

Risk factors in the delay of treatment of childhood tuberculosis in a Peruvian Hospital

Factores de riesgo en el retraso de tratamiento de tuberculosis infantil en un hospital peruano

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What do we know about the subject matter of this study?

Following the diagnosis of childhood pulmonary tuberculosis (c-PTB), the immediate initiation of treatment is critical, as delays are often associated with poor prognosis and increased mortality in endemic areas.

What does this study contribute to what is already known?

A low level of education of the guardian represents a risk factor for the delayed initiation of c-PTB treatment in children under the age of 15. Therefore, belonging to the health care network A of Callao, Peru, is a factor that decreases the risk of tuberculosis in this study group.

Abstract

Childhood tuberculosis (c-TB) continues to be one of the causes of morbidity and mortality in children, but there is still little information on the delay in the initiation of specific treatment. **Objective:** To determine the risk factors associated with delayed initiation of tuberculosis (TB) treatment in children under 15 years of age. **Patients and Method:** Case-control study. Patients <15 years of age with a diagnosis of childhood pulmonary tuberculosis (c-PTB) with delayed treatment initiation >24 hours were included. Clinical and epidemiological variables were evaluated: age, gender, guardian's education, poverty level, origin, family history of TB, altered imaging findings, symptomatic, PPD >10mm, histology, bacteriology, resistance to treatment, and healthcare network. Bi and multivariate logistic regression analysis was performed, through which odds ratios were calculated. **Results:** We evaluated 116 patients with c-PTB with a delayed initiation of specific treatment of more than 24 hours, and 264 with start of treatment in the first 24 hours. The delay in anti-tuberculosis treatment had a median of 3 days with an interquartile range of 2 to 7 days. The patient with the least educated guardian had a delay in treatment initiation with an odds ratio of 7.47 (95%CI: 4.13 - 13.52). Belonging to the healthcare network A of Callao decreased the probability of having tuberculosis by 0.224 times (95%CI:0.11 - 0.46). **Conclusion:** Incomplete education level of the guardian is a risk factor associated with delayed initiation of c-PTB treatment in children under 15 years of age while belonging to the Callao healthcare network A is a factor that decreases the risk in the group under study.

Keywords:
Tuberculosis;
Risk Factors;
Time-to-Treatment;
Child;
Peru

Introduction

Worldwide, childhood tuberculosis (c-TB) is one of the most important causes of morbidity and mortality. The World Health Organization (WHO) reports figures of up to one million children infected with c-TB each year and it accounts for the death of up to 400 children per day, despite being a preventable and curable disease¹⁻³. Following the diagnosis of childhood pulmonary tuberculosis (c-PTB), the immediate initiation of treatment is critical, as delays are often associated with poor prognosis and increased mortality in endemic areas⁴⁻⁶. To ensure timely treatment, interventions are required to address the barriers that delay the initiation of anti-tuberculosis treatment and to facilitate the continuum of care for this disease⁶.

One of the causes of delayed treatment is late diagnosis; this is due to nonspecific symptoms, the low socioeconomic level of the household of origin, limited knowledge of the disease, and the deficiencies of the Peruvian healthcare system for the detection of tuberculosis on a large scale^{5,7,8}. The deficiencies of the system include a shortage of health personnel (specialists and subspecialists), lack of supplies, obsolete or malfunctioning equipment, suboptimal administrative processes, and stigmatizing behaviors in the care of tuberculosis patients⁶.

Although the Peruvian government established a law for the prevention and control of tuberculosis, implementing units such as primary care health centers and hospitals often fail to comply with it, using the allocated budget for other expenses⁹.

Other factors related to the delay in starting treatment are the socioeconomic and sociodemographic conditions of the patients, since populations in rural areas, with a low socioeconomic level, represent groups at high risk of infection of the disease and treatment abandonment^{10,11}. Likewise, families with children with tuberculosis and single caregivers constitute a barrier to treatment initiation, especially when there is more than one infected individual in the household^{6,11}. Also, in some contexts, the incomplete level of education of parents or guardians and the lack of knowledge about the disease lead to a delay in the initiation of treatment or non-compliance with treatment⁶.

Currently, the exact time delay in the initiation of anti-tuberculosis treatment in an urban area that could significantly increase morbidity and mortality in pediatric patients is unknown. Tuberculosis is one of the main health problems in the Callao Region, so it is necessary to identify the social determinants of health that could be associated with its delayed treatment, as well as the approximate time of delay in order to propose strategies that can mitigate the impact of this disease on the population¹².

The objective of this research was to determine the factors associated with delay in the initiation of treatment for c-PTB in children under 15 years of age.

Patients and Method

Design

Case-control study. Two groups of pediatric patients with c-PTB were formed, cases with delayed initiation of specific treatment and controls with timely initiation, in a 1:2 ratio.

Population, sample

The Regional Health Directorate (DIRESA) of the Regional Government of Callao, Constitutional Province of Callao, Peru¹³, is made up of four hospitals, one of third-level of care (III-1) and three second-level hospitals. The III-1 hospital of national reference is the *Hospital Nacional Daniel Alcides Carrión* (HNDAC), which is not exclusively for patients with tuberculosis. The DIRESA Callao has 49 first-level care facilities, organized into three health care networks. The patients in this study belonged to the three networks of the Callao Region (Network A or BEPECA, Network B or Bonilla, and Network C or Ventanilla)^{12,14}.

This study included the entire population of patients under 15 years of age, of both sexes, with the diagnosis of c-PTB according to Stegen-Toledo criteria: clinical, epidemiological, radiological, immunological (tuberculin test and/or immunodiagnostic interferon-gamma release assay "IGRA"), histological, and bacteriological (culture or PCR positive for *Mycobacterium tuberculosis* "MTB") criteria. Patients received specific treatment between January 2014 and December 2019 according to Technical Health Standard 104-Ministry of Health (MINSA) General Directorate of People's Health-V.01 for the comprehensive healthcare of people affected by tuberculosis⁴.

To guarantee the results obtained, the power of the test was calculated according to the study by Valvi et al.¹⁵ in relation to the sex variable; a proportion of exposed cases and controls of 43% and 59%, respectively, was assumed with a 95% CI. Thus, obtaining 88% statistical power.

Patients with c-PTB with incomplete and illegible medical records were considered as exclusion criteria. The study was approved by the Ethics Committee of the Faculty of Human Medicine of Ricardo Palma University and by the Ethics and Research Committee of the HNDAC. The ethical considerations of the Declaration of Helsinki and the World Medical Association were followed.

Variables under study

The dependent variable was the delay in starting anti-tuberculosis treatment more than 24 hours after diagnosis.

The independent variables were patient's age (0 to 4 years/5 to 14 years), patient's sex (male/female), guardian's educational level (primary/complete secondary/incomplete secondary), poverty level (lower and middle/upper)¹⁶, place of origin (Callao/other), history of family member with TB (yes/no), altered radiography (yes/no), respiratory symptomatic -i.e., those with productive cough equal to or greater than 15 days- (yes/no), PPD >10mm (yes/no), histology (yes/no), positive bacteriology (yes/no), MTB in sputum or gastric content or culture or positive PCR or Interferon Gamma or Quantiferon-TB (yes/no), resistance to treatment (yes/no), and the health care network of origin (Network A, Network B, and Network C)¹². In addition, the number of days elapsed from diagnosis to initiation of treatment was calculated.

The data was obtained from the patients' medical records retrospectively using data collection cards; the technique used was documentation.

Statistical analysis

Data analysis was performed using IBM SPSS version 25. Frequencies and percentages were used for qualitative variables, while median and interquartile range were used for quantitative variables. Hypothesis tests were contrasted at a significance level of 0.05, with a 95% CI. In addition, a bi- and multivariate logistic regression analysis was performed, through which crude and adjusted odds ratio (OR) were calculated.

Results

During the study period, 380 patients with a diagnosis of c-PTB were included, 116 cases and 264 controls. Regarding the PPD skin test, 69% of the cases were recorded as PPD positive (+), 20.7% as PPD negative (-), and 10.3% of the cases did not undergo PPD due to lack of reagent. Of the controls, 57.2% were PPD (+), 31.8% PPD (-), and 11% of the cases did not have a PPD skin test due to lack of reagent. In most of the patients, the PPD test reading was recorded in the clinical history as positive or negative; no record of the induration reading in millimeters was found.

In this study, both sexes were similarly distributed, the median age was 6 years, and 70.7% of the guardians of the cases had incomplete education. The Callao B and C healthcare networks had almost all the cases of c-PTB with 38.8% and 50.9%, respectively. The poverty level of the cases was 75.9% (lower/medium), 92.2%

of the cases had a family history of tuberculosis, and 8.6% had a positive smear test (Table 1).

The delay in the initiation of anti-tuberculosis treatment had a median of 3 days with an interquartile range of 2-7 days. Figure 1 shows the histogram of the days of delay in starting treatment.

In the bivariate analysis, the following variables were statistically significant: the educational level of the guardian with an odds ratio of 6.81 (95%CI: 4.20 - 11.07); health care network with an odds ratio of 0.19 (95%CI: 0.10 - 0.38), and poverty level with an odds ratio of 2.04 (95%CI: 1.25 - 3.34). In the multivariate analysis, it was found that a lower educational level increases the probability of delay in treatment initiation by 7.47 times (95%CI:4.13 - 13.52), and belonging to the healthcare network A decreases the probability by 0.22 times (95%CI:0.11 - 0.46) (Table 2).

Discussion

In this work, globally, a median of 3 days is observed for the initiation of anti-tuberculosis treatment; therefore, once the patient is diagnosed with c-PTB, the initiation of treatment is relatively fast despite that, by definition, there is a delay in initiation. This is similar to what was observed in India in Kalra's study¹⁷ but the range was wider. However, Valvi et al.¹⁵ in the same country identified a longer median (51 days) delay in treatment initiation. Another study in China reported a delay of 30 days in patients with childhood pleural tuberculosis; a similar result was reported in Ethiopia. These differences can be explained by the heterogeneity in the conceptualization of the variable delay in treatment initiation and from what moment it is considered present. It should be noted that delay in treatment, especially in c-TB, constitutes a latent threat at a global level with respect to the development of this disease^{18,19}.

Through the Tuberculosis Control Program (TCP), active intervention is carried out at the different levels of healthcare to detect the largest number of patients with suspected tuberculosis to corroborate the diagnosis and initiate timely anti-tuberculosis treatment to achieve successful control of the disease^{2,20}. It is necessary to establish comprehensive and individualized care in the treatment and prevention of this pathology, the implementation of specific tests for the early diagnosis of TB in children, and the capacity in terms of infrastructure and knowledge of the healthcare personnel of the first and second level of care since these are variables of great importance according to studies carried out in Latin America^{22,23}.

In patients with c-TB, the clinical and radiological characteristics are less specific compared with adults;

Table 1. Factors associated with delay in TB treatment in children under 15 years in the outpatient clinic of Daniel Alcides Carrión National Hospital for the period of 2014-2019

Variables	Characteristics	Case		Control		Total	P-Value	OR ^A	CI(95%) ^B
		n	%	n	%				
Age	Until 4 years of age	44	37.9%	119	45.1%	163	0.195	0.75	(0.48 - 1.16)
	5 to 14 years of age	72	62.1%	145	54.9%	217			
Gender	Female	60	51.7%	129	48.9%	189	0.608	1.12	(0.72 - 1.74)
	Male	56	48.3%	135	51.1%	191			
Place of origin	Callao	51	44.0%	139	52.7%	190	0.119	0.71	(0.46 - 1.10)
	Ventanilla	56	48.3%	50	18.9%	106			
	Others	9	7.8%	75	28.4%	84			
Tutor's educational level	Incomplete studies	82	70.7%	69	26.1%	151	< 0.001	6.82	(4.20 - 11.07)
	Complete studies	34	29.3%	195	73.9%	229			
Care network	Network A (BEPECA) ^C	12	10.3%	100	37.9%	112	< 0.001	0.19	(0.10 - 0.38)
	Network B(Bonilla)/ Network C (Ventanilla)	104	89.7%	164	62.1%	268			
Level of poverty	Lower/middle	88	75.9%	160	60.6%	248	0.004	2.04	(1.25 - 3.34)
	Superior	28	24.1%	104	39.4%	132			
Family history of TB	Si	107	92.2%	239	90.5%	346	0.590	0.80	(0.36 - 1.78)
	No	9	7.8%	25	9.5%	34			
Clinical symptomatology	Si	75	64.7%	189	71.6%	264	0.176	1.38	(0.87 - 2.19)
	No	41	35.3%	75	28.4%	116			
Chest X-ray (+)	Si	113	97.4%	256	97.0%	369	0.812	0.85	(0.22 - 3.26)
	No	3	2.6%	8	3%	11			
Positive smearoscopy	Si	10	8.6%	26	9.8%	36	0.707	1.16	(0.54 - 2.49)
	No	106	91.4%	238	90.2%	344			

The qualitative variables are described with frequencies and percentages, whilst the quantitative variables, with measures of central tendency (mean, median, standard deviation and percentiles). P-values were calculated using the Chi-square test. ^AOR: Odds Ratio. ^B95% CI: 95% confidence interval. ^CBEPECA: Bellavista/La Perla/Callao. ^DICR: interquartile range.

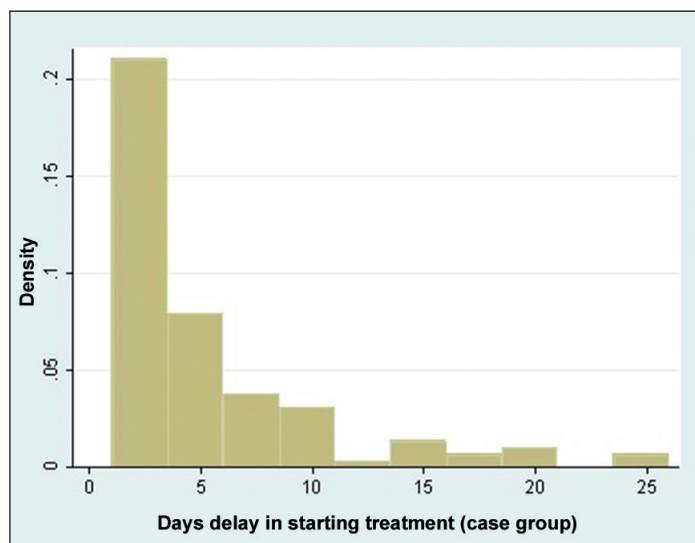


Figure 1. Histogram of the delayed days in the initiation of the case's treatment.

however, epidemiological suspicion, the tuberculin test (Mantoux), and chest X-ray continue to be important for diagnosis^{2,19}.

Bacteriological confirmation is often presumed rather than confirmed because the lesions are paucibacillary/closed, and because of the difficulty in collecting the sputum sample (aspiration and gastric lavage methods). There are reports where the microbiological identification of MTB in children is less than 50%^{2,19}; even the culture is positive in 30 to 40% of the cases^{2,20}. In this research, regarding the clinical characteristics presented by the patients, it was determined that clinical symptomatology, chest X-ray, and smear microscopy did not have a statistically significant association in relation to the late initiation of treatment in c-TB ($p = 0.176$, $p = 0.812$, and $p = 0.707$, respectively). These results differ from a study where an association was found between clinical manifestations and delay in treatment since this time can be decreased by con-

Table 2. Multivariate analysis of the delayed initiation of tuberculosis treatment and associated factors in children under the age of 15 for the period 2014-2019.

Variables	Análisis bivariado		Análisis multivariado	
	ORC ^a (IC 95%) ^c	Valor p	ORA ^b (IC 95%) ^c	Valor p
Tutor's level of education	6.81 (4.20 - 11.07)	< 0.001	7.473 (4.13 - 13.52)	< 0.001
Care network	0.19 (0.10 - 0.38)	< 0.001	0.224 (0.11 - 0.46)	< 0.001
Poverty level	2.04 (1.25 - 3.34)	0.004	0.579 (0.30 - 1.14)	0.111

P-values are calculated using the Chi-square test. ^aORC: Crude Odds Ratio. ^bORA: Adjusted Odds Ratio ^c95% CI: 95% confidence interval.

sidering the appearance of this symptomatology in patients. In addition, the use of imaging is also related to the decrease in the time it takes to provide treatment for c-TB according to a study conducted in Bangladesh^{19,23}.

In this study, the educational level of the guardian with incomplete education was a risk factor for delayed initiation of c-TB treatment. This is similar to what was reported in Brazil in 2014, where incomplete education of the guardian coupled with low socioeconomic status is associated with delayed initiation of anti-tuberculosis treatment in pediatric patients with this disease²¹. In India, in 2017, they also reported a delay in the initiation of treatment associated with guardians with incomplete education, a poor health system, and a population with traditional beliefs, such as “shaman” or “healer”, who use physical and/or spiritual means to heal and are the ones who are usually consulted before attending a healthcare center¹⁷.

Deficient education of the guardian, as reported in other studies, leads to the risk of delayed initiation of treatment of the patient with c-TB due to the lack of knowledge of the disease^{11,25} or the severity of the symptoms^{26,27}, which induces the abandonment of the patient's treatment²⁸.

Patients in the Callao Healthcare Network A initiated anti-c-TB treatment on time, which can be explained by the Tuberculosis Infection Prevention and Control Program implemented in 2019²⁸. This is relevant since one of the barriers to timely treatment of tuberculosis is access and responsiveness of health services, which was documented by Sullivan et al.¹¹ since the existence of structural and organizational problems in the health systems would prevent compliance with timely anti-tuberculosis treatment with prioritized emphasis on high-risk groups and areas.

Besides, what was observed in the jurisdiction of the other Healthcare Networks (B and C) can be explained by the fact that the activities for the re-

cruitment and home follow-up of patients with c-PTB were limited by the lack of personnel, violence generated by gangs in the area, and the distance to the health center²⁸.

The main limitation of this study is that, given its retrospective design, a secondary source was used (HCL, attendance control card, and administration of drugs with scheme one), which does not allow making conclusive statements, as there is the possibility of some type of bias in the information collected.

In conclusion, the educational level of the guardian with incomplete studies and Healthcare Networks B and C of Callao were risk factors associated with delay in the initiation of treatment in children under 15 years of age.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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