



Association between the radiological presentation and elapsed time for the diagnosis of pulmonary tuberculosis in the emergency department of a university hospital

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ABSTRACT

Objective: To evaluate the radiological presentation of patients with pulmonary tuberculosis diagnosed in the emergency department and to investigate its association with the time to diagnosis. **Methods:** This was a prospective observational study involving patients diagnosed with pulmonary tuberculosis in the emergency department of a tertiary university hospital in southern Brazil. Chest X-rays taken on admission were evaluated by a radiologist. The various patterns of radiological findings and locations of the lesions were described. The main study outcome was the total time elapsed between the initial radiological examination and the diagnosis of tuberculosis. **Results:** A total of 78 patients were included in the study. The median time from chest X-ray to diagnosis was 2 days, early and delayed diagnosis being defined as a time to diagnosis < 2 days and ≥ 2 days, respectively. Sputum smear positivity was associated with early diagnosis ($p = 0.005$), and positive culture was associated with delayed diagnosis ($p = 0.005$). Early diagnosis was associated with the presence of sputum ($p = 0.03$), weight loss ($p = 0.047$), cavitation ($p = 0.001$), and consolidation ($p = 0.003$). Pulmonary cavitation was found to be an independent predictor of early diagnosis ($OR = 3.50$; $p = 0.028$). **Conclusions:** There is a need for tuberculosis-specific protocols in emergency departments, not only to avoid delays in diagnosis and treatment but also to modify the transmission dynamics of the disease.

Keywords: Tuberculosis/diagnosis; Emergency medical services; Radiography, thoracic.

INTRODUCTION

Tuberculosis is one of the most lethal communicable diseases. It is estimated that approximately 10 million people developed the disease in 2017, leading to 1.3 million deaths, with an additional 300,000 deaths in individuals who were coinfecting with HIV.⁽¹⁾ There is a socioeconomic component, as evidenced by the fact that 90% of all tuberculosis cases are distributed among 22 developing countries, including Brazil.⁽²⁾

Early diagnosis and treatment are essential for tuberculosis control. In areas of high tuberculosis prevalence, early diagnosis can be defined as that occurring within the first two to three weeks after the onset of respiratory symptoms, whereas delayed diagnosis can be defined as that occurring four weeks or more after the onset of such symptoms.⁽³⁾ Despite the fact that tuberculosis control programs have prioritized making the diagnosis at the primary health care level, many cases are still diagnosed at hospitals, especially public referral hospitals.⁽⁴⁾ Porto Alegre has one of the highest tuberculosis incidence rates among all Brazilian cities, and the rate of in-hospital diagnosis of tuberculosis in the city is 39%.⁽⁵⁾

Imaging studies play an important role in the diagnostic evaluation of patients with suspected pulmonary tuberculosis (PTB).⁽⁶⁾ There have been few studies evaluating the radiological findings related to patients diagnosed with PTB in the emergency department. One study showed that a radiological pattern other than the typical one (of apical infiltrates or cavitations) was associated with delayed clinical suspicion of tuberculosis.⁽⁷⁾ In this context, it is important to analyze the radiological findings among patients diagnosed with PTB in the emergency department. We hypothesize that this information will alert physicians to the difficulties of diagnosing PTB, thus helping reduce the burden of hospitalization for tuberculosis.

This study aims to evaluate the radiological presentation of patients with PTB diagnosed in the emergency department and to investigate its association with the time to diagnosis.

METHODS

This was a prospective cohort study involving patients with active PTB who were diagnosed in the emergency

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department of a tertiary university hospital in the city of Porto Alegre, located in the state of Rio Grande do Sul, in southern Brazil. We assessed the radiological presentations and their association with the time elapsed between the initial radiological examination and the diagnosis of PTB.

All procedures were performed in accordance with the ethical standards of the local institution and with Brazilian National Health Council Resolution no. 466/12, as well as with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of the Porto Alegre *Hospital de Clínicas* (Registration no. 14-0130; Protocol no. 1686812800005327), and all participating patients gave written informed consent.

We included patients who were ≥ 14 years of age, were suspected of having active PTB, and had undergone radiological examination. Patients for whom chest X-rays were unavailable were excluded, as were those in whom the diagnosis of tuberculosis was unconfirmed, those already being treated for tuberculosis, those who had previously abandoned tuberculosis treatment, and those who had exclusively extrapulmonary tuberculosis (EPTB).

The diagnosis of PTB followed the criteria established in the Third Brazilian Thoracic Association Guidelines on Tuberculosis⁽²⁾: positive sputum smear microscopy (Ziehl-Neelsen staining) in two samples; positive sputum smear microscopy (Ziehl-Neelsen staining) in one sample and a positive result for *Mycobacterium tuberculosis* in one culture (in Löwenstein-Jensen medium); positive sputum smear microscopy (Ziehl-Neelsen staining) in one sample and radiological findings consistent with tuberculosis; a positive result for *M. tuberculosis* in one culture (in Löwenstein-Jensen medium) alone; or the presence of clinical, epidemiological, and radiological characteristics consistent with tuberculosis. Therefore, some subjects were initially diagnosed and treated on the basis of the presence of clinical, epidemiological, and radiological characteristics consistent with tuberculosis, the diagnosis subsequently being confirmed by a positive culture. In all cases, the diagnosis was also confirmed by the response to tuberculosis treatment. The diagnosis of EPTB was based on the results of clinical and laboratory tests indicating the location of the disease.

A researcher conducted the interview and clinical evaluation of all patients identified as having been diagnosed with tuberculosis. The demographic characteristics, clinical features of the disease, and the presence of comorbidities were determined in the clinical evaluation and by reviewing electronic medical records with a specific collection instrument. The following data were collected: date of admission to the emergency department; date of the first radiological examination; date of the diagnosis of tuberculosis; smoking status; symptoms; and comorbidities, including HIV infection and lung diseases. At the time of the interview, we asked the patients to estimate the time in days from the onset of any symptoms.

To avoid and prevent a conscious or unconscious interpretation bias, the chest X-rays taken at admission were evaluated by a radiologist who was a member of the research team and was blinded to the other clinical characteristics of the patients. The different patterns of radiological findings and the locations of the lesions were described by the radiologist and categorized as follows: suggestive of primary tuberculosis; suggestive of post-primary tuberculosis; indeterminate; or suggestive of another diagnosis (mentioned).

The main study outcome was the total elapsed time between the initial radiological examination and the diagnosis of PTB. Secondary endpoints were the correlations of HIV infection with the various radiological presentations and the correlations of the radiological presentation with the diagnostic test results.

Data were entered into a Microsoft Excel database, being processed and analyzed using the Predictive Analytics Software package, version 18.0 (SPSS Inc., Chicago, IL, USA). For the purpose of statistical analysis, patients were stratified into two groups, according to the time elapsed between the initial radiological examination and the diagnosis of PTB: early diagnosis, comprising those for whom the time to diagnosis was below the median for this variable; and delayed diagnosis, comprising those for whom the time to diagnosis was equal to or above the median. Quantitative data are expressed as mean \pm standard deviation or as median (interquartile range). Qualitative data are expressed as absolute and relative frequencies. In the analysis of continuous variables with normal distributions, we used Student's t-tests for independent samples. In the analysis of continuous variables with non-normal distributions, we used the Mann-Whitney U test. For categorical variables, we used the chi-square test and, if necessary, Yates' correction or Fisher's exact test. All statistical tests were two-tailed, and the level of significance was set at 5%. We performed multivariate logistic regression in which the dependent variable was an acceptable time to diagnosis (early diagnosis) and the independent variables were demographic, clinical, and radiological characteristics that showed statistical significance in the univariate analysis. Potential predictors were selected for the final multiple regression model by the Enter method, based on clinical judgment, the analysis of non-collinearity, and statistical significance ($p < 0.1$), and the model was adjusted for gender and age. The sample size calculation was based on that employed in a previous study,⁽⁶⁾ in which a radiological pattern other than the typical one (of apical infiltrates or cavitations) was associated with delayed clinical suspicion of tuberculosis. Considering a prevalence of atypical radiological patterns of 30%, with an amplitude of the confidence interval of 0.20 and a confidence level of 95%, we determined that it would be necessary to include 81 patients in the study.

RESULTS

Between September of 2014 and December of 2015, we evaluated 134 potential candidates for inclusion in

the study. Of those 134 individuals, 56 were excluded, for one of the following reasons: lack of confirmation of the diagnosis; exclusively EPTB; and previous abandonment of tuberculosis treatment. Therefore, the final sample comprised 78 patients.

Table 1 shows the descriptive characteristics of the sample. The median duration of symptoms was 47 days. In most individuals (52%), tuberculosis was diagnosed on the basis of a positive result on sputum smear microscopy for AFB. The median time elapsed from the initial chest X-ray to the diagnosis of PTB was 2 days (interquartile range, 0-58 days). The most common radiological findings were consolidation (in 67%) and reticular infiltrate (in 47%). It is noteworthy that 5% of the chest X-rays were classified as normal.

Table 2 shows the comparative analysis according to the time elapsed between the initial radiological examination and the diagnosis of PTB. The frequency of sputum smear positivity was higher in the early diagnosis group than in the delayed diagnosis group (75% vs. 40%; $p = 0.005$). There were also differences between those two groups regarding symptoms such as sputum production (64.3% vs. 36.0%; $p = 0.03$) and weight loss (89.3% vs. 66.0%; $p = 0.047$). As can be seen in Table 3, the proportion of patients in whom a chest X-ray showed cavitation was higher in the early diagnosis group than in the delayed diagnosis group (64.3% vs. 22.0%; $p = 0.001$), as was that of

those in whom a chest X-ray showed consolidation (89.3% vs. 54.0%; $p = 0.003$).

Table 4 shows the multivariate logistic regression of factors associated with early diagnosis. The presence of cavitation on a chest X-ray was identified as an independent predictor of early diagnosis (OR = 3.50; 95% CI: 1.14-10.72; $p = 0.028$).

DISCUSSION

In this prospective observational study, we evaluated the association between the radiological presentation and the time to the diagnosis of PTB in the emergency department of a tertiary care hospital. We found a median elapsed time from the first chest X-ray to tuberculosis diagnosis of 2 days. Cavitation and consolidation were more common in the early diagnosis group than in the delayed diagnosis group, the presence of cavitation being found to be an independent predictor of early diagnosis.

There is no consensus on what is considered an acceptable delay in diagnosis. Previous studies have suggested that the time to diagnosis is related to health care services and the local epidemiology.⁽⁸⁾ It has been demonstrated that the time to the diagnosis of tuberculosis is shorter at hospitals located in areas where the prevalence of the disease is high.⁽⁹⁾ The in-hospital time to diagnosis is particularly important, especially in places with high tuberculosis incidence

Table 1. Characteristics of patients diagnosed with pulmonary tuberculosis.

Characteristic	(N = 78)
Age (years), mean \pm SD	41.88 \pm 16.45
Male gender, n (%)	47 (60.3)
Smoking status, n (%)	
Current smoker	32 (41.0)
Former smoker	20 (25.6)
HIV/AIDS, n (%)	33 (42.3)
Non-HIV-related immunosuppression, n (%)	9 (11.5)
Drug dependence, n (%)	31 (39.7)
Duration of symptoms (days), median (IQR)	30 (13-75)
Diagnostic criteria, n (%)	
AFB-positive smear	41 (52.6)
Positive culture	15 (19.2)
AFB-positive smear + positive culture	22 (28.2)
Days from chest X-ray to PTB diagnosis, median (IQR)	2 (1-7)
Chest X-ray findings	
None	4 (5.1)
Cavitation	29 (37.1)
Reticular infiltrate	37 (47.4)
Consolidation	52 (66.7)
Residual fibrosis	19 (24.4)
Miliary pattern	8 (10.3)
Pleural effusion	22 (28.2)
Bronchiectasis	1 (1.3)
Atelectasis	18 (23.1)
Hilar lymphadenopathy	3 (3.8)

IQR: interquartile range; and PTB: pulmonary tuberculosis.

Table 2. Comparative analysis of patient characteristics, by group (early and delayed diagnosis of pulmonary tuberculosis).

Characteristic	Group		p
	Early diagnosis* (n = 28)	Delayed diagnosis† (n = 50)	
Age (years), mean ± SD	39.21 ± 12.80	43.4 ± 18.1	0.241
Male gender, n (%)	18 (64.3)	29 (58.0)	0.762
Diagnostic criteria, n (%)			
AFB-positive smear	21 (75.0)	20 (40.0)	0.005
Positive culture	1 (3.6)	14 (28.0)	
AFB-positive smear + positive culture	6 (21.1)	16 (32.0)	
Smoking status, n (%)			
Never smoker	7 (25.0)	19 (38.0)	0.412
Former smoker	7 (25.0)	13 (26.0)	
Current smoker	14 (50.0)	18 (36.0)	
Symptoms, n (%)			
Asthenia	25 (89.3)	37 (64.0)	0.190
Cough	25 (89.3)	36 (72.0)	0.137
Sputum	18 (64.3)	18 (36.0)	0.030
Fever	19 (67.9)	31 (62.0)	0.786
Weight loss	25 (89.3)	33 (66.0)	0.047
Dyspnea	13 (46.4)	22 (44.0)	1.000
Hemoptysis	5 (17.9)	4 (8.0)	0.270
Night sweats	13 (46.4)	20 (40.0)	0.755
Chest pain	8 (28.6)	13 (26.0)	1.000
Drug dependence, n (%)	14 (50.0)	17 (34.0)	0.253
Alcohol dependence	7 (25.0)	9 (18.0)	0.658
HIV/AIDS	10 (35.7)	23 (46.0)	0.520
Immunosuppression, n (%)			
Corticosteroid use	2 (7.1)	6 (12.0)	0.704
Immunosuppressive therapy	1 (3.6)	5 (10.2)	0.408
Transplant recipient	0 (0.0)	4 (8.0)	0.291
Previous tuberculosis, n (%)	6 (21.4)	9 (18.0)	0.945
Chronic lung disease, n (%)			
COPD	1 (3.6)	6 (12.0)	0.411
Other	1 (3.6)	2 (4.0)	1.000
Malignancy, n (%)			
Lung cancer	0 (0.0)	1 (2.0)	1.000
Other	0 (0.0)	2 (4.0)	0.534

* < 2 days from the initial radiological examination to the diagnosis of pulmonary tuberculosis. † ≥ 2 days from the initial radiological examination to the diagnosis of pulmonary tuberculosis.

rates, such as Porto Alegre, where the rate of in-hospital diagnosis of tuberculosis is nearly 40%,⁽⁶⁾ because a delay in diagnosis has been associated with higher mortality.⁽⁹⁾ Another study,⁽⁶⁾ also conducted in Porto Alegre, reported a median time to diagnosis of 6 days. However, in that study, the sample also included patients with EPTB, which accounted for a significant delay in diagnosis.

In the present study, cavitation and consolidation on a chest X-ray were associated with early diagnosis. In fact, the presence of cavitation was found to be an independent predictor of a time to diagnosis < 2 days (i.e., early diagnosis). Cavitation is considered a typical radiological feature in PTB, having been shown to be associated with a shorter time to diagnosis.⁽⁷⁾

The location of radiological findings did not differ significantly between the early diagnosis and delayed diagnosis groups, as was also the case for the presence of residual fibrotic alterations. In a study conducted in the same emergency department as our study,⁽⁵⁾ residual fibrosis, which is suggestive of previous tuberculosis, was identified as a factor associated with a health care system-related diagnostic delay.

In our univariate analysis, sputum smear positivity was associated with early diagnosis and a positive culture was associated with delayed diagnosis. It is well known that smear-negative PTB is associated with a delay in diagnosis and, consequently, higher mortality.^(5,10,11) In the present study, the presence of

Table 3. Comparative analysis of radiological findings, by group (early and delayed diagnosis of pulmonary tuberculosis).

Characteristic	Group		p
	Early diagnosis*	Delayed diagnosis [†]	
	(n = 28) n (%)	(n = 50) n (%)	
Chest X-ray findings			
Normal	0 (0.0)	4 (8.0)	0.291
Cavitation	18 (64.3)	11 (22.0)	0.001
Reticular infiltrate	16 (57.1)	21 (42.0)	0.294
Consolidation	25 (89.3)	27 (54.0)	0.003
Residual fibrosis	7 (25.0)	12 (24.0)	1.000
Miliary pattern	1 (3.6)	7 (14.0)	0.247
Pleural effusion	5 (17.9)	17 (34.0)	0.209
Bronchiectasis	0 (0.0)	1 (2.0)	1.000
Atelectasis	8 (28.6)	10 (20.0)	0.561
Lymphadenopathy	0 (0.0)	3 (6.0)	0.549
Location of lesions			
APUL	16 (57.1)	21 (42.0)	0.294
B6	9 (32.1)	14 (28.0)	0.900
AUL	12 (42.9)	14 (28.0)	0.278
Middle lobe	1 (3.6)	3 (6.0)	1.000
Lingula	1 (3.6)	2 (4.0)	1.000
Basal pyramid	8 (28.6)	11 (22.0)	0.709
Diffuse	7 (25.0)	13 (26.0)	1.000
Parenchymal damage			
None	0 (0.0)	4 (8.0)	
Left lung	5 (17.9)	11 (22.0)	0.432
Right lung	9 (32.1)	14 (28.0)	
Bilateral	14 (50.0)	21 (42.0)	
Radiologist conclusion			
Post-primary tuberculosis	16 (57.0)	21 (42.0)	0.332
Another diagnosis	6 (21.4)	11 (22.0)	
Undetermined	6 (21.4)	14 (28.0)	
Normal	0 (0.0)	4 (8.0)	

APUL: anterior and posterior upper lobe; B6: superior segment of the lower lobe; and AUL: anterior upper lobe. * < 2 days from the initial radiological examination to the diagnosis of pulmonary tuberculosis. [†] ≥ 2 days from the initial radiological examination to the diagnosis of pulmonary tuberculosis.

sputum is associated with a shorter time to diagnosis, as previously demonstrated.^(5,7)

Another symptom associated with early diagnosis was weight loss. Solari et al.⁽¹²⁾ developed a clinical prediction rule, based on information obtainable on admission, to permit rapid identification of patients with PTB in emergency departments. The authors found that weight loss was an independent predictor of the diagnosis of tuberculosis. In addition, other studies have shown that weight loss is associated with a delay in diagnosis and in the initiation of treatment.^(13,14) On the basis of the findings of our study, we may suppose that physicians have sufficient understanding of the importance of the association between weight loss and tuberculosis diagnosis, which could explain the association between this symptom and the early diagnosis of tuberculosis.

Drug dependence and HIV infection are major problems in Porto Alegre, where the incidence of tuberculosis/HIV coinfection is 25.2%, which is among

the highest among cities in Brazil.⁽¹⁵⁾ However, in the present study, neither HIV infection nor drug dependence showed an association with a delay in the diagnosis of PTB. Other studies have also shown that HIV infection is not associated with delayed diagnosis of PTB,^(16,17) despite the possibility of atypical presentations of tuberculosis.^(18,19) In addition, drug dependence has been shown to be associated only with patient-related delays and not with health care system-related delays.⁽⁵⁾ Our finding that important clinical and radiological variables (asthenia, fever, night sweats, HIV infection, immunosuppression, a miliary pattern, and the location of the lesions) were not associated with the time to diagnosis should alert physicians to the difficulty of diagnosing PTB in the emergency department.

Our study has some limitations. It was conducted at a single center, we did not evaluate previous chest X-rays, and we did not investigate patient-related delays. In addition, we did not use imaging techniques that are more advanced, such as CT, because such

Table 4. Multivariate regression to identify factors associated with the time elapsed between the initial radiological examination and the diagnosis of pulmonary tuberculosis.

Variable	B	Wald	p	OR	95% CI
Age	0.014	0.660	0.416	1.010	0.98-1.05
Gender	0.309	0.305	0.581	1.360	0.45-4.09
Cavitation*	1.252	4.804	0.028	3.500	1.14-10.72
Consolidation	1.155	2.426	0.119	3.170	0.74-13.58
AFB-positive smear	1.608	2.054	0.152	4.990	0.55-44.98
Constant	-1.315	0.839	0.117	0.268	-

*Cavitation on a chest X-ray was identified as an independent predictor of early diagnosis (within the first 2 days after the initial radiological examination).

techniques are more costly and are not widely available. Nevertheless, our results underscore the message that a typical radiological presentation, particularly cavitation, is associated with a shorter time to PTB diagnosis.

In summary, we demonstrated a median elapsed time from the initial chest X-ray to the diagnosis of PTB of 2 days. We also found that cavitation was an

independent predictor of early diagnosis. Reducing diagnostic delays may require greater awareness on the part of health care professionals and a review of health care facility practices. Specific strategies, such as the use of tuberculosis-specific protocols in the emergency department, should be developed, not only to expedite diagnosis and treatment but also to modify the transmission dynamics of tuberculosis.

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