Scientific Research Publishing

Advances in Microbiology, 2024, 14, 287-302
https://www.scirp.org/journal/aim
ISSN Online: 2165-3410
ISSN Print: 2165-3402

Epidemiology and Clinical Features of *Mycobacterium avium* Complex Pulmonary Disease in a Brazilian Amazon Cohort

Jose Tadeu Colares Monteiro[1,2,3*], Adriana Rodrigues Barretto[1], Ruan Seguin Azevedo Quaresma[1], Bianca Miranda Gouveia[1], Ismari Perini Furlaneto[3], Victória Menezes da Costa[1], Yan Corrêa Rodrigues[4], Layana Rufino Ribeiro[4], Ricardo J. de Paula Souza e Guimarães[5], Alex Brito Souza[4], Ana Roberta Fusco da Costa[2,3], Karla Valéria Batista Lima[2,4*]

[1]Joao de Barros Barreto University Hospital, Federal University of Pará, Belém, Brazil
[2]Center for Biological and Health Sciences, Ph.D. Program in Parasitic Biology in the Amazon Region (PPGBPA), State University of Pará (UEPA), Belém, Brazil
[3]Department of Medicine, Centro Universitário do Pará CESUPA, Belém, Brazil
[4]Bacteriology and Mycology Section, Evandro Chagas Institute (SABMI/IEC), Ministry of Health, Ananindeua, Brazil
[5]Geoprocessing Laboratory, Evandro Chagas Institute/SVSA/MS, Ananineua, Brazil
Email: *cephujbb@yahoo.com.br, *tadeucolares@hotmail.com, *karlalima@iec.gov.br

How to cite this paper: Monteiro, J.T.C., Barretto, A.R., Quaresma, R.S.A., Gouveia, B.M., Furlaneto, I.P., da Costa, V.M., Rodrigues, Y.C., Ribeiro, L.R., de Paula Souza e Guimarães, R.J., Souza, A.B., da Costa, A.R.F. and Lima, K.V.B. (2024) Epidemiology and Clinical Features of *Mycobacterium avium* Complex Pulmonary Disease in a Brazilian Amazon Cohort. *Advances in Microbiology*, **14**, 287-302.
https://doi.org/10.4236/aim.2024.146021

Received: January 10, 2024
Accepted: June 4, 2024
Published: June 7, 2024

Abstract

The incidence of *Mycobacterium avium* complex pulmonary disease (MACPD) has been globally increasing. The present study aims to provide a comprehensive analysis of clinical characteristics and treatment response among patients in the Amazon region of Brazil and conduct a retrospective cohort study at a prominent referral hospital in the State of Pará, Brazil, from 2012 to 2020. The *M. avium* group represented 58.9% of cases, followed by *M. intracellulare* (35.7%), *M. colombiense* (3.6%), and *M. chimaera* (1.8%). The majority of patients (73.2%) were female and with an average age of 63 years. Primary clinical manifestations included persistent cough and sputum production. The Charlson comorbidity index (CCI) averaged 2.47, with 36.3% of patients having a CCI score equal to higher than 3. Notably, over 70% of patients had received treatment for pulmonary tuberculosis before initiating treatment for MAC infection. The fibrocavitary radiologic form was the most prevalent (55.4%), frequently exhibiting a bilateral distribution (53.6%). Antimicrobial susceptibility revealed a significant prevalence of MAC resistance to drugs in the therapeutic regimen. Despite this, most of the patients experienced clinical improvement (50%). In conclusion, this study highlights a higher prevalence of MAC infections among middle-aged women, with a history of pulmonary tuberculosis treatment and presenting the fibrocavitary radiological form was predominant.

Keywords

MACDP, Nontuberculous Mycobacteria, *Mycobacterium avium* Lung Disease

1. Introduction

Recent data have shown increasing infections caused by nontuberculous mycobacteria (NTM), particularly, the pulmonary disease caused by the *Mycobacterium avium* complex pulmonary disease (MACPD) as an emerging and relevant pathology on a global scale [1]. Most individuals affected by MACPD have underlying pulmonary complications, such as chronic obstructive pulmonary disease (COPD) and bronchiectasis. Additionally, another group at higher risk for developing disseminated mycobacterial disease includes those with compromised immune systems due to HIV/AIDS, organ transplants, or immunosuppressive therapies [2].

Notable differences are observed regarding the prevalence of NTM species causing infections, in which the regional disparities are usually attributed to environmental and climatic conditions, exposure to contaminated water sources, and specific individual factors. Globally, Brazil and Portugal account for approximately 50% of NTM cases attributed to the MAC [3]. Furthermore, notable regional disparities in NTM infection prevalence in Brazil are evident, with *M. kansasii* being highly prevalent in the South and Southeast regions, while MAC and *M. abscessus* are more frequent in the North and Northeast regions [4] [5]. Data from the state of Ceará (Brazilian Northeast) present an epidemiological scenario predominantly characterized by cases among males (73.9%), with pulmonary (60.9%) and disseminated manifestations (27.5%), presenting a significant association with HIV infection (69.6%), and cases primarily linked to *M. avium* (24.6%) and *M. fortuitum* (10.1%) species [6]. In the Brazilian Northern region, the State of Pará reports one of the highest national averages in terms of mycobacterial infections: between 2013 and 2019, the state recorded over 100 cases of NTM, highlighting MAC as the predominant pathogen in Pará state. Additionally, the state exhibits a concerning rate of 49.4% of tuberculosis (TB) cases per 100,000 inhabitants officially documented in 2022 [6] [7]. For the diagnosis of MACPD, it is essential to consider not only the clinical characteristics, but also the microbiological and radiological aspects. Finally, categorizing the disease into fibrocavitary or nodular-bronchiectatic forms plays a crucial role in clinical management and therapy response [8] [9] [10] [11].

Treating patients with MACPD can be challenging due to several factors, including the extended duration of treatment and respective side effects. Furthermore, the inherent manifestation of antimicrobial resistance by NTM species can further complicate therapeutic success. In this context, careful monitoring and an individualized approach are necessary to achieve satisfactory clinical outcomes [12] [13] [14] [15] [16].

To facilitate the development of control strategies and improve the management of MACPD infections in Brazil, it is imperative to understand the regional factors, considering the vast Brazilian territory and, especially, the significant socioeconomic, geographical, and environmental disparities existing in the Amazon region. Therefore, studies focusing on specific regions are important to provide insights into a particular locality and enable the Brazilian healthcare system to effectively monitor and mitigate the impact of MACPD nationwide.

2. Materials and Methods

Study design and data collection

This retrospective observational study was conducted at the João de Barros Barreto University Hospital (Belém, State of Pará, Brazil), within the most populous state in the Northern region of Brazil. Records of 139 patients with pulmonary NTM isolates treated between January 2012 and December 2020 were reviewed, and 56 patients were identified with MACPD. Patients over 18 years of age, diagnosed according to the 2020 American Thoracic Society (ATS/IDSA) criteria, and who completed treatment between January 2012 and December 2020 were included [8] [9]. In this study, 13 patients who did not meet these criteria were excluded from the analysis, and by using available medical records, 43 patients were analyzed including data on sociodemographic, clinical, microbiological, medical imaging aspects (High-Resolution Computed Tomography) and therapeutic responses.

The Charlson comorbidity index (CCI) was used to assess known comorbidities association with mortality, including myocardial infarction, diabetes mellitus, cancer, chronic lung disease, liver disease, chronic kidney failure, stroke, peptic ulcer, autoimmune disease, cirrhosis, leukemia, and AIDS [16] [17] [18]. Also, the history of prior treatment for pulmonary tuberculosis, using the therapeutic regimen composed of rifampicin, ethambutol, pyrazinamide, and isoniazid, was evaluated.

For the relative risk analysis, patients were divided into two groups: the "*M. avium* group" and "other species" group (including patients with *M. intracellulare*, *M. chimaera*, *and M. colombiense*). Regarding the primary outcome, variables and determining factors associated with treatment response were examined, comparing characteristics of cured and non-cured patients. The definition of cure included the completion of antimycobacterial treatment, with documented culture conversion, and absence of failure and/or recurrence within 24 months after antimycobacterial treatment. Patients not meeting these criteria were classified as non-cured [19].

Molecular identification of isolates and drug susceptibility testing (DST)

The molecular identification of isolates involved the sequencing of specific regions of the 16S rRNA, *hsp65*, and *rpoB* genes, followed by the obtained data comparison using the basic local alignment search tool (BLAST) in the National Center for Biotechnology Information database [20] [21].

For the drug susceptibility testing (DTS) experiments, the first isolate obtained from each patient were included and the minimum inhibitory concentration (MIC) was determined using the microdilution method SLOMYCO Sensititre®, provided by Trek Diagnostic Systems. Out of 43 initial isolates, only 41 isolates were tested, and the results were standard analyzed following the guidelines by the Clinical and Laboratory Standards Institute (CLSI) [22]. All experiments were conducted under the responsibility of the regional tuberculosis laboratory, in the Bacteriology and Mycology section, at the Evandro Chagas Institute, affiliated with the Brazilian Ministry of Health (IEC/PA/MS).

Spatial distribution of Mycobacterium avium complex cases

The spatial distribution analysis was conducted and organized into 13 distinct regional health centers. Each address was tabulated in Microsoft Office Excel 2019, and geographical coordinates were acquired using the Freegeocoding and Google Maps tools. Subsequently, ArcGIS (https://www.arcgis.com) and Terra-View 10.5 software were utilized for case mapping. The kernel density estimator (EDK) spatial analysis technique, available in TerraView, was applied to explore point patterns through exploratory interpolation. Results obtained from this estimator were depicted using a color scheme, associating green with the Low-Occurrence category, yellow with Medium Occurrence, orange with High Occurrence, and red with Very High Occurrence [23] [24]. A map was built for visualization of this distribution, emphasizing the locations of MAC species and their respective occurrences in the State of Pará.

Protocols and therapeutic approaches for Mycobacterium avium complex pulmonary disease (MACPD)

The initial treatment plan involved three medications: rifamycin, ethambutol, and a macrolide (clarithromycin mainly). For severe and cavitary forms, an aminoglycoside (amikacin mainly) was added to the initial protocol. Other drugs, like azithromycin, streptomycin, and rifabutin, were used in creating various therapeutic protocols, particularly in specific situations such as cases of intolerance or allergy. The treatment was maintained for 12 months until achieving negative culture conversion or meeting the established criteria for cure [8] [9].

The adopted definition of cure encompassed the successful completion of antimycobacterial therapy, as evidenced by documented culture conversion and the absence of any indications of failure or recurrence for a period of up to 24 months following the completion of antibiotic treatment. Furthermore, clinical improvement of symptoms with regression, especially in symptoms like cough, sputum, and fever, was taken into consideration. As for signs, weight loss would be considered. Patient-reported and/or objective improvement of symptoms throughout antimycobacterial treatment was also considered, with this improvement sustained until the conclusion of the treatment, even in the absence of available culture data to confirm microbiological conversion. Patients failing to meet these specific criteria were classified as not cured [19].

Statistical analysis

In this study, the MAC species were divided into two groups based on molecular identification: the *M. avium* group and the group of other species (*M. intracellulare*, *M. chimaera*, *and M. colombiense*). The collected data underwent a comprehensive statistical analysis, incorporating both descriptive and inferential statistics to account for the properties of the variables. The Shapiro-Wilk test was employed to assess the normal distribution of the data. In cases where the variables exhibited a non-parametric distribution, the Mann-Whitney test was applied to conduct comparative analyses between two independent groups. To estimate the degree of association between the selected exposure variables and the resulting event, measures of relative risk were calculated, along with the corresponding 95% confidence intervals for each variable.

Ethical considerations

The study protocol received approval from the ethics committee of the João de Barros Barreto University Hospital and registered under CAAE: 53327321.0.0000.0017 on May 20, 2022. Given the retrospective nature of the study, written informed consent was not obtained. Also, the research adhered to the guidelines presented in the Declaration of Helsinki Brazilian and by the Brazilian National Health Council.

3. Results

Species identification

According to obtained data, the most prevalent MAC species was *M. avium* (58.9%; 33/56), followed by *M. intracellulare* (35.7%; 20/56), *M. colombiense* (3.6%; 2/56), and *M. chimaera* (1.8%; 1/56). The identified isolates were distributed throughout the State of Pará (**Figure 1**). The application of the Kernel Density Estimator (KDE) technique demonstrated that the areas of higher incidence were concentrated in the metropolitan region of the capital, Belém (**Figure 2**).

Clinical characteristics of patients

In the present cohort, the female population represented a substantial majority, accounting for 73.0% (31/43) of the study participants. Regarding age, the highest representation across all species was found in individuals aged between 70 and 79, constituting 25.0% of cases. Additionally, when comparing patients in the group consisting of other species, it was noted that, on average, they were about 10 years older than patients in the *M. avium* group ($p = 0.0317$). Furthermore, in the group of other species, the age ranged from 25 to 90 years, with an average age of 63 years (**Table 1** and **Table 2**). Regarding clinical manifestations, cough and sputum showed statistically significant proportions ($p < 0.0001$) among the participants. The mean CCI score was 2.47, with 36.3% of patients having a CCI score of 3 or higher. However, no difference was observed when comparing the Charlson comorbidity index between patients infected with other species and *M. avium* ($p = 0.0752$) (**Table 2**).

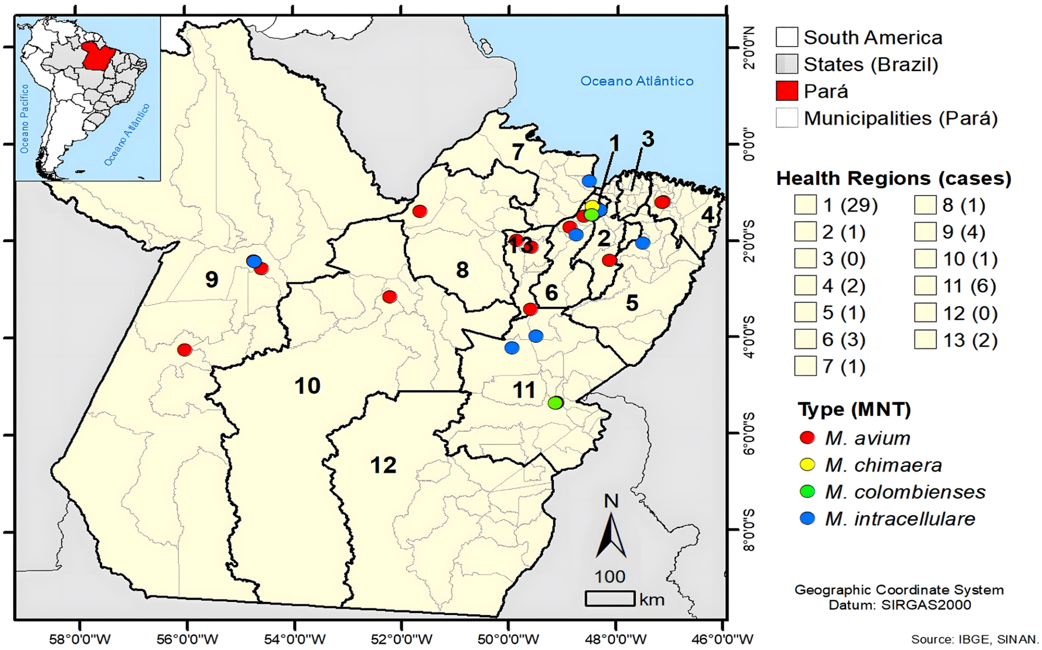

Figure 1. Distribution of *Mycobacterium avium* complex species cases associated with pulmonary disease in the State of Pará, Brazil, Amazon Region. Source: Evandro Chagas Institute (IEC/PA), 2023.

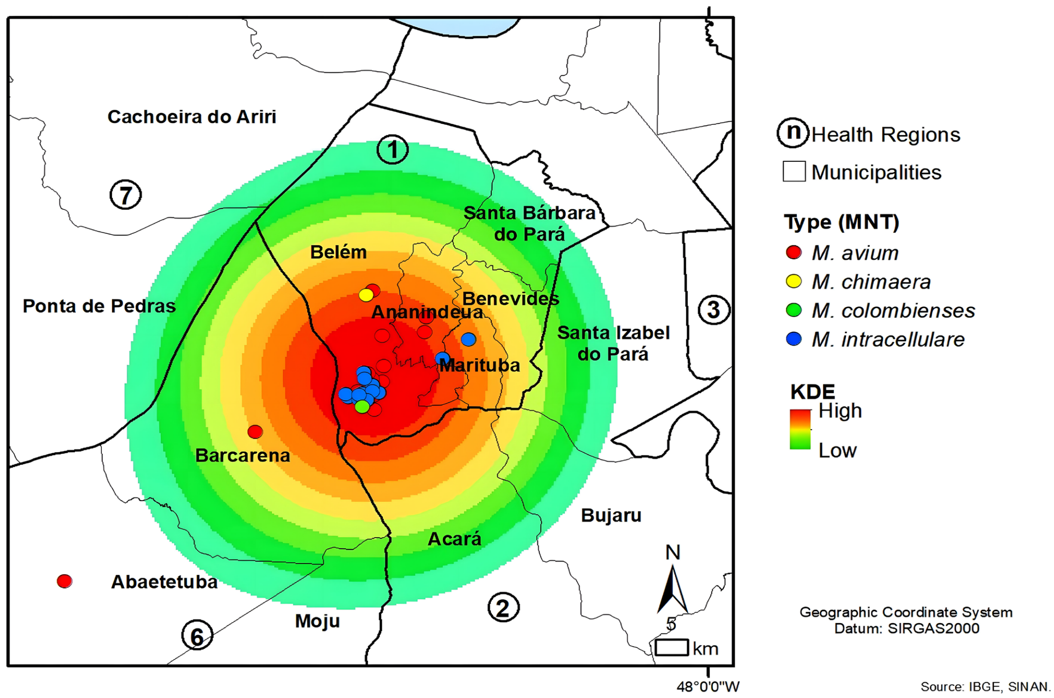

Figure 2. Spatial distribution of *Mycobacterium avium* complex species concentrated in the metropolitan region of the capital, Belém. Source: Evandro Chagas Institute (IEC/PA), 2023.

Regarding previous treatments for pulmonary tuberculosis, 70% of patients with *M. avium* and 81% of patients with *M. intracellulare*, undergone the regimen. Also, some patients undergone more than two treatments, both in the *M. avium* group (33%) and in the *M. intracellulare* group (62.5%) (Table 3).

Table 1. Demographic characteristics of patients.

Epidemiological data	Frequency	% (N = 43)
Sex		
Female	31	73.0%
Male	12	27.0%
Age	**Frequency**	**% (N = 43)**
<50	8	20.0%
50 - 59	7	18.0%
60 - 69	8	20.0%
70 - 79	11	25.0%
≥80	9	17.0%
Minimum/average/maximum	**25/63.0 ± 16.7/90 years**	

Source: NTM Outpatient Clinic—HUJBB, 2023.

Table 2. Comparison of age and Charlson comorbidity index among MACPD patients according to *Mycobacterium avium* group and other species group (including patients with *M. intracellulare*, *M. chimaera*, and *M. colombiense*) and observed outcome. HUJBB, 2012-2020.

Variable	*MACPD*		p-value
	Other MAC species	*M. avium*	(Mann-Whitney)
Age			
Min. - Max.	25 - 85	32 - 90	
Average ± standard deviation	69.5 ± 15.4	59.6 ± 16.4	0.0317
CI 95%	61.3 - 77.7	52.7 - 66.5	
Median (DIQ)	73.5 (61.8 - 80.8)	58.5 (43 - 72.3)	
Charlson comorbidity index			
Min. - Max.	0 - 5	0 - 6	
Median (DIQ)	4 (2.3 - 4)	2 (1 - 3.8)	0.0752
CI 95%	2 - 4	1 - 3	

Source: NTM Outpatient Clinic—HUJBB, 2023.

Table 3. Treatments for pulmonary tuberculosis prior to the diagnosis of MAC

MAC	Treatment for pulmonary Tb	>2 treatments for pulmonary Tb
M. avium (24/43)	17 (70%)	8 (33%)
M. intracellulare (16/43)	13 (81%)	10 (62.5%)
M. colombiense (2/43)	x	2 (100%)
M. *chimaera* (1/43)	1 (100%)	x

Source: NTM Outpatient Clinic—HUJBB, 2023.

In this study, results indicate an increased relative risk among women with a history of previous treatments for pulmonary TB compared to those without such a history. The calculated relative risk estimate (RR) demonstrates a statistically significant association between previous treatment and subsequent *M. avium* infection, even after adjustment for potential confounding factors, with a risk ratio of 4.750 [1.191 - 26.880] (95% confidence interval, p-value < 0.05). These results highlight the importance of considering previous pulmonary TB treatment as a risk factor when assessing *M. avium* infection rates among women.

Radiologic features

The fibrocavitary and bilateral forms were the most prevalent, representing 72.1% (31/43) and 69.8% (30/43) of cases. It is worth noting that no statistical significance was observed for these values (p > 0.05) (**Table 4** and **Figure 3**).

Drug susceptibility testing (DST) and treatment of Mycobacterium avium complex pulmonary disease (MACPD)

The DST indicated considerable resistance to common antimycobacterial agents such as rifampicin and ethambutol. However, it was observed that *M. avium* isolates showed significantly higher resistance rates to clarithromycin and amikacin when compared to other species within the *M. avium* complex (**Table 5**). Concerning treatment and medications schemes by patients, a significant correlation was observed in the administration of clarithromycin and ethambutol (p < 0.0001), with utilization rates of 67.5% and 100%, respectively. Rifampicin demonstrated a statistically significant prevalence, being utilized by 74.5% of the patient population. Additionally, other medications, such as streptomycin (35.7%), amikacin (33.9%), and azithromycin (32.5%), among others, were administered as detailed in **Table 6**.

Table 4. Radiological features presented by MACPD patients in the State of Pará.

Radiologic features	Frequency	% (N = 43)
Unilateral	15	34.9%
Bilateral	30	69.8%
Fibrocavitary	31	72.1%
Bronchiectasis	24	55.8%
Opacities	8	18.6%
Fibrosis	6	14.0%
Nodules	11	25.6%
Atelectasis	4	9.3%
Tree-in-bud	3	7%
Calcification	2	4.7%
Pleural thickening	2	4.7%

Source: NTM Outpatient Clinic—HUJBB, 2023.

Table 5. Antimicrobial resistance profile of *M. avium* complex isolates in patients from the State of Pará (2012-2020).

Tested drugs	Breakpoint	*M. avium* N = 23 (%)	*M. intracellulare* N = 15 (%)	*M. colombiense* N = 2 (%)	*M. chimaera* N = 1 (%)	Nres (%)
Rifampin	≥1	23 (100%)	15 (100%)	0	1 (100%)	95.1
Rifabutin	≥2	20 (87.0%)	5 (33.3%)	0	0	60.1
Ethambutol	≥8	23 (100%)	15 (100%)	2 (100%)	1 (100%)	100
Clarithromycin	≥32	11 (47.8%)	5 (33.3%)	1 (50%)	0	41.6
Moxifloxacin	≥4	21 (91.3%)	12 (80%)	2 (100%)	1 (100%)	87.8
Amikacin	≥64	16 (69.6%)	7 (46.7%)	0	0	56.1
Linezolid	≥32	22 (95.7%)	10 (66.6%)	2 (100%)	1 (100%)	85.3

Nres: resistant isolates; the number provided corresponds to the quantity of antibiotic-resistant samples for the respective antibiotic; susceptibility testing (ST) results were available for only 41 patients.

Table 6. Medications used in the treatment of patients with *MACPD*.

Medications	Frequency	% (N = 43)
Etambutol*	43	100%
Claritromicin*	29	67.5%
Rifampicin**	32	74.5%
Estreptomicin	15	35.7%
Amicacin	19	33.9%
Azitromicin	14	32.5%
Rifabutin	11	25.5%

*p < 0.0001 and **p = 0.0008 Chi-Square Goodness-of-Fit Test. Source: NTM Outpatient Clinic—HUJBB, 2023.

Figure 3. Cavitary form of *Mycobacterium intracellulare* pulmonary disease in a 52-year-old female patient. Chest high-resolution computed tomography (HRCT) reveals bilateral cavitation, centrolobular nodule in the middle lobe and upper right lobe, and left lung volume reduction. Source: NTM Outpatient Clinic—HUJBB, 2023.

Consequently, responses to treatment were assessed, revealing clinical improvement in 25 patients (58.1%). Weight gain was observed in 14 patients (32.6%), while radiological improvement manifested in 11.6% of cases. Subsequently, a significant proportion of the patient cohort (65.1%) achieved cure compared to those who experienced treatment failure (30.2%) and those who abandoned treatment (14.0%), as presented in Table 7.

Table 7. Treatment-related variables.

Treatment response	Frequency	% (N = 43)
Clinical improvement	25	58.1%
Weight gain	14	32.6%
Radiologic improvement	5	11.6%
Outcomes	**Frequency**	**% (N = 43)**
Cure*	28	65.1%
Failure	13	30.2%
During treatment	6	14.0%
Abandon	6	14.0%
Relapse	3	7.0%

*All the definitions used here are described in the methodology [20]. Source: NTM Outpatient Clinic—HUJBB, 2023.

4. Discussion

The pulmonary infection by *M. avium* Complex was identified at a high prevalence among women in this cohort, aligning with early reports of Lady Windermere Syndrome. Data from a study involving 35 women indicated significantly higher estrogen levels in patients undergoing MAC treatment, while DHEA-S (dehydroepiandrosterone sulfate) levels were comparatively lower [25] [26]. Several studies suggested a plausible correlation between hormonal factors and senescence as prominent elements in MACPD. In a study with 220 individuals with pulmonary NTM, 30% exhibited bronchiectasis in computed tomography scans. In this specific group, a higher proportion was demonstrated among women ($p = 0.002$), and the average age was considerably high ($p = 0.005$). Additionally, these patients tended to have significantly lower body weight (below 50 kg) and height ≤ 155 cm ($p < 0.0001$ and $p = 0.018$, respectively) [25] [26] [27]. In the present study, the elderly emerged as significant predictors of MACPD, with patients affected by the group of other species, mainly represented by *M. intracellulare*, having an average age ten years higher ($p = 0.0317$) than those affected by the MAC group. These results are aligned with previously data, where patients infected with *M. avium* and *M. intracellulare* had average ages of 59 and 64 years, respectively [28].

According to the study by Koh *et al.* [28], 267 cases of pulmonary disease by MACPD were examined, of which 45% were attributed to the *M. intracellulare* species. The affected patients were older (64 years, $p = 0.002$), had a lower body mass index (19.5 kg/m^2, $p < 0.001$), and a higher frequency of respiratory symptoms, such as cough (84%, $p = 0.005$). Moreover, a higher percentage of patients had a previous history of tuberculosis treatment (51% versus 31%, $p < 0.001$), and were more likely to present the fibrocavitary form of the disease (26% versus 13%, $p < 0.001$). In the present cohort, patients with *M. intracellulare* presented similar findings; however, they were older, had multiple clinical symptoms (on average, more than four symptoms), and the fibrocavitary form was more evident (although statistically significant differences were not observed). This study also highlighted the predominance of bilateral fibrocavitary forms, which could be explained by the high prevalence of previous treatment for pulmonary TB among patients (occurring in more than 70% of cases), especially among women in the *M. avium* group [29] [30] [31]. This association indicates a nearly five times higher relative risk (4.750 [1.191 - 26.880]) for infection. Unfortunately, in Brazil, the routine use of sputum cultures before starting treatment for pulmonary tuberculosis is not consistently practiced in most cases. This lack of diagnostic precision leads to the administration of inadequate treatment regimens for NTM patients, such as infected by MAC species [8] [9] [32]. The delay in initiating specific treatment for MAC, including fibrocavitary forms, may contribute to the exacerbation of pulmonary deterioration evidenced in imaging studies, consequently leading to a higher prevalence of more severe presentations [17] [32] [33] [34] [35].

Regarding comorbidities, bronchiectasis was the most frequently identified condition (41.1%). In a recent systematic review, respiratory conditions such as bronchiectasis showed a robust association for NTM-PD (bronchiectasis [OR, 21.43; 95% CI, 5.90 - 77.82], similar to those found in the present analysis for a previous history of TB [OR, 12.69; 95% CI, 2.39 - 67.26]) [36].

Commonly used antimycobacterial drugs in treatment include clarithromycin, ethambutol, and rifampicin, which are the most recommended non-resistant regimens. Additionally, the values of MIC in susceptibility tests were high, revealing considerable resistance to rifampicin, ethambutol, moxifloxacin, clarithromycin, and amikacin. However, it was observed that clarithromycin and amikacin presented significantly higher resistance rates among *M. avium*. This finding supports the hypothesis of increased resistance in these isolates, raising additional epidemiological concerns. This is particularly relevant considering that the use of aminoglycosides is strongly advised in the treatment of cavitary and severe forms caused by *M. avium*. Therefore, the resistance demonstrated by these isolates can indeed have negative implications for the clinical progression of patients, as therapeutic responses improved symptoms in only about 50% of cases [11]. Additionally, the precise measurement of NTM susceptibility to antibiotics should include assessments of biofilms and intracellular environments, representing considerable challenges and some of the main difficulties in discovering suitable antibiotic regimens [10].

Another evaluation observed therapeutic success rates of 60.0%, but there was a dropout rate of 16.0%, which can be attributed to the long duration of treatment, multiple drug regimens, and severe adverse effects [32]. Currently, according to updated data from the Brazilian registry, MAC has become the most prevalent species in the North, Central-West, and South regions of Brazil between 2013 and 2019, highlighting the importance of clinical studies with regional perspectives in a country with a vast geographic territory like Brazil. An epidemiological description involving 29 cases in Pará found that a previous history of pulmonary tuberculosis was the most critical risk factor for NTM pulmonary disease, specifically among 52-year-old women. At that time, *M. abscessus* and the *M. simiae* complex were the predominant species in the region [30]. Another study conducted in Rondônia, a state also located in the Amazon region, demonstrated that the most frequently found NTM species were *M. abscessus* and *M. avium* [31]. Therefore, the development of controlled clinical studies is crucial to improve the management and conduct of treatments to achieve more effective clinical outcomes among patients.

The present study acknowledges certain limitations, including a reduced sample size that may limit the generalizability of our findings, incomplete medical records that could hinder a comprehensive analysis of patient histories, and the absence of drug susceptibility testing (DST) for all patients, impacting our ability to fully assess antimicrobial resistance patterns. Nonetheless, these challenges underscore the importance of robust data collection and highlight potential areas for future research, aiming to enhance our understanding of *M. avium* complex pulmonary disease and improve patient outcomes through more informed treatment strategies.

5. Conclusion

The present study provides relevant information on demographic characteristics, clinical manifestations, antibiotic susceptibility profiles, and therapeutic response MAC infections in the State of Pará. Examining the history of treatment for pulmonary tuberculosis, it is relevant to note that more than 70% of the patients had been previously treated for tuberculosis. Some had even undergone more than two treatments before initiating the therapeutic regimen for MAC. Conditions that can significantly influence the approach, bring implications for the management and outcome of NTM treatment. These are valuable insights portraying the epidemiological scenario in the Amazon region during the study period and underscore the need for additional epidemiological surveillance research, especially studies evaluating drug resistance in therapeutic regimens for NTM, particularly by MAC, which notably, showed considerably higher resistance rates to clarithromycin and amikacin antimicrobials.

Funding

The APC was funded by Evandro Chaga Institute (IEC/PA). Yan Corrêa Rodrigues scholarship is funded by PDPG—Pós-Doutorado Estratégico (PDPG-POSDOC), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES/Edital 16/2022).

Data Availability Statement

All relevant data is provided within the manuscript.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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