven cases were defined as those with positive TB culture and/or TB polymerase chain reaction (PCR). Non-microbiologically proven cases were defined as those with negative TB culture or PCR but positive TB smear, tuberculin skin test, interferon gamma release assay (IGRA) in the presence of clinical diagnosis of TB or suggestive chest X-ray (CXR). EPTB was defined as any active TB case involving organs other than lungs and pleural.

Multi-organ TB was defined as active TB involving 2 or more organs and was considered EPTB. CNS TB (subset of EPTB) was defined as TB meningitis or meningoencephalitis.

Close contact was defined as living in the same household or in frequent contact with smear positive pulmonary TB case. Immunodeficiency was either primary immune disorders or secondary to an underlying disease or immunosuppressive drugs. Definitions of symptoms were adapted from the South African Guidelines 2013 (9);

- Significant cough was defined as cough duration of ≥ 14 days
- Significant fever was defined as temperature ≥ 38°C for ≥ 14 days
- Significant weight loss was defined as ≥ 1kg for ≥ 1 month. Weight loss was further expressed as a percentage of body weight at diagnosis.
- Fatigue: Patient's or parents' complaint of reduced playfulness or lethargy

In our center, T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom) is the preferred type of IGRA used for children ≥ 2 years old because of the lower rate of indeterminate results compared to QuantiFERON-TB Gold and QuantiFERON-TB In-tube (10). Tuberculin skin test (TST) might be performed when T-spot was not available (i.e. out of office hours). Positive TST was defined as reading of ≥ 10mm at 48 hours. All patients had CXR performed and reported by in-house radiologists. All our patients had microbiological investigations. Consecutive fluid specimens were sent for acid-fast bacilli (AFB) smear and culture. The TB culture method was by the automated MGIT960 system for liquid growth and Lowenstein Jensen slants for solid growth (10, 11). Multi-drug-resistant TB (MDR-TB) was defined as resistance to both rifampicin and isoniazid.

Statistical analysis

Analysis was carried out using SPSS version 19 (IBM, Armonk, New York, USA). Categorical data were expressed as counts and percentages whereas continuous data were expressed as median and interquartile ranges (IQR). Differences between categorical data were analysed by chi-square tests or Fisher's exact test when cell sizes were less than 5. Differences between continuous data were analysed by Mann-Whitney test. All statistical tests were 2-tailed and a P value of <0.05 was statistically significant.

RESULTS

Seventy-five patients were included; 49 (65%) had PTB and 26 (35%) had EPTB. Further breakdown of EPTB: 5 lymphatic; 7 central nervous system (CNS); 1 pericardial, 2 gastro-intestinal; 1 eye, 2 musculoskeletal and 8 multi-organ TB. All cases of CNS TB were TB meningitis. Of the multi-organ TB: 2 had involvement of pulmonary and CNS, 1 patient each had involvement of CNS and lymphatics; GIT and MSK; pulmonary and GIT; pulmonary and lymphatics; GIT, lymphatics and MSK; GIT and pulmonary.

Table 1 describes the differences between PTB and EPTB. Patients with EPTB were younger [Median age 5.05 years (IQR 1.23, 10.23) vs 10.10 years (IQR 3.47, 13.45), p=0.03], more likely to be immunodeficient (35% vs 6%, p<0.01) and had lower hemoglobin (Hb) level [Median Hb level 11.15 g/dL (IQR 10.23, 11.90) vs 12.00 g/dL (IQR 10.50, 13.85), p=0.01]. Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). However, only 20 (27%) of our patients presented with ≥ 2 significant symptoms. Patients with PTB were more likely to have significant cough whereas those with EPTB were more likely to present with significant fever and/or lymphadenopathy (Table 1). Twenty-eight patients (37%) had positive TB contact; 26 household contacts and 2 school contacts. Only 4 (5%) patients had ≥ 2 significant symptoms and positive contact history.

Abnormal CXR was found in 51 patients (68%) with the following changes: pulmonary infiltrates (n=24, 32%), hilar adenopathy (n=7, 9%), miliary (n=4, 5%), lobar collapse (n=3, 4%), pleural changes (n=2, 3%), cavitation (n=2, 3%), widened mediastinum (n=1, 1%) and combination of findings (n=8, 11%). Patients with PTB were more likely to have abnormal CXR compared to those with EPTB (84% vs 39%, p<0.01).

More than half of PTB and EPTB had microbiologically proven disease (53% and 73% respectively). T-Spot was performed in 41 (55%) patients: 32 (78%) positive, 6 (15%) negative and 3 (7%) indeterminate. TST was performed in 31 patients (41%): 26 (84%) positive with median reading was 14.5 mm (IQR 11.0, 20.0). However, there were no significant differences in the percentage of positive smear, culture, PCR, TST or T-Spot disease between PTB and EPTB. There were no cases of MDR-TB in our cohort.

All patients received isoniazid and rifampicin with pyrazinamide and/or ethambutol. Patients with EPTB needed longer duration of treatment compared to those with PTB [Median 12 (IQR 9, 12) vs 6 (IQR 6, 9) months, $p<0.01$]. Twelve (16.0%) patients were immunodeficient; Table 2 describes the types of immunodeficiences in both PTB and EPTB patients Patients who were immunodeficient were also treated for a longer period compared to immunocompetent patients [Median 12 (IQR 10, 12) vs 6 (IQR 6, 9) months, $p<0.01$].

Overall mortality rate was 8.0%. Mortality rate of PTB and EPTB was 4% and 15% respectively. Event-free survival in PTB patients compared to EPTB was 57% vs 27% ($p=0.01$). Of the 4 deaths in EPTB, 2 patients (50%) had TB meningitis. Mortality rate of TB meningitis was 29%. Septic shock accounted for 3 out of 6 deaths in both PTB and EPTB. Table 3 describes the details of sequelae, mortality and relapse cases of PTB and EPTB.

DISCUSSION

Our study compares the demographics, clinical spectrum, investigation results and outcomes of PTB and EPTB.

The median age of patients with EPTB was significantly younger than PTB [Median age 5.05 vs 10.10 years, p=0.03], similar to another paediatric TB study (12). EPTB had lower recovery rate, high mortality, relapse and sequelae rates compared to PTB. Similar to other studies, this implied that younger children had higher risk of serious TB (13, 14). The mortality of TB meningitis from our review had decreased drastically from a peak of 60% in 1955 (7, 8). Mass BCG vaccination campaign, implemented in 1957, was one of the key interventions that led to a marked decrease in TB mortality rates, especially EPTB and for children < 5 years old (15, 16). A retrospective pediatric study in China showed that EPTB was more prevalent in the BCG unvaccinated group (59% vs 41%, p=0.05); our small study failed to show any significant difference (12). This finding suggests that children who received BCG vaccination have less chance of contracting EPTB.

Children with TB rarely present with classical symptoms as seen in a survey from a high burden community (17). This is similar to our study in which only 27% of patients presented with ≥ 2 out of 5 significant symptoms stated by South African Society for Pediatric Infectious Diseases (9). Marais et al stated that the index of suspicion should be increased when symptoms such as prolonged cough of more than 2 weeks, significant weight loss and fatigue exist together with positive TB contact (18). Four (5%) of our patients with TB had ≥ 2 significant symptoms and positive contact history. Nevertheless, available scoring systems should not be used for predicting pediatric TB infection as they lack sensitivity and specificity (19).

Sixty-eight percent of patients had abnormal CXR, which was higher than a large-scale multicenter center study conducted in India (20). This can be explained by significant variation between radiologists when interpreting pediatric CXR (21). Moreover, CXR had a high sensitivity but low specificity for detecting active TB as many radiological changes seen in TB could be present in other infections (22).

A positive microbiological culture remains the gold standard for diagnosis of active TB but is often limited by the prolonged turnover time. In this study, the percentage of patients with eventual positive TB culture (49.0% and 57.5%) was more than those with ≥1 positive AFB smear (26.5% and 28.0%) in both the PTB and EPTB group, which could lead to a delay in identification and treatment of active TB disease. Our higher TB culture rates compared to 15.7% in China and 34% in USA could be due to more aggressive sampling methods or different culture methods (12, 23).

Immunological investigations such as TST and IGRA can aid in the diagnosis of TB but each has its own limitations. In children < 4 years old, T-Spot is preferred as it has lower rate of indeterminate results compared to QuantiFERON-TB test (24). While IGRA and TST are good predictors of latent TB infection, their sensitivity for active TB infection are much more limited (25, 26). Regardless of TST or IGRA results, treatment for TB should not be delayed if factors are strongly suggestive of TB (contact history, radiologic and microbiologic) (27).

The limitations of this study were the small sample size and its retrospective nature. It was not powered to correlate the effect of age, gender, and symptoms to laboratory results. This study only included patients who received inpatient treatment for TB in KKH, potentially missing the less severe group who received outpatient therapy.

CONCLUSION

Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate and higher sequelae rate. As TB culture has a long turnover time, treatment for TB should not be delayed if other factors are strongly suggestive of TB. Clinicians should have a high index of suspicion for EPTB and should pay special attention to the younger age group.

What is already known on this topic

Diagnosis of pediatric TB can be challenging as presentation ranges from non-specific symptoms to severe clinical presentation. The proportion of EPTB has increased in the adult population. However, little is known about the global impact of pediatric EPTB.

What this study adds

Common clinical presentations involving a third of patients with both PTB and EPTB were significant fever, cough and weight loss. Patients with EPTB were more likely to be immunodeficient. Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate and higher sequelae rate.

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Table 1. Comparison of Pulmonary and Extra-pulmonary TB

	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)	P value
Median age (years)	10.1 (IQR 3.5, 13,5)	5.1 (IQR 1.2, 10.2)	0.03
Gender			
Males	25 (51)	14 (54)	0.82
Females	24 (49)	12 (46)	
Nationality			
Singapore residents	37 (76)	16 (62)	0.21
Non-Singapore residents	12 (24)	10 (38)	
Received BCG vaccine	41 (89)	19 (76)	0.14
Comorbidities			
Immunodeficient	3 (6)	9 (35)	<0.01
Not immunodeficient	46 (94)	17 (65)	
Contact history			
Positive contact	22 (45)	6 (23)	0.06
No contact history	27 (55)	20 (77)	
Symptoms			
Significant fever	9 (19)	11 (48)	0.01
Significant cough	22 (51)	3 (14)	<0.01
Significant weight loss	18 (39)	6 (27)	0.34
Median weight loss (%body weight)	10.6 (IQR 5.8, 20.0)	16.3 (IQR 13.6, 40.6)	0.29
Fatigue	2 (4)	2 (8)	0.60
Lymphadenopathy	2 (4)	8 (31)	<0.01
≥ 2 symptoms stated above	14 (29)	5 (23)	0.61
No symptom stated above	22 (45)	11 (42)	0.83
Hematological results			
Median hemoglobin (g/dL)	12.0 (IQR 10.5, 13.9)	11.2 (IQR 10.2, 11.9)	0.03
Median white blood cells ($x10^9$/L)	11.2 (IQR 7.5 15.6)	10.2 (IQR 7.6, 12.0)	0.15
Median Platelet ($x10^9$/L)	376.5 (IQR 281.5, 451.0)	377.0 (IQR 339.5, 507.0)	0.38
Median ESR (mm/hr)	40.0 (IQR 15.0, 85.0)	34.0 (IQR 19.0, 54.5)	0.61
Median CRP (mg/L)	36.0 (IQR 16.5, 84.4)	32.4 (IQR 8.6, 69.3)	0.43
Immunological results			
Positive TST	20 (41)	6 (23)	0.10
Positive IGRA	20 (41)	12 (46)	0.80
Microbiological			
Microbiologically proven	26 (53)	19 (73)	0.10
Not microbiologically proven	23 (47)	7 (27)	
Microbiological results			
≥ 1 site/sample positive AFB smear	13 (27)	7 (28)	0.89
≥ 1 site/sample positive AFB culture	24 (49)	15 (58)	0.47
≥ 1 site/sample positive TB PCR	14 (40)	12 (60)	0.15
Abnormal CXR	41 (84)	10 (39)	<0.01
Treatment outcome			
Recovered	28 (57)	7 (27)	0.01
Death	2 (4)	4 (15)	0.17
Relapsed	1 (2)	1 (4)	-
Sequelae	10 (20)	9 (35)	0.18
Lost to follow up	8 (16)	3 (12)	0.73
Still completing treatment	0 (0)	2 (8)	-
Median duration of treatment (months)	6.0 (IQR 6.0, 9.0)	12.0 (IQR 9.0, 12.0)	<0.01

Table 2. Types of immunodefiencies in Pulmonary and Extra-pulmonary TB

Types of immunodeficiencies	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)
HIV	2 (4)	2 (8)
Malignancy	0 (0)	2 [b] (8)
Primary immune deficiency	0 (0)	2 [c] (8)
Others	1 [a] (2)	3 [d] (12)

[a] Ebstein Barr Virus-related haemophagocytic lymphohistiocytosis

[b] 1 Medulloblastoma on chemotherapy, 1 Neuroblastoma on chemotherapy

[c] Severe combined immunodeficiency

[d] 1 Crohn's disease on immunosuppressant, 1 Juvenile idiopathic arthritis on biologics, 1 Mendelian susceptibility to mycobacterial disease

Table 3. Outcomes of Pulmonary and Extra-pulmonary TB

	Pulmonary N = 49			Extrapulmonary N = 26		
		n	%		n	%
Types of sequelae	Bronchus compression	3	6	Intestinal perforation	1	4
	Bronchiectasis	3	6	Kyphosis	1	4
	Restrictive lung disease	2	4	CNS infarct	1	4
	Complications from underlying condition	2	4	Complications from underlying condition	2	8
				Developmental delay	2	8
				Seizures	2	8
Reasons for mortality [a]	Septic shock	1	2	Septic Shock	2	8
	Pulmonary haemorrhage	1	2	Severe Cerebral edema	1	4
				Underlying malignancy	1	4
Reasons for relapse	Reactivation of pulmonary TB with pericarditis (cause unknown)	1	2	Recurrent TB lymphadenitis (cause unknown)	1	4

[a] Of 4 EPTB: 2 TB meningitis, 1 pericardial TB, 1 multiorgan TB

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PAEDIATRIC TUBERCULOSIS IN SINGAPORE – A RETROSPECTIVE REVIEW

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Conflicts of interest: None

ABSTRACT

Background: Tuberculosis (TB) is a major cause of mortality and morbidity in the world. Each case represents on-going transmission and has a significant public health burden. We aim to (i) examine the clinical profile of paediatric TB and (ii) compare pulmonary TB (PTB) with extra-pulmonary TB (EPTB) in Singapore.

Methods: Retrospective study of patients admitted to KK Women's and Children's Hospital, Singapore, from January 2008 to September 2017 for active TB disease. We compared clinical characteristics and outcomes of patients with PTB and EPTB.

Results: Seventy-five patients were diagnosed as active TB; 65% PTB and 35% EPTB. Patients with EPTB were more likely to be younger [Median age 5.1 (interquartile range (IQR) 1.2, 10.2) vs 10.1 (IQR 3.5, 13.5) years], immunodeficient (35% vs 6%), had lower haemoglobin count [Median 11.5 (IQR 10.2, 11.9) vs 12.0 (IQR 10.5, 13.9) g/dL], lower recovery rate (27% vs 57%) and required longer duration of treatment [Median 12 (IQR 9, 12) vs 6 (IQR 6,9) months]. Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). Overall mortality was 8% with septic shock responsible for 3 of the 6 deaths.

Conclusion: Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate.

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Analysis was carried out using SPSS version 19 (IBM, Armonk, New York, USA). Categorical data were expressed as counts and percentages whereas continuous data were expressed as median and interquartile ranges (IQR). Differences between categorical data were analysed by chi-square tests or Fisher's exact test when cell sizes were less than 5. Differences between continuous data were analysed by Mann-Whitney test. All statistical tests were 2-tailed and a P value of <0.05 was statistically significant.

RESULTS

Seventy-five patients were included; 49 (65%) had PTB and 26 (35%) had EPTB. Further breakdown of EPTB: 5 lymphatic; 7 central nervous system (CNS); 1 pericardial, 2 gastro-intestinal; 1 eye, 2 musculoskeletal and 8 multi-organ TB. All cases of CNS TB were TB meningitis. Of the multi-organ TB: 2 had involvement of pulmonary and CNS, 1 patient each had involvement of CNS and lymphatics; GIT and MSK; pulmonary and GIT; pulmonary and lymphatics; GIT, lymphatics and MSK; GIT and pulmonary.

Table 1 describes the differences between PTB and EPTB. Patients with EPTB were younger [Median age 5.05 years (IQR 1.23, 10.23) vs 10.10 years (IQR 3.47, 13.45), p=0.03], more likely to be immunodeficient (35% vs 6%, p<0.01) and had lower hemoglobin (Hb) level [Median Hb level 11.15 g/dL (IQR 10.23, 11.90) vs 12.00 g/dL (IQR 10.50, 13.85), p=0.01]. Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). However, only 20 (27%) of our patients presented with ≥ 2 significant symptoms. Patients with PTB were more likely to have significant cough whereas those with EPTB were more likely to present with significant fever and/or lymphadenopathy (Table 1). Twenty-eight patients (37%) had positive TB contact; 26 household contacts and 2 school contacts. Only 4 (5%) patients had ≥ 2 significant symptoms and positive contact history.

Abnormal CXR was found in 51 patients (68%) with the following changes: pulmonary infiltrates (n=24, 32%), hilar adenopathy (n=7, 9%), miliary (n=4, 5%), lobar collapse (n=3, 4%), pleural changes (n=2, 3%), cavitation (n=2, 3%), widened mediastinum (n=1, 1%) and combination of findings (n=8, 11%). Patients with PTB were more likely to have abnormal CXR compared to those with EPTB (84% vs 39%, p<0.01).

More than half of PTB and EPTB had microbiologically proven disease (53% and 73% respectively). T-Spot was performed in 41 (55%) patients: 32 (78%) positive, 6 (15%) negative and 3 (7%) indeterminate. TST was performed in 31 patients (41%): 26 (84%) positive with median reading was 14.5 mm (IQR 11.0, 20.0). However, there were no significant differences in the percentage of positive smear, culture, PCR, TST or T-Spot disease between PTB and EPTB. There were no cases of MDR-TB in our cohort.

All patients received isoniazid and rifampicin with pyrazinamide and/or ethambutol. Patients with EPTB needed longer duration of treatment compared to those with PTB [Median 12 (IQR 9, 12) vs 6 (IQR 6, 9) months, $p<0.01$]. Twelve (16.0%) patients were immunodeficient; Table 2 describes the types of immunodeficiences in both PTB and EPTB patients Patients who were immunodeficient were also treated for a longer period compared to immunocompetent patients [Median 12 (IQR 10, 12) vs 6 (IQR 6, 9) months, $p<0.01$].

Overall mortality rate was 8.0%. Mortality rate of PTB and EPTB was 4% and 15% respectively. Event-free survival in PTB patients compared to EPTB was 57% vs 27% ($p=0.01$). Of the 4 deaths in EPTB, 2 patients (50%) had TB meningitis. Mortality rate of TB meningitis was 29%. Septic shock accounted for 3 out of 6 deaths in both PTB and EPTB. Table 3 describes the details of sequelae, mortality and relapse cases of PTB and EPTB.

DISCUSSION

Our study compares the demographics, clinical spectrum, investigation results and outcomes of PTB and EPTB.

The median age of patients with EPTB was significantly younger than PTB [Median age 5.05 vs 10.10 years, p=0.03], similar to another paediatric TB study (12). EPTB had lower recovery rate, high mortality, relapse and sequelae rates compared to PTB. Similar to other studies, this implied that younger children had higher risk of serious TB (13, 14). The mortality of TB meningitis from our review had decreased drastically from a peak of 60% in 1955 (7, 8). Mass BCG vaccination campaign, implemented in 1957, was one of the key interventions that led to a marked decrease in TB mortality rates, especially EPTB and for children < 5 years old (15, 16). A retrospective pediatric study in China showed that EPTB was more prevalent in the BCG unvaccinated group (59% vs 41%, p=0.05); our small study failed to show any significant difference (12). This finding suggests that children who received BCG vaccination have less chance of contracting EPTB.

Children with TB rarely present with classical symptoms as seen in a survey from a high burden community (17). This is similar to our study in which only 27% of patients presented with ≥ 2 out of 5 significant symptoms stated by South African Society for Pediatric Infectious Diseases (9). Marais et al stated that the index of suspicion should be increased when symptoms such as prolonged cough of more than 2 weeks, significant weight loss and fatigue exist together with positive TB contact (18). Four (5%) of our patients with TB had ≥ 2 significant symptoms and positive contact history. Nevertheless, available scoring systems should not be used for predicting pediatric TB infection as they lack sensitivity and specificity (19).

Sixty-eight percent of patients had abnormal CXR, which was higher than a large-scale multicenter center study conducted in India (20). This can be explained by significant variation between radiologists when interpreting pediatric CXR (21). Moreover, CXR had a high sensitivity but low specificity for detecting active TB as many radiological changes seen in TB could be present in other infections (22).

A positive microbiological culture remains the gold standard for diagnosis of active TB but is often limited by the prolonged turnover time. In this study, the percentage of patients with eventual positive TB culture (49.0% and 57.5%) was more than those with ≥1 positive AFB smear (26.5% and 28.0%) in both the PTB and EPTB group, which could lead to a delay in identification and treatment of active TB disease. Our higher TB culture rates compared to 15.7% in China and 34% in USA could be due to more aggressive sampling methods or different culture methods (12, 23).

Immunological investigations such as TST and IGRA can aid in the diagnosis of TB but each has its own limitations. In children < 4 years old, T-Spot is preferred as it has lower rate of indeterminate results compared to QuantiFERON-TB test (24). While IGRA and TST are good predictors of latent TB infection, their sensitivity for active TB infection are much more limited (25, 26). Regardless of TST or IGRA results, treatment for TB should not be delayed if factors are strongly suggestive of TB (contact history, radiologic and microbiologic) (27).

The limitations of this study were the small sample size and its retrospective nature. It was not powered to correlate the effect of age, gender, and symptoms to laboratory results. This study only included patients who received inpatient treatment for TB in KKH, potentially missing the less severe group who received outpatient therapy.

CONCLUSION

Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate. As TB culture has a long turnover time, treatment for TB should not be delayed if other factors are strongly suggestive of TB. Clinicians should have a high index of suspicion for EPTB and should pay special attention to the younger age group.

What is already known on this topic

Diagnosis of pediatric TB can be challenging as presentation ranges from non-specific symptoms to severe clinical presentation. The proportion of EPTB has increased in the adult population. However, little is known about the global impact of pediatric EPTB.

What this study adds

Common clinical presentations involving a third of patients with both PTB and EPTB were significant fever, cough and weight loss. Patients with EPTB were more likely to be immunodeficient. Extra-pulmonary TB is more common in the younger age group and is associated with lower recovery rate.

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Table 1. Comparison of Pulmonary and Extra-pulmonary TB

	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)	P value
Median age (years)	10.1 (IQR 3.5, 13,5)	5.1 (IQR 1.2, 10.2)	0.03
Gender			
Males	25 (51)	14 (54)	0.82
Females	24 (49)	12 (46)	
Nationality			
Singapore residents	37 (76)	16 (62)	0.21
Non-Singapore residents	12 (24)	10 (38)	
Received BCG vaccine	41 (89)	19 (76)	0.14
Comorbidities			
Immunodeficient	3 (6)	9 (35)	<0.01
Not immunodeficient	46 (94)	17 (65)	
Contact history			
Positive contact	22 (45)	6 (23)	0.06
No contact history	27 (55)	20 (77)	
Symptoms			
Significant fever	9 (19)	11 (48)	0.01
Significant cough	22 (51)	3 (14)	<0.01
Significant weight loss	18 (39)	6 (27)	0.34
Median weight loss (%body weight)	10.6 (IQR 5.8, 20.0)	16.3 (IQR 13.6, 40.6)	0.29
Fatigue	2 (4)	2 (8)	0.60
Lymphadenopathy	2 (4)	8 (31)	<0.01
≥ 2 symptoms stated above	14 (29)	5 (23)	0.61
No symptom stated above	22 (45)	11 (42)	0.83
Hematological results			
Median hemoglobin (g/dL)	12.0 (IQR 10.5, 13.9)	11.2 (IQR 10.2, 11.9)	0.03
Median white blood cells ($x10^9$/L)	11.2 (IQR 7.5 15.6)	10.2 (IQR 7.6, 12.0)	0.15
Median Platelet ($x10^9$/L)	376.5 (IQR 281.5, 451.0)	377.0 (IQR 339.5, 507.0)	0.38
Median ESR (mm/hr)	40.0 (IQR 15.0, 85.0)	34.0 (IQR 19.0, 54.5)	0.61
Median CRP (mg/L)	36.0 (IQR 16.5, 84.4)	32.4 (IQR 8.6, 69.3)	0.43
Immunological results			
Positive TST	20 (41)	6 (23)	0.10
Positive IGRA	20 (41)	12 (46)	0.80
Microbiological			
Microbiologically proven	26 (53)	19 (73)	0.10
Not microbiologically proven	23 (47)	7 (27)	
Microbiological results			
≥ 1 site/sample positive AFB smear	13 (27)	7 (28)	0.89
≥ 1 site/sample positive AFB culture	24 (49)	15 (58)	0.47
≥ 1 site/sample positive TB PCR	14 (40)	12 (60)	0.15
Abnormal CXR	41 (84)	10 (39)	<0.01
Treatment outcome			
Recovered	28 (57)	7 (27)	0.01
Death	2 (4)	4 (15)	0.17
Relapsed	1 (2)	1 (4)	-
Sequelae	10 (20)	9 (35)	0.18
Lost to follow up	8 (16)	3 (12)	0.73
Still completing treatment	0 (0)	2 (8)	-
Median duration of treatment (months)	6.0 (IQR 6.0, 9.0)	12.0 (IQR 9.0, 12.0)	<0.01

Table 2. Types of immunodefiencies in Pulmonary and Extra-pulmonary TB

Types of immunodeficiencies	Pulmonary N= 49 (%)	Extra-pulmonary N= 26 (%)
HIV	2 (4)	2 (8)
Malignancy	0 (0)	2 [b] (8)
Primary immune deficiency	0 (0)	2 [c] (8)
Others	1 [a] (2)	3 [d] (12)

[a] Ebstein Barr Virus-related haemophagocytic lymphohistiocytosis

[b] 1 Medulloblastoma on chemotherapy, 1 Neuroblastoma on chemotherapy

[c] Severe combined immunodeficiency

[d] 1 Crohn's disease on immunosuppressant, 1 Juvenile idiopathic arthritis on biologics, 1 Mendelian susceptibility to mycobacterial disease

Table 3. Outcomes of Pulmonary and Extra-pulmonary TB

	Pulmonary N = 49			Extrapulmonary N = 26		
		n	%		n	%
Types of sequelae	Bronchus compression	3	6	Intestinal perforation	1	4
	Bronchiectasis	3	6	Kyphosis	1	4
	Restrictive lung disease	2	4	CNS infarct	1	4
	Complications from underlying condition	2	4	Complications from underlying condition	2	8
				Developmental delay	2	8
				Seizures	2	8
Reasons for mortality [a]	Septic shock	1	2	Septic Shock	2	8
	Pulmonary haemorrhage	1	2	Severe Cerebral edema	1	4
				Underlying malignancy	1	4
Reasons for relapse	Reactivation of pulmonary TB with pericarditis (cause unknown)	1	2	Recurrent TB lymphadenitis (cause unknown)	1	4

[a] Of 4 EPTB: 2 TB meningitis, 1 pericardial TB, 1 multiorgan TB