Research article

Frequency of Nontuberculous Mycobacteria Pulmonary Disease During the COVID-19 Pandemic at Southern Texas

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Background: **Nontuberculous mycobacteria (NTM) pulmonary disease (PD) is a growing global concern. COVID-19 exhibits varying severity, particularly among those with existing lung conditions, making it essential to examine NTM PD prevalence in the context of the pandemic.**

Methods: **Our cross-sectional study investigated NTM PD frequency, causative NTM species, patient demographics, and treatment outcomes by reviewing electronic health records.**

Results: **We found a higher prevalence of NTM PD in patients aged 65 and older with underlying medical conditions. *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* were the most frequently isolated NTM species. Despite increased acid-fast bacillus (AFB) culture testing during the COVID-19 pandemic, NTM PD cases decreased from 2.78% pre-pandemic to 0.78% during the pandemic. Notably, one patient who had both NTM PD and COVID-19 had a much longer recovery time.**

Conclusions: **The insights from our study are valuable for healthcare providers, public health officials, and policymakers, deepening our understanding of NTM infections amid pulmonary diseases, including COVID-19.**

Keywords: Nontuberculous Mycobacteria Pulmonary Disease; COVID-19, frequency, *Mycobacterium avium* complex, *Mycobacterium abscessus*

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Introduction

Nontuberculous mycobacteria (NTM) pulmonary disease (PD) is a chronic lung infection garnering increased attention from public health professionals worldwide. Common clinical manifestations of this infection typically include persistent cough with sputum production, low-grade fever, dyspnea, fatigue, and hemoptysis.[1] NTM species responsible for NTM PD are acid-fast microorganisms that inhabit the environment and are transmitted via contaminated food or water, inhalation, or skin abrasions. Historically, NTM are known to be harmless to human health. However, epidemiological evidence has shown that some NTM species, such as *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus*, can indeed cause pulmonary infection in humans.[1-3]. NTM PD poses heightened challenges for individuals with pre-existing lung diseases or immune-deficiencies. For example, Agizew *et al.*, showed that 228 out of 408 patients with HIV were diagnosed with NTM PD.[4] A seven-year follow-up study in Beijing, China demonstrated that 17.2% of patients diagnosed with NTM PD had chronic obstructive pulmonary disease (COPD), and 24.1% had bronchiectasis.[5] Additionally, an Italian study reported that 47 out of 373 (12.6%) patients diagnosed with bronchiectasis also had NTM PD.[6]

Prior to the COVID-19 pandemic, the global prevalence and incidence of NTM PD were on a noticeable rise. In the United States (US), specifically among patients enrolled in US Medicare Advantage programs, the annual prevalence of NTM PD significantly increased from 19.5 to 43.1 cases per 100,000 individuals between 2008 and 2015.[7] Similarly, in Korea, the prevalence of NTM PD rose from 1.2 (in 2003) to 33.3 (in 2016) cases per 100,000 individuals.[8] Among the cohort of patients afflicted with NTM PD, certain demographic subgroups demonstrated a heightened prevalence when compared to others, specifically females, individuals aged 65 or older, patients with underlying medical conditions, and immunocompromised individuals.[7,9]

COVID-19 has had extensive and multifaceted adverse effects on human health, with a particularly notable effect on individuals with pre-existing structural lung diseases. This infectious disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which inflicts damages on the pulmonary system. As of March 2023, the World Health Organization (WHO) reported nearly 750 million documented COVID-19 cases globally.[10] Studies have elucidated that severe COVID-19 cases entail substantial alterations in B and T cells during the course of hospitalization.[11] The changes induced in the lungs and immune system by the SARS-CoV-2 virus may render COVID-19 patients more susceptible to opportunistic infections like NTM PD, which has been observed in patients with other lung diseases. Given that both COVID-19 and NTM PD lead to pulmonary damage and exhibit overlapping symptoms, suggesting a potential interrelationship, where one condition may serve as a precursor for the other. As evidence, a study conducted in Korea underscores this connection, revealing that individuals with NTM PD exhibited a 2.1% higher incidence of COVID-19 when compared to the general population.[12] This observation, considering the predisposing impact of pulmonary diseases on the host immune system in the context of COVID-19 infection, suggests that the frequency of NTM lung diseases may continue to rise. However, it is noteworthy that, up to this juncture, there has been little evidence to substantiate a direct association between NTM and SARS-CoV-2 infection. This study aimed to compare the frequency of NTM PD in an academic teaching hospital before and during the COVID-19 pandemic.

Material and methods

Study design

In this cross-sectional study, data from the electronic medical record (EMR) of an academic teaching hospital (666 beds, Level 1 Trauma Center in Southeast Texas) were analyzed to investigate changes in NTM PD

prevalence during the COVID-19 pandemic. The study encompassed patients with acid-fast bacilli (AFB) culture orders and resulted in the EPIC Laboratory information system from March 1, 2017, to March 1, 2023. These patients were divided into two groups: the pre-pandemic group (March 1, 2017 - February 29, 2020), and the COVID pandemic group (March 1, 2020 – March 1, 2023). Vulnerable populations such as incarcerated patients, pregnant women, and children under 18, were excluded from this study, as well as patients with AFB cultures positive for tuberculosis (TB) and leprosy. This study was reviewed by our Institutional Review Board (IRB) and was determined to meet the criteria for exemption from review (IRB # 23-0022).

Data collection

Data collected include the following: patient demographics (age, gender, and race), AFB culture results from all respiratory samples (including but not limited to expectorated sputum samples, bronchial washing, bronchoalveolar lavage, or lung biopsy). Diagnosis of pulmonary mycobacterial infection and any concurrent comorbidities was determined through International Classification of Diseases-10 (ICD-10) codes: A31.0 for NTM PD; J42, J44 for COPD; J47 for bronchiectasis; J45 for asthma; B20 for HIV; E84 for cystic fibrosis; and U07.1 for COVID-19 to identify subjects who had received a diagnosis of NTM PD and any concurrent comorbidities.

We also collected information about prescribed antibiotic treatments for diagnosed NTM PD, which was categorized as “treatment success” or “treatment failure”. Treatment success meant clinical improvement, having at least one negative AFB culture following their last positive cultures for the same causative NTM species, and completing the antibiotic therapy. Treatment failure included persistent positive AFB cultures, reinfection with the same NTM species, ongoing treatment, or death.

Data analysis

Descriptive statistics examined demographic variables (age, gender, and race) and medical history. Variables were presented as counts and percentages. We employed Chi-square to test for differences in the rates of NTM PD between pre-COVID and during COVID periods. Positivity rates or frequency of NTM PD were calculated by dividing the number of patients with positive AFB cultures for NTM PD by the total number of patients who had AFB cultures ordered on their respiratory samples. A p-value < 0.05 indicated statistical significance. Microsoft Excel and SPSS were used for data analysis.

Results

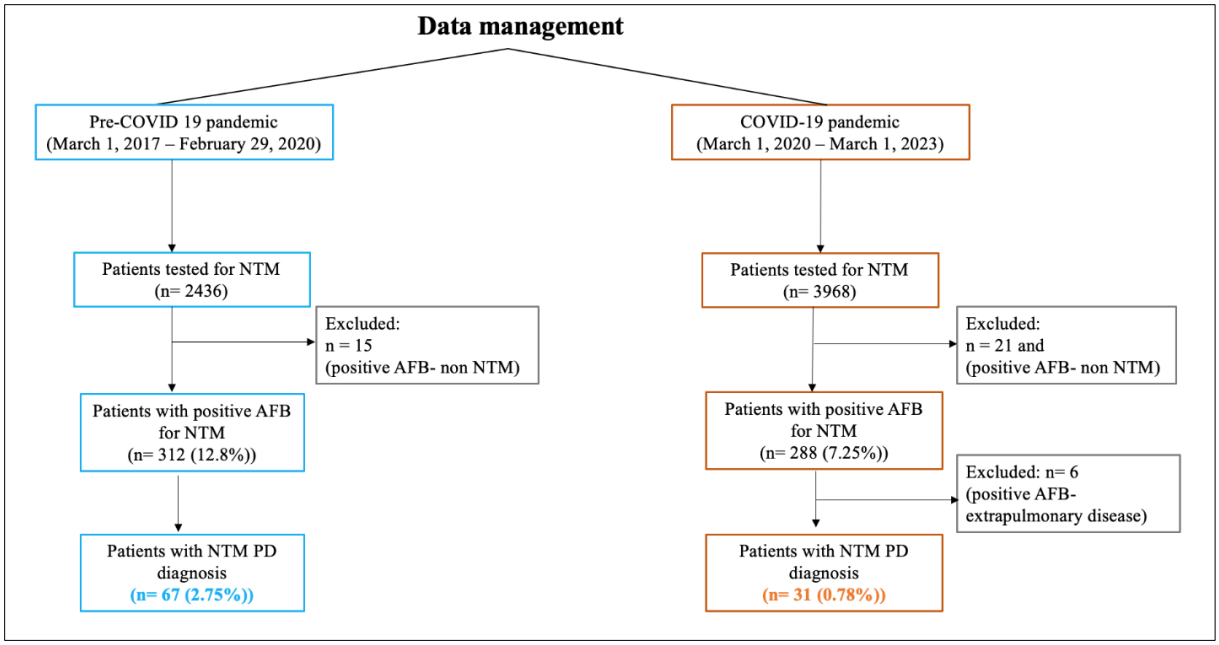
Frequency of NTM PD before and during the COVID-19 pandemic

A total of 6,404 patients had AFB cultures on their respiratory samples during our defined study period. Among these individuals, 2,436 patients fulfilled the inclusion criteria for the pre-COVID-19 group (cohort 1), while 3,968 were classified within the COVID-19 group (cohort 2), as delineated in Figure 1.

Anticipating an increase in NTM cases during the COVID-19 pandemic, we calculated the positivity rate, reflecting the frequency of patients who ultimately received a diagnosis of NTM PD for each cohort. Surprisingly, the positivity rate of NTM PD-diagnosed patients in cohort 1 was higher than in cohort 2, with rates of 2.75% and 0.78%, respectively. This observed difference was found to be statistically significant ($p < 0.05$), highlighting a notable disparity in the frequency of patients with NTM PD between the two cohorts.

Demographic variables and identified NTM organisms in study patients

Table 1 summarized demographic variables for patients with NTM PD, contrasting data from the periods before and during the COVID-19 pandemic. The variables encompass gender,



***Note**. Blue color represents patients in the pre-COVID 19 pandemic groups; Orange color indicate patients in the COVID 19 pandemic groups. NTM = Nontuberculous mycobacteria; PD = pulmonary disease; AFB = acid-fast bacilli. The positivity rate was used to calculate the frequency of NTM PD before and during the pandemic with p < 0.05.*

Figure 1. Classifications of patients who had AFB tested for NTM according to AFB culture result and NTM PD diagnosis.

Table 1. Cohort demographics and characteristics of patients with NTM PD pre-COVID and during COVID pandemic.

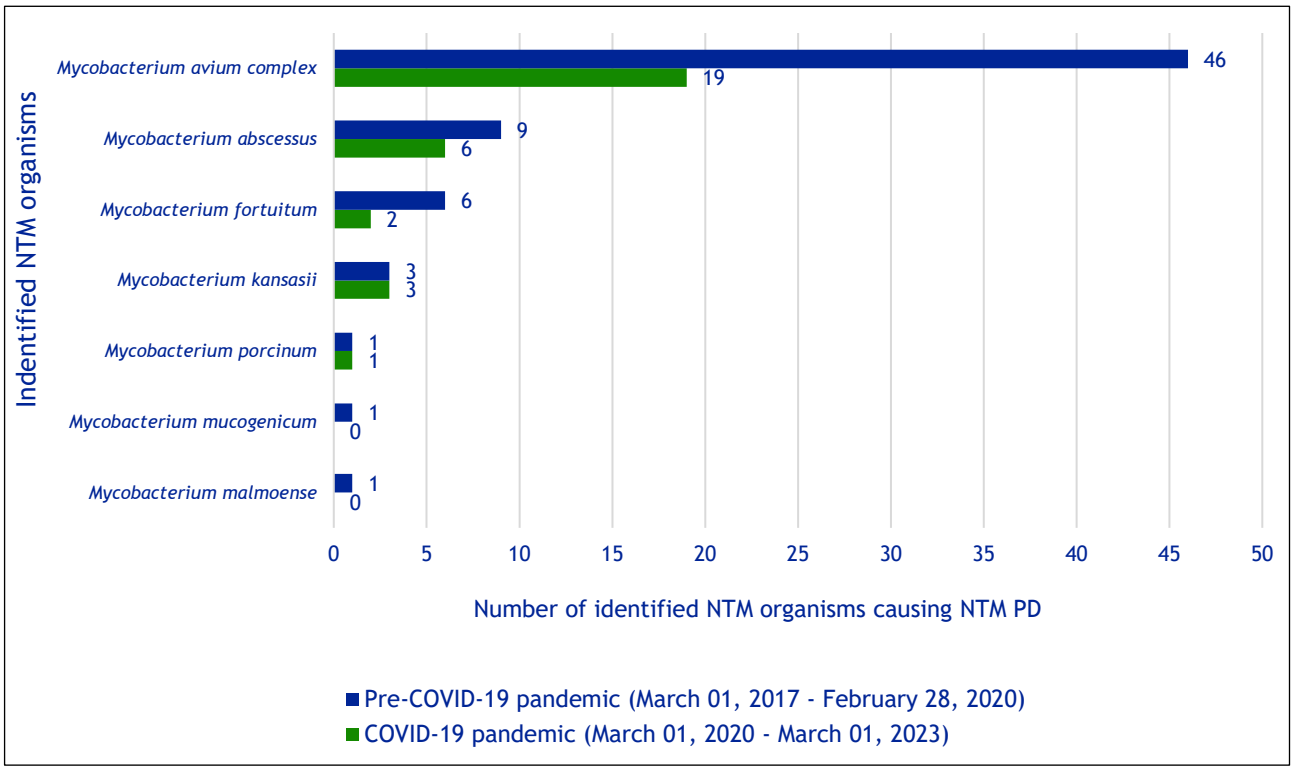
Demographic variables	**NTM PD (pre-pandemic) Cohort 1 n = 67**		**NTM PD (pandemic) Cohort 2 n = 31**		**p-value**
	n	%	n	%	
Age (years)	66 (22-94), 16*		66 (32-96), 11*		p = 0.866
Age (<65 years)	29	43.28	12	38.7	p = 0.966
Age (> 65 years)	38	56.72	19	61.3	p = 0.228
Gender					
Female	34	50.7	16	51.6	p = 0.936
Male	33	49.3	15	48.4	
Race					
Caucasian/White	49	73.1	20	64.5	p = 0.719
Black	9	13.4	4	12.9	
Asian	2	3	2	6.45	
Hispanic	7	10.4	5	16.1	
Medical history					
COPD	30	44.8	9	29	p = 0.134
Bronchiectasis	23	34.3	8	25.8	p = 0.394
Asthma	12	17.9	5	16.1	p = 0.828
HIV	3	4.5	1	3.22	p = 0.766
CF	1	1.5	0	0	p = 0. 382
Antibiotics (initiated)	41	61.2	25	80.6	p = 0.056

**Median (range), interquartile range*

age, race, and comorbidities, and the initiation of antibiotic treatment. No statistically significant differences were observed among patients with NTM PD before and during the COVID-19 pandemic for any of these variables. In terms of patient age, both cohorts displayed the same median age of 66. The racial distribution of NTM PD cases also exhibited no statistical disparities between the two study periods. With comorbidities, patients in both cohorts had at least one underlying medical condition, such as COPD, bronchiectasis, asthma, HIV, and CF. Although there were no statistically significant differences in the frequency of these comorbidities between the two groups, it is noteworthy that COPD and bronchiectasis were the most frequently observed comorbidities in both cohorts. Additionally, regarding initiation of antibiotic treatment, there was no significant difference in the commencement of therapy between the two cohorts.

Identified causative NTM organisms responsible for NTM PD

A comparative analysis of the pathogenic NTM species identified between the pre-COVID-19 and during-COVID-19 groups revealed that MAC was the most frequently isolated species in patients with NTM PD in both cohorts (68.7% & 61.2%, respectively), followed by *M. abscessus* (13.4% & 19.3%, respectively). Additionally, several other NTM species were identified in smaller numbers, as illustrated in Figure 2. The Likelihood ratio test indicated that there was no statistical difference in the causative NTM organisms between the two study cohorts ($p = 0.745$). Further detailed analysis demonstrated that the proportions of MAC and *M. abscessus* did not exhibit substantial differences between the two groups either ($p = 0.538$).



Note. *Each blue and green bar corresponds to identified NTM organisms that cause NTM PD in the pre-COVID-19 and during COVID-19 periods, respectively. The likelihood ratio showed no significant difference in identified NTM organisms in both study periods. Mycobacterium avium complex (MAC) and M. abscessus were the most common isolates. NTM = Nontuberculous mycobacteria; PD = pulmonary disease.*

Figure 2. Causative organisms in patients with NTM PD before and during the COVID-19 pandemic.

Table 2. Treatment outcomes in patients who had NTM PD only and in patients who had NTM PD and COVID-19.

Treatment outcomes	NTM PD only (Pre-pandemic) n = 67	NTM PD only (Pandemic) n = 27	NTM PD and COVID-19 n = 4	p-value[a]
Treatment success, n (%)	14 (20.8)	4 (14.8)	1 (25)	0.87
Duration of treatment (days)[b]	385 (219 – 698)	515.5 (223-714)	967	ND[c]
Treatment failure, n (%)	30 (44.8)	12 (44.4)	1 (25)	0.87
Other[d], n (%)	23 (34.3)	11 (40.7)	2 (50)	0.87

[a]p-value corrected using the Likelihood ratio & Bonferroni post hoc statistics method when the expectation was below 5.
[b]Median (range)
[c]ND = p-value could not be obtained due to the small sample size.
[d]Other: include loss to follow-up, patients experiencing adverse effects, resistant strains, or deceased patients.

NTM PD patients with COVID-19

Among the 31 patients with NTM PD during the COVID-19 pandemic, four of them (12.9%) were identified as having concurrent COVID-19 infections. Many of them were Caucasian females who were older than 65 years old (75%). One patient had NTM PD before contracting SARS-CoV-2, and three patients were diagnosed with COVID-19 after their NTM PD diagnosis. The pathogenic NTM species were MAC (75%) and *M. kansasii* (25%).

Treatment outcomes

To evaluate treatment outcomes in all patients with NTM PD during the study period, we assessed treatment success and treatment failure rates across three categories: (1) patients with NTM PD before the pandemic, (2) patients with NTM PD during the pandemic, and (3) patients with both NTM PD and SARS-CoV-2 coinfections. As seen in table 2, our results demonstrate that the treatment success and failure rates remained consistent between patients with NTM PD only (before and during the pandemic) and those with both NTM PD and COVID-19 infections (p = 0.870).

We also compared the duration of treatment success in these three subgroups to ascertain whether patients who had COVID-19 took longer to recover from NTM PD than patients without COVID-19. Due to the small sample size, p-values could not be obtained. However, we observed that patients with COVID-19 took approximately two to three times longer to recover from NTM PD than those with NTM PD only (Table 2).

Discussion

The present study, which investigated the impact of COVID-19 pandemic on the prevalence of NTM PD, has yielded several important findings. These findings shed light on the complex interactions between respiratory infections, demographic factors, and treatment outcomes.

In this study, a noteworthy and significant decrease in the frequency of NTM PD cases was observed in Galveston, Texas during the first three years of the COVID-19 pandemic. Contrary to previous research that had indicated a global increase in NTM PD prevalence before the COVID-19 pandemic, our study findings did not align with this trend.[7-8,13] Furthermore, even after the onset of the pandemic, Kim *et al.*, reported a continued rise in the prevalence of NTM PD from 11.4 cases/100,000 in 2010 to 56.7 cases/100,000 in 2021.[13] This inconsistency between our findings and the existing literature raises the possibility that the COVID-19 pandemic might have played a role in reducing the number of NTM PD cases. Several factors may contribute to this phenomenon. One plausible explanation is the reluctance of patients to seek medical intervention during the pandemic due to stay-at-home orders and heightened concerns about COVID-19 infection. Patients may have delayed or avoided healthcare facilities for non-COVID-19 related issues, including the diagnosis and

management of NTM PD. Similar trends have been observed in other respiratory diseases during the COVID-19 pandemic. For instance, a Turkish study on pulmonary tuberculosis (TB) infection demonstrated a 22% reduction in the number of patients diagnosed with TB during the first year of the pandemic.[14]

While the frequency of NTM PD cases decreased during the COVID-19 pandemic, our study observed an interesting and somewhat unexpected trend: the number of patients tested for NTM PD during the pandemic was higher than before the pandemic. This intriguing discrepancy raises the possibility that there might have been a change in physician behavior during the pandemic possibly influenced by the similarities in respiratory symptoms between NTM PD and COVID-19. Physicians, in their efforts to diagnose and provide appropriate care, may have ordered AFB tests more frequently during the pandemic to evaluate patients with respiratory symptoms. These tests could have been utilized to either confirm or rule out NTM PD, given the shared respiratory symptomatology of NTM PD and COVID-19.

Previous studies have consistently shown that NTM PD was more commonly observed in certain demographic groups, including females, individuals aged over 65, and immune-compromised adults with pre-existing pulmonary diseases.[5-7,9,13] However, the equal gender distribution in our study, contrary to the typical female predominance, might be explained by COVID-19 indirectly influencing the gender distribution of NTM PD cases.

In our study period, we observed that MAC was the most common isolate among the causative NTM species, in agreement with previous studies.[2-3] Existing evidence suggests that the frequent use of chlorinated, piped water may confer a selective advantage to NTM species in the environment.[15] NTM species have demonstrated more resistance to chlorine, potentially posing a threat to individuals with weak immune systems. Although our study did not directly investigate this phenomenon, it is conceivable that the environmental selective advantage associated with chlorinated water sources could contribute to the predominance of MAC in our study. Besides MAC, *M. abscessus* was the second most common causative pathogen in our investigation, a pattern consistent with prior findings that highlight the prevalence of *M. abscessus* in the Southeastern US, including Texas.[16]

Given the limited sample size within the cohort of patients presenting with both NTM PD and COVID-19, our study lacks the statistical power necessary to definitively establish whether treatment outcomes in this specific subgroup are significantly superior or inferior to those observed in patients with NTM PD alone. The coinfection of SARS-CoV-2 alongside other pathogens poses a significant challenge to healthcare systems. Recent studies have highlighted the potential for SARS-CoV-2 to exacerbate infections with other viruses like influenza A and respiratory syncytial virus (RSV), and bacterial coinfections such as tuberculosis, *Candida albicans*, and *Legionella pneumophila*.[14,17-19] A case study in Florida reported the unfortunate death of a patient with severe pneumonia resulting from an exacerbated complication of both COVID-19 and *M. abscessus* infection after 12 days of hospitalization.[20] However, the influence of COVID-19 on the treatment outcomes of patients with NTM PD remains poorly understood, with limited evidence available. In our study, only one patient with a confirmed COVID-19 diagnosis exhibited treatment success after a prolonged 967 days of antibiotic therapy, a duration two or three times longer than that of patients with NTM PD alone. This observation leads us to propose a potential link between extended treatment duration in patients with COVID-19 coinfection and the dysfunction of lymphocytes. Shuwa *et al.,* have demonstrated decreased lymphocyte activities in patients with COVID-19, which may create a more permissive environment for secondary infections.[11] Building on this concept, Bak *et al.,* have also noted reduced T17 lymphocyte function in patients with both MAC infection

and comorbid asthma.[21] While our data is limited, these preliminary findings underscore the importance of ongoing research to monitor treatment outcomes in patients with NTM PD, particularly in the context of concurrent COVID-19 infection.

There are several limitations of this study to be acknowledged here. First, lack of radiographic information which is recommended by the American Thoracic Society/ Infectious Diseases Society of America (ATS/ IDSA).[22] The absence of this information may limit a comprehensive understanding of disease presentation. Second, the data were sourced exclusively from a single hospital, restricting the generalizability of our findings to all patients with NTM PD in the US. Regional and institutional differences may influence the characteristics and outcomes of NTM PD cases. Third, despite covering the first three years of the pandemic, the sample size remained relatively small. This limitation is due to the study's duration, which may not capture the full spectrum of patients with NTM PD. Fourth, patients categorized as "NTM PD only" during the COVID-19 period might have also had concurrent COVID-19, but their COVID-19 status was not consistently documented in their medical records. This lack of information may affect the interpretation of the results. Therefore, larger, and more diverse datasets to validate and expand upon the findings of this study is needed. A more comprehensive dataset would provide a more robust foundation for understanding the interplay between NTM PD and COVID-19.

Conclusion

In conclusion, this study highlights the reduced number of NTM PD cases during the COVID-19 pandemic, contrary to previous trends of increasing prevalence. This reduction may be associated with changes in healthcare-seeking behavior, heightened COVID-19 concerns, or the similarity of respiratory symptoms between NTM PD and COVID-19. NTM PD predominantly affected older patients with underlying conditions, and MAC and *M. abcessuss* were the primary causative NTM species. Treatment outcomes revealed persistent challenges, with high treatment failure rates, potentially attributed to antibiotic resistance and relapse. This study emphasizes the need for further research on NTM infections in the context of pandemics like COVID-19 and underscores the importance of tailored management strategies for NTM PD patients.

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Ethical Approval

This study was reviewed by the IRB and considered it to meet the criteria for exemption from review (IRB # 23-0022).

Conflict of interest statements

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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