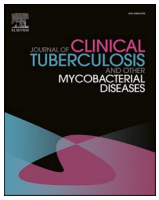
Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 36 (2024) 100441

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube



Pediatric tuberculosis in Mexico: A retrospective analysis of 100 patients

Enrique G. Villarreal [a,b], Emilia Ramos-Barrera [a], Ricardo J. Estrada-Mendizabal [a], Pablo D. Treviño-Valdez [b], Oscar Tamez-Rivera [a,*]

[a] Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Ave. Morones Prieto 3000, Monterrey, N.L. 64710, Mexico
[b] Department of Pediatrics, Secretaría de Salud del Gobierno del Estado de Nuevo León, Hospital Regional de Alta Especialidad Materno Infantil de Monterrey, Ave. San Rafael 450, Guadalupe, N.L. 67140, Mexico

ARTICLE INFO

Keywords:
Tuberculosis
Pediatrics
Epidemiology
Mexico
Meningeal tuberculosis
Public health

ABSTRACT

Background: Analyzing the epidemiology and clinical manifestations of pediatric tuberculosis in endemic regions is crucial to meet the goal of ending tuberculosis. The objective was to assess the various clinical scenarios of tuberculosis in a large pediatric cohort in Mexico.

Methods: This retrospective study from a pediatric referral center in Mexico included patients diagnosed with tuberculosis from 2012 to 2021. We analyzed clinical data and diagnostic study results, including demographic characteristics, underlying medical conditions, BCG vaccination, clinical presentation, imaging findings, microbiologic data, treatment, and clinical outcomes. Basic descriptive statistics and Chi-squared analysis were performed to summarize the metadata of pediatric patients with different clinical presentations of tuberculosis and evaluate their association with mortality, respectively.

Results: A total of 100 patients were included with a mean age of 7.76 years ± 1.49 years. The most prevalent clinical presentation was pulmonary tuberculosis ($n = 51$). Only 51 patients were immunized with Bacillus Calmette–Guérin vaccine. The most commons symptoms were fever, cough and weight loss. Among patients with meningeal tuberculosis ($n = 14$), the most common clinical signs were seizures, fever, and vomiting. Cure was achieved in 52 patients, 12 patients died, and 36 continue in treatment. Clinical presentation of tuberculosis (p-value = 0.009) and immunodeficiency (p-value = 0.015) were significantly associated with mortality.

Conclusions: Increasing the visibility of tuberculosis is imperative to end this disease. We report relevant clinical data of a large pediatric tuberculosis cohort, stratified by the different forms of disease. A high index of suspicion of tuberculosis is required for a timely diagnosis and treatment initiation, particularly among immunocompromised individuals, in whom mortality is higher.

1. Introduction

Tuberculosis (TB) is a global health issue that confers high morbidity and mortality. This disease is caused by *Mycobacterium tuberculosis* complex, mainly by *M. tuberculosis*; however, other clinically relevant mycobacteria cause atypical and extrapulmonary types of TB [1]. From a clinical and epidemiological perspective, TB can be classified as latent and active [2]. Latent TB infection (LTBI) refers to a non-contagious asymptomatic form of TB, while active TB infection is the contagious and symptomatic disease, which can be further divided into pulmonary and extrapulmonary disease [3,4].

The World Health Organization (WHO) estimates that annually, 1 million children develop TB, with around 210,000 child deaths [5,6]. Assessing the global burden in pediatrics is challenging due to diagnosis difficulties, frequent extrapulmonary manifestations, and low public health priority for pediatric TB [7]. Pediatric TB mirrors that of adults, with a heavy burden of disease in sub-Saharan Africa and Asia [6]. Despite the United States being a low-incidence country with less than 4 cases per 100,000 population, its southern neighbor, Mexico, faces a challenging scenario with an incidence rate of 28 cases per 100,000

Abbreviations: ATBI, Active tuberculosis infection; BCG, Bacillus Calmette–Guérin; CN, Cranial nerve; CSF, Cerebrospinal fluid; CT, Computerized tomography; EMB, Ethambutol; HIV, Human Immunodeficiency Virus; INH, Isoniazid; IQR, Interquartile range; LP, Lumbar puncture; LTBI, Latent tuberculosis infection; MRI, Magnetic resonance imaging; NAAT, Nucleic acid amplification test; PZA, Pyrazinamide; RIF, Rifampin; TB, Tuberculosis; WHO, World Health Organization.

* Corresponding author at: Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Ave. Ignacio Morones Prieto 3000, Monterrey, N.L., Mexico.
E-mail addresses: quique_villarreal93@hotmail.com (E.G. Villarreal), emiramos19@gmail.com (E. Ramos-Barrera), restrada97@outlook.com (R.J. Estrada-Mendizabal), pablotreva_@hotmail.com (P.D. Treviño-Valdez), oscar.tamez@tec.mx (O. Tamez-Rivera).

https://doi.org/10.1016/j.jctube.2024.100441

Available online 19 April 2024

reported in 2023. In 2020, compared to the previous year, Mexico observed a 5 % increase in TB-related mortality, resulting in 2,300 documented deaths due to the disease [8]. Although regulatory policies in the country establish the mandatory notification of new cases, underreporting is a prevalent phenomenon.

Information on pediatric TB is often eclipsed by the enormous amount of available data from adult populations. Children tend to manifest a pauci-symptomatic form of the disease, which requires a high index of suspicion from the clinicians to diagnose TB. A detailed and comprehensive description of the clinical and diagnostic study results features of the various forms of TB in children is required. Our main objective was to characterize the clinical presentation, diagnostic modalities, radiological findings, and treatment outcomes of 100 pediatric patients with TB in Mexico. Additionally, we explored possible associations with mortality.

2. Methods

2.1. Study design, location, and population

This is a retrospective, cross-sectional, descriptive study carried out at a pediatric tertiary referral center that admits patients from north-east Mexico. During the study, we examined electronic medical records of pediatric patients aged 0 to 18 years, who were diagnosed with any form of tuberculosis between February 2012 and January 2021. Clinical data and diagnostic test results of these patients were analyzed.

2.2. Diagnostic criteria for pediatric TB

TB diagnosis was established according to the Mexican National Health System guidelines with a combination of clinical, radiologically, laboratory, pathological and microbiological criteria (Supplementary Table 1). Diagnosing pulmonary tuberculosis in children presents challenges as microbiological confirmation is frequently elusive. Hence, diagnosis primarily relies on clinical symptoms in conjunction with findings from chest radiographs. As highlighted in previous studies published in the Journal of Pediatric Radiology, intrathoracic lymphadenopathy, such as hilar, mediastinal, and paratracheal lymphadenopathy, has been included within the pulmonary TB group for the purpose of our study [9,10].

2.3. Diagnostic criteria for meningeal TB

The diagnosis of meningeal TB was made on a combination of clinical, radiological [brain computerized tomography (CT) or magnetic resonance imaging (MRI)], cerebrospinal fluid (CSF) and microbiological findings. Regarding the CSF analysis, pleocytosis was defined as > 5 cells/microL, hyperproteinorrhachia as > 60 mg/dL and hypoglycorrhachia as < 50 mg/dL [11,12].

2.4. Statistical analysis

Descriptive statistics were performed to summarize the demographic, clinical characteristics and diagnostic test results of pediatric patients with TB, according to their form of disease. To evaluate the association between several variables of interest (age, sex, living location, Bacillus Calmette–Guérin [BCG] vaccination status and immunosuppression) with mortality, a Chi-squared univariate analysis was performed. SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, considering a bilateral *p-value* ≤ 0.05 as statistically significant.

2.5. Ethical review approval

The study has been approved by the Institutional Review Board of *Hospital Regional Materno Infantil de Alta Especialidad* with the protocol number PR-190121063. We followed the STROBE guidelines, to ensure that results are reported as fully and accurately as possible.

3. Results

3.1. Epidemiological characteristics according to TB clinical presentation (Table 1)

A total of 100 patients with pediatric TB were included in this study. Pulmonary TB was the most common clinical presentation ($n = 51$), followed by lymph node, meningeal, miliary, and skeletal TB; respectively. A male predominance was observed (54 %). Half of the patients were between the ages of 5–12 years, and most of the patients lived in metropolitan areas (79 %). Fifty-seven patients had positive community bacillus exposure (COMBE). Common index cases were mothers and grandparents ($n = 13$; each). Only half of the patients had a positive history of BCG vaccination. Most of the patients were previously healthy ($n = 77$) with no chronic comorbidities, underlying conditions or immunosuppression. According to the weight-for-age malnutrition classification, 42 patients had some degree of malnutrition. Most patients with miliary TB had moderate to severe malnutrition (68 %).

Fifty-two patients have been successfully cured, with 36 patients still receiving antituberculous treatment. At the time of the analysis, the case fatality rate was of 12 %. Proportionally, meningeal TB was the most fatal clinical presentation (5 out of 14 patients; 36 %). In contrast, only 6 % (3 out of 51 patients) of patients with pulmonary TB died. Additionally, no deaths were observed in the lymph node group.

3.2. General signs and symptoms by TB clinical presentation (Table 2)

Signs and symptoms were analyzed according to the different clinical presentation of TB. Fever was the most common sign, followed by cough and weight loss. Fever was a prevalent sign in all the different forms of TB (47.6–85.7 %). Cough was frequent only in the pulmonary (84.3 %) and miliary TB (71.4 %). Weight loss was an uncommon sign among patients with localized forms of TB. Cervical lymph nodes (85.7 %) were the most affected lymph nodes. Night sweats, fatigue and hepatosplenomegaly were infrequent among our population. Four out of six patients with hepato- or splenomegaly had the miliary form of disease.

3.3. Clinical, radiological, and cerebrospinal fluid characteristics in meningeal TB (Table 3)

Our cohort shows that 10 out of 14 patients who presented with meningeal tuberculosis had generalized seizures and fever. Vomiting was present in half of the patients with meningeal TB; vomiting was only present in this clinical presentation. Meningeal signs were present in 42.9 % of the patients. Headache was present in one third of the patients and most of the patients described it as an intense holocranial pain. Three patients had cranial nerve (CN) alterations: two had facial paralysis (CN-VII) and one had hypoacusia (CN-VIII).

Central nervous system imaging (CT or MRI) was performed in all patients with meningeal TB. Of note, all patients with meningeal TB had an abnormal study with at least one radiological alteration. Hydrocephalus was the most common finding (71.4 %), closely followed by basal arachnoiditis (64.3 %). Vascular damage (vasculitis, hemorrhage, and infarction) was uncommon (28.6 %). Tuberculoma and cerebral edema were only present in 2 patients, respectively (14.3 %).

Lumbar puncture (LP) for CSF analysis was performed in 13 patients. From the 13 CSF samples, only one was reported within normal cell count, proteins, and glucose ranges. Pleocytosis occured in 11 patients, with a median of 120 cells/microL. Severe pleocytosis (>100 cells/microL) was present in 7 patients. We did not notice a significant cellular predisposition between neutrophils and lymphocytes, with 6 patients showing neutrophil predominance and 5 showing lymphocyte predominance. Hyperproteinorrhachia was present in 10 patients with a

Table 1
Epidemiological characteristics according to tuberculosis clinical presentation.

TB presentation	Pulmonary TB[a] (n = 51)	Ganglionic TB (n = 21)	Meningeal TB (n = 14)	Miliary TB (n = 7)	Skeletal TB (n = 4)	Other[b] (n = 3)	Total (N = 100)
Sex							
No. (%)							
Male	27 (53)	10 (48)	8 (57)	5 (71)	3 (75)	1 (33)	54
Female	24 (47)	11 (52)	6 (43)	2 (29)	1 (25)	2 (67)	46
Age							
Mean (SD)							
Years	10.32 (4.14)	7.76 (4.86)	5.1 (5.17)	9.18 (5.3)	2.5 (1.3)	11.67 (4.16)	7.76 (1.49)
Age groups according to NICHD pediatric terminology							
No. (%)							
<1 year (neonatal and infancy)	1 (2)	0 (0)	4 (29)	1 (14)	0 (0)	0 (0)	6
1–4 years (Toddler and early childhood)	6 (12)	7 (33)	4 (29)	1 (14)	4 (100)	0 (0)	22
5–12 years (middle childhood)	21 (42)	10 (48)	4 (29)	2 (29)	0 (0)	1 (33)	38
13–18 years (Adolescence)	23 (46)	4 (19)	2 (14)	3 (43)	0 (0)	2 (67)	34
Living area							
No. (%)							
Metropolitan (population > 50,000)	38 (75)	17 (81)	11 (79)	6 (86)	4 (100)	3 (100)	79
Micropolitan (population < 50,000)	13 (25)	4 (19)	3 (21)	1 (14)	0 (0)	0 (0)	21
Community Bacillus Exposure							
No. (%)							
Positive	35 (69)	8 (38)	6 (43)	5 (71)	2 (50)	1 (33)	57
Negative	16 (31)	13 (62)	8 (57)	2 (29)	2 (50)	2 (67)	43
Bacillus Calmette–Guérin vaccination status							
No. (%)							
Non-vaccinated	21 (41)	11 (52)	9 (64)	4 (57)	2 (50)	2 (66)	49
Vaccinated	30 (59)	10 (48)	5 (36)	3 (43)	2 (50)	1 (33)	51
Comorbidities							
No. (%)							
HIV infection	2 (4)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	3
Cancer[c]	1 (2)	0 (0)	1 (7)	0 (0)	0 (0)	1 (33)	3
Cystic Fibrosis	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2
Asthma	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2
Down Syndrome	0 (0)	1 (5)	0 (0)	1 (14)	0 (0)	1 (33)	3
Other Comorbidities[d]	5 (10)	2 (10)	0 (0)	1 (14)	0 (0)	1 (33)	10
Malnutrition (according to weight-for-age classification by Gomez et al.[e])							
No. (%)							
Mild (Grade 1, 75–90 %)	11 (21)	7 (33)	2 (14)	1 (14)	0 (0)	1 (33)	22
Moderate (Grade 2, 60–74 %)	4 (8)	2 (10)	3 (21)	2 (29)	0 (0)	1 (33)	12
Severe (Grade 3, <60 %)	5 (10)	0 (0)	1 (7)	2 (29)	0 (0)	0 (0)	8
Outcome							
No. (%)							
Cured	29 (57)	13 (62)	5 (36)	1 (14)	2 (50)	2 (67)	52
Ongoing therapy	19 (37)	8 (38)	4 (29)	4 (57)	1 (25)	0 (0)	36
Died	3 (6)	0 (0)	5 (36)	2 (29)	1 (25)	1 (33)	12

Abbreviations: HIV, Human Immunodeficiency Virus; NICHD, National Institute of Child Health and Human Development; TB, tuberculosis.
[a] We included patients with pleural involvement in this TB clinical presentation.
[b] Other: Intestinal or renal tuberculosis.
[c] Cancer: Two patients with acute lymphoblastic leukemia and one patient with Hodgkin lymphoma.
[d] Other comorbidities: hypothyroidism, systemic erythematous lupus, diabetes mellitus, chronic granulomatous disease unspecified dysmorphic syndrome and unspecified pneumopathy. One patient had multiple comorbidities such as chronic renal failure, Cushing syndrome, and renal transplant.
[e] Gomez malnutrition classification.

median of 112 mg/dL. Hypoglycorrhachia was also a common CSF feature of children with meningeal TB (10 patients) with a median glucose of 25 mg/dL. Three patients had severe hypoglycorrhachia (<10 mg/dL) and 2 patients had significant hyperproteinorrhachia (>1 gr/dL). Severe hypoglycorrhachia (<10 mg/dL) and hyperproteinorrhachia (>1 gr/dL) were present in three and two patients, respectively.

3.4. Chest imaging findings (Table 4)

All patients in our cohort had a chest imaging (chest x-ray and/or CT scan) performed during their workup and 68 % of them had an abnormal report. Intrathoracic lymphadenopathy was the most frequent imaging finding (70.5 %). Among lung parenchymal abnormalities, pulmonary infiltrates were the most common finding (48.5 %). Pleural effusion was a relatively prevalent finding in 30.9 %, with 3 patients having bilateral pleural effusion. We report the presence of cavitary lesions in 10 patients, of which 6 were adolescents. Calcifications were reported in 10.3 % of the patients; the most common site of these were perihilar calcifications. Atelectasis, pneumothorax, bronchiectasis, and pericardial effusion were infrequent findings in our cohort.

Table 2
Signs and symptoms in children according to their clinical presentation of tuberculosis.

	Pulmonary TB[a] (*n = 51*)	Ganglionic TB (*n = 21*)	Meningeal TB (*n = 14*)	Miliary TB (*n = 7*)	Skeletal TB (*n = 4*)	Other[b] (*n = 3*)	Total (*N = 100*)
Fever *No. (%)*	36 (70.6)	10 (47.6)	9 (64.3)	6 (85.7)	2 (50)	2 (66.7)	65
Cough *No. (%)*	43 (84.3)	1 (4.8)	5 (35.7)	5 (71.4)	1 (25)	1 (33.3)	56
Weight loss *No. (%)*	23(45.1)	3 (14.3)	5 (35.7)	4 (57.1)	0 (0)	2 (66.7)	37
Lymphadenopathy *No. (%)*	6 (11.8)	21(100)	2 (14.3)	3 (42.9)	0 (0)	2 (66.7)	34
Hyporexia *No. (%)*	17 (33.3)	4 (19)	5 (35.7)	2 (28.6)	0 (0)	2 (66.7)	30
Asthenia/Adynamia *No. (%)*	14 (27.5)	3 (14.3)	6 (42.9)	2 (28.6)	0 (0)	2 (66.7)	27
Night sweats *No. (%)*	3 (5.9)	3 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	6
Fatigue *No. (%)*	3 (5.9)	0 (0)	3 (21.4)	0 (0)	0 (0)	0 (0)	6
Hepatomegaly *No. (%)*	1 (2)	0 (0)	0 (0)	3 (42.9)	0 (0)	1 (33.3)	5
Splenomegaly *No. (%)*	0 (0)	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	1

Abbreviation: TB, tuberculosis.
[a] We included patients with pleural involvement in this TB clinical presentation.
[b] Other: Intestinal and renal TB.

Table 3
Clinical, radiological, and cerebrospinal fluid characteristics in meningeal tuberculosis.

Signs and symptoms (*n* = 14)	**No. (%)**
Generalized seizures	10 (71.4)
Fever	10 (71.4)
Vomiting	7 (50.0)
Meningeal signs[a]	6 (42.9)
Headache	5 (35.7)
Irritability	5 (35.7)
Weight loss	5 (35.7)
Dizziness	4 (28.6)
Cranial nerve alterations	3 (21.4)
Other[b]	7 (50)
Brain imaging findings (CT or MRI) (*n* = 14)	**No. (%)**
Hydrocephalus	10 (71.4)
Basal arachnoiditis	9 (64.3)
Vasculitis	2 (14.3)
Tuberculoma	2 (14.3)
Cerebral edema	2 (14.3)
Parenchymal infarction	1 (7.1)
Parenchymal hemorrhage	1 (7.1)
Cerebrospinal fluid characteristics (*n* = 13)[c] – Frequency	**No. (%)**
Pleocytosis (>5 cells/microL)	11 (84.6)
Hyperproteinorrhachia (>60 mg/dL)	10 (76.9)
Hypoglycorrhachia (<50 mg/dL)	10 (76.9)
Cerebrospinal fluid characteristics (*n* = 13)[c] – Numerical	**Median (IQR)**
Cytology (cells/microL)	120 (30–227)
Proteins (mg/dL)	112 (78–576)
Glucose (mg/dL)	25 (16–47)

Abbreviation: CT, computerized tomography; MRI, magnetic resonance imaging; TB, tuberculosis.
[a] Meningeal signs: nuchal rigidity, Kernig's sign, Brudzinski's sign or jolt accentuation headache.
[b] Other: altered state of consciousness, macrocephalus, hypotonia, altered reflexes.
[c] Lumbar puncture was not performed in one patient due to an extensive sacral ulcer. Percentages, medians, and interquartile ranges (IQRs) were measured using 13 patients as the sample size.

3.5. Mycobacterial isolates and drug susceptibility

Mycobacterial culture information was available from 41 % of the total sample. The rest of the patients were diagnosed via: 18 % by nucleic acid amplification test (NAAT), 13 % by acid-fast bacilli (AFB), and 38 % in a combination of clinical, radiological, and epidemiologic information. Mycobacterial growth was documented in 22 patients with pulmonary TB, all of them due to *M. tuberculosis*. Only one patient had a multi-drug resistant (MDR) strain of *M. tuberculosis* which was resistant to both Isoniazid (INH) and Rifampin (RIF). This patient had a positive history of household contact with confirmed MDR pulmonary TB. This patient was treated and cured after a 20-month treatment regimen consisting of levofloxacin, bedaquiline, linezolid, and clofazimine. Nine patients from the lymph node group had a positive mycobacterial culture, 6 of them reporting drug susceptible *M. tuberculosis,* and 3 drug suspectable *M. bovis*. Drug susceptible *M. tuberculosis* was isolated in 7 cases of meningeal TB and in 3 cases of skeletal TB.

Table 4
Chest imaging abnormalities in children with tuberculosis.

Imaging abnormalities (*n* = 68)	**No. (%)**
Lymphadenopathy	48 (70.5)
Pulmonary infiltrates	33 (48.5)
Interstitial infiltrates	26 (38.2)
Miliary infiltrates	7 (10.3)
Pleural effusion	21 (30.9)
Cavitations	10 (14.7)
Calcifications	7 (10.3)
Atelectasis	5 (7.4)
Pneumothorax	1 (1.5)
Bronchiectasis	1 (1.5)
Pericardial effusion	1 (1.5)

3.6. Treatment outcomes (Table 5)

Cure was achieved in 52 % of the total sample, and 36 % are still receiving antituberculous treatment with good clinical response to date. Twelve patients died during hospitalization. TB clinical presentation has a significant impact on mortality (*p-value* = 0.009). The clinical presentations with the highest proportion of mortality were miliary (66.6 %) and meningeal TB (44.4 %). One-third of the patients who died had some form of immunodeficiency, and half of the patients with immunodeficiency died (*p-value* = 0.015). We did not observe statistically significant differences between age, sex, living area and BCG vaccination status with mortality.

Table 5
Clinical outcomes of children with TB according to their epidemiological characteristics.

Characteristic	Cured ($n = 52$)	Died ($n = 12$)	*p-value*	Total[d] ($n = 64$)
TB clinical presentation — *No. (%)*				
Pulmonary TB[a]	29 (828)	6 (17.1)	*0.009**	35
Ganglionic TB	13 (100)	0 (0)		13
Meningeal TB	5 (55.5)	4 (44.4)		9
Miliary TB	1 (33.3)	2 (66.6)		3
Skeletal TB	2 (100)	0 (0)		2
Other[b]	2 (100)	0 (0)		2
Age — *No. (%)*				
< 1 year	1 (33.3)	2 (66.6)	*0.174*	3
1–4 years	14 (87.5)	2 (12.5)		16
5–12 years	19 (82.6)	4 (17.4)		23
13–18 years	18 (81.8)	4 (18.1)		2
Sex — *No. (%)*				
Male	28 (84.9)	5 (15.1)	*0.447*	33
Female	24 (77.4)	7 (22.6)		31
Location — *No. (%)*				
Metropolitan (population > 50,000)	14 (87.5)	2 (12.5)	*0.460*	16
Micropolitan (population < 50,000)	38 (79.1)	10 (20.9)		48
Bacillus Calmette–Guérin vaccination status — *No. (%)*				
Vaccinated	28 (87.5)	4 (12.5)	*0.2*	32
Not vaccinated	24 (75)	8 (25)		32
Immunodeficiency[c] — *No. (%)*				
Yes	4 (50)	4 (50)	*0.015**	8
No	48 (85.7)	8 (14.3)		56

Abbreviation: TB, tuberculosis.
[a] We included patients with pleural involvement in this tuberculosis clinical presentation.
[b] Other tuberculosis clinical presentation: Intestinal or renal tuberculosis.
[c] Immunodeficiencies: Cancer, human immunodeficiency virus infection, chronic granulomatous disease, systemic lupus erythematosus.
[d] 36 patients who were undergoing treatment at the time of the study were excluded from this analysis.
* A *p-value* less than 0.05 is considered statistically significant.

4. Discussion

TB disease exhibits a global distribution. The WHO established a strategy to *End TB* by setting milestones addressing incidence rates, mortality, access to medications, among others·1 In recent years, a global setback in the fight against TB has been reported [13]. This phenomenon has also been observed in the Americas; where countries like Venezuela and Argentina have almost doubled their incidence rates, and Haiti (151 per 100,000) and Peru (135 per 100,000) exceed the global mean incidence rate (134 per 100,000) [13–16]. According to the WHO Country Profile for TB, Mexico belongs to the top 10 countries with the highest incidence of TB in the Americas, with a reported rate of 28 per 100,000 (range 19–32) [8].

Although the incidence of TB in Mexico is below the global rate, TB disease has an alarming burden that impacts economic, social, and health levels of the community. Additionally, like many countries, Mexico faces the complex challenge of underdiagnosis and unreported cases of TB, as well as an uneven geographic distribution that shows a higher burden in the country's northern region. As most of the available data of TB is focused on adult population, it is imperative to address the knowledge gap of pediatric TB in Mexico. [8,13].

Our study features one of the largest single-center pediatric TB cohorts, enabling comparisons with similar studies. In our population, TB presentation was evenly split between pulmonary and extrapulmonary TB, aligning with findings from other large pediatric cohorts [17,18]. Despite pulmonary TB being more common in the community, our cohort's even distribution was anticipated, given the inclusion of hospitalized patients requiring tertiary care, while outpatient clinics handle most pulmonary TB cases. Children face a higher risk of extrapulmonary TB than adults [19]. Lymph node TB emerged as the most common extrapulmonary form in our cohort, consistent with prior studies highlighting lymph nodes as a primary site for extrapulmonary TB, possibly due to the predominant lymphohematogenous spread of tuberculous bacilli in children [20–23].

TB is one of the most significant infections in immunosuppressed patients due to its high frequency, morbidity, and mortality [24]. In our cohort, comorbidities that lead to an immunosuppressive state (secondary immunodeficiency) was present in 7 patients. Three patients had HIV, three patients were in chemotherapeutic treatment and one patient was immunosuppressed due to renal transplant. Lancella et al. recommended that all immunosuppressed patients who develop TB should be referred to a TB reference center [25].

In our cohort, fever was the most common clinical manifestation, followed by cough and weight loss. This distribution is similar to other cohorts of pediatric TB [26–29]. These clinical signs are nonspecific and can be observed in other infectious diseases, highlighting the importance of a complete diagnostic workup. Symptom chronicity lasting more than two weeks should raise the suspicion of TB [30]. As expected, cough was a highly frequent sign among patients with pulmonary (84.3 %) and miliary TB (71.4 %). Likewise, lymphadenopathy was present in all patients with TB lymphadenitis. The classic symptom of night sweats was present in only 6 % of patients, defying the historical dogma that it is a classical sign of TB [2,31]. Our findings suggest that the absence of night sweats should not rule out the possibility of TB in children.

Our cohort features a substantial proportion of meningeal TB (14 %), allowing in-depth analysis of this clinical presentation. Early signs and symptoms of meningeal TB are non-specific and may include headache, vomiting, and irritability. However, children with more advanced disease present overt manifestations, such as: meningeal signs, signs of intracranial hypertension, altered state of consciousness, and seizures [32]. As our cohort is limited to hospitalized patients, late- disease imaging and clinical manifestation, such as seizures (71.4 %) and meningeal signs (42.9 %), were highly prevalent. Meningeal TB may include focal cranial nerve manifestations, particularly abducent nerve (VI) and facial nerve (VII) involvement [33]. In our sample, only three patients with meningeal TB (21.4 %) presented cranial nerve alterations.

Central nervous system (CNS) neuroimaging studies are essential in the diagnosis of meningeal TB. Although the best imaging modality is magnetic resonance imaging (MRI) with gadolinium, contrast-enhanced computed tomography (CT) can be a comparable imaging study with greater accessibility in developing countries [34]. The most prevalent imaging findings in our cohort are similar to those described in the literature. These include communicating hydrocephalus and basal arachnoiditis (71.4 % and 64.3 %, respectively). Only 2 patients presented with vasculitis, tuberculoma or cerebrovascular disease.

CSF analysis is also essential in the workup for meningeal TB. Most patients had the classical triad found in CSF analysis: 11 patients with pleocytosis with lymphocytic predominance, 10 patients with hyperproteinorrhachia, and 10 patients with hypoglycorrhachia. A glucose level of less than 40 mg/dL and proteins greater than 1 g/L are highly indicative of CNS TB. Solomons et al. observed that the diagnostic utility of CSF analysis in pediatric patients with meningeal TB has a high specificity (94 %), but suboptimal sensitivity (78 %) [35]. Among the fourteen cases of meningeal TB in our cohort, only three had > 1 g/L CSF protein levels, and six had glucose levels < 40 mg/dL. This highlights the limited sensitivity of CSF chemistry in detecting meningeal TB.

Prompt TB meningitis identification is critical, as early diagnosis decreases morbidity and mortality. Studies indicate that 65 % of TB meningitis survivors face neurological deficits, including motor, sensory, and cognitive impairments. Early treatment mitigates the likelihood of developing sequalae, such as cerebral palsy, sensory impairment, intellectual disability, and neurodevelopmental disorders. Detecting mycobacterial infection is challenging due to its paucibacillary nature. In our cohort, only four patients with meningeal TB had a positive NAAT, while none had positive CSF cultures. Huynh proposed a

diagnostic algorithm based on clinical presentation and risk factors, recommending rapid complementary diagnostic techniques such as AFB, NAAT, and neuroimaging [36,37]. Additionally, a treatment regimen comprising antituberculous drugs for more than 12 months is suggested, with corticosteroid therapy during the first eight weeks.

Chest imaging studies aid in the diagnosis of pulmonary TB and are also useful for evaluating treatment response and assessing disease-specific complications. The most predominant radiological manifestation in our cohort was lymphadenopathy, with a frequency of 48 cases (70.5 %), consistent with previous reports in the literature. Lymphadenopathy involving the hilum and mediastinum is a frequent finding in pediatric TB and may represent the sole radiological finding [38]. Chest CT scan is the gold standard for detecting lymphadenopathy and can identify lymph node involvement in up to 60 % of patients who present with a normal chest X-ray [39].

In our cohort ($n = 33$), pulmonary parenchymal infiltrates are prevalent in imaging studies. Among these, interstitial infiltrates ($n = 26$) often occur during latent infection reactivation via bronchogenic dissemination. This occurs in 20 % of secondary TB patients, affecting upper lobe apical segments due to high oxygenation levels [40,41]. High-resolution CT scans reveal 2–4 mm centrilobular nodules with branching opacities (tree-in-bud sign), indicating bronchiole caseous necrosis [42]. Miliary infiltrates ($n = 7$) are a pathognomonic feature of miliary TB, appearing as numerous < 2 mm non-calcified pulmonary nodules on chest imaging due to hematogenous infection dissemination in both primary and secondary disease, affecting young children and immunocompromised individuals[43,44].

Interestingly, pleural effusion was present in 21 patients with abnormal chest imaging. This finding is uncommon in children and its prevalence increases with age [45,46]. Effusions result from lymphatic blockage or hypersensitivity, making microorganism isolation rare. Mycobacteria may be detected if effusion is caused by hematogenous spread or proximity to a caseating granuloma near the pleura [41]. Chest ultrasound is the first-line study when effusion is suspected; additionally, chest CT can measure the effusion and detect bronchopleural fistulas.

As TB confers high mortality risk, we explored possible associations with mortality in our cohort. Among the studied variables, only TB clinical presentation (*p-value* = 0.009) and immunodeficiency (*p-value* = 0.015) were significantly associated with mortality. We observed heterogeneity in mortality rates based on the clinical presentation, with severe types of tuberculosis, such as meningeal and miliary TB, showing higher mortality rates compared to pulmonary TB. These findings are consistent with those from a similar study conducted in China, where severe types of TB were associated with significantly higher mortality rates with an odds ratio of 1.71 (95 % CI: 1.24–2.36) [18].

Our study revealed that mortality was significantly elevated (*p-value* = 0.015) in patients with immunodeficiency. It is well known that immunocompromised individuals, especially those with HIV, are at higher risk of disease progression [47,48]. In a recent meta-analysis, TB-HIV co-infection was shown to have a markedly higher fatality rate [49]. The advent of antiretroviral therapy has significantly modified the incidence, morbidity, and mortality of TB in this population [47]. For instance, a study conducted in the Democratic Republic of Congo demonstrated that antiretroviral treatment significantly reduced the incidence from 20.4 to 10.2 per 100 person-years [50].

The progression of TB disease is influenced by several factors, including the relative immaturity of the immune system at early ages [6]. Young patients (<4 years) are at a higher risk of developing active TB and severe forms of the disease; however, we did not find a significant association between age and mortality (*p-value* = 0.174). The BCG vaccination status was relatively low, despite the vaccine being included in the Mexican immunization schedule, where all children should be vaccinated at birth. Factors such as vaccine hesitancy and transient supply shortage in the country have contributed to a decline in immunization coverage. However, vaccination status was not found to be statistically related to mortality (*p-value* = 0.2), despite being described as a protective measure against disseminated TB. BCG prevents an estimated 117,000 deaths annually [51]. Although not statistically significant, both patients who died from TB under the age of one didn't receive the vaccine and mortality was twice as high in the unvaccinated patients.

Our study has limitations, primarily due to its retrospective nature, sample size and limited power. Firstly, the sample was derived from a referral hospital, leading to a potential sampling bias as these cases are typically more severe. Also, the limited sample size and the insufficient statistical power may compromise the precision and generalizability of our results. Secondly, certain demographic, clinical data or diagnostic workup were incomplete or absent in medical records. Additionally, patients with a delayed/incorrect diagnosis, were not included in our study. Despite these limitations, our study provides valuable insights into outcomes and associated factors in this hospital that serves as the primary referral center for pediatric TB in northern Mexico, offering a nationally representative investigation.

5. Conclusion

Increasing the visibility of tuberculosis is imperative to end this disease. We report relevant clinical data and diagnostic study results of a large pediatric tuberculosis cohort, stratified by the different forms of disease. A high index of suspicion of tuberculosis is required for a timely diagnosis and treatment initiation, particularly among immunocompromised individuals, in whom mortality is higher.

6. Prior presentation of study data

This work was previously presented as a poster in IDWeek, October 2022, at Washington DC. This is the joint annual meeting of the Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), the HIV Medicine Association (HIVMA), the Pediatric Infectious Diseases Society (PIDS), and the Society of Infectious Diseases Pharmacists (SIDP).

7. Reprint request

None.

Funding sponsors

There are no sources of funding to disclose for this work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Database linking

Deidentified participant data is readily available in an open access repository and can be accessed and downloaded at: https://data.mendeley.com/datasets/zg7pgwznnf/draft?a=3ab346e8-8938-4261-a799-34495fbc1c05.

Compliance with ethical standards

All study procedures complied with the ethical standards of the Helsinki Declaration and has been approved by the Institutional Review Board of *Hospital Regional Materno Infantil de Alta Especialidad* and was given the protocol number PR-190121063 with an approval date of 01/24/2021.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100441.

References

[1] Orcau À, Caylà JA, Martínez JA. Present epidemiology of tuberculosis. Prevention and control programs. Enferm Infecc Microbiol Clin 2011;29(Suppl 1):2–7. https://doi.org/10.1016/s0213-005x(11)70011-8.

[2] Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nat Rev Dis Primers 2016;2:16076. https://doi.org/10.1038/nrdp.2016.76.

[3] Ramírez-Lapausa M, Menéndez-Saldaña A, Noguerado-Asensio A. Extrapulmonary tuberculosis. Rev Esp Sanid Penit 2015;17:3–11. https://doi.org/10.4321/s1575-06202015000100002.

[4] Banta JE, Ani C, Bvute KM, Lloren JIC, Darnell TA. Pulmonary vs. extra-pulmonary tuberculosis hospitalizations in the US [1998-2014]. J Infect Public Health 2020;13:131–9. https://doi.org/10.1016/j.jiph.2019.07.001.

[5] Lamb GS, Starke JR. Tuberculosis in Infants and Children. Microbiol Spectr 2017;5. https://doi.org/10.1128/microbiolspec.TNMI7-0037-2016.

[6] Thomas TA. Tuberculosis in Children. Pediatr Clin North Am 2017;64:893–909. https://doi.org/10.1016/j.pcl.2017.03.010.

[7] Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004;8:636–47.

[8] Tuberculosis profile: Mexico. World Health Organization, 2021.

[9] Andronikou S, Smith B, Hatherhill M, Douis H, Wilmshurst J. Definitive neuroradiological diagnostic features of tuberculous meningitis in children. Pediatr Radiol 2004;34:876–85. https://doi.org/10.1007/s00247-004-1237-1.

[10] George A, Andronikou S, Pillay T, Goussard P, Zar HJ. Intrathoracic tuberculous lymphadenopathy in children: a guide to chest radiography. Pediatr Radiol 2017;47:1277–82. https://doi.org/10.1007/s00247-017-3890-1.

[11] Østergaard AA, Sydenham TV, Nybo M, Andersen ÅB. Cerebrospinal fluid pleocytosis level as a diagnostic predictor? A cross-sectional study. BMC Clin Pathol 2017;17:15. https://doi.org/10.1186/s12907-017-0053-0.

[12] Shahan B, Choi EY, Nieves G. Cerebrospinal Fluid Analysis. Am Fam Physician 2021;103:422–8.

[13] Global tuberculosis report 2021 Geneva: World Health Organization, 2021.

[14] Ranzani OT, Pescarini JM, Martinez L, Garcia-Basteiro AL. Increasing tuberculosis burden in Latin America: an alarming trend for global control efforts. BMJ Glob Health 2021;6:e005639.

[15] Tuberculosis profile: Haiti. World Health Organization: World Health Organization, 2022.

[16] Tuberculosis profile: Peru. World Health Organization: World Health Organization, 2021.

[17] Sreeramareddy CT, Ramakrishnareddy N, Shah RK, Baniya R, Swain PK. Clinico-epidemiological profile and diagnostic procedures of pediatric tuberculosis in a tertiary care hospital of western Nepal-a case-series analysis. BMC Pediatr 2010;10:57. https://doi.org/10.1186/1471-2431-10-57.

[18] Wu XR, Yin QQ, Jiao AX, Xu BP, Sun L, Jiao WW, et al. Pediatric tuberculosis at Beijing Children's Hospital: 2002–2010. Pediatrics 2012;130:e1433–40. https://doi.org/10.1542/peds.2011-3742.

[19] Maltezou HC, Spyridis P, Kafetzis DA. Extra-pulmonary tuberculosis in children. Arch Dis Child 2000;83:342. https://doi.org/10.1136/adc.83.4.342.

[20] Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician 2005;72:1761–8.

[21] Santiago-García B, Blázquez-Gamero D, Baquero-Artigao F, Ruíz-Contreras J, Bellón JM, Muñoz-Fernández MA, et al. Pediatric Extrapulmonary Tuberculosis: Clinical Spectrum, Risk Factors and Diagnostic Challenges in a Low Prevalence Region. J Pediatric Infect Dis Soc 2016:35.

[22] Leung AN. Pulmonary Tuberculosis: The Essentials. Radiology 1999;210:307–22. https://doi.org/10.1148/radiology.210.2.r99ja34307.

[23] Kaba Ö, Kara M, Odacılar CA, Kamer İ, Sütçü M, Demir S, et al. Evaluation of cases of pediatric extrapulmonary tuberculosis: a single center experience. Turk Pediatri Ars 2019;54:86–92. https://doi.org/10.14744/TurkPediatriArs.2019.33239.

[24] Machuca I, Vidal E, de la Torre-Cisneros J, Rivero-Román A. Tuberculosis in immunosuppressed patients. Enferm Infecc Microbiol Clin (Engl Ed) 2018;36:366–74. https://doi.org/10.1016/j.eimc.2017.10.009.

[25] Lancella L, Galli L, Chiappini E, Montagnani C, Gabiano C, Garazzino S, et al. Recommendations Concerning the Therapeutic Approach to Immunocompromised Children With Tuberculosis. Clin Ther 2016;38:180–90. https://doi.org/10.1016/j.clinthera.2015.10.012.

[26] Cano APG, Romaneli MTN, Pereira RM, Tresoldi AT. Tuberculosis in pediatric patients: how has the diagnosis been made? Rev Paul Pediatr 2017;35:165–70. https://doi.org/10.1590/1984-0462/;2017;35;2;00004.

[27] Lotfian F, Bolursaz MR, Khalilzadeh S, Baghaie N, Hassanzad M, Velayati A. Features of Adolescents Tuberculosis at a Referral TB's Hospital in Tehran, Iran. Mediterr J Hematol Infect Dis 2016;8:e2016005.

[28] Galli L, Lancella L, Tersigni C, Venturini E, Chiappini E, Bergamini BM, et al. Pediatric Tuberculosis in Italian Children: Epidemiological and Clinical Data from the Italian Register of Pediatric Tuberculosis. Int J Mol Sci 2016:17. https://doi.org/10.3390/ijms17060960.

[29] Turel O, Kazanci S, Gonen I, Aydogmus C, Karaoglan E, Siraneci R. Paediatric Tuberculosis at a Referral Hospital in Istanbul: Analysis of 250 Cases. Biomed Res Int 2016;2016:6896279. https://doi.org/10.1155/2016/6896279.

[30] Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. Chapter 1: introduction and diagnosis of tuberculosis in children. Int J Tuberc Lung Dis 2006;10:1091-1097.

[31] Viera AJ, Bond MM, Yates SW. Diagnosing night sweats. Am Fam Physician 2003;67:1019–24.

[32] Chatterjee S. Brain tuberculomas, tubercular meningitis, and post-tubercular hydrocephalus in children. J Pediatr Neurosci 2011;6:S96–s100. https://doi.org/10.4103/1817-1745.85725.

[33] Sharma P, Garg RK, Verma R, Singh MK, Shukla R. Incidence, predictors and prognostic value of cranial nerve involvement in patients with tuberculous meningitis: a retrospective evaluation. Eur J Intern Med 2011;22:289–95. https://doi.org/10.1016/j.ejim.2011.01.007.

[34] van Toorn R, Solomons R. Update on the Diagnosis and Management of Tuberculous Meningitis in Children. Semin Pediatr Neurol 2014;21:12–8. https://doi.org/10.1016/j.spen.2014.01.006.

[35] Solomons RS, Visser DH, Donald PR, Marais BJ, Schoeman JF, van Furth AM. The diagnostic value of cerebrospinal fluid chemistry results in childhood tuberculous meningitis. Childs Nerv Syst 2015;31:1335–40. https://doi.org/10.1007/s00381-015-2745-z.

[36] Huynh J, Abo YN, du Preez K, Solomons R, Dooley KE, Seddon JA. Tuberculous Meningitis in Children: Reducing the Burden of Death and Disability. Pathogens 2021:11. https://doi.org/10.3390/pathogens11010038.

[37] Huynh J, Donovan J, Phu NH, Nghia HDT, Thuong NTT, Thwaites GE. Tuberculous meningitis: progress and remaining questions. Lancet Neurol 2022;21:450–64. https://doi.org/10.1016/s1474-4422(21)00435-x.

[38] Concepcion NDP, Laya BF, Andronikou S, Daltro PAN, Sanchez MO, Uy JAU, et al. Standardized radiographic interpretation of thoracic tuberculosis in children. Pediatr Radiol 2017;47:1237–48. https://doi.org/10.1007/s00247-017-3868-z.

[39] Delacourt C, Mani TM, Bonnerot V, de Blic J, Sayeg N, Lallemand D, et al. Computed tomography with normal chest radiograph in tuberculous infection. Arch Dis Child 1993;69:430–2. https://doi.org/10.1136/adc.69.4.430.

[40] Marais BJ, Gie RP, Schaaf HS, Starke JR, Hesseling AC, Donald PR, et al. A proposed radiological classification of childhood intra-thoracic tuberculosis. Pediatr Radiol 2004;34:886–94. https://doi.org/10.1007/s00247-004-1238-0.

[41] Van Dyck P, Vanhoenacker FM, Van den Brande P, De Schepper AM. Imaging of pulmonary tuberculosis. Eur Radiol 2003;13:1771–85. https://doi.org/10.1007/s00330-002-1612-y.

[42] Hadlock FP, Park SK, Awe RJ, Rivera M. Unusual radiographic findings in adult pulmonary tuberculosis. AJR Am J Roentgenol 1980;134:1015–8. https://doi.org/10.2214/ajr.134.5.1015.

[43] Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med 2012;367:348–61. https://doi.org/10.1056/NEJMra1008049.

[44] Kwong JS, Carignan S, Kang EY, Müller NL, FitzGerald JM. Miliary tuberculosis. Diagnostic accuracy of chest radiography. Chest 1996;110:339–42. https://doi.org/10.1378/chest.110.2.339.

[45] Nachiappan AC, Rahbar K, Shi X, Guy ES, Mortani Barbosa EJ, Jr., Shroff GS, Ocazionez D, Schlesinger AE, Katz SI, Hammer MM. Pulmonary Tuberculosis: Role of Radiology in Diagnosis and Management. Radiographics 2017;37:52-72. doi: 10.1148/rg.2017160032.

[46] Andronikou S, Vanhoenacker FM, De Backer AI. Advances in imaging chest tuberculosis: blurring of differences between children and adults. Clin Chest Med 2009;30:717-744, viii. doi: 10.1016/j.ccm.2009.08.022.

[47] Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC Infect Dis 2014;14(Suppl 1):S5. https://doi.org/10.1186/1471-2334-14-s1-s5.

[48] Holmberg PJ, Temesgen Z, Banerjee R. Tuberculosis in Children. Pediatr Rev 2019;40:168–78. https://doi.org/10.1542/pir.2018-0093.

[49] Jenkins HE, Yuen CM, Rodriguez CA, Nathavitharana RR, McLaughlin MM, Donald P, et al. Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2017;17:285–95. https://doi.org/10.1016/s1473-3099(16)30474-1.

[50] Edmonds A, Lusiama J, Napravnik S, Kitetele F, Van Rie A, Behets F. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. Int J Epidemiol 2009;38:1612–21. https://doi.org/10.1093/ije/dyp208.

[51] Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. Clin Infect Dis 2014;58:470–80. https://doi.org/10.1093/cid/cit790.