Age-specific Clinical Presentation and Risk Factors for Extrapulmonary Tuberculosis Disease in Children

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Background: Clinical presentation for extrapulmonary tuberculosis (EPTB) in children can be variable and nonspecific, leading to delayed diagnosis, disease and death. We describe the age-specific clinical presentation and identify risk factors for EPTB among children in Pakistan.

Methods: In 2015–2016 in 4 facilities in Sindh, Pakistan, children were diagnosed with TB either through bacteriologic confirmation or clinical-radiologic criteria. EPTB comprised any form of TB disease that did not involve the lungs. Among children with TB disease, we report demographics, clinical characteristics and symptoms, family medical history and diagnostic test results for children with and without EPTB. We conduct age-specific regression analyses to identify factors associated with an EPTB diagnosis among children age 0–4, 5–9 and 10–14 years.

Results: A total of 1163 children were diagnosed with TB disease, of which 157 (13.5%) had EPTB. Of those, 46 (29.3%) were 0–4, 53 (33.8%) were 5–9 and 58 (36.9%) were 10–14 years old. Of children with EPTB, the most frequently reported sites were lymph node (113, 72.4%) and abdominal (31, 19.9%). Weight loss was associated with an increased risk of EPTB in the 0–4-year-old (adjusted odds ratio: 2.80, 95% confidence interval: 1.05–7.47) and 10–14-year-old (adjusted odds ratio: 2.79, 95% confidence interval: 1.28–6.07) groups, and the presence of cough was associated with a decreased risk of EPTB.

Conclusions: This study provides new knowledge about age-specific clinical presentation and risk factors of EPTB in children in Pakistan. Our results can help to optimize clinical algorithms designed to achieve a timely diagnosis in children with EPTB along with improved treatment outcomes.

Key Words: pediatric, epidemiology, diagnosis, extrapulmonary

(*Pediatr Infect Dis J* 2022;41:620–625)

In 2019, extrapulmonary tuberculosis (EPTB) accounted for about 16% of 7.1 million reported TB cases globally.[1] Children are more likely to present with EPTB compared with adults, with younger age and developing immunity contributing to elevated disease risk.[2,3] In 2020, 1.1 million children (<15 years old) were estimated to develop TB.[4] The global burden of EPTB among children specifically remains unknown.

Challenges to estimating the burden of EPTB include difficulty with bacteriologic confirmation of pediatric disease as well as under-reporting of pediatric cases.[5] The pathogenesis of EPTB generally consists of primary lung disease with hematogenous dissemination of the *Mycobacterium tuberculosis* to other parts of the body.[3] Specific barriers for diagnosing EPTB include variable and nonspecific clinical presentation, which present unique diagnostic challenges.[6] These lead to delays in diagnosis of EPTB, which in turn contributes to poor treatment outcomes. There is an urgent need to understand which children are at higher risk of EPTB to improve TB diagnosis, prompt treatment initiation and subsequent treatment outcomes.

As a top 30 high TB burden country, Pakistan accounts for 5.8% of all estimated incident TB cases worldwide.[4] Additionally, Pakistan has a high number of EPTB cases, which accounts for 20% of all notified TB cases.[2] Children in Pakistan are burdened with high levels of acute and chronic malnutrition, which contribute to these high TB burdens.[7] A descriptive analysis performed in Pakistan among 3607 children (age 0–14 years) with TB registered nationwide in 2016 found the following frequency of EPTB disease by site: abdominal TB (38.4%), lymphatic TB (22.4%), pleural TB (14.0%), central nervous system (CNS; 6.0%), osteoarticular (3.9%) and site not specified (12.1%).[2] Beyond that report, there are limited data in the literature about the clinical presentation of EPTB and risk factors for EPTB in children, by age group.

To fill this gap, we describe the age-specific clinical presentation and risk factors for EPTB among children diagnosed with TB disease in Pakistan.

MATERIALS AND METHODS

Setting, Intervention and Definitions

Between October 2014 and March 2016, 4 public sector health facilities in Jamshoro District, Pakistan, implemented a screening program designed to improve diagnosis of children with TB disease. Children were screened for symptoms and contact history by health workers and were referred to a TB medical officer for a clinical evaluation for TB. Elsewhere, we describe details of the screening procedures used.[8–10] Children received a clinical evaluation, including chest radiograph, complete blood count and erythrocyte sedimentation rate, and—if they could produce sputum—additional testing such as Xpert MTB/RIF assay and acid fast bacilli smear. If indicated, abdominal ultrasound, computed tomography and/or fine-needle aspiration/biopsy were performed. Gastric aspirates and induced sputum procedures were not available. During the first quarter of the program (October 2014 to December

2014), audit of the clinical data raised a possibility of overdiagnosis of abdominal TB. We retrained all the project medical officers in the next quarter (January 2015 to March 2015) and put in place a mechanism that required discussion of EPTB diagnosis with the project pediatrician. A random sample of all TB patients diagnosed was also independently validated by the district TB coordinator throughout the remainder of the program. Thus, in this analysis, we include children diagnosed with EPTB after the implementation of quality checks to improve EPTB diagnoses, between April 2015 and March 2016.

A case of TB disease was determined by a physician on review of the clinical, laboratory, radiologic and/or histopathologic test results. A case of EPTB disease was defined as having any form of TB disease that did not involve the lungs. Pulmonary TB (PTB) was defined as having TB disease with lung involvement. A patient with both PTB and EPTB was classified as a case of PTB.[11] Children diagnosed with TB were started on treatment per the National TB Program guidelines of Pakistan.[12]

Study Population and Data Collection

Children were included in this analysis if they were between 0 and 14 years of age. Demographic and clinical characteristics were collected and entered into a custom-built electronic data collection tool.[8] Demographic information included sex and age. Clinical characteristics included weight-for-age percentile, recorded using the World Health Organization's (WHO) growth charts for children 0–2 years old and the U.S. Centers for Disease Control and Prevention's growth charts for children older than 2 years old.[13] We classified each child according to whether their weight-for-age was at or below the fifth percentile, or higher than the fifth percentile. Other clinical characteristics recorded were symptoms—such as cough for 2 weeks or longer, cough duration (characterized as no cough, less than 2 weeks, between 2 and 3 weeks, and greater than 3 weeks), fever lasting 2 or more weeks, and weight loss—and the presence of Bacillé Calmette-Guerin (BCG) vaccination scars. Family medical history included history of TB, family member TB type (EPTB or PTB), family member with TB (mother, father, or other) and whether the family member was sputum positive. Diagnostic test results included chest examination, abdominal examination, lymph node examination, chest radiograph, abdominal ultrasound and histopathology suggestive of TB. Type of TB was characterized as EPTB or PTB. Sites of EPTB disease included abdominal, lymph node, bone, CNS, pleural or other.

Statistical Analysis

We report demographics, symptoms, medical and family history and clinical examination results for children diagnosed with any form of TB disease and compare these characteristics across children diagnosed with PTB and EPTB using χ^2 or Fisher exact tests. We report the odds ratios (OR), 95% confidence intervals (CIs) and P values produced from univariable and multivariable analyses for 6 different regression analyses.

TABLE 1. Demographics, Clinical Characteristics and Symptoms, Family Medical History, and Diagnostic Results of Children With Pulmonary and Extrapulmonary Tuberculosis (N = 1163)

Characteristics	Total Children With TB N = 1163 (100%) (n, %)	Children With EPTB N = 157 (13.5%) (n, %)	Children With PTB N = 1006 (86.5%) (n, %)	P Value
Demographic information				
Female	499 (42.9)	73 (46.5)	426 (42.4)	0.328
Age				
0–4	565 (48.6)	46 (29.3)	519 (51.6)	<0.001
5–9	346 (29.8)	53 (33.8)	293 (29.1)	
10–14	252 (21.7)	58 (36.9)	194 (19.3)	
Clinical characteristics and symptoms				
Weight percentile <5th (N = 1150)	948 (81.5)	87 (57.2)	861 (86.3)	<0.001
Cough (N = 1122)	1072 (92.2)	115 (78.8)	957 (98.1)	<0.001
Cough duration (N = 1066)				
No cough	86 (7.4)	56 (50.0)	30 (3.1)	<0.001
<2 wk	90 (7.7)	12 (10.7)	78 (8.2)	
2–3 wk	289 (24.8)	19 (17.0)	270 (28.3)	
>3 wk	601 (51.7)	25 (22.3)	576 (60.4)	
Fever (N = 1162)	1000 (86.0)	145 (92.4)	855 (85.1)	0.014
Weight loss (N = 1158)	889 (76.4)	135 (87.1)	754 (75.2)	0.001
Presence of a BCG scar (N = 1056)	741 (63.7)	91 (65.5)	650 (70.9)	0.194
Family medical history				
Family history of TB	1092 (93.9)	139 (88.5)	953 (94.7)	0.003
Family TB type EPTB (N = 1082)	1078 (92.7)	133 (97.1)	945 (100.0)	N/A
Family member with TB (N = 1090)				
Mother	1043 (89.7)	125 (89.9)	918 (96.5)	<0.001
Father	3 (0.3)	0 (0)	3 (0.3)	
Other	44 (3.8)	14 (10.1)	30 (3.2)	
Family member with sputum positive TB (N = 1091)	1041 (89.5)	129 (92.8)	912 (95.8)	0.115
Diagnostic test results				
Chest examination suggestive of TB (N = 1105)	992 (85.3)	39 (27.9)	953 (98.8)	<0.001
Abdominal examination suggestive of TB (N = 1105)	60 (5.2)	38 (27.1)	22 (2.3)	<0.001
Lymph node examination suggestive of TB (N = 1105)	128 (11.0)	95 (67.9)	33 (3.4)	<0.001
Chest radiograph suggestive of TB (N = 1145)	1021 (87.8)	38 (26.6)	983 (98.1)	<0.001
Ultrasound abdomen suggestive of TB (N = 98)	94 (8.1)	39 (97.5)	55 (94.8)	0.643*
Histopathology suggestive of TB (N = 19)	19 (1.6)	18 (100.0)	1 (100.0)	N/A

*Fisher's exact text used; otherwise, χ^2 test used.

Model 1 identifies risk factors associated with being diagnosed with EPTB for all children (0–14 years old) who were diagnosed with any form of TB disease. Models 2–4 also identify risk factors for EPTB for children in each of the following age groups: 0–4-, 5–9-, and 10–14-year-olds. Models 5 and 6 aim to identify risk factors associated with being diagnosed with abdominal and lymph node TB, respectively, for all children (0–14 years old) who were diagnosed with EPTB. These EPTB subtypes were chosen as they are known to be the most prevalent in children in Pakistan.[2]

All univariable analyses assessed the associations of gender, age, weight percentile, cough, cough duration, fever, weight loss, presence of a BCG scar and family history of TB with the specific outcome. Multivariable analyses were restricted to only the following variables being eligible for potential inclusion: cough, fever and weight loss were eligible for models 1–4; age group, cough, fever and weight loss were eligible for models 5 and 6. Backward selection was used to determine inclusion of these potential variables in the final multivariable models; those with a *P* value <0.05 were retained in the final model. Among children with EPTB, we also assessed the percentage that had EPTB at 6 different sites (abdomen, lymph node, bone, CNS, pleural and other) by age group. Analyses were completed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Ethics

Ethics review was conducted by the Institutional Review Board of Interactive Research and Development, Karachi, Pakistan, for the original screening study. Verbal informed consent was obtained from all children's guardians as well as from children over the age of 7. The Harvard Medical School Institutional Review Board determined analysis of the deidentified dataset to be exempt from review.

RESULTS

A total of 1166 children were diagnosed with TB disease during the intervention period. Of those, the type of TB (PTB or EPTB) was reported in 1163 (99.7%) children; 1006 (86.5%) had PTB while 157 (13.5%) had EPTB. Of those with EPTB, 46 (29.3%) were 0–4, 53 (33.8%) were 5–9 and 58 (36.9%) were 10–14 years old (Table 1). This age breakdown was significantly different from that observed for children with PTB, in which 519 (51.6%) were 0–4, 293 (29.1%) were 5–9 and 194 (19.3%) were 10–14 years old (*P* < 0.001). Compared with children with PTB, less children with EPTB were under the 5th weight percentile (86.3% vs. 57.2%; *P* < 0.001), reported cough (98.1% vs. 78.8%; *P* < 0.001), had a family history of TB (94.7% vs. 88.5%; *P* = 0.003) and had a chest radiograph suggestive of TB disease (98.1% vs. 26.6%; *P* < 0.001). On the contrary, compared with children with PTB, more children with EPTB reported a fever (85.1% vs. 92.4%; *P* = 0.014) or weight loss (75.2% vs. 87.1%; *P* = 0.001).

Among children with EPTB, the most frequently reported sites were the abdomen (19.9% overall; 43.5%, 5.8%, and 13.8% in children 0–4, 5–9 and 10–14 years old, respectively) and lymph nodes (72.4% overall; 50.0%, 84.6% and 79.3% in children 0–4, 5–9 and 10–14 years old, respectively; Fig. 1). The site of disease was not reported for 1 child with EPTB.

In univariable regression analysis, we observed that increasing age, presence of fever and weight loss were all associated with increased odds of EPTB disease in children 0–14 years old who were diagnosed with TB (Table 2). Weight below the 5th percentile, presence of cough, and a family history of TB were all associated with lower odds of EPTB disease. In multivariable analysis, cough was associated with lower odds of having EPTB disease (OR: 0.18, 95% CI: 0.14–0.24; *P* < 0.001) while weight loss was associated with higher odds of EPTB (OR: 2.02, 95% CI: 1.29–3.14; *P* = 0.002).
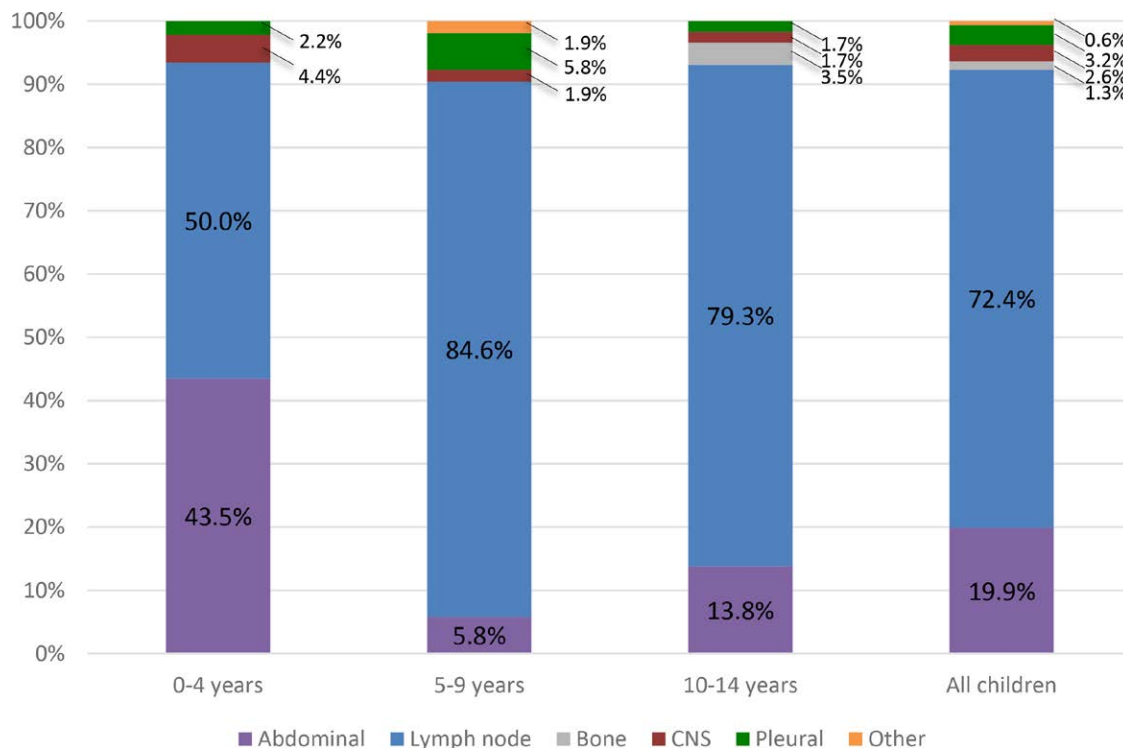

FIGURE 1. Age-specific percentages of site of EPTB disease in children (n = 156).

TABLE 2. Risk Factors for EPTB in Children 0–14 Years Old With TB Disease (n = 1163)

Characteristics	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female	1.16 (0.86–1.55)	0.328		
Age				
0–4	Ref	Ref		
5–9	1.88 (1.30–2.73)	<0.001		
10–14	2.83 (1.98–4.04)	<0.001		
Weight percentile <5th	0.29 (0.22–0.38)	<0.001		
Cough	0.17 (0.13–0.23)	<0.001	0.18 (0.14–0.24)	<0.001
Cough duration				
No cough	Ref	Ref		
<2 wk	0.20 (0.12–0.35)	<0.001		
2–3 wk	0.10 (0.06–0.16)	<0.001		
>3 wk	0.06 (0.04–0.10)	<0.001		
Fever	1.96 (1.11–3.44)	0.020		
Weight loss	2.04 (1.30–3.20)	0.002	2.02 (1.29–3.14)	0.002
Presence of a BCG scar	0.81 (0.58–1.11)	0.192		
Family history of TB	0.50 (0.33–0.77)	0.002		

Across univariable models for all 3 separate age groups, weight below the 5th percentile, presence of cough and increasing cough duration was significantly associated with lower odds of EPTB (Table 3). Additionally, in the 0–4- and 10–14-year-old models, weight loss was associated with higher odds of EPTB; and in the 0–4-year-old model, the presence of BCG scars and family

TABLE 3. Age Group-specific Risk Factors for EPTB in Children 0–4, 5–9 and 10–14 Years Old Who Were Diagnosed With TB

Characteristics	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
0–4-year-old model (n = 565)				
Female	0.94 (0.53–1.65)	0.820		
Weight-for-age <5th percentile	0.23 (0.13–0.41)	<0.001		
Cough	0.11 (0.07–0.19)	<0.001	0.12 (0.07–0.19)	<0.001
Cough duration				
No cough	Ref	Ref		
<2 wk	0.20 (0.07–0.57)	0.002		
2–3 wk	0.12 (0.05–0.28)	<0.001		
>3 wk	0.06 (0.02–0.13)	<0.001		
Fever	6.89 (0.96–49.2)	0.055		
Weight loss	3.04 (1.11–8.33)	0.031	2.80 (1.05–7.47)	0.039
BCG scars	0.53 (0.29–0.97)	0.040		
Family history of TB	0.31 (0.16–0.59)	<0.001		
5–9-year-old model (n = 346)				
Female	0.88 (0.53–1.47)	0.628		
Weight percentile <5th	0.24 (0.15–0.39)	<0.001		
Cough	0.22 (0.13–0.39)	<0.001	0.22 (0.13–0.39)	<0.001
Cough duration				
No cough	Ref	Ref		
<2 wk	0.17 (0.06–0.49)	0.001		
2–3 wk	0.10 (0.05–0.20)	<0.001		
>3 wk	0.04 (0.02–0.10)	<0.001		
Fever	1.93 (0.73–5.11)	0.184		
Weight loss	1.37 (0.70–2.67)	0.359		
BCG scars	1.08 (0.61–1.90)	0.805		
Family history of TB	0.48 (0.20–1.13)	0.091		
10–14-year-old model (n = 252)				
Female	1.47 (0.93–2.35)	0.102		
Weight percentile <5th	0.35 (0.23–0.55)	<0.001		
Cough	0.24 (0.16–0.34)	<0.001	0.25 (0.18–0.35)	<0.001
Cough duration				
No cough	Ref	Ref		
<2 wk	0.35 (0.16–0.76)	0.008		
2–3 wk	0.12 (0.05–0.29)	<0.001		
>3 wk	0.12 (0.07–0.22)	<0.001		
Fever	1.38 (0.67–2.81)	0.383		
Weight loss	2.50 (1.19–5.23)	0.015	2.79 (1.28–6.07)	0.010
BCG scars	0.71 (0.43–1.18)	0.183		
Family history of TB	0.86 (0.39–1.90)	0.717		

TABLE 4. Logistic Regression Results to Identify Risk Factors for Abdominal and Lymph Node TB in Children Diagnosed With EPTB

Characteristics	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Abdominal TB model (n = 156)				
Female	0.74 (0.39–1.41)	0.358		
Age				
0–4	Ref	Ref	Ref	Ref
5–9	0.13 (0.04–0.42)	<0.001	0.12 (0.04–0.37)	<0.001
10–14	0.32 (0.15–0.65)	0.002	0.30 (0.15–0.60)	<0.001
Weight percentile <5th	6.87 (2.18–21.60)	0.001		
Cough	2.54 (0.83–7.80)	0.104	3.04 (1.04–8.91)	0.043
Cough duration				
No cough	Ref	Ref		
<2 wk	18.33 (4.44–75.70)	<0.001		
2–3 wk	13.03 (3.08–55.02)	<0.001		
>3 wk	9.90 (2.31–42.52)	0.002		
Fever	2.50 (0.37–16.77)	0.345		
Weight loss	2.16 (0.56–8.38)	0.264		
BCG scars	0.06 (0.02–0.19)	<0.001		
Family history of TB	1.89 (0.49–7.27)	0.354		
Lymph node TB model (n = 156)				
Female	1.11 (0.91–1.34)	0.303		
Age				
0–4	Ref	Ref	Ref	Ref
5–9	1.69 (1.24–2.31)	<0.001	1.69 (1.24–2.31)	<0.001
10–14	1.59 (1.16–2.18)	0.004	1.59 (1.16–2.18)	0.004
Weight percentile <5th	0.67 (0.55–0.81)	<0.001		
Cough	1.05 (0.80–1.37)	0.729		
Cough duration				
No cough	Ref	Ref		
<2 wk	0.36 (0.16–0.80)	0.013		
2–3 wk	0.40 (0.22–0.72)	0.002		
>3 wk	0.69 (0.51–0.94)	0.017		
Fever	0.86 (0.65–1.13)	0.273		
Weight loss	1.05 (0.77–1.42)	0.778		
BCG scars	2.51 (1.70–3.70)	<0.001		
Family history of TB	0.85 (0.68–1.08)	0.178		

history of TB also associated with higher odds of EPTB. In multivariable analyses, cough was associated with lower odds of EPTB in children 0–4 (OR: 0.12, 95% CI: 0.07–0.19; *P* < 0.001), 5–9 [OR: 0.22 (95% CI: 0.13–0.39); *P* < 0.001] and 10–14 (OR: 0.25, 95% CI: 0.18–0.35; *P* < 0.001). In children 0–4 and 10–14, weight loss was associated with higher odds of EPTB (OR: 2.80, 95% CI: 1.05–7.47; *P* = 0.039 and OR: 2.79, 95% CI: 1.28–6.07; *P* = 0.010, respectively).

In multivariable analysis in the cohort of children with EPTB, compared with children age 0–4 years, older age groups [age 5–9 (OR: 0.12, 95% CI: 0.04–0.37; *P* < 0.001) and 10–14 (OR: 0.30, 95% CI: 0.15–0.60; *P* < 0.001)] were associated with lower odds of abdominal TB disease, while the presence of cough (OR: 3.04, 95% CI: 1.04–8.91; *P* = 0.043) was associated with higher odds of abdominal TB disease (Table 4). Compared with children age 0–4 years, older age groups [age 5–9 (OR: 1.69, 95% CI: 1.24–2.31; *P* < 0.001) and 10–14 (OR: 1.59; 95% CI: 1.6–2.18; *P* < 0.004)] were associated with higher odds of lymph node TB.

DISCUSSION

Our study highlights the variable clinical presentation and risk factors for children with EPTB by age group. For clinical presentation, we found that lymph node TB was the most commonly reported site of EPTB for children in all groups, followed by abdominal TB. In the age 5–9 group, abdominal TB and pleural TB had similar percentages (5.8%). Our findings are consistent with

prior literature on EPTB in children, as lymph node TB is the most common form of extrathoracic TB in children.[3,14] Our findings are also consistent with a prior study of EPTB in Pakistan, which found that abdominal TB and lymphatic TB were the most common clinical manifestations of EPTB in children.[2]

We found that weight loss was associated with increased risk of EPTB for all age groups (except age 5–9). Of note, the symptom of weight loss was associated with EPTB in our study, while weight percentile was not associated with EPTB. Since 81.5% of children in our cohort had a weight percentile <5th percentile, one explanation for this finding is that if the children experienced weight loss, it was less pronounced given that it made up a small absolute amount, though a significant proportion of their initial weight. In all age groups, cough was associated with decreased risk of EPTB. This is consistent with our definition of EPTB as any form of TB disease that did not involve the lungs. Prior studies have evaluated risk factors for EPTB in children. In the low TB burden setting of Spain, EPTB in children was found to be associated with immigrant status, immune disorders and drug resistance.[6] In the high TB burden setting of China, age less than 5 years and female sex were associated with extrathoracic TB.[15]

In terms of the risk factors for subtypes of EPTB, our study found that cough was associated with an increased risk of abdominal TB, while ages 5–9 and 10–14 was associated with a decreased risk of abdominal TB. Our finding that, compared with younger children, those children ages 5–9 and 10–14 have a lower risk of abdominal TB is a unique finding, given that prior studies in Pakistan have not examined the presentation of EPTB by age group in

children.[2] For lymph node TB, our study found that ages 5–9 and 10–14 were associated with an increased risk of lymph node TB. This is consistent with findings from a study performed in Ethiopia, another high TB burden country, which reported a higher prevalence of lymph node TB in older children (5–14 years), compared with children under 5.[16] Hypotheses for increased risk of lymph node TB in older children include age-specific pathophysiology and missed diagnoses of EPTB in younger children.[3]

Overall, the proportion of EPTB in our cohort of pediatric TB cases was 13.5%. This is on the lower end of the range reported in prior studies, which found that the proportion of EPTB cases ranged between 13% and 50% from both high and low TB burden settings.[2,6,17,18] Compared with children with PTB, children with EPTB reported significantly more fever or weight loss. Prior literature supports the association of fever and weight loss with EPTB in children.[19] We did not find significant variations in gender between children with EPTB and PTB. The role of malnutrition on the clinical presentation of EPTB remains unclear, particularly as malnutrition is a key driver of TB, but TB also leads to malnutrition.[2] There also may also be geographic differences in clinical presentation of TB, as there are different percentages of extrapulmonary TB reported across the WHO regions.[1]

Strengths of our study include analysis of a prospectively collected data set with comprehensive information on demographics, symptoms, medical and family history and clinical examination results for children diagnosed with EPTB in a high burden TB country. An additional strength is that clinicians refined their diagnostic algorithm and underwent quality assurance measures when diagnosing children with TB.[8]

Limitations to our study include the inability to assess all variables in the multivariable analysis when broken down by age group. However, it is important to note that our sample size is relatively large in relation to overall EPTB literature. We may have underestimated the number of EPTB diagnoses due to the limitations of classification of EPTB. We were unable to assess the impact of HIV status, immunocompromised status or disseminated disease for our cohort as this information was not collected in the data set.

Several challenges exist in relation to diagnosis and characterization of childhood EPTB. There are diagnostic challenges, given various and nonspecific clinical manifestations and difficulties of culture diagnosis in children. In addition, there is a broad differential for lymphadenopathy and other EPTB findings, including malignancy and other alternative diagnoses.[20] Given that EPTB contributes less to transmission than PTB, EPTB may receive less attention when designing TB case-finding interventions. In addition, EPTB is characterized in various ways in different studies. In children, extrapulmonary TB can also be referred to as "extrathoracic" tuberculosis, which refers to disease outside of the chest cavity that excludes miliary TB, pleural effusion and mediastinal lymphadenopathy.[3] In addition, there are studies that define children with both PTB and EPTB as cases of EPTB,[6] and others that characterize both PTB and EPTB as disseminated TB.[21] Our study characterized EPTB according to the WHO definition, which may explain the lower proportion of EPTB cases in this cohort.[11]

Our study adds important knowledge about age-specific clinical presentation and risk factors for EPTB disease in children in Pakistan. Our results can be used to optimize clinical algorithms to ensure that children with EPTB receive a timely diagnosis and have successful outcomes. It is important to recognize fever, weight loss, cervical lymphadenopathy and abdominal pain as presenting signs of EPTB. Further studies are needed to evaluate the risk of EPTB disease by individual age and determine clinical rationale for high rates of lymph node and abdominal TB in children.

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