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FACTORS ASSOCIATED WITH DRUG-RESISTANT TUBERCULOSIS IN THE STATE OF MARANHÃO, IN THE PERIOD FROM 2010 TO 2015

***[1]Andréia Cristina da Silva Ribeiro, [2]Elza Lima da Silva, [3]Tereza Cristina Silva, [4]Vanessa Moreira da Silva Soeiro and [5]Arlene de Jesus Mendes Caldas**

[1]Master in Nursing from the Federal University of Maranhão
[2]PhD in Clinical and Experimental Physiopathology, Professor, Department of Nursing, Federal University of Maranhão
[3]PhD in Public Health, Professor, Biology Department, Federal Institute of Education, Science and Technology of Maranhão
[4]PhD student in Public Health, Substitute professor, Nursing Department, Federal University of Maranhão
[5]PhD in Human Pathology, Professor, Department of Nursing, Federal University of Maranhão

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ABSTRACT

Objective: To analyze the factors associated with drug-resistant tuberculosis (DRTB) in the State of Maranhão, from 2010 to 2015. **Methods:** An analytical cross-sectional study with DRTB cases of the Tuberculosis Special Treatment Information System (SITETB) using the model to identify associations. Estimated prevalence and 95% confidence intervals (95% CI). **Results:** Between 2010 and 2015, 124 (1.13%) cases of DRTB were reported. In the unadjusted analysis, the following were associated with BDRB: retreatment (95% CI = 1.71-3.84, OR = 2.56), closure because of non-cure (CI = 2.15-4.41, OR = (95% CI = 2.66-9.73, OR = 5.09), and use of illicit drugs (95% CI = 1.01-2.71, OR = 1.66), positive sputum smear microscopy. After adjusting for the model, the following were maintained: retreatment (95% CI = 1.05-2.48, OR = 1.61), closure for non-cure (95% CI = 2.01-4.35, OR = 2.96), and positive sputum smear microscopy (95% CI = 2.26-8.87, OR = 4.47). **Conclusion:** the prevalence of DRTB in Maranhão was low in relation to the country, however, entry by retreatment, closure due to non-cure and positive smear microscopy may be contributing to the maintenance of this rate.

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INTRODUCTION

Tuberculosis (TB), although one of the oldest reported diseases, still causes great social impact, constituting a major public health problem, where sociocultural factors contribute to the burden of disease (Silva *et al*, 2014; Sagili *et al*, 2016)Worldwide, the TB is responsible for the largest number of deaths when considering a single infectious agent (Coutinho *et al*, 2012). Brazil is part of the group of 22 high-load countries prioritized by the World Health Organization (WHO), which concentrate 80% of TB cases in the world, occupying the 16th position in absolute number of cases (WHO, 2015; WHO, 2016). In Brazil, in the period from 2005 through 2014, an average of 73 thousand new cases of TB were diagnosed per year, and, in 2013, there were 4,577 deaths (Brasil, 2017). In Brazil, the TB is one of the Diseases of Compulsory Notification (DCN) throughout the national territory, with the establishment of the National System for Notification Worsening (SINAN – *Sistema Nacional de Agravos de Notificação*) as a notification mechanism. According to data obtained by SINAN, in 2015, in the state of Maranhão, there were 2,390 cases of TB, thus establishing, in the last five years, the fourth place among the Northeast states that have the highest incidence rates of TB per 100 thousand inhabitants, as well as the fifth cause of mortality in the state (Brasil, 2017). TB is a curable disease in almost 100% of cases

****Corresponding author: Andréia Cristina da Silva Ribeiro***
Master in Nursing from the Federal University of Maranhão

sensitive to anti-tuberculosis drugs, if the basic principles of therapy and the proper operation of the treatment are followed. These principles consist of administering the proper medication association, in correct doses correct and in sufficient time for the treatment, thus preventing the development of resistance to drugs and ensuring the cure of the patient (WHO, 2015; WHO, 2016). One of the problems of TB relapses, in both advanced as developing countries, is the phenomenon of multidrug resistance. One of the most worrisome and discussed problems, aggravated by the increased misery, co-infection with HIV/Aids, deterioration of health services and gradual reduction of care resources (Zanoti, 2010). Despite the efforts and some advances in the control of tuberculosis, the DRTB is an important public health problem. In the last 20 years, studies of the WHO have highlighted a significant increase in DRTB, representing a serious obstacle to the control of the disease, especially in areas where its prevalence is high (WHO, 2015; WHO, 2016). The DRTB is a disease caused by *M. tuberculosis* strains that are resistant to rifampicin (R) and isoniazid (H) simultaneously, which is the therapeutic pair with the greatest bactericide and sterilizing potential in the treatment of disease (Keshavjee and Farmer, 2012). This worries, whether by the possibility of dissemination of multidrug-resistant strains, or by the difficulties establishing efficient and effective regimens (Medeiros *et al*, 2011). Resistance to drugs have been studied since the 1940's; however, only 0.5% of individuals newly diagnosed with DRTB receive adequate treatment, and those who do not receive continue to feed the global pandemic of resistance (Udwadia, 2012). The DRTB is not evenly across different regions, varying according to the evolution, epidemiological moment and quality of the control of the disease. In this context, the present study becomes necessary once it allows offering subsidies for planning actions for the control of tuberculosis. Therefore, the objective was to analyze the factors associated with drug-resistant tuberculosis (DRTB) in the state of Maranhão, in the period from 2010 through 2015.

MATERIALS AND METHODS

This was a cross-sectional, analytical and retrospective study with DRTB cases reported in the state of Maranhão in the period from 2010 through 2015. The state of Maranhão is part of the Brazilian Northeast macro region. Its current population is of 6,954,036 inhabitants, its area is of 331,937.450 km^2 and its population density is of 19.81 inhabitants/km^2. It is divided into 217 municipalities, distributed into five mesoregions, north, south, east, west and central (IBGE, 2013). The study population included all cases of DRTB residing in the state of Maranhão notified in the Information System of Special Treatments of Tuberculosis (SITETB - *Sistema de Informação de Tratamentos Especiais da Tuberculose*) and TB cases in young adults (20 through 49 years) reported in the SINAN, which served as a parameter to define the factors associated with the DRTB, in the period from 1 January 2010 through 31 december 2015. The inclusion criteria were individuals presenting with any type of drug resistance to anti-tuberculosis treatment, and exclusion: cases with incomplete and inaccurate information and duplicates. A new case referred to a patient with pulmonary tuberculosis who has never been submitted to antituberculosis chemotherapy or has used tuberculostatic drugs for less than 30 days; cure case, the patient with pulmonary tuberculosis, initially positive, who presented, during the treatment, at least two negative sputum smear or who completed the treatment based on clinical and radiological criteria; primary resistance, the patient that has never received any treatment for tuberculosis, infected by resistant strains; acquired resistance, patients with initially sensitive TB, who, after irregular exposure to medications, present resistance in culture; default mono-resistance, resistance to a first-line drug; standard multidrug resistance, resistance to at least isoniazid and rifampicin; default poly-resistance, resistance to more than one drug in the sensitivity testing (ST); and standard extensive resistance, multidrug resistance and resistance to a fluoroquinolone and one of the three second-line injectable drug (amikacin, capreomycin, kanamycin). The data relating to DRTB were collected from the SITETB databaseof the Health Department of Maranhão; and the data of sensitive TB were collected from the SINAN. All variables identifying individuals were excluded to protect their anonymity, and inconsistencies (inaccurate information), incompleteness (incomplete information) and duplicates (two or more records for the same case) were removed for better data analysis.

The variables used in the study were: gender (male, female), age in years (age range: ≤ 20, 20 - 39, 40 - 59, ≥ 60), race/color (white, non-white), schooling in years of study (< 8, ≥ 8, uninformed), entry type (new case, retreatment), clinical form (extrapulmonary and pulmonary) closure (cure, no cure), smear microscopy (negative and positive), anti-HIV test (negative, positive), worsening (yes, no; alcoholism, diabetes, AIDS, smoking, illicit drugs), type of resistance (primary, acquired, uninformed), pattern of resistance (mono-resistancemultidrug resistance, poly-resistance, extensive resistance), resistance to ofloxacin(sensitive, resistant, uninformed), resistance to ethambutol (sensitive, resistant, uninformed), resistance to amikacin (sensitive, resistant, uninformed), resistance to rifampicin (sensitive, resistant, uninformed), resistance to isoniazid (sensitive, resistant, uninformed), resistance to streptomycin (sensitive, resistant, uninformed), resistance to capreomycin (sensitive, resistant, uninformed), resistance to kanamycin (sensitive, resistant, uninformed), treatment regimen (DRTB 1, DRTB2, DRTB3 , DRTB4). Data were collected from the SITETB and SINAN databases, saved in the Tabwin application version 3.5, and exported to Excel. Statistical analyses were performed using STATA software, version 11.0. The prevalence was calculated by the ratio between the number of cases of DRTB in the studied period divided by the total number of tuberculosis cases, multiplied by 100. Descriptive analysis was performed (absolute number and frequency) for resistance cases of DRTB. To identify associations between the independent variables and the DRTB, Poisson regression model was used. A univariate analysis was initially performed, with an estimate of the unadjusted prevalence ratios and 95% confidence interval (95% CI).

The variables whose p value was ≤0.20 were included in the multivariate Poisson regression model. The variables were selected by the stepwise method with retrograde elimination of variables. Only the variables with a value p≤0.05 remained in the final model, for which the prevalence ratios (ORS) and their respective 95% confidence intervals (95% CI) were estimated. An OR of 1.00 was attributed to the categories. Since this is a cross-sectional study, the odds ratio (OR) was chosen because the prevalence of DRTB cases is less than 10%, once OR tends to overestimate the associations and produce false positives when the prevalence of the event is high (usually above 10%). The present study is part of the

main project entitled "Prognostic factors for the outcome of pulmonary tuberculosis". In compliance with the requirements demanded by the Resolution 466/2012 of the National Health Council, Research Ethics Committee of the HUUFMA analyzed and approved the study, under opinion 473.975/2013.

RESULTS

In the study period, there were 10,944 cases of tuberculosis in the state of Maranhão; of these, 10,820 (98.9%) were TB sensitive cases, being 1,021 cases in young adults (20 through 49 years) and 124 (1.13%) DRTB cases. Thus, the DRTB prevalence in Maranhão, in the period from 2010 through 2015, was 1.13%. The highest prevalence of DRTB cases occurred in 2014 (1.62%) and the lowest, in 2010 (0.17 %) (Figure 1). Regarding the profile of resistance of DRTB cases (Table 3), there as predominance of acquired resistance (83.9%), and multidrug resistance pattern (74.2%); the greatest resistance was recorded for isoniazid (87.1%) and rifampicin (82.3%), followed by streptomycin (26.6%), ethambutol

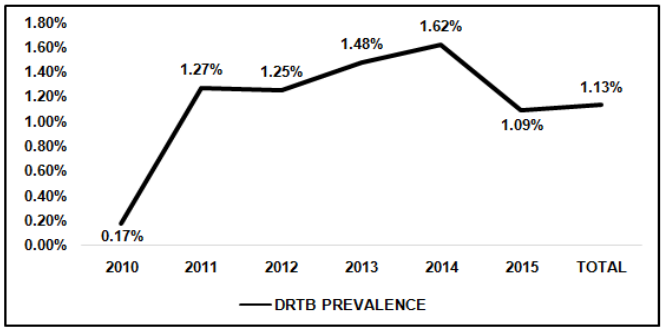

Figure 1. Prevalence of DRTB cases, in Maranhão, by notification year, in the period from 2010 to 2015

Table 1. Resistance profile of drug resistant tuberculosis cases (DRTB) reported in the State of Maranhão, between 2010 and 2015. São Luís-MA, 2017

Variable	*DRTB (n= 124)		
	n	(%)	**$CI_{95\%}$
Type of resistance			
Primary	15	12,1	(6,3 – 17,9)
Acquired	104	83,9	(77,3 – 90,4)
Uninformed	5	4,0	(0,5 – 0,7)
Pattern of resistance			
Monoresistance	21	16,9	(10,2 – 23,6)
Multiresistance	92	74,2	(66,4 – 82,0)
Polyresistance	8	6,4	(2,1 – 10,8)
Extensiveresistance	3	2,4	(0,3 - 5,2)
Ofloxacinresistance			
Sensintive	29	23,4	(15,8 - 30,9)
Resistant	12	9,7	(4,4 - 14,9)
Uninformed	83	66,9	(58,5 - 75,3)
Ethambutolresistance			
Sensintive	79	63,7	(55,1 - 72,3)
Resistant	32	25,8	(17,9 - 33,6)
Uninformed	13	10,5	(5,0 - 15,9)
Amikacinresistance			
Sensintive	37	29,8	(21,7 - 38,0)
Resistant	4	3,2	(0,1 - 6,3)
Uninformed	83	66,9	(58,5 - 75,3)
Rifampicinresistance			
Sensintive	14	11,3	(5,6 - 16,9)
Resistant	102	82,3	(75,4 - 89,1)
Uninformed	8	6,45	(2,1 - 10,8)
Isoniazidresistance			
Sensintive	6	4,8	(1,0 - 8,7)
Resistant	108	87,1	(81,1 - 93,1)
Uninformed	10	8,1	(3,2 - 12,9)
Streptomycinresistance			
Sensintive	80	64,5	(55,9 - 73,1)
Resistant	33	26,6	(18,7 - 34,5)
Uninformed	11	8,9	(3,8 - 13,9)
Capreomycinresistance			
Sensintive	38	30,6	(22,4 - 38,9)
Resistant	2	1,6	(0,6 - 3,8)
Uninformed	84	67,7	(59,4 - 76,1)
Kanamycinresistance			
Sensintive	37	29,8	(21,6 - 38,00)
Resistant	3	2,4	(0,3 - 5,1)
Uninformed	84	67,7	(59,4 - 76,1)
Treatmentregimen			
DRTB* 1	13	10,5	(5,0 - 15,9)
DRTB2	59	47,6	(38,7 - 56,5)
DRTB3	12	9,7	(4,4 - 14,9)
DRTB4	15	12,1	(6,3 - 17,9)
Uninformed	25	20,2	(13,0 - 27,3)

*Drug-resistant TB**Confidence interval

(25.8%), ofloxacin (9.7%), amikacin (3.2%), kanamycin (2.4%) and capreomycin (1.6%). The predominant treatment regimen was the MDR-TB 2, with a rate of 47.6%. The adjusted and non-adjusted analyses considered only 119 DRTB cases, because five of the 124 cases were excluded due to lack of information regarding the selected variables. In the non-adjusted analysis, the variables associated with the DRTB (Table 2) were: retreatment entry ($CI_{95\%}$=1.71-3.84; OR=256; *p<0.001*), no cure closure ($CI_{95\%}$=2.15-4.41, OR=3.08, *p=0.001*), positive sputum smear ($CI_{95\%}$=2.66-9.73; OR=5.09; p=0.001), and use of illicit drugs ($CI_{95\%}$=1.01-2.71,OR=1.66; *p=0.043*); and the variables considered as protective association were: education with <8 years ($CI_{95\%}$=0.31-0.64; OR=0.44; *p<0.001*) and positive anti-HIV test ($CI_{95\%}$= 0.08-0.79; OR=0.25; *p=0.019*). After the adjustment of the model, the variables that remained associated with the DRTB

Table 2. Unadjusted analysis of the factors associated with cases of drug-resistant tuberculosis (DRTB) reported in the State of Maranhão, from 2010 to 2015

	TUBERCULOSIS			
	SENSITIVE (n=1021)	*DRTB (n=119)		
Variable	n (%)	n (%)	OR ($CI_{95\%}$)	*p-value*
Sex				
Female	326 (88,4)	43 (11,6)	1	
Male	695 (90,3)	76 (9,8)	0,84 (0,58 – 1,22)	0,380
Age (years)				
≤39	511 (87,9)	70 (12,1)		
40 a 59	343 (90,3)	37 (9,7)	0,80 (0,54 – 1,20)	0,295
≥ 60	167 (93,3)	12 (6,7)	0,55 (0,30 – 1.02)	0,061
Race/color				
White	116 (88,5)	15 (11,4)	1	
Not White	905 (89,7)	104 (10,3)	0,90 (0,52 – 1,54)	0,703
Schooling (years)				
<8	283 (82,9)	58 (17,0)	1	
≥8	738 (92,4)	61 (7,6)	0,44 (0,31 – 0,64)	<0,001
Input				
New case	910 (91,3)	87 (8.73)	1	
Retreatment	111 (77,6)	32 (22,4)	2,56 (1,71 – 3,84)	<0,001
Form				
Extrapulmonary	42 (97,6)	1 (2,33)		
Pulmonary	979 (89,2)	118 (10,76)	4,62 (0,64 – 33,10)	0,127
Closing				
Cure	816 (92,9)	62 (7,1)		
Not cure	205 (78,2)	57 (21,7)	3,08 (2,15 – 4,41)	<0,001
Sputum smear microscopy				
Negative	353 (97,2)	10 (2,7)		
Positive	668 (85,9)	109 (14,0)	5,09 (2,66 – 9,73)	<0,001
HIV test				
Negative	918 (88,7)	116 (11,2)		
Positive	103 (97,2)	3 (2,8)	0,25 (0,08 – 0,79)	0,019
Alcoholism				
Not	888 (90,2)	96 (9,7)		
Yes	133 (85,2)	23 (14,7)	1,51 (0,96 – 2,38)	0,075
Diabetes				
Not	918 (88,9)	114 (11,1)		
Yes	103 (95,4)	5 (4,6)	0,42 (0,17 – 1,02)	0,057
Aids				
Not	931 (88,9)	116 (11,1)		
Yes	90 (96,7)	3 (3,2)	0,29 (0,09 – 0,91)	0,035
Smoking				
Not	878 (89,3)	105 (10,7)		
Yes	143 (91,1)	14 (8,9)	0,83 (0,47 – 1,46)	0,526
Drugs				
Not	923 (90,2)	100 (9,8)		
Yes	98 (83,7)	19 (16,2)	1,66 (1,01 – 2,71)	0,043

* Drug-resistant TB **Confidence interval

Table 3. Adjusted analysis of factors associated with cases of drug-resistant tuberculosis (DRTB) reported in the State of Maranhão, from 2010 to 2015

Variable	OR ($IC_{95\%}$)	*p-value*
Schooling (years)		
≥8 anos	1	
<8 anos	0,46 (0,32 – 0,66)	<0.001
Input		
New case	1	
Retreatment	1,61 (1,05 – 2,48)	0,030
Closing		
Cure	1	
Not cure	2,96 (2,01 – 4,35)	<0.001
Sputum smear microscopy		
Negative	1	
Positive	4,47 (2,26 – 8,87)	<0.001

* Drug-resistant TB **Confidence interval

(Table 3) were: retreatment entry ($CI_{95\%}$=1.05-2.48; OR=1.61; *p=0.030*), no cure closure ($CI_{95\%}$=2.01-4.35, OR=2.96; *p<0.001*), and positive sputum smear ($CI_{95\%}$=2.26-8.87; OR=4.47; *p<0.001*); the variable that remained as protective association was: schooling with <8 years ($CI_{95\%}$=0.32-0.66; OR=0.46; *p<0.001*).

DISCUSSION

Tuberculosis in the state of Maranhão remains a public health problem and multidrug-resistance cases contribute to worsening this problem, with a prevalence of 1.13%. This prevalence is below the one found in Brazil, which, in the period from 1995 through 1997, was 10.6% (Almeida *et al*, 2014). Moreover, this difference may relate to both the study period as possible failures that occur during the treatment of sensitive TB when there is early detection of treatment failure. Other factors may contribute to these variations, such as epidemiological moment, quality of services and even the quality of information systems. In relation to the type of resistance, most cases presented acquired resistance. Several other studies also found similar results, ranging from 7.9% (Ribeiro *et al*, 2012), 12% (Micheletti *et al*, 2014) and up to 20.3% (Marques *et al*, 2017). Melo found a percentage of 74%, which is closer to our result (83.9%) (Melo, 2010). Considering that acquired resistance of DRTB occurs in previously treated patients, the results reinforce that this kind of resistance arises from errors during the TB treatment, i.e., inappropriate prescriptions of the drug association, monotherapy and patient's non-adherence to the treatment. This situation may also be related to an inadequate anti bacilar therapeutic adherence by patients, mainly due to the abandonment of treatment or relapse (Câmara *et al*, 2016). The most frequent resistance pattern was the multidrug resistance. The result of our study is above the recommendation of the WHO, which is 4.8%, and higher than estimates for Brazil (1.4%), Latin America (3.5%), MatoGrosso do Sul (4.9%), Ceará (1.1%), and Porto Alegre (4.7%) (Marques *et al*, 2017; Micheletti *et al*, 2014). Multidrug resistance is a long-known phenomenon and its development results from multiple factors, especially human actions, and may reflect failures in the control of sensitive TB. The treatment of multidrug-resistant forms is much more complex, more expensive and likely to fail, which favors the spread of resistant strains.

This fact may hinder the control of TB in Maranhão with this high rate of DRTB. Regarding isolated resistance, the largest number of cases was resistance to isoniazid and rifampicin. Coelho *et al*. found a similar situation. The resistance to rifampicin and isoniazid is rather worrying, because they are the most powerful drugs used in the treatment of TB (Coelho *et al*, 2012), in addition to their easy handling, low cost, presentation via oral route and duration of treatment of six months (Fregona *et al*, 2017). Various hypotheses have been suggested to explain this phenomenon. Some authors have reported non-adherence to treatment as the most plausible explanation for these cases (Almeida *et al*, 2014). Other studies have reported that the occurrence of resistance to rifampicin and isoniazid results from changes in the RNA polymerase enzyme or from the impermeability of the bacterial cell. In relation to this event, there should be association of drugs, in which the germs resistant to isoniazid will be affected by rifampicin and the ones resistant to rifampicin, by isoniazid (Coelho *et al*, 2012).

The results of the present study pointed out the retreatment entry, no cure closure and positive sputum smear as factors that increase the chance of developing DRTB. One of the greatest challenges today, for the control of DRTB in Brazil are retreatment cases. This group, formed by relapse and readmission cases, has greater chance of developing an unfavorable outcome for the disease. Few studies have investigated the issue of retreatment, which represents an important monitoring indicator of the National Program for the Control of Tuberculosis (NTCP – *Programa Nacional de Controle de Tuberculose*), because it allows identifying the performance of the program in relation to recall of cases (Câmara *et al*, 2016). Micheletti *et al*., in Porto Alegre, also found that the retreatment is associated with the occurrence of DRTB (Micheletti *et al*, 2014). The no-cure closure condition is also associated to DRTB, caused by the patient's abandonment of treatment, considered the greatest obstacle to the healing of DRTB. Several factors may contribute to this, such as professional-patient relationship, prejudice, non-acceptance of the disease, predominance of young adults, use of medication during insufficient time and/or incorrectly (Basta *et al*, 2013).

Special strategies are necessary to monitor this clientele, seeking to reduce the abandonment rate. The positive sputum smear was another variable associated with the DRTB. Coelho *et al*. found the same result when they observed that the sputum smear microscopy was performed in most of the notified cases, and most results were positive (Coelho *et al*, 2012). Augusto *et al*. state that the sputum smear microscopy is the main method of diagnosis of DRTB, being an examination of easy implementation and low cost, useful for the coverage of patients with respiratory symptoms, justifying the large number of requests for this test (Augusto *et al*, 2013). The sputum smear microscopy is also recommended for monthly follow-up of the treatment (Pires *et al*, 2014). The interpretation of the results should take into account some limitations of the study, such as the analysis of secondary data, which can be influenced by lack of completeness. However, despite the limitations, the results are consistent with the literature, and can be used to subsidize public policies aimed at improving the control of DRTB, contribute to the qualification of professionals working in the area and guide them about the factors that may indicate a negative prognosis and qualify the existing databases. The study contributed to the characterization of DRTB in Maranhão, drawing the panorama of resistance. The DRTB requires special attention, since the emergence of multidrug-resistant and extensively resistant strains suggests weakness in properly diagnosing and treating cases of DRTB.

Therefore, the improvement of the quality of assistance throughout the state is extremely important. One of the biggest challenges that public health still has in relation to the control of DRTB is decreasing its incidence, and improving patients' adherence to treatment. Thus, more investments are necessary in the fight against this disease through the dissemination of information to the public about the risk that the DRTB presents. In addition, measures to expand access to early diagnosis and treatment need to be strengthened in order to achieve an effective control of the disease. The data analyzed in this study may indicate comparative parameters for use in new researches. The knowledge of the problem of resistance to anti-tuberculosis drugs by health professionals must reach the care provided to patients, improving the initial approach,

aiming at a more accurate anamnesis and identification of possible factors that might interfere with the adherence to treatment.

Conflict of Interests: The authors declare no conflict of interest.

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