Factors associated with pulmonary tuberculosis among patients seeking medical attention at referral clinics for tuberculosis*,**

Fatores associados à tuberculose pulmonar em pacientes que procuraram serviços de saúde de referência para tuberculose

Cid Carlos Soares de Alcântara, Afrânio Lineu Kritski, Valéria Goes Ferreira, Mônica Cardoso Façanha, Ricardo Soares Pontes, Rosa Salani Mota, Terezinha do Menino Jesus Silva Leitão

Abstract

Objective: The identification of behavioral and clinical factors that are associated with pulmonary tuberculosis might improve the detection and treatment of the disease, thereby reducing its duration and transmission. Our objective was to identify sociodemographic, clinical, and behavioral factors that are associated with the diagnosis of pulmonary tuberculosis. **Methods:** This was a cross-sectional study conducted between April of 2008 and March of 2009 at three health care clinics in the city of Fortaleza, Brazil. We selected 233 patients older than 14 years of age who spontaneously sought medical attention and presented with cough for ≥ 2 weeks. Sociodemographic, clinical, and behavioral data were collected. Sputum smear microscopy for AFB and mycobacterial culture were also carried out, as were tuberculin skin tests and chest X-rays. The patients were divided into two groups (with and without pulmonary tuberculosis). The categorical variables were compared by the chi-square test, followed by logistic regression analysis when the variables were considered significant. **Results:** The prevalence of pulmonary tuberculosis was 41.2%. The unadjusted OR showed that the following variables were statistically significant risk factors for pulmonary tuberculosis: fever (OR = 2.39; 95% CI, 1.34-4.30), anorexia (OR = 3.69; 95% CI, 2.03-6.75), and weight loss (OR = 3.37; 95% CI, 1.76-6.62). In the multivariate analysis, only weight loss (OR = 3.31; 95% CI, 1.78-6.14) was significantly associated with pulmonary tuberculosis. **Conclusions:** In areas with a high prevalence of tuberculosis, weight loss could be used as an indicator of pulmonary tuberculosis in patients with chronic cough for ≥ 2 weeks.

Keywords: Mycobacterium tuberculosis; Tuberculosis, pulmonary/epidemiology; Risk factors.

Resumo

Objetivo: A identificação de fatores comportamentais e clínicos associados à tuberculose pulmonar pode melhorar a detecção e o tratamento dessa doença, consequentemente reduzindo sua duração e transmissão. Nosso objetivo foi identificar fatores sociodemográficos, clínicos e comportamentais associados à tuberculose pulmonar. **Métodos:** Estudo transversal realizado entre abril de 2008 e março de 2009 em três unidades de saúde na cidade de Fortaleza (CE). Foram selecionados 233 pacientes maiores de 14 anos que procuraram atendimento médico espontaneamente e que apresentavam tosse por ≥ 2 semanas. Foram coletados dados sociodemográficos, clínicos e comportamentais. Foram realizadas baciloscopia direta para BAAR e cultura de micobactérias, bem como testes tuberculínicos e radiografias de tórax. Os pacientes foram divididos em dois grupos (com e sem tuberculose pulmonar). As variáveis categóricas foram comparadas com o teste do qui-quadrado, seguido de análise de regressão logística quando as variáveis foram consideradas significativas. **Resultados:** A prevalência de tuberculose pulmonar foi 41,2%. As OR não ajustadas indicaram que as seguintes variáveis foram fatores de risco significativos para tuberculose pulmonar: febre (OR = 2,39; IC95%: 1,34-4,30), anorexia (OR = 3,69; IC95%: 2,03-6,75) e perda de peso (OR = 3,37; IC95%: 1,76-6,62). Na análise multivariada, apenas perda de peso (OR = 3,31; IC95%: 1,78-6,14) associou-se significativamente com tuberculose pulmonar. **Conclusões:** Em áreas com elevada prevalência de tuberculose, a perda de peso poderia ser utilizada como um indicador de tuberculose pulmonar em pacientes com tosse crônica por ≥ 2 semanas.

Descritores: Mycobacterium tuberculosis; Tuberculose pulmonar/epidemiologia; Fatores de risco.

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* Study carried out in the Department of Community Health, Federal University of Ceará School of Medicine, Fortaleza, Brazil. Correspondence to: Terezinha do Menino Jesus Silva Leitão. Avenida dos Expedicionários, 4435, Montese, CEP 60410-411, Fortaleza, CE, Brasil.
Tel. 55 85 9994-6710. Fax: 55 85 3366-8044. E-mail: tsilva@ufc.br
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Introduction

A delay in the diagnosis of pulmonary tuberculosis can accelerate the progression of the disease, increase the risk of death, and contribute to the transmission of tuberculosis in the community.[1] Various studies have investigated risk factors for pulmonary tuberculosis in an attempt to accelerate the identification of cases.[2-4] The intention was to identify hospitalized patients in a timely manner in order to reduce transmission[2,3] or to establish diagnostic criteria for tuberculosis among patients with AFB-negative sputum smears.[4] Similarly, various studies have investigated the impact of demographic, socioeconomic, and cultural factors on active tuberculosis,[5] as well as variables related to the development of tuberculosis in HIV-infected patients.[6]

Given the high worldwide incidence of respiratory diseases and the millions of people with latent tuberculosis, a 2-3 week history of cough in patients residing or working in areas where tuberculosis is common is a finding that can contribute to earlier diagnosis, thus improving the outcomes and reducing the transmission of the disease.[7] In a study involving patients seeking medical attention at a primary health care clinic in the city of Rio de Janeiro, Brazil, the authors compared those with cough for ≥ 1 week and those with cough for ≥ 3 weeks in terms of the impact of tuberculosis screening on the rate of diagnosis.[8] The authors found that the probability of detecting tuberculosis was influenced by the reason for seeking medical attention rather than by the duration of cough. The probability of detecting pulmonary tuberculosis was significantly higher among those seeking medical attention for respiratory symptoms than among those seeking attention for other reasons (7.9% vs. 0.3%). The authors suggested that tuberculosis screening in patients seeking medical attention for respiratory symptoms and presenting with cough for ≥ 1 week in settings with a high prevalence of tuberculosis might significantly increase the detection of tuberculosis cases. The identification of other variables that can hasten the laboratory investigation and increase the detection of pulmonary tuberculosis might contribute to early treatment initiation and therefore become a useful tool in health care clinics.

In the state of Ceará, Brazil, the crude incidence of pulmonary tuberculosis increased from 41.9 cases per 100,000 population in 2007 to 45.5 per 100,000 population in 2010. Ceará ranks fourth among the Brazilian states with the highest number of pulmonary tuberculosis cases,[9] the cure rate for the state being 69%. This rate is much lower than that recommended by the World Health Organization (i.e., 85%)[10] and lower than that reported for Brazil (i.e., 73%).[10]

Patients seeking medical attention at any of three referral health care clinics in the city of Fortaleza, Brazil, and presenting with cough for ≥ 2 weeks were invited to participate in the present study. Our objective was to identify sociodemographic, clinical, and behavioral factors that are associated with the diagnosis of pulmonary tuberculosis.

Methods

This was a cross-sectional study conducted between April of 2008 and March of 2009 at three health care clinics in the city of Fortaleza, which is the capital of the state of Ceará, in northeastern Brazil, and has a population of 2,473,614 inhabitants. The patients included in the present study were selected from among those being treated at the *Centro de Saúde Cesar Cals* (a primary health care clinic), the *Centro de Saúde Carlos Ribeiro* (a primary health care clinic), or the Messejana Hospital Outpatient Clinic.

The three health care clinics are referral centers for tuberculosis, and the vast majority of individuals with suspected tuberculosis are referred to those clinics for routine investigation. The patients were enrolled in the study when they presented to one of the abovementioned clinics for a medical consultation and were interviewed by trained investigators.

The eligibility criteria were as follows: being older than 14 years of age; having sought medical attention spontaneously; presenting with a ≥ 2 week history of cough; being willing to provide at least one sputum sample and undergo chest X-ray. The exclusion criteria included being pregnant and having declined to give written informed consent. All of the adult participants gave written informed consent, as did the parents/guardians of the children included in the present study. The study project was approved by the Research Ethics Committees of the Federal University of Ceará (Protocol no. 158/08) and the Messejana Hospital (Protocol no. 547/08) in October of 2008.

Patients with pulmonary tuberculosis were defined either as those with a positive culture for *Mycobacterium tuberculosis* or an AFB-positive sputum smear or as those who had clinical and radiological characteristics suggestive of pulmonary tuberculosis and who showed improvement (as determined by the study coordinator) after six months of antituberculosis treatment alone. Patients without pulmonary tuberculosis were defined as those with an AFB-negative sputum smear and a negative culture for *M. tuberculosis* and no chest X-ray changes after a six-month follow-up period. Six months after having interviewed the patients without pulmonary tuberculosis, we searched the Brazilian Ministry of Health *Sistema Nacional de Informação de Agravos de Notificação* (SINAN, National Case Registry Database) in order to determine whether any of those patients had been diagnosed with tuberculosis elsewhere.

Sociodemographic data included age, gender, marital status, level of education of the head of the household, place of birth, place of residence, prior institutionalization, housing, and employment status. Smoking and illicit drug use were evaluated as behavioral variables; alcohol consumption was evaluated by the **C**ut down, **A**nnoyed, **G**uilty, and **E**ye-opener (CAGE) questionnaire.[11] Household contacts with tuberculosis cases were also investigated.

We gathered clinical information (including history of tuberculosis, previous hospitalization, and presence of other chronic respiratory diseases) and asked the participants whether they had experienced any of the following symptoms: cough, pulmonary secretion, hemoptysis, night sweats, chest pain, fever, anorexia, weakness, hoarseness, dyspnea, or adenopathy. In addition, we collected information regarding past and present body weight (as reported by the study participants).

The participants underwent chest X-ray and tuberculin skin test (with PPD RT23). Sputum samples for smear microscopy for AFB and mycobacterial cultures were collected on the day of the medical consultation at one of the clinics and in the following morning, the study participants having been instructed on how to collect sputum properly. Cultures for *M. tuberculosis* were performed on Löwenstein-Jensen medium and were followed by biochemical speciation.[12] The chest X-rays were evaluated by a radiologist working at the clinic where the patient was being treated. The chest X-ray reports were reviewed by the study coordinator, who used a standardized form in order to classify the findings in accordance with previously established criteria.[13] Findings that were considered characteristic of pulmonary tuberculosis included the presence of infiltrates, consolidations, or cavities (unilateral or bilateral in the upper lungs), with or without mediastinal or hilar lymphadenopathy, and bilateral miliary infiltrates.

In order to construct a database, we used Epi Info, version 6.04b. The patients were divided into two groups (i.e., with and without pulmonary tuberculosis). We used contingency tables in order to describe the categorical variables, which were organized by group. We used the chi-square test in order to compare the categorical variables, which were grouped into sociodemographic characteristics, living conditions, behavioral aspects, history of tuberculosis, and symptoms.

After adjustment for possible confounding factors, a stepwise logistic regression analysis was carried out. The final model was constructed in three steps. First, we selected variables within each group, the criterion being a value of $p < 0.20$; second, we obtained a model with dummy variables, the OR being adjusted by multiple logistic regression; and third, we used an adjusted logistic regression model in order to create a reduced model with dummy variables. A value of $p < 0.05$ was considered statistically significant.

Data analysis was performed with the STATA program, version 7 (StataCorp LP, College Station, TX, USA), the level of significance being set at 5%.

Results

The initial sample consisted of 265 patients selected from among those being treated at any of the abovementioned health care clinics. Of those 265 patients, 32 were excluded: 15 did not provide a sputum sample, and 17 did not undergo chest X-ray. The final sample therefore consisted of 233 patients, the prevalence of pulmonary tuberculosis being 41.2% (n = 96).

Most of the participants resided in Fortaleza (97.42%). In addition, most of the participants were either single (37.77%) or married (30.47%). The median age was 42.62 years, and there was a slight predominance of females (51.93%).

As shown in Table 1, the patients who reported having been cured of tuberculosis after previous

treatment were significantly less likely to be diagnosed with pulmonary tuberculosis (OR = 0.45; 95% CI, 0.20-0.98).

The unadjusted OR showed that the variables age, gender, place of birth, level of education of the head of the household, and employment status were not statistically significant risk factors for pulmonary tuberculosis. In addition, illicit drug or alcohol use, a history of smoking, previous hospitalization, emphysema, housing, and household contact with a tuberculosis patient were found to have no significant association with pulmonary tuberculosis (Table 1). In our sample, only 4 patients were homeless. Illicit drug use (OR = 2.35; 95% CI, 1.14-4.94), *cachaça* consumption—*cachaça* being a popular Brazilian spirit (alcohol by volume, 40-50%)—(OR = 15.09; 95% CI, 4.31-79.87), and a history of imprisonment (OR = 11.76; 95% CI, 1.61-514.62) were significantly more common in males than in females.

Certain symptoms, such as anorexia (OR = 3.69; 95% CI, 2.03-6.75), weight loss (OR = 3.37; 95% CI, 1.76-6.62), and fever (OR = 2.39; 95% CI, 1.34-4.30), were significantly associated with pulmonary tuberculosis. However, classic symptoms such as hemoptysis (OR = 1.84; 95% CI, 0.92-3.67), weakness (OR = 1.66; 95% CI, 0.92-2.99), night sweats (OR = 1.24; 95% CI, 0.71-2.17), and chest pain (OR = 1.59; 95% CI, 0.88-2.89) were not (Table 2).

Among the patients with tuberculosis, the disease was diagnosed by sputum smear microscopy or culture in 78.2% and by clinical, radiological, and epidemiological characteristics followed by clinical and radiological improvement after tuberculosis treatment alone in 21.8%. Although HIV testing was offered to all 233 participants, only 141 (60.5%) agreed to be tested. Of those, only 3 tested positive. Of those 3 patients, 1 had tuberculosis. None of the patients classified as not having pulmonary tuberculosis matched the tuberculosis cases included in the SINAN database.

The variables with a value of $p > 0.2$ were used to construct a logistic regression model (Tables 1 and 2). After the model was adjusted at a level of significance of 5%, only weight loss remained significantly associated with pulmonary tuberculosis (OR = 3.31; 95% CI, 1.78-6.14; Table 3).

Discussion

The proportion of pulmonary tuberculosis cases was higher in the present study (41.2%) than in other studies. Façanha et al. studied a group of patients with respiratory symptoms in a poor community in Fortaleza and found the prevalence of tuberculosis to be 8%.[14] In our study, rather than recruiting patients with respiratory symptoms, we included only those who were suspected of having active pulmonary tuberculosis and who sought medical attention for chronic cough and other respiratory or systemic symptoms.

In our sample (patients over 14 years of age seeking medical attention at a referral clinic in an endemic area and presenting with a ≥ 2 week history of cough), weight loss was the only symptom that was found to be significantly associated with pulmonary tuberculosis. Similarly, in a recent study involving 1,435 children living in an area with a high burden of tuberculosis in Africa, where the prevalence of the disease was 1.3%, weight loss was the only clinical variable that differed significantly between the patients with tuberculosis and those without.[15]

Unlike other studies,[8,16,17] the present study found that patients under 40 years of age were similar to those over 40 years of age in terms of the prevalence of active tuberculosis. Carvalho et al. found that tuberculosis/HIV co-infection was significantly more common among patients over 40 years of age and among those with a lower level of education (i.e., fewer than 8 years of schooling).[6] In our study, although HIV testing was offered to all of the patients who were suspected of having tuberculosis, only 141 (60.5%) agreed to be tested. This underscores the importance of policy decisions targeting that specific population.

We found that the 44 patients with a history of tuberculosis treatment and cure were less likely to present with pulmonary tuberculosis. This finding differs from those reported in South Africa, where high rates of tuberculosis were found among those who had previously received treatment; indeed, 75% of the cases of postprimary disease were attributable to exogenous reinfection.[18] Our results are in line with the unitary concept of pathogenesis, which states that previously treated patients are at a lower risk of developing tuberculosis because most tuberculosis cases result from endogenous reactivation.

Table 1 - Epidemiological characteristics of the patients with and without pulmonary tuberculosis.

Variable	Diagnosis of pulmonary tuberculosis		Unadjusted OR (95% CI)	p
	Yes	No		
	n (%)	n (%)		
Gender				
Male	52 (46.43)	60 (53.57)	1.51 (0.86-2.65)	0.11
Female	44 (36.36)	77 (63.64)	1	
Age, years				0.05
< 40	51 (48.11)	55 (51.89)	1.68 (0.96-2.96)	
≥ 40	45 (35.43)	82 (64.57)	1	
Place of birth				
Fortaleza	60 (42.86)	80 (57.14)	1.13 (0.63-2.05)	0.65
Ceará state	33 (39.76)	50 (60.24)	1	
Other states	03 (30.00)	07 (70.00)	0.57 (0.09-2.64)	0.42
Level of education of head of household, years of schooling				
0	12 (42.85)	16 (57.15)	1.08 (0.44-02.57)	0.84
1-4	29 (37.18)	49 (62.82)	0.77 (0.42-01.40)	0.37
5-12	45 (45.45)	54 (54.54)	1.35 (0.77-02.37)	0.25
> 12	09 (40.90)	13 (59.09)	0.98 (0.35-02.62)	0.97
No data	01 (16.67)	05 (83.33)	1	
Employment status				
Unemployed	32 (45.71)	38 (54.29)	1.13 (0.53-2.40)	0.72
Self-employed	12 (48.00)	13 (52.00)	1.34 (0.35-5.10)	0.61
Employed	26 (42.62)	35 (57.38)	1	
No data	26 (33.76)	51 (66.24)		
Household contact with tuberculosis				
Yes	33 (46.48)	38 (53.52)	1.36 (0.74-2.48)	0.27
No	63 (38.89)	99 (61.11)	1	
Smoking status				
Current smoker	25 (37.88)	41 (62.12)	1.03 (0.50-2.10)	0.91
Former smoker	38 (48.72)	40 (51.28)	1.61 (0.83-3.13)	0.12
Never smoker	33 (37.08)	56 (62.92)	1	
Illicit drug use				
Yes	021 (45.65)	25 (54.35)	1.25 (0.61-2.52)	0.49
No	075 (40.10)	112 (59.90)	1	
Alcohol consumption (CAGE)				
Heavy	22 (50.00)	22 (50.00)	1.50 (0.57-3.90)	0.35
Sporadic	16 (40.00)	24 (60.00)	1	
Nondrinker	58 (38.92)	91 (61.08)		
History of tuberculosis followed by full treatment				
Yes	12 (27.27)	32 (72.73)	0.45 (0.20-0.98)	0.03
No	84 (44.91)	103 (55.09)	1	
No data	00 (00.00)	02 (100.00)		
Hospitalization in the last two years				
Yes	24 (50.00)	24 (50.00)	1.56 (0.78-3.12)	0.16
No	72 (38.92)	113 (61.08)	1	
Emphysema				
Yes	56 (45.53)	67 (54.47)	1.47 (0.84-2.60)	0.14
No	39 (36.11)	69 (63.89)	1	
Uncertain	01 (50.00)	01 (50.00)		

CAGE: **C**ut down, **A**nnoyed, **G**uilty, and **E**ye-opener (questionnaire).

Table 2 - Symptoms reported by the patients with and without pulmonary tuberculosis.

Variable	Diagnosis of pulmonary tuberculosis		Unadjusted OR (95% CI)	p
	Yes	No		
	n (%)	n (%)		
Anorexia				
Yes	69 (55.20)	56 (44.80)	3.69 (2.03-6.75)	0.001
No	27 (25.00)	81 (75.00)	1	
Weight loss				
Yes	78 (50.32)	77 (49.68)	3.37 (1.76-6.62)	0.001
No	18 (23.08)	60 (76.92)	1	
Fever				
Yes	64 (50.79)	62 (49.21)	2.39 (1.34-4.30)	0.001
No	31 (30.10)	72 (69.90)	1	
Uncertain	01 (33.33)	03 (66.67)		
Hemoptysis				
Yes	26 (53.06)	23 (46.94)	1.84 (0.92-3.67)	0.05
No	68 (37.99)	111 (62.01)	1	
Uncertain	02 (40.00)	03 (60.00)		
Weakness				
Yes	66 (45.83)	78 (54.17)	1.66 (0.92-2.99)	0.06
No	30 (33.71)	59 (66.29)	1	
Chest pain				
Yes	67 (45.27)	81 (54.73)	1.59 (0.88-2.89)	0.09
No	29 (34.12)	56 (65.88)	1	

Table 3 - Independent variables associated with pulmonary tuberculosis, as determined by logistic regression analysis.

Variable	p	Adjusted OR	95% CI
Complete model			
Weight loss	0.002	2.78	1.44-5.34
Hemoptysis	0.12	1.70	0.86-3.38
Fever	0.14	1.61	0.84-3.06
Weakness	0.64	1.16	0.60-2.22
Chest pain	0.85	0.94	0.49-1.79
Model adjusted to $p < 0.05$			
Weight loss	0.0002	3.31	1.78-6.14

In the present study, the diagnosis of tuberculosis was based on clinical, radiological, and epidemiological evidence in 21.8% of the patients, a proportion that is similar to those reported by other authors.[5,19] Gordin et al. evaluated 139 patients who had undergone tuberculosis treatment on the basis of a presumptive diagnosis of pulmonary tuberculosis. Of those 139 patients, 66 (48%) had active tuberculosis, 16 (24%) had positive culture results, 43 (65%) showed radiological improvement after treatment, and 7 (11%) showed clinical improvement. In the present study, all of the patients who received a diagnosis of pulmonary tuberculosis were followed for at least 6 months and showed clinical or radiological improvement.[19]

The association between active pulmonary tuberculosis and males has been previously described.[5] This might due to the fact that males are more likely to be exposed to certain risk factors for infections, including consuming alcoholic beverages, using illegal drugs, being an ex-convict, and smoking. Although we found that the proportion of males with pulmonary tuberculosis was higher than was that of females, we found no association between the male gender and pulmonary tuberculosis. It is of note that the four risk factors mentioned above were found to be significantly associated with the male gender.

In our study, neither smoking nor a history of smoking was significantly associated with pulmonary tuberculosis. Tobacco has been shown to be a factor that not only increases the risk of pulmonary tuberculosis but also delays its diagnosis because coughing is commonly attributed to smoking.[20] Machado et al. studied 218 pulmonary tuberculosis patients in the state of Rio de Janeiro, Brazil, and reported that those

with cough were over eleven times more likely to delay seeking medical attention.[21]

Approximately 10% of all tuberculosis cases worldwide can be attributed to alcohol consumption. In a recent systematic review of 53 studies, Rehm et al. reported a strong correlation between heavy alcohol use/alcohol use disorders and tuberculosis.[22] We found no association between pulmonary tuberculosis and alcohol use, which is probably due to our sample size. In addition, in order to detect alcohol use, we used the CAGE screening questionnaire, which is a tool that mainly identifies patients who drink heavily.

Our univariate analysis showed that anorexia, weight loss, and fever were associated with pulmonary tuberculosis. Although Bastos et al.[8] found that fever, weight loss, and night sweats were significantly associated with pulmonary tuberculosis in patients seeking medical attention at primary health care clinics, they found no associations between hemoptysis and pulmonary tuberculosis or between anorexia and pulmonary tuberculosis in those patients.[8]

Our logistic regression analysis with a significance level of 5% showed that weight loss was independently associated with a diagnosis of pulmonary tuberculosis. In areas with a high incidence of common respiratory diseases and tuberculosis, weight loss could aid in establishing an early diagnosis of pulmonary tuberculosis in patients with cough for ≥ 2 weeks, thus contributing to the control of the disease in regions with limited resources.

In conclusion, weight loss could be used as an indicator of pulmonary tuberculosis in patients with chronic cough for ≥ 2 weeks in areas with a high prevalence of tuberculosis.

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About the authors

Cid Carlos Soares de Alcântara
Master's Student. Department of Community Health, Federal University of Ceará School of Medicine, Fortaleza, Brazil.

Afrânio Lineu Kritski
Full Professor. Federal University of Rio de Janeiro School of Medicine, Rio de Janeiro, Brazil.

Valéria Goes Ferreira
Associate Professor. Federal University of Ceará School of Medicine, Fortaleza, Brazil.

Mônica Cardoso Façanha
Associate Professor. Federal University of Ceará School of Medicine, Fortaleza, Brazil.

Ricardo Soares Pontes
Associate Professor. Federal University of Ceará School of Medicine, Fortaleza, Brazil.

Rosa Salani Mota
Adjunct Professor. Department of Statistics and Mathematics, Federal University of Ceará, Fortaleza, Brazil.

Terezinha do Menino Jesus Silva Leitão
Associate Professor. Federal University of Ceará School of Medicine, Fortaleza, Brazil.