



Clinical Manifestations of Pulmonary Tuberculosis in Childhood

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Abstract

Objective: To determine clinical presentations related to pulmonary tuberculosis in children.

Methods: A retrospective descriptive study was conducted in children less than 15 years old who were diagnosed with pulmonary tuberculosis at the Department of Pediatrics, Faculty of Medicine Vajira Hospital between January 1st, 2009 - January 1st, 2021. The quantitative data were analyzed into mean and standard deviation and compared between groups by unpaired t-test. The qualitative data were reported by percentage and compares between groups by Chi-square test.

Results: A total of 96 patients were included. The average age was 10.3 ± 4.6 years (6 months to 15 years old); 36.5% of patients were male and 63.5% were female, while 84.4% of the patients presented with 2 or more clinical features. Signs and symptoms described in the Thai CPG for Tuberculosis in Children 2019 that were found in this study were cough ≥ 2 weeks (58.3%), fever ≥ 7 days (57.3%), anorexia (42.7%), weight loss (25.0%), inactivity (8.3%), and poor weight gain (1%). Signs and symptoms not included in the Thai CPG for Tuberculosis in Children 2019 were afebrile (34.4%), cough < 2 weeks (28.1%), fatigue (28.1%), hemoptysis (19.8%), night sweat (15.6%), no cough (13.5%), dyspnea (12.5%), chest pain (9.4%), tachypnea (9.4%), fever < 7 days (8.3%), lymphadenopathy (8.3%), chronic vomiting and diarrhea (1%), and asymptomatic (2.1%). Ninety-two patients (95.8%) always had at least 1 clinical feature that was described in the Thai Tuberculosis CPG 2019. However, 4 patients (4.2%) in this study only presented with clinical features not included in the Thai Tuberculosis CPG 2019, including 1 patient who presented with only chest pain, 1 patient who presented with only hemoptysis, and 2 asymptomatic patients.

Conclusion: Most of the pediatric patients with pulmonary tuberculosis presented with 2 or more clinical features and almost always had at least 1 symptom that was described in the Thai Tuberculosis CPG 2019.

Keywords: childhood, pulmonary tuberculosis, clinical manifestations



ลักษณะทางคลินิกของวัณโรคปอดในเด็ก

มีดี มีผลประไพ พ.บ.¹

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาอาการและอาการแสดงที่เป็นไปได้ของผู้ป่วยเด็กที่ได้รับการวินิจฉัยวัณโรคปอด

วิธีดำเนินการวิจัย: ทำการศึกษาเชิงพรรณนาย้อนหลัง ในผู้ป่วยอายุน้อยกว่า 15 ปี ที่ได้รับการวินิจฉัยวัณโรคปอด ในภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์วชิรพยาบาล ระหว่างวันที่ 1 มกราคม พ.ศ. 2552 ถึงวันที่ 1 มกราคม พ.ศ. 2564 วิเคราะห์ข้อมูลเชิงปริมาณด้วยค่าเฉลี่ย และส่วนเบี่ยงเบนมาตรฐาน เปรียบเทียบค่าเฉลี่ยระหว่างกลุ่มโดย unpaired t-test วิเคราะห์ข้อมูลเชิงคุณภาพด้วยการนำเสนอเป็นร้อยละ เปรียบเทียบระหว่างกลุ่มโดย Chi-square test

ผลการวิจัย: พบผู้ป่วยเด็กจำนวน 96 ราย อายุเฉลี่ย 10.3 ± 4.6 ปี (6 เดือน - 15 ปี) เป็นผู้ป่วยชายร้อยละ 36.5 ผู้ป่วยหญิงร้อยละ 63.5 ที่ได้รับการวินิจฉัยวัณโรคปอด พบว่าผู้ป่วยร้อยละ 84.4 มีอาการ ≥ 2 อาการขึ้นไป ร่วมกัน โดยพบอาการที่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ได้แก่ ไอมากกว่าหรือเท่ากับ 2 สัปดาห์ (ร้อยละ 58.3) ไข้มากกว่าหรือเท่ากับ 7 วัน (ร้อยละ 57.3) เบื่ออาหาร (ร้อยละ 42.7) น้ำหนักลดไม่ทราบสาเหตุ (ร้อยละ 25.0) ซึม ไม่เล่น (ร้อยละ 8.3) และน้ำหนักไม่เพิ่มขึ้น (ร้อยละ 1) พบอาการที่นอกเหนือจากแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ได้แก่ ไม่มีไข้ (ร้อยละ 34.4) ไอน้อยกว่า 2 สัปดาห์ (ร้อยละ 28.1) อ่อนเพลีย (ร้อยละ 28.1) ไอเป็นเลือด (ร้อยละ 19.8) เหงื่อออกกลางคืน (ร้อยละ 15.6) ไม้ออ (ร้อยละ 13.5) หายใจลำบาก (ร้อยละ 12.5) เจ็บหน้าอก (ร้อยละ 9.4) หายใจเร็ว (ร้อยละ 9.4) ใช้น้อยกว่า 7 วัน (ร้อยละ 8.3) คลำได้ก้อนต่อมน้ำเหลือง (ร้อยละ 8.3) อาเจียนและถ่ายเหลวเรื้อรัง (ร้อยละ 1) และไม่มีอาการ (ร้อยละ 2.1) ผู้ป่วย 92 คน (ร้อยละ 95.8) เป็นผู้มีอาการและอาการแสดงที่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ร่วมด้วยอย่างน้อย 1 อาการ อย่างไรก็ตาม พบผู้ป่วย 4 ราย (ร้อยละ 4.2) ในการศึกษาครั้งนี้มีเฉพาะอาการที่ไม่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ได้แก่ เจ็บหน้าอกอย่างเดียว 1 ราย ไอเป็นเลือดอย่างเดียว 1 ราย และไม่มีอาการ 2 ราย

สรุป: ผู้ป่วยเด็กที่เป็นวัณโรคปอด ส่วนมากมีอาการและอาการแสดงตั้งแต่ 2 อาการขึ้นไป และเกือบทั้งหมดมีอาการและอาการแสดงที่อยู่ในแนวทางเวชปฏิบัติการรักษาวัณโรคในเด็ก พ.ศ. 2562 ร่วมด้วยอย่างน้อย 1 อาการ

คำสำคัญ: เด็ก วัณโรคปอด ลักษณะทางคลินิก

Introduction

Thailand is one of the 22 high-burden tuberculosis countries on the WHO's list¹. The estimated number of incidences is around 120,000 cases per year², but the incident reports for childhood tuberculosis in Thailand are markedly lower than in other countries¹. Identifying and treating TB infections in children provides long-term benefits in TB control. However, diagnosis of TB in children is a difficult task because of its unspecific signs and symptoms³ and radiological findings⁴. Moreover, microbiological confirmations are hard to obtain because younger patients are unlikely to expectorate sputum as effectively as adults⁵.

The Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019² was established to help diagnose tuberculosis in children based on clinical features (fever more than 7 days, cough more than 2 weeks, weight loss, poor weight gain, inactivity, and anorexia) along with contact exposures and/or tuberculin skin test and radiographic findings.

Previous studies showed that weight loss⁶⁻⁷, chronic cough⁷⁻⁸, and fatigue⁷⁻⁸ were significantly associated with pulmonary tuberculosis in children whereas persistent fever and/or chest pain were found in 25% of the patients⁸. However, some of patients diagnosed with pulmonary tuberculosis presented with fever of less than 7 days⁹⁻¹⁰ and cough less than 14 days¹⁰. Devrim I found that 13% of children diagnosed with pulmonary tuberculosis presented without fever, cough, malaise, and weight loss at the same time¹¹. In addition, 2-44.6% of patients were reported to have other symptoms such as dyspnea^{9,12}, night sweat¹¹, hemoptysis¹²⁻¹³, diarrhea⁹, vomiting⁹, hepatomegaly⁹, and lymphadenopathy⁹, or were asymptomatic⁹.

The diagnosis of pulmonary tuberculosis in children is a major challenge due to various clinical features. This study aimed to determine the typical signs and symptoms of pulmonary tuberculosis according to the Thai CPG of Treatment for Tuberculosis in Children 2019, as well as signs and symptoms that are not included in the CPG.

This information may provide benefits for clinicians to recognize typical and atypical signs and symptoms of pulmonary tuberculosis, which may improve screening and treatment for pulmonary TB.

Methods

This is a retrospective descriptive study. The study protocol was reviewed and approved by the Ethics Committee for Research in Humans, Institutional Review Board (COA 059/2563). The inclusion criteria were patients younger than 15 years old at the Department of Pediatrics, Faculty of Medicine Vajira Hospital, Navamindradhiraj University who were diagnosed with pulmonary tuberculosis from January 1st, 2009 - January 1st, 2021. The exclusion criteria were patients with latent tuberculosis infection, congenital tuberculosis, extrapulmonary tuberculosis, immunocompromised host or receiving immunosuppressive agents, and incomplete medical record.

Criteria for the diagnosis of pulmonary tuberculosis were defined according to the Thai Clinical Practice Guideline of the Treatment of Tuberculosis in Children 2019 that considers 3 elements of the following for diagnosis: 1) Signs and symptoms compatible with tuberculosis: fever > 7 days (persistent unexplained fever > 38°C reported by a guardian or objectively recorded at least once¹⁴), weight loss (an unexplained reduction of weight of more than 5% within 3 months¹⁴), poor weight gain (inability to maintain the percentile curve of the growth chart or a percentile drop during the period prior to TB diagnosis⁹), inactive (unexplained lethargy or decrease in activity reported by a parent or caregiver¹⁴), cough > 2 weeks (persistent, non-remitting cough > 2 weeks¹⁴) and anorexia; 2) Contact with a TB index case or a positive result for tuberculin skin test (TST), and 3) Abnormal radiographic finding such as hilar adenopathy, Ghon's complex, intrapulmonary calcification, miliary infiltration, cavity, lobar or segmental atelectasis, or pleural effusion. Pulmonary tuberculosis was defined as one of the following:

- 1) Patients who presented with all three criteria;
- 2) Patients who presented with signs and symptoms and abnormal radiographic findings who did not improve after receiving treatment for bacterial pneumonia, and 3) Patients with military infiltration.

Statistical analysis

A sample size of 96 was estimated by the infinite population size formula¹⁵

$$n = \frac{Z_{\alpha/2}^2 p(1 - p)}{d^2}$$

in which *p* is the prevalence of signs and symptoms in a pediatric patient with pulmonary tuberculosis in line with the research of Tarunotai U.¹², (*p* = 0.514), acceptable type I error is set at 5% (*α* = 0.05) and *d* (Error) equal to 0.1

The statistical analysis was performed using SPSS version 22.0. The quantitative data such as age and weight were analyzed into means and standard deviations and compared between groups by unpaired t-test. The qualitative data such as the result of microbiological confirmations, criteria for diagnosis, and clinical manifestations were reported by percentage and compared between groups by Chi-square test.

Results

This study collected data from pediatric patients at Vajira Hospital who were diagnosed with pulmonary tuberculosis from January 1st, 2009 - January 1st, 2021. A total of 96 patients were included (figure 1). Thirty-five patients (36.5%) were male and 61 (63.5%) patients were female, with an age ranging from 6 months to 15 years old. The average age was 10.3 ± 4.6 years and most of the children were 10 to 15 years old. Among the cases, 8.3% had underlying diseases, including 2 patients with asthma and one patient each with bronchiectasis, G6PD deficiency, congenital cystic adenomatoid malformation, epilepsy, Down syndrome, and thalassemia (table 1).

There were 78.2% of the patients who met all three criteria of Thai Clinical Practice Guideline of the Treatment of Tuberculosis in Children 2019 as shown in Table 1, with 36.5% of this group having at least one microbiological confirmation. There were 18.8% of the patients who met only two criteria, including clinical features and radiological abnormality, but because of their positive microbiological results, the diagnosis can be made.

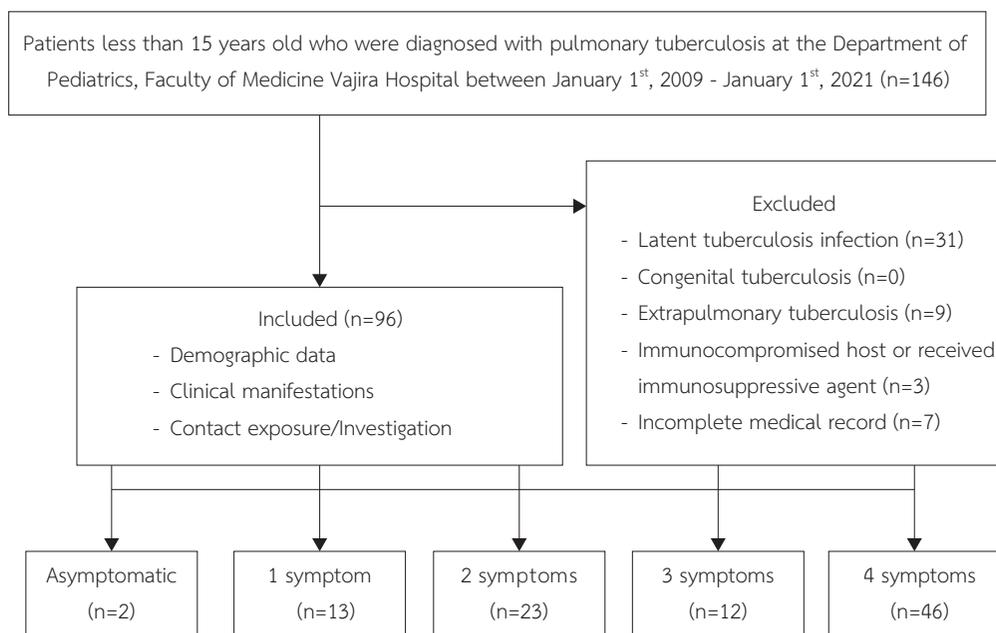


Figure 1 Subjects flowchart

Table 1:

Demographic data of childhood pulmonary TB patients (n=96)

	Number (%)
Age distribution (years)	
<1 year	3 (3.1)
1-4 years	13 (13.5)
5-9 years	17 (17.7)
10-15 years	63 (65.6)
Body weight (percentile)	
< P3	4 (4.2)
P3 – P97	83 (86.4)
≥ P97	9 (9.4)
TB contact history	59 (61.5)
TST positive	54 (81)
Microbiological examination	
AFB positive	47 (51.6)
Culture for <i>M. tuberculosis</i> positive	14 (16.9)
PCR for <i>M. tuberculosis</i> positive	7 (30)
Criteria diagnosis for pulmonary TB	
Clinical + TST/Contact history + Radiological finding	40 (41.7)
Clinical + TST/Contact history + Radiological finding + Microbiological confirmation	35 (36.5)
Clinical + Radiological finding + Microbiological confirmation	18 (18.8)
TST/Contact history + Radiological finding	2 (2.1)
Clinical + Radiological finding	1 (1.0)

There were 2 cases (2.1%) who were asymptomatic, and met only the two criteria of contact history and abnormal CXR findings; both were treated with anti-TB drugs. The chest x-ray findings improved as the treatment was completed. There was 1 patient, a 13-year-old boy, who presented with hemoptysis of 1 week, who had been diagnosed with pulmonary TB only from clinical and radiological criteria, with neither a history of TB contact nor positive TST, and the microbiological confirmation was also negative. The CXR showed reticular infiltration in both upper lungs, therefore, CT chest was performed as an additional investigation. The findings were infiltration and consolidation at the right upper lung and left upper lung, with a tree-in-bud pattern, suggesting

pulmonary TB. The patient was treated with anti-TB drugs and was successfully cured.

The outcome of the treatment revealed that 86 (89.6%) of the children were cured, 6 (6.3%) continued treatment at other hospitals, 4 (4.2%) were lost to follow up and none died.

The most common of the signs and symptoms in our study was cough (86.5%), followed by fever (65.6%), anorexia (42.7%), fatigue (28.1%), weight loss (25%), and hemoptysis (19.8%) as displayed in Table 2. There were 4 patients (4.2%) without any signs and symptoms described in the Thai Clinical Practice Guideline of the Treatment of Tuberculosis in Children 2019², including one patient who presented with only chest pain, another with only hemoptysis, and 2 patients without any symptoms.

Table 2 Clinical manifestations of childhood pulmonary TB patients

Signs and symptoms described in Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019*	Number (%)
Cough \geq 2 weeks	56 (58.3)
Fever \geq 7 days	55 (57.3)
Anorexia	41 (42.7)
Weight loss	24 (25.0)
Inactive	8 (8.3)
Poor weight gain	1 (1.0)
Signs and symptoms not included in Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019*	Number (%)
Afebrile	33 (34.4)
Cough < 2 weeks	27 (28.1)
Fatigue	27 (28.1)
Hemoptysis	19 (19.8)
Night sweat	15 (15.6)
No cough	13 (13.5)
Dyspnea	12 (12.5)
Tachypnea	9 (9.4)
Chest pain	9 (9.4)
Fever < 7 days	8 (8.3)
Lymphadenopathy	8 (8.3)
Chronic vomiting and diarrhea	1(1.0)
Asymptomatic	2 (2.1)

*Each patient may have more than 1 of the signs and/or symptoms.

In 63 patients presenting with fever, 55 of them (87.3%) had a fever for more than 7 days; 8 (12.7%) had fever for fewer than 7 days, while 33 (34.4%) patients were afebrile. Therefore 41 of 96 patients (42.7%) had a fever for fewer than 7 days or had no fever. Also, in 83 patients presenting with cough, 56 (64.7%) had a cough for more than 2 weeks and 27 (32.5%) had a cough for less than 2 weeks, while 13 (13.5%) patients did not have a cough. Hence, 40 of 96 patients (41.6%) had a cough for less than 2 weeks or did not have a cough at all.

Thirty patients (31.2%) were reported to have both fever for more than 7 days and cough

for more than 2 weeks, whereas 15 (15.6%) had both fever for fewer than 7 days and cough for less than 2 weeks. The number of patients with either fever for more than 7 days or cough for more than 2 weeks was 81 (84.4%).

Most of the patients (47.9%) presented with 4 or more clinical features, 13 (13.5%) presented with 1 symptom, 23 (24%) presented with 2 symptoms, 12 (12.5%) presented with 3 symptoms, and 2 (2.1%) were asymptomatic, as shown in Table 3. The maximum number of symptoms (8 symptoms) was found in 1 patient, including fever, cough, hemoptysis, tachypnea, dyspnea, chest pain, fatigue, and night sweat.

Table 3 Summary of signs and symptoms for each individual patient

	Number (%)
1 symptom	13 (13.5)
Only cough \geq 2 weeks	8 (8.3)
Only fever \geq 7 days	3 (3.1)
Only hemoptysis*	1 (1.0)
Only chest pain*	1 (1.0)
2 symptoms	23 (24.0)
Fever \geq 7 days and cough \geq 2 weeks	6 (6.3)
Cough \geq 2 weeks and hemoptysis*	5 (5.2)
Fever \geq 7 days and cough $<$ 2 weeks*	4 (4.2)
Cough \geq 2 weeks and anorexia	4 (4.2)
Cough $<$ 2 weeks* and anorexia	2 (2.1)
Cough \geq 2 weeks and chest pain*	1 (1.0)
Fever \geq 7 days and fatigue*	1 (1.0)
3 symptoms	12 (12.5)
Cough \geq 2 weeks, hemoptysis* and fatigue*	2 (2.1)
Fever \geq 7 days, cough \geq 2 weeks and weight loss	2 (2.1)
Fever \geq 7 days, weight loss and lymphadenopathy*	2 (2.1)
Fever \geq 7 days, cough \geq 2 weeks and anorexia	2 (2.1)
Fever \geq 7 days, cough $<$ 2 weeks* and anorexia	1 (1.0)
Fever $<$ 7 days*, cough $<$ 2 weeks* and anorexia	1 (1.0)
Fever \geq 7 days, cough $<$ 2 weeks* and hemoptysis*	1 (1.0)
Fever \geq 7 days, cough $<$ 2 weeks* and fatigue*	1 (1.0)
\geq 4 symptoms	46 (47.9)
No symptoms	2 (2.1)

* Not included in the Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019

Discussion

A majority of the patients (78.2%) met all three diagnostic criteria for pulmonary tuberculosis described in the Thai Clinical Practice Guideline of Treatment for Tuberculosis in Children 2019² with or without having the microbiological confirmation for diagnosis. Among this group, 2.1% of the patients only had symptoms that were not included in the Thai

Tuberculosis CPG 2019² (only chest pain and only hemoptysis at the time of presentation), while 18.8% of the patients met only two criteria, including clinical features and radiological abnormality, but because of their positive microbiological results, the diagnosis can be made. There were 2.1% of the patients who were asymptomatic and were diagnosed with pulmonary tuberculosis due to a history of

contact tuberculosis and abnormal radiological findings, while 1% of the patients had clinical features and abnormal radiological findings without a history of contact with tuberculosis. Therefore, the Thai CPG of Treatment for Tuberculosis in Children 2019² can establish the diagnosis of pulmonary TB in most of the patients, but there are some limitations in those who have a history of contact exposure but are asymptomatic or presented with symptoms not included in the CPG.

In our study, signs and symptoms described in the Thai CPG 2019² were reported, including cough for more than 2 weeks (58.3%), fever for more than 7 days (57.3%), anorexia (42.7%), weight loss (25%), inactivity (8.3%), and poor weight gain (1%). Cough and fever are the main symptoms of pulmonary tuberculosis, as reported by Devrim I¹¹ and Tarunotai U¹² who stated that cough and fever were reported in 81.5 – 94.4% and 33.7 – 71.4%, respectively. Anorexia was also found in a study from Marais BJ⁶ (22.2%). The number of patients who had weight loss in this study was close to that of the study of Marais BJ⁶ (27.8%). Nevertheless, most of the patients did not have all of the signs and symptoms that were included in the Thai tuberculosis CPG² at the same time. We found that 84.4% presented with 2 or more clinical features, and among those were clinical features both included and not included in this CPG.

Signs and symptoms not included in the Thai tuberculosis CPG 2019² that were found in this study included afebrile (34.4%), cough for less than 2 weeks (28.1%), no cough (13.5%), and fever for less than 7 days (8.3%). There were 15.6% of patients who presented with neither cough for more than 2 weeks nor fever for more than 7 days, which was relatively lower than in Zar HJ¹⁰ (21%) and Soriano-Arandes A⁹ (38.6%). Other signs and symptoms not mentioned in the Thai tuberculosis CPG 2019² that were also found in this study were as follows: fatigue (28.1%), hemoptysis (19.8%), night sweat (15.6%),

dyspnea (12.5%), tachypnea (9.4%), and chest pain (9.4%). These were clinical features that were also reported in Marais BJ⁶. In addition, 8.3% of the patients in this study had lymphadenopathy, which was slightly higher than in Soriano-Arandes A⁹ and Limpokaiyakul P¹³ in which lymphadenopathy was found in 2% and 4.4% of the patients, respectively. Chronic diarrhea and vomiting were reported in 1% of the patients, which was also reported in Soriano-Arandes A⁹ who found 5% of the patients presented with vomiting and 6.9% presented with diarrhea. In addition, there were asymptomatic patients reported at 2.1% in this study, which was lower than in Devrim I¹¹ and Marais BJ⁶ (13-50%).

Most of the patients who presented with clinical features not included in Thai tuberculosis CPG 2019² almost always had other clinical features that were described in this CPG concurrently, making the diagnosis of pulmonary tuberculosis more convenient. However, 4 patients (4.2%) in this study were an exception. They presented with only clinical features not included in tuberculosis CPG 2019² including 1 patient who presented with only chest pain, 1 patient with only hemoptysis, and 2 asymptomatic patients. Therefore, other information, such as history of contact exposure or radiographic features compatible with pulmonary tuberculosis became an important factor for making the diagnosis of pulmonary tuberculosis in childhood.

The limitation of this study is that we gathered information in a retrospective manner, using data collected from medical records in the past, so some of the data may be incomplete or have information errors due to recording errors.

Conclusion

The clinical features of pulmonary tuberculosis in childhood are varied. Patients may have signs and symptoms included or not included in the Thai Clinical Practice Guideline of Treatment for Tuberculosis in

Children 2019. A majority of the patients had 2 or more symptoms, while 95.8% of the patients had at least 1 symptom described in the CPG and could be diagnosed with pulmonary TB based on clinical symptoms described in the Thai CPG criteria. Only 4.2% presented with clinical features not included in the CPG and were diagnosed based on contact exposure or radiographic features compatible with pulmonary tuberculosis. This made the Thai CPG a suitable guideline for the diagnosis of pulmonary tuberculosis in childhood.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Lolekha R, Anuwatnonthakate A, Nateniyom S, Sumnapun S, Yamada N, Wattanaamornkiat W, et al. Childhood TB epidemiology and treatment outcomes in Thailand: a TB active surveillance network, 2004 to 2006. *BMC Infect Dis* 2008;8:94.
2. Division of Tuberculosis, Department of Disease Control Ministry of Public Health and Pediatric Infectious Disease Society of Thailand. Clinical practice guideline of treatment for tuberculosis in children 2019. [cited 2021 Jan 2]. Available from: <https://pidst.net/A717.html>.
3. Eamranond P, Jaramillo E. Tuberculosis in children: reassessing the need for improved diagnosis in global control strategies. *Int J Tuberc Lung Dis* 2001;5(7):594-603.
4. Thomas TA. Tuberculosis in children. *Pediatr Clin North Am* 2017;64(4):893-909.
5. Osborne CM. The challenge of diagnosing childhood tuberculosis in a developing country. *Arch Dis Child* 1995;72(4):369-74.
6. Marais BJ, Obihara CC, Gie RP, Schaaf HS, Hesselning AC, Lombard C, et al. The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high burden community. *Arch Dis Child* 2005;90(11):1166-70.
7. Marais BJ, Gie RP, Hesselning AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics* 2006;118(5):e1350-9.
8. Marais BJ, Gie RP, Obihara CC, Hesselning AC, Schaaf HS, Beyers N. Well defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis. *Arch Dis Child* 2005;90(11):1162-5.
9. Soriano-Arandes A, Brugueras S, Rodríguez Chitiva A, Noguera-Julian A, Orcau À, Martín-Nalda A, et al. Clinical presentations and outcomes related to tuberculosis in children younger than 2 years of age in Catalonia. *Front Pediatr* 2019;7:238.
10. Zar HJ, Workman LJ, Little F, Nicol MP. Diagnosis of pulmonary tuberculosis in children: assessment of the 2012 National Institutes of Health Expert Consensus Criteria. *Clin Infect Dis* 2015;61Suppl 3(Suppl 3): S173-8.
11. Devrim I, Aktürk H, Bayram N, Apa H, Tulumoğlu S, Devrim F, et al. Differences between pediatric extra-pulmonary and pulmonary tuberculosis: a warning sign for the future. *Mediterr J Hematol Infect Dis* 2014;6(1):e2014058.
12. Tarunotai U, Sirikunakorn P, Apiwathnasorn R. Tuberculosis in pediatric patients in Faculty of Medicine Vajira Hospital. *Vajira Med J* 2013;57:27-35.
13. Limpokaiyakul P. Contact TB investigation for children at Krabi Hospital. *Thai J of Pediatr* 2015;54:117-25.

14. Graham SM, Ahmed T, Amanullah F, Browning R, Cardenas V, Casenghi M, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis* 2012;205 Suppl 2(Suppl 2):S199-208.
15. Daniel WW. *Biostatistics: a foundation for analysis in the health sciences*. 6th ed. Hoboken: John Wiley&Sons;1995. p.1-777.