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Profile of Nontuberculous Mycobacteria and *Mycobacterium Tuberculosis* Detected in the Sputum of Pulmonary Tuberculosis Retreatment Patients at Dr. Soetomo General Hospital

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Abstract

Tuberculosis (TB) remains one of the leading infectious diseases worldwide. Despite global efforts to control TB, it remains a major public health issue, affecting 10.6 million people annually in 2021, with significant morbidity and mortality, particularly in resource-limited settings. Effective treatment of TB requires strict adherence to long-term medication, but challenges such as treatment failure, relapse, and loss to follow-up complicate outcomes. This is especially concerning for patients with comorbidities such as diabetes, HIV, or hypertension, which not only increase the risk of TB but also hinder its treatment and elevate the likelihood of nontuberculous mycobacteria (NTM) infections. This study aimed to analyze 326 pulmonary TB retreatment cases at Dr. Soetomo General Academic Hospital from October 2023 to April 2024. The retrospective design identified that 323 cases involved MTB and 3 involved NTM. The findings show that loss to follow-up was the most common reason for retreatment, particularly among males and older adults. Comorbidities were found to exacerbate treatment challenges, with some retreatment cases lasting up to 24 months. The study concludes that loss to follow-up remains a major risk factor for TB retreatment, particularly in MTB cases, and highlights the importance of managing comorbidities to improve treatment outcomes.

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INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), remains one of the most critical public health issues worldwide.[1] In 2021, the World Health Organization (WHO) reported 10.6 million TB cases globally, with 969,000 cases occurring in Indonesia, marking an increase from 2020's estimate of 10 million cases. TB treatment requires strict adherence to a long-term regimen of antituberculosis drugs, and any interruptions in treatment can lead to complications such as treatment failure, relapse, or loss to follow-up.[2] When these outcomes occur, patients must undergo retreatment to achieve complete bacterial eradication. In 2021, the treatment success rate (TSR) in East Java was 89.13%, indicating that 10.87% of cases still required retreatment.[3]

Comorbid conditions such as HIV, malignancies, diabetes, and other chronic diseases further complicate TB treatment by weakening the immune system. HIV-1 targets CD4+ T cells and macrophages, while *Mycobacterium tuberculosis* mainly impacts macrophages, which rely on CD4+ T cells to help eliminate intracellular pathogens. Consequently, the decline in CD4+ T cells due to HIV-1 infection is believed to significantly contribute to the heightened risk of tuberculosis in individuals infected with HIV-1[4]. Associated mechanisms of TB and malignancy lead to a persistent and intense inflammatory response contributes to the development and advancement of cancer through various mechanisms. Multiple theories connect DNA damage in lung epithelial cells to free radical-induced harm and the sustenance of a cytokine network that is both pro-inflammatory and immunosuppressive.[5] Several biological factors can weaken the immune system and increase the risk of tuberculosis in people with diabetes (DM). High insulin levels are linked to reduced T helper 1 (Th1) immunity, lowering the T helper 1 to T helper 2 cell ratio and the interferon-gamma (IFN-γ) to interleukin-4 (IL-4) ratio. People with diabetes also have lower IFN-γ levels, which are negatively correlated with HbA1c, a blood sugar measure. Additionally, neutrophils in diabetics show decreased movement and bacteria-killing ability.[6] Studies have shown that TB patients with comorbid diabetes mellitus are ten times more likely to have poor TB treatment outcomes than people without diabetes mellitus due to diminished treatment responses. [7,8] Moreover, patients with a history of comorbidities such as chronic obstructive pulmonary disease (COPD), bronchiectasis, tumors, or immunosuppressant use are at a heightened risk of developing nontuberculous mycobacteria (NTM) infections.[9]

Nontuberculous mycobacteria (NTM) are becoming recognized as a crucial opportunistic pathogen for humans. NTM mostly affect the lungs and may lead to progressive disease in susceptible hosts, mainly in people with chronic lung diseases, including COPD, bronchiectasis, cystic fibrosis, and a history of tuberculosis.[10] The most prevalent nontuberculous mycobacterial species includes slow-growing such as *Mycobacterium avium* complex and *Mycobacterium kansasii*, as well as fast-growing such as *Mycobacterium abscessus* and *Mycobacterium chelonae*. [11]

Despite advances in TB treatment, there remains a significant gap in understanding the relationship between comorbidities, NTM infections, and treatment outcomes in TB retreatment cases. Current research has not fully explored the profile of NTM and MTB in TB retreatment patients, particularly in

Indonesia. Addressing this gap is crucial to improving treatment success rates and reducing retreatment cases.

This research provides valuable insights into the challenges faced by patients, particularly those with comorbidities like diabetes and HIV. Analyzing 326 cases revealed that loss to follow-up was the primary reason for retreatment, especially among older males. The study underscores the significant impact of comorbidities on treatment outcomes, demonstrating that effective management of these conditions is crucial for improving recovery rates in TB patients. This research highlights the need for targeted interventions to enhance treatment adherence and ultimately reduce TB-related complications.

MATERIALS AND METHODS

Population and Sample

This study utilizes a comprehensive dataset derived from secondary data, specifically the medical records of pulmonary tuberculosis (TB) retreatment patients at Dr. Soetomo General Academic Hospital, covering the period from January 2020 to March 2023. The dataset includes detailed records for patients aged 18 years and older who underwent sputum examination and met specific inclusion criteria. This approach ensures a robust and complete dataset for analysis. Cases with incomplete data were excluded to enhance the reliability and validity of the findings.

Methods

A descriptive retrospective design was employed to investigate the profiles of nontuberculous mycobacteria (NTM) and *Mycobacterium tuberculosis* (MTB) identified in the sputum samples of retreatment TB patients. Data were systematically organized and analyzed using Microsoft Excel (version 2406), facilitating a detailed breakdown of key variables, including demographic information, sputum culture results, and treatment outcomes. Statistical analyses were performed to identify trends and patterns within the patient population, allowing for a comprehensive understanding of the prevalence of NTM and MTB in the studied cohort.

RESULTS AND DISCUSSION

Table 1 shows that 28.4% of pulmonary TB cases required retreatment, largely due to relapse, treatment failure, or loss to follow-up, consistent with global studies.[12] Various factors contribute, including limited healthcare access, socioeconomic challenges, non-adherence to treatment, comorbidities like HIV or diabetes, and exogenous reinfections.[13]

The majority (99.07%) of retreated TB patients were infected by MTB, with only 0.93% by NTM, similar to findings by Limo (2016) in Kenya. NTM infections mimic MTB symptoms, such as chronic cough, fever, and weight loss, complicating diagnosis, especially in TB-endemic regions.[14] Additionally, NTM's slow growth makes diagnosis challenging.[15]

Drug resistance was found in 42.11% of the patients, presenting a significant challenge, as noted by Adé et al. (2016). The occurrence of drug resistance is often due to biological and clinical interactions, including poor compliance, and molecular mechanisms.[16,17]

Of those with NTM, 100% were drug sensitive (DS TB) patients, with previous TB history increasing susceptibility.[18] Co-infection with NTM and MTB poses a greater risk, particularly in those with pulmonary cavitation, which may act as a reservoir for NTM.[19]

Table 1. Proportion of new and retreated pulmonary TB patients, the mycobacterium, and the drug classification

	Amount	Percentage
Proportion		
TB	822	71.6
TB retreatment	326	28.4
Mycobacterium		
MTB	323	99.07
NTM	3	0.93
Drug sensitive		
MTB	187	57.89
NTM	3	100
Drug resistance		
MTB	136	42.11
NTM	0	0

The analysis of retreated pulmonary TB patients based on Table 2 reveals that the majority of cases occurred in adults aged 19-59 years, with 82.02% of MTB infections and 66.67% of NTM infections found in this age group. These findings align with prior research indicating that TB is most prevalent in individuals of productive age.[20,21] High mobility and socioeconomic factors contribute to the spread and severity of the disease, increasing both morbidity and mortality rates in this demographic.[22]

In contrast, adolescents (under 18 years old) represented only a small proportion of cases, with 0.62% for MTB and 33.33% for NTM. Risk factors like diabetes, smoking, and poor living conditions exacerbate the susceptibility of this age group to TB.[18] Meanwhile, elderly patients (over 60 years old) accounted for 17.67% of MTB infections, with no NTM cases. Elderly individuals, due to weakened immune systems and comorbidities, are particularly vulnerable to TB, leading to higher infection rates.[23]

Regarding gender, men represented 59.4% of MTB cases and 66% of NTM cases. This data are consistent with global trends, where TB and NTM infections are more prevalent in males.[24] Alcohol abuse is much higher in men than women. Furthermore, smoking is the most significant risk factor for COPD and lung cancer and is related to pulmonary TB. Overall, men smoke more than women. As a result, alcohol abuse and smoking are greater contributors to the TB disease burden in men.[25,26]

Table 2. Retreated pulmonary TB patients by age and gender

	Amount	Percentage
Age (MTB)		
Teenager (18 years)	2	0.62
Adult (19-59 years)	264	82.02
Elderly (60+ years)	57	17.67
Age (NTM)		
Teenager (18 years)	1	33.33
Adult (19-59 years)	2	66.67
Elderly (60+ years)	0	0
Gender (MTB)		
Male	192	59.4
Female	131	40.6
Gender (NTM)		
Male	2	66
Female	1	34

The data in Table 3 highlight common comorbidities in pulmonary TB patients. Diabetes mellitus affected 18.2% of MTB patients, which impairs immune function, leading to higher TB retreatment rates. This is consistent with findings from Siddiqui et al. (2016) and Tan et al. (2021), emphasizing how hyperglycemia disrupts immune responses and facilitates TB progression.[27]

Additionally, HIV/AIDS was present in 8.9% of MTB cases, a well-known risk factor due to its detrimental effect on T-cells and macrophages. Research by Mahtab and Coetzee (2017) and Tan et al. (2021) confirms that co-infection accelerates disease progression, making TB harder to control.[28] In HIV-1

infection, it targets CD4+ T cells and macrophages. Mycobacterium tuberculosis primarily impacts macrophages, which depend on CD4+ T cells to help eliminate intracellular pathogens. As a result, the decrease in CD4+ T cells due to HIV-1 infection is believed to significantly contribute to the increased risk of tuberculosis in HIV-1-infected individuals.[4] Hypertension was less common but still significant, as immune response disruptions can lead to pulmonary hypertension, supported by findings from Huamán et al. (2015) and Bhattacharyya et al. (2016). It is hypothesized that tuberculosis can lead to hypertension by triggering immune responses that impair endothelial function, increasing the risk of cardiovascular disease (CVD) and hypertension. TB may cause damage to lung tissue, affecting vascular structures and leading to conditions like vasculitis and endarteritis, which can reduce the cross-sectional area of pulmonary blood vessels and result in pulmonary hypertension. Additionally, if TB infects the kidneys, it can damage renal tissue, decrease kidney function, and impair blood pressure regulation, potentially causing hypertension.[29]

For NTM patients, comorbidities like hepatitis B and pituitary gland tumors were reported in 33% of cases. Studies by Khan et al. (2021) highlight the risks of drug-induced hepatotoxicity in co-infected patients. Tumors, meanwhile, worsen TB reactivation due to immune system suppression.[30] A persistent and intense inflammatory response contributes to the onset and advancement of cancer through various mechanisms. Multiple theories connect DNA damage in lung epithelial cells to free radical-induced harm and the establishment of a cytokine network that is both pro-inflammatory and immunosuppressive.[5] Lastly, the relationship between tumors and TB highlights a bi-directional link where both diseases facilitate each other's progression.[31]

Table 3. Comorbidities of pulmonary TB patients on retreatment

	Amount	Percentage
Comorbidities (MTB)		
Diabetes Mellitus	59	18.2
HIV	29	8.9
Hypertension	3	0.92
Comorbidities (NTM)		
Hepatitis B	1	33.33
Tumor	1	33.33

Based on Table 4, the majority of pulmonary TB patients on retreatment due to MTB faced loss to follow-up, accounting for 49.5%, followed by 37.5% experiencing treatment failure and 13% relapse. For patients with pulmonary TB caused by NTM, 60% encountered treatment failure, and 40% faced loss to follow-up, with no recorded relapses.

These findings align with research by Lin et al. (2021), who reported 15.9% loss to follow-up and 0.3% treatment failure. Additionally, research by Dedefo et al. (2019) in Ethiopia found 72.6% relapse, 19.6% treatment failure, and 7.8% loss to follow-up cases.

Table 4. TB treatment status of the patient

	Amount	Percentage
TB Status (MTB)		
Treatment failure	159	37.5
Relapse	54	13
Loss to follow up	207	49.5
TB Status (NTM)		
Treatment failure	3	60
Relapse	0	0
Loss to follow up	2	40

Loss to follow-up in tuberculosis cases can result from factors such as limited healthcare access, socioeconomic status, lack of family support, and non-compliance with treatment.[10] Risk factors for treatment failure and relapse include HIV infection, diabetes, malnutrition, and drug resistance.[32,33]

The data in Table 5 highlight that the longest duration of treatment for pulmonary TB was 24 months. Most drug sensitive (DS TB) patients had retreatment durations of either six months (45.26%) or 12 months (37.36%). For DR-TB (drug-resistant TB), most patients had retreatment durations of 11 months (56.61%) or 20 months (24.26%).

Table 5. Duration of treatment for pulmonary TB patients

	Amount	Percentage
Duration (Drug sensitive TB)		
6 months	86	45.26
7 months	9	4.73
8 months	10	5.26
9 months	1	0.52
11 months	2	1.05
12 months	71	37.36
13 months	4	2.10
15 months	1	0.52
16 months	1	0.52
18 months	2	1.05
20 months	1	0.52
22 months	1	0.52
23 months	1	0.52
Duration (Drug-resistant TB)		
6 months	1	0.73
9 months	5	3.67
10 months	9	6.61
11 months	77	56.61
16 months	1	0.73
18 months	8	5.88
20 months	33	24.26
21 months	1	0.73
24 months	1	0.73

Treatment duration varies due to the need for adjustments based on how patients respond to therapy. Soeroto et al. (2022) found that 43.08% of DR-TB patients required shorter treatments (9-11 months). But, the next research found 91.62% of patients with long-standing DR-TB needed longer treatment due to complications like culture conversion time or comorbidities such as malnutrition, HIV, and CKD. These factors significantly reduce the treatment success rate.[34]

For NTM infections caused by Mycobacterium avium complex, treatment typically includes three drugs—macrolides, ethambutol, and rifampicin—and must continue for 12 months after culture conversion.[35] These findings underline the importance of tailoring TB treatment based on specific patient factors to optimize recovery outcomes.

STRENGTH AND LIMITATION

The strength of this study lies in its focus on retreatment patients affected by *Mycobacterium tuberculosis* and nontuberculous mycobacteria, providing valuable insights into both types of infections. However, the research was limited by the inability to determine the specific NTM species, types of drug resistance, and the total number of patient fatalities.

CONCLUSIONS

The primary risk factor for retreated pulmonary tuberculosis, particularly in patients infected with MTB, is a high rate of loss to follow-up. Additionally, comorbid conditions exacerbate the outcomes, further complicating treatment success.

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ETHICAL CLEARANCE

The research protocol and use of medical record data was approved by Dr. Soetomo Surabaya General Hospital ethics committee (Ref. No.: 1459/LOE/301.4.2/IX/2023).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in relation to this study.

AUTHOR CONTRIBUTION

All authors were actively involved in the study design, drafting, and approval for publication.

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