Clinical forms and diagnosis of tuberculosis in children and adolescents during the COVID-19 pandemic

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Submitted:
Accepted:

Study carried out at the Instituto de Puericultura e Pediatria Martagão Gesteira - IPPMG - Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.

ABSTRACT

Objective: The present study aimed to describe the clinical forms and the time taken to diagnose new tuberculosis cases and to statistically analyze the isolated and combined forms of the disease in children and adolescents treated at a university hospital in Rio de Janeiro during the first year of the COVID-19 pandemic in Brazil. **Methods:** This was a cross-sectional study that used retrospective data on children (0–9 years old) and adolescents (10–18 years old) with pulmonary (PTB), extrapulmonary (EPTB), and combined tuberculosis (PTB + EPTB) followed up at the outpatient clinic from January 2019 to March 2021. Categorical data were analyzed by descriptive statistics and expressed as frequency and proportions. Categorical variables were compared using the Chi-square test, and numerical variables using Student's T-test. **Results:** A total of 51 cases were included, 63% (32/51) of which comprised patients in the year of the pandemic (group A), while 37% (19/51) were patients attended in previous years (group B). In group A, 19% (6/32) of the patients presented PTB, 59% (16/32) had EPTB, and 31% (10/32) had PTB+EPTB. In group B, 42% (8/19) of the patients presented PTB, 42% (8/19) had EPTB, and 16% (3/19) had PTB+EPTB. **Conclusion:** Our study revealed more tuberculosis cases in the first year of the pandemic than in the same period of the previous year, with greater variation of sites affected by the disease, including rarer and more severe forms.

Keywords: pandemic, children, adolescents, tuberculosis, coronavirus.

INTRODUCTION

Tuberculosis is a communicable disease that constitutes one of the leading causes of death worldwide. Since 1993, it has been considered a global emergency and a challenging public health problem. In 2019, approximately ten million people contracted tuberculosis, with 73,864 new cases in Brazil. At the end of that year, the global indicators of tuberculosis disease burden declined, and access to prevention and treatment improved.[1-3]

The coronavirus disease (COVID-19) pandemic has reversed years of progress. For the first time in more than a decade, the number of deaths due to tuberculosis has increased, and the reduced disease incidence achieved in previous years has decreased. Approximately half of the people with tuberculosis had no access to healthcare in 2020 and, therefore, were not reported. A recent study published by the Stop Tuberculosis Partnership organization showed that social isolation measures, which reduce the demand for services, may consequently lead to 6.3 million new cases and 1.3 million more deaths due to the disease

by 2025. However, the impact of tuberculosis has been estimated to be much worse in 2021 and 2022.[3-6]

In 2020, economic and human health resources were reallocated due to the high priority of COVID-19, interrupting current health programs and reducing the early diagnosis and treatment of several diseases, including tuberculosis. The impact of the pandemic on the care of infectious diseases may have been greater in the area of pulmonary diseases than in others, as specialized teams concentrated their efforts to control COVID-19, thus dismantling specific tuberculosis services.[7] The negative impact of these measures could lead to an increase of up to 20% in the number of deaths by tuberculosis in the next five years.[6,8] Tuberculosis control measures have failed to achieve the global goals established by the United Nations (UN). Approximately 19.8 million people were treated for tuberculosis from 2018 to 2020, corresponding to only half of the 5-year goal of 40 million (2018–2022). In the same period, only 1.4 million children were treated, equivalent to 41% of the 5-year goal of 3.5 million. In 2020, the global

expenditure on tuberculosis services was US$5.3 billion, half of what is needed to control the disease, and preventive treatment decreased by 22% when compared to the previous year.[4] In Rio de Janeiro, there was a 16% increase in tuberculosis cases from 2015 to 2020, with 7,050 new cases in 2021. As for spatial distribution, the cases were more concentrated in areas of high population density and greater social vulnerability. The cure rates in laboratory-confirmed tuberculosis cases showed a significant decrease of 60.1% in 2020, with progressively increasing mortality (2019–2020) and treatment abandonment (2017–2021).[9]

The aim of the present study was to describe the clinical forms and the time taken to diagnose new tuberculosis cases and to statistically analyze the isolated and combined forms of tuberculosis in children and adolescents treated at a university hospital in Rio de Janeiro during the first year of the COVID-19 pandemic in Brazil.

METHODS

This cross-sectional study used retrospective data on children (0–9 years old) and adolescents (10–18 years old) with pulmonary (PTB), extrapulmonary (EPTB), and combined tuberculosis (PTB + EPTB) who were followed up at the pediatric pulmonology outpatient clinic of the Instituto de Puericultura e Pediatria Martagão Gesteira – (IPPMG), a reference university pediatric hospital in Rio de Janeiro, from January 1, 2019, to March 1, 2021.

The inclusion criteria were patients identified in the tuberculosis case registry book who were followed up at the IPPMG during the disease treatment period. Clinical and epidemiological data were obtained from medical records; patients whose medical records were not found were excluded.

The evaluated variables included disease history (fever, cough, weight loss, adynamia, dyspnea, and adenomegaly); contact with tuberculosis; diagnostic score of the Ministry of Health - Brazil (MoH-Brazil); alterations in chest radiography (lymph node hilum enlargement, miliary pattern, expansile pneumonia, cavitations, calcifications, pleural effusion, and atelectasis);[10] acid-fast bacilli (AFB) on Ziehl-Neelsen smears; culture of *Mycobacterium tuberculosis* (M.tb); Gene Xpert MTB-RIF and Gene Xpert Ultra tests (Cepheid – USA); tuberculin skin test (TST) positivity (≥ 5 mm); antibody tests for human immunodeficiency virus (HIV), and healthcare prior to PTB diagnosis (antibiotic therapy for common germs without improvement).

The diagnosis of PTB was established according to the MoH-Brazil clinical score (more than 40 points, very likely; 30–35 points, possible; less than 25 points, unlikely) based on epidemiological and clinical-radiological criteria, TST (positive ≥ 5 mm; negative < 5 mm), and bacteriological analyses.[11]

The diagnosis of EPTB, in turn, was based on clinical and epidemiological criteria, TST, and invasive biopsy results compatible with tuberculosis. Patients with a diagnosis based on these criteria and whose response to treatment with antituberculosis drugs was satisfactory after two months of initiation were classified as having tuberculosis and included in the study.

The tuberculosis patients were divided into two groups: group A - from March 2020 to March 2021, corresponding to the first year of the COVID-19 pandemic; and group B - from January 2019 to February 2020, the period corresponding to the year before the pandemic.

The Gene Xpert MTB-RIF Ultra (Ultra) test was used when appropriate in patients in group A, and the Gene Xpert MTB-RIF (Xpert) test was used in patients in group B. Ultra's bacterial load detection is categorized as high, medium, low, and positive traces. In EPTB, positive traces indicate a positive M.tb result.[12]

Data were entered into a Microsoft Excel 12.0 (Office 2007) spreadsheet. The categorical data were analyzed by descriptive statistics and expressed as frequency and proportions, whereas non-categorical data were analyzed by numerical variables as minimum and maximum values and median and expressed as a box plot. Categorical variables were compared using the Chi-square test, and numerical variables using Student's T-test; p-values < 0.05 were considered significant.

The present study was approved by the Research Ethics Committee (REC) of the IPPMG, Federal University of Rio de Janeiro - UFRJ, under Certificate of Presentation for Ethical Appreciation (CAAE) No. 45439221.3.0000.5264.

RESULTS

A total of 51 patients were attended from 2019 to 2021. Group A included 32 patients: 60% (19/32) male and 47% (15/32) from the city of Rio de Janeiro. The age range varied from two to 205 months (median of 109 months), with 47% (15/32) adolescents and 53% (17/32) children. Group B comprised 19 patients: 58% (11/19) female and 84% (16/19) from the city of Rio de Janeiro. The age range varied from four to 182 months (median of 84 months), with 37% (7/19) adolescents and 63% (12/19) children.

Group A showed a 68% increase in the number of tuberculosis cases when compared to the previous year (group B). Both groups had a higher prevalence of children; however, group A had a higher frequency of adolescents than group B.

Figure 1 shows the number of new cases identified since the first case in group B, through the first case of COVID-19 in Brazil, the declaration of COVID-19 as a pandemic (3/11/2020), and the beginning and end of the lockdown (May to October 2020), up to

the implementation of new restrictive measures (3/26/2021).

As for the case outcomes, three patients died in group A, while none died in group B.

Figure 2 shows the forms of tuberculosis presentation in each group.

The data on clinical history, contact with tuberculosis patients, TST results, and healthcare prior to the final diagnosis in patients with PTB, EPTB, and PTB + EPTB in groups A and B are described in Table 1.

The radiological aspects of children and adolescents with PTB and PTB + EPTB were distributed in groups A and B. The three main forms observed were: expansile pneumonia, pleural effusion, and lymph node hilum enlargement. In group A, they represented 62% of the cases, with 28% (9/32) exhibiting expansile pneumonia, 25% (8/32) pleural effusion, and 9% (3/32) lymph node hilum enlargement. Meanwhile,

in group B, they represented 84% of the cases, with 42% (8/19) with expansile pneumonia, 31% (6/19) pleural effusion, and 11% (2/19) lymph node hilum enlargement.

The 14 patients with PTB presented clinical scores equal to or greater than 30 points, with 100% of the patients in group A (6/6) and 87% in group B (7/8). The laboratory tests used are described in Table 2.

In group A, six patients showed detectable results in the Ultra test, while in group B, two showed detectable results in the Xpert test. In groups A and B, 33% (3/19) and 25% (8/32) of the patients, respectively, were diagnosed with tuberculosis and started treatment during hospitalization.

The types of EPTB in groups A and B are detailed in Table 3.

Coinfection with HIV was identified in 2/19 of the tested patients: one patient in group A (with severe
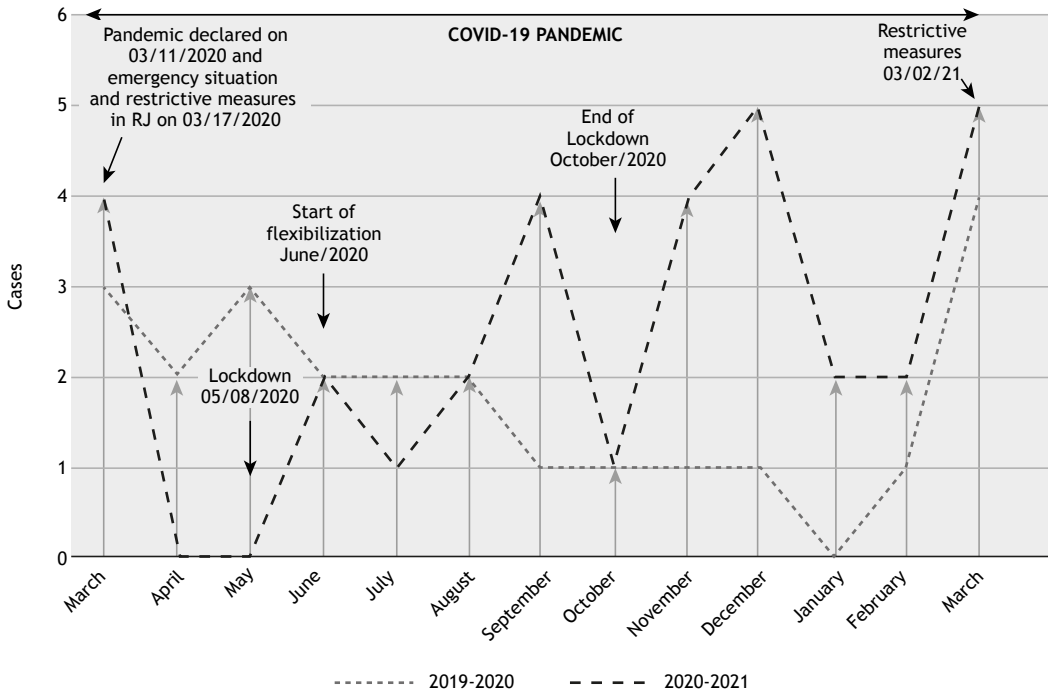

Figure 1. Graph indicating the number of active tuberculosis cases diagnosed at the IPPMG-UFRJ from 2019–2021.
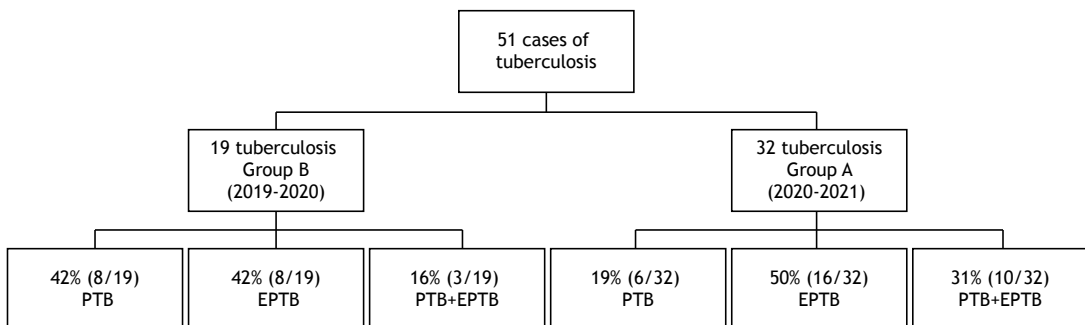

Figure 2. Flowchart of tuberculosis distribution by clinical presentation. EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis. Group A - 2020–2021; Group B - 2019–2020.

Table 1. Clinical data, diagnosis, and therapeutic course from 2019–2021.[a]

		TOTAL (n = 51)		PTB (n = 14)		EPTB (n = 24)		PTB + EPTB (n = 13)	
		Group							
		A (n = 32)	B (n = 19)	A (n = 6)	B (n = 8)	A (n = 16)	B (n = 8)	A (n = 10)	B (n = 3)
Clinical History	Fever	25 (78%)	13 (68%)	6 (100%)	5 (62%)	13 (81%)	5 (62%)	6 (60%)	3 (100%)
	Cough	10 (32%)	7 (37%)	5 (83%)	6 (75%)	1 (6%)	0 (0%)	4 (40%)	1 (33%)
	Weight loss	11 (35%)	6 (30%)	2 (33%)	5 (62%)	6 (40%)	0 (0%)	3 (30%)	1 (33%)
	Adynamia	11 (35%)	2 (10%)	2 (33%)	2 (25%)	7 (43%)	0 (0%)	3 (30%)	0 (0%)
	Adenomegaly	14 (45%)	7 (37%)	0 (0%)	0 (0%)	9 (60%)	7 (87%)	5 (50%)	0 (0%)
	Dyspnea	8 (25%)	5 (25%)	4 (66%)	1 (12%)	0 (0%)	3 (20%)	4 (40%)	3 (100%)
Prior Service Attention	Yes	20 (63%)	14 (73%)	3 (50%)	5 (62%)	10 (63%)	8 (100%)	7 (70%)	1 (34%)
Contact with Tuberculosis	Yes	11 (35%)	11 (58%)	1 (12%)	5 (62%)	6 (40%)	5 (45%)	4 (40%)	1 (33%)
	Group	A (n = 28)	B (n = 15)	A (n = 5)	B (n = 5)	A (n = 13)	B (n = 8)	A (n = 10)	B (n = 2)
Positive Tuberculin Test	Yes	16 (52%)	12 (63%)	2 (40%)	4 (80%)	7 (54%)	6 (75%)	7 (70%)	2 (100%)

EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis. Group A (2020–2021); Group B (2019–2020). [a]Values expressed as n (%).

immunosuppression according to the Center for Disease Control and Prevention (CDC) classification)[13] and one patient in group B. Both had a previous diagnosis of HIV and were using antiretroviral therapy, but with poor adherence by the patient in group A. The graph in Figure 3 represents the time expended from symptom onset (days) until the final diagnosis of tuberculosis in groups A and B.

Group A presented greater variability than group B; this value dispersion resulted in a significant variation in the number of days since symptom onset. Outliers were found on different days in group A. The median number of days for the diagnosis of tuberculosis was 56 days in group A and 42 days in group B (p < 0.01).

DISCUSSION

The present study was conducted at a referral hospital in Rio de Janeiro (RJ), Brazil, and showed that the COVID-19 pandemic in Brazil led to delayed tuberculosis diagnoses in children and adolescents.

The COVID-19 pandemic reduced the demand for care at health centers. This, added to poverty and confinement in households where many people live together in small physical spaces, which are mostly poorly ventilated,[14] increased the number of tuberculosis cases in Brazil, an effect that was also identified at our service.

Our study shows that there were more tuberculosis cases in the first year of the pandemic than in the same period in the previous year, predominantly in children over five years of age, in both years. According to the World Health Organization, 11% of the children in the world had tuberculosis in 2020. With respect to adults, men were found to be more affected than women.[15] Although the age group

was different, this pattern was observed herein in the patients from group A; however, the same did not occur in group B. As for clinical presentation, symptoms of fever and cough were more prevalent when evaluating PTB and combined cases, which contributed to the MoH-Brazil clinical score. Group B also presented low laboratory test (AFB and culture) positivity, corroborating the fact that children are paucibacillary or bacillus-negative. Nevertheless, with the replacement of the Gene Xpert MTB-RIF cartridge with the Ultra cartridge, in 2020, a greater number of patients in group A had their diagnosis of tuberculosis confirmed; this was due to the fact that the latter method increases the sensitivity of the diagnosis on account of its lower detection limit for M.tb.[12] The Ultra test has a detection limit of M.tb of less than 15.6 CFU, while the Xpert assay has a limit of 116 CFU. Despite the use of this new technique, considering the singularities of PTB in children and adolescents, MoH-Brazil recommends that the diagnosis in this age group be performed based on the scoring system. This system values clinical, radiological, and epidemiological data and does not include bacteriological confirmation.[11]

In group A, the EPTB cases showed a greater variety of sites affected by the disease, including rarer and more severe forms than in group B. The lack of access to healthcare services and the non-specificity of symptoms, which can be confused with other diseases, may have contributed to this finding.[6]

Likewise, the emergency care that was previously available and the greater delay in the diagnosis in group A can be attributed to the difficult immediate diagnosis in the period from 2020 to 2021 due to the greater demand for emergency services caused by the pandemic.[6]

Table 2. Laboratory characteristics of children and adolescents with tuberculosis in groups A and B.[a]

AFB	TOTAL (n = 43)		p-value*	PTB (n = 13)		p-value*	EPTB (n = 17)		p-value*	PTB + EPTB (n = 10)		p-value*
Group	A (n = 29)	B (n = 14)		A (n = 6)	B (n = 7)		A (n = 12)	B (n = 5)		A (n = 8)	B (n = 2)	
Positive	3 (9%)	4 (28%)	<0.17	2 (33%)	3 (43%)	<0.7	0 (0%)	0 (0%)	<0.8	1 (12%)	1 (50%)	<0.2
Negative	23 (91%)	10 (72%)		4 (67%)	4 (57%)		12 (100%)	5 (100%)		7 (88%)	1 (50%)	
Culture *M.tb.*	TOTAL (n = 31)		p-value*	PTB (n = 11)		p-value*	EPTB (n = 14)		p-value*	PTB + EPTB (n = 6)		p-value*
Group	A (n = 21)	B (n = 10)		A (n = 5)	B (n = 6)		A (n = 11)	B (n = 3)		A (n = 5)	B (n = 1)	
Positive	3 (15%)	3 (30%)	<0.3	1 (20%)	2 (33%)	<0.6	0 (0%)	1 (33%)	<0.04	2 (40%)	0 (0%)	<0.5
Negative	18 (85%)	7 (70%)		4 (80%)	4 (67%)		11 (100%)	2 (67%)		3 (60%)	1 (100%)	
XPERT	TOTAL (n = 33)		p-value*	PTB (n = 10)		p-value*	EPTB (n = 15)		p-value*	PTB + EPTB (n = 9)		p-value*
Group	A (n = 23)	B (n = 10)		A (n = 5)	B (n = 5)		A (n = 12)	B (n = 3)		A (n = 7)	B (n = 2)	
Detectable[+]	18 (77%)	3 (30%)	<0.01	4 (80%)	2 (40%)	<0.19	8 (67%)	0 (0%)	<0.03	6 (86%)	1 (50%)	<0.2
Not Detectable	6 (23%)	7 (70%)		1 (20%)	3 (60%)		4 (33%)	3 (100%)		1 (14%)	1 (50%)	

EPTB: extrapulmonary tuberculosis; PTB: pulmonary Tuberculosis; Group A (2020–2021); Group B (2019–2020). [a]Values expressed as n (%). *Chi-square test. [+]In the Ultra test, the category trace was included as detectable.

The analysis of the time taken until the diagnosis of tuberculosis in group A, even with patients seeking emergency care, showed a greater number of previous visits and a longer time to establish the diagnosis in group A than in the previous year (group B). Thus, these patients may have had their access and clinical support for tuberculosis diagnosis affected by the interruption of tuberculosis services during the COVID-19 pandemic. Reduced tuberculosis diagnoses during the pandemic were observed worldwide, based on the lower number of notifications.[4]

In the context of tuberculosis-HIV coinfection, the number of cases found in this study was lower than 10%, corroborating what happens at the state level, in which the proportion of tuberculosis-HIV cases in the study period ranged from 7.9–8.6% of cases.[9] The only patient diagnosed during the pandemic had severe immunosuppression, which may have contributed to the unfavorable progression of the disease. Supposedly, this severity is due to the possible delay in seeking care and poor adherence, with partial or complete interruption of HIV control treatment, observed in the same period in the country and around the world, as occurred with the tuberculosis programs.[11]

It was not possible to identify the source of disease in most cases in group A; however, when identified, it was due to close contact with infected individuals. This finding may have been caused by the delayed diagnosis of active tuberculosis due to social isolation. Even though this protective measure helped reduce the spread of COVID-19, it has favored intra-household exposure to tuberculosis. Prolonged contact at the household level is one of the risk factors that increase active tuberculosis transmission.[15,16]

Our study showed a decrease in tuberculosis diagnoses in the first four months after the beginning of the pandemic, after the introduction of restrictive measures and lockdown, with no tuberculosis cases diagnosed in the two consecutive months. This may be justified by the reduced accessibility of patients to medical services due to interrupted or difficult access to public transport or canceled follow-up visits.[7] As a result of less restrictive measures, more than twice as many cases were recovered over the following months, peaking after the end of the lockdown period with four times more cases than at the beginning of the pandemic in the state of Rio de Janeiro.

More deaths were observed in group A, possibly as a result of restrictive measures and the increased time for diagnosis during the COVID-19 pandemic. In Rio de Janeiro, the mortality rate that had been decreasing up to 2017 has risen progressively since 2019, with the highest rate of 4.81 per 100,000 inhabitants in 2021. Thus, an increase of up to 20% in tuberculosis deaths can be expected in the next five years.[6,8,9]

This study had some limitations. The hospital where it was conducted is a reference center for

Table 3. Types of active EPTB from 2019–2021.[a]

Extrapulmonary forms Tuberculosis Group	TOTAL (n = 37)		EPTB (n = 24)		PTB + EPTB (n = 13)	
	A (n = 26)	B (n = 11)	A (n = 16)	B (n = 8)	A (n = 10)	B (n = 3)
Peripheral adenopathy	11 (42%)	5 (45%)	8 (52%)	5 (62%)	3 (30%)	0 (0%)
Pleural	5 (19%)	5 (45%)	1 (6%)	2 (25%)	4 (40%)	3 (100%)
Peritoneal	2 (7%)	1 (10%)	2 (12%)	1 (13%)	0 (0%)	0 (0%)
Meningitis	1 (4%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Bone	2 (8%)	0 (0%)	1 (6%)	0 (0%)	1 (10%)	0 (0%)
Cutaneous	1 (4%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Others *	4 (16%)	0 (0%)	2 (12%)	0 (0%)	2 (20%)	0 (0%)

CNS: central nervous system; EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis; Group A (2020–2021); Group B (2019–2020). [a]Values expressed as n (%). *Total of four patients: one with meningitis + ophthalmic tuberculosis; one with peritoneal + skin tuberculosis; one with pleural + ganglionic tuberculosis, and one with bone + pleural + pericardial tuberculosis.
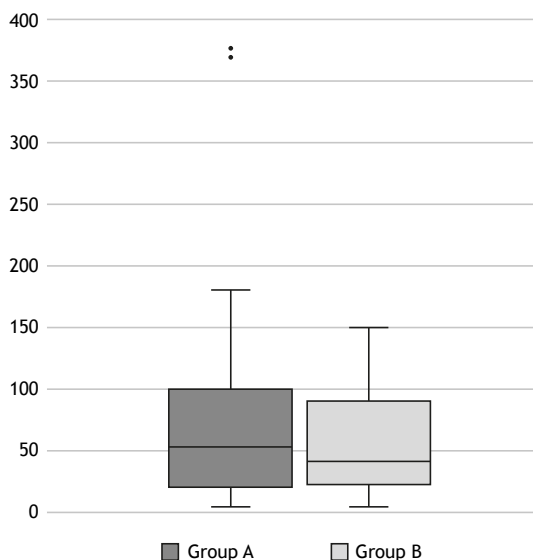

Figure 3. Box plot graph for the time variable for tuberculosis diagnosis in the period from 2019–2021.

tuberculosis, not necessarily reflecting what takes place in basic healthcare units, which are the centers for COVID-19 cases that are more accessible to the population.

The negative impact of the pandemic on tuberculosis programs will still promote repercussions on society for several years to come; therefore, there is an urgent need to adopt actions to mitigate and reverse this impact. The immediate priority is to restore access to and the provision of essential tuberculosis services without neglecting care for other diseases, including COVID-19 and AIDS.

AUTHOR CONTRIBUTIONS

Study design: MASP, RBA, AAAIP, CCS, MFBPS, ACCF, CBH, TFA, SF. Data collection: MASP. Data analysis: MASP, RBA, ACCF, CBH, TFA, CCS. Manuscript writing: MASP. Manuscript revision: RBA, ARF, AAAIP, ACCF, CBH, TFA, SF, MFBPS, CCS. Study supervision: CCS.

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