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Original Article

Nontuberculous mycobacterial infection after lung transplantation: A single-center experience in South Korea

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Abstract *Purpose:* Nontuberculous mycobacteria (NTM) infection is an important issue after lung transplantation. However, a large-scale epidemiological study on this issue in Korea is lacking. We aimed to evaluate the epidemiology of NTM infection after lung transplant surgery in Korea.
Methods: Between October 2012 and December 2018, we retrospectively evaluated lung transplant recipients in a referral hospital in South Korea. A total of 215 recipients were enrolled. The median age at transplantation was 56 years (range, 17—75), and 62% were men. Bronchoscopy was performed according to the surveillance protocol and clinical indications. A diagnosis of NTM infection was defined as a positive NTM culture from a bronchial washing, bronchoalveolar lavage sample, or two separate sputum samples. We determined NTM pulmonary disease (NTM-PD) according to the American Thoracic Society/Infectious Disease Society of America 2007 guidelines. The Kaplan—Meier method and log-rank test were used for conditional survival analysis in patients with follow-up of ≥12 months.
Results: Fourteen patients (6.5%) were diagnosed with NTM infection at a median of 11.8

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months (range, 0.3–51.4) after transplantation. Nine patients (4.2%) were diagnosed with NTM-PD, and the incidence rate was 1980/100,000 person-years. *Mycobacterium abscessus* was the most common species causing NTM-PD (66%), followed by *M. avium* complex (33%). The presence of NTM infection did not influence all-cause mortality among those who underwent follow-up for ≥12 months ($N = 133$, log-rank $P = 0.816$).
Conclusion: The incidence of NTM-PD was considerably high among lung-transplant recipients. *M. abscessus* was the most common causative species of NTM-PD after lung transplantation.

Introduction

Lung transplantation is an effective treatment modality for chronic respiratory failure.[1] In recent years, more than 4000 patients annually receive lung transplants (LTXs) worldwide.[2] Between 1-month and 1-year post-surgery, infection is the leading cause of death for LTX recipients; it accounts for approximately 35% of deaths within the first year after lung transplantation.[2] Despite recent improvements in surgical techniques and postoperative management, there is still a high risk of morbidity and mortality, mainly due to the immunosuppression that is associated with LTX surgery.[3]

Nontuberculous mycobacteria (NTM) are environmental organisms commonly found in nature, households, and hospitals.[4] Human tissues and bodily fluids are often infected by NTM, resulting in pulmonary and extrapulmonary diseases.[5] Factors associated with host vulnerability, such as structural lung disease or an immunosuppressed status, are important risk factors for NTM pulmonary disease (NTM-PD).[6] The incidence and prevalence of NTM-PD continue to increase globally.[7]

Several studies have been published concerning the epidemiology of NTM infection after LTX in western countries[8–16] and Japan.[17] However, the nature of NTM infection after LTX is not fully understood, and data from Korea have not been reported. The geographic distribution of NTM widely differs, primarily due to the environmental nature of these microorganisms.[18] Therefore, we aimed to evaluate the epidemiology of NTM infection after LTX surgery at a tertiary referral hospital in Korea. To the best of our knowledge, this is the first study reporting the epidemiology of NTM lung infection in LTX recipients in Korea.

Methods

Study design and data collection

The Institutional Review Board of Severance Hospital approved the study protocol (4-2020-0009). The committee waived the need to obtain informed consent from the recipients due to the retrospective design of this study.

We retrospectively obtained data on age, sex, body mass index, comorbidities, and NTM-PD treatment regimen from medical records. The last day of follow-up in this study was October 31, 2019. We analyzed the mycobacterial culture records of 215 LTX recipients who underwent surgery between October 2012 and December 2018 at Severance Hospital, a tertiary referral hospital in Seoul, South Korea. In our institution, routine surveillance bronchoscopy is performed on postoperative day 1, as well as in postoperative months 1, 3, 6, 12, and 24. The culture results from the post-transplant pulmonary specimens—including those from sputum, bronchial washing fluid, and bronchoalveolar lavage (BAL)—were included, while the results from extrapulmonary samples were excluded. Cultures of the donor BAL were routinely performed before harvesting.

Immunosuppressive regimen

Immunosuppressive regimens were maintained with tacrolimus, steroids, and mycophenolate mofetil (MMF). All patients received tacrolimus with target blood concentrations between 8 and 10 ng/mL. Prednisolone was initially administered at a dose of 0.25 mg/kg/day, then gradually tapered to 0.15 mg/kg/day. In combination with tacrolimus and steroids, 500 mg MMF was prescribed twice daily, except in cases where the white blood cell count was lower than 3.0×10^9/L.

Microbiological examination

Respiratory specimens were stained according to the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) 2007 guidelines and manual of laboratory tests for tuberculosis.[5,19] Samples were decontaminated with 4% NaOH, homogenized, and centrifuged. Detailed information on specimen processing has been published previously.[20]

A reverse-hybridization line probe assay was used for species identification and was conducted at a supranational reference laboratory, the Korean Institute of Tuberculosis (Cheongju, Korea), until December 2016 and at the Seoul Clinical Laboratories (Yongin, Korea) after January 2017. In this study, *Mycobacterium abscessus* represented the *M. abscessus* subspecies *abscessus*.

All drug susceptibility tests were conducted at the Korean Institute of Tuberculosis using broth microdilution methods as described by the Clinical and Laboratory Standards Institute.[21] Clarithromycin susceptibility was defined as a minimal inhibitory concentration (MIC) ≤8 mcg/mL for the *Mycobacterium avium* complex (MAC). For *M. abscessus*, MIC ≤2 mcg/mL and ≥8 mcg/mL were considered as susceptible and resistant, respectively. Inducible resistance of clarithromycin was assessed with the MIC on both day three and day 14 of culture.

Definitions of NTM infection and treatment response

The diagnosis of NTM infection required one positive culture result from bronchial washing or lavage fluids, or at least two positive results from sputum on different days. The NTM infection group was classified based on the presence of NTM-PD according to the ATS/IDSA 2007 guidelines. Criteria for NTM-PD were defined as combined respiratory symptoms and radiographic correlations on chest computed tomography (CT) that indicated NTM infection.[5] Those who never developed NTM-PD were classified as having NTM colonization.

Sputum culture conversion was defined as three consecutively negative NTM respiratory sample results. No positive culture results with causative species after sputum culture conversion was defined as a microbiologic cure. We defined cure as a combination of microbiological cure and improvement in symptoms.

Radiologic evaluation

The radiologic patterns of NTM-PD were classified according to the chest radiography and CT findings. The nodular bronchiectatic form was defined as bilateral bronchiectasis with multiple nodules and tree-in-bud opacities.[5]

Statistical analysis

The incidence rate of NTM-PD was calculated as the number of patients with NTM-PD divided by the total number of study subjects and follow-up years. The categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test, while the continuous variables were analyzed with the Wilcoxon signed-rank test. We performed conditional survival analysis for those with follow-up of $\geq$12 months, as LTX recipients have high mortality in the early postoperative period.[22,23] The Kaplan–Meier method was used to estimate overall survival. Differences in survival between the two groups were analyzed using the log-rank test. All statistical analyses were conducted using R (v3.6.2), and a two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the study population. Lung transplantation was performed in 215 patients during the study period. The median age of LTX recipients was 56 years (range, 17–75), and 62% were men. The majority of patients received a bilateral LTX, and idiopathic pulmonary fibrosis was the most common indication for surgery.

We observed NTM infection in 14 (6.5%) LTX recipients. The NTM infection group had a lower proportion of hypertension and a longer follow-up duration (Table 1). Nine patients were diagnosed with NTM-PD during a follow-up of 454 person-years; therefore, the cumulative incidence rate of NTM-PD was 1980 per 100,000 person-years. There were no differences in clinical characteristics between the NTM-PD group and the others.

NTM species observed after transplantation

M. abscessus was the most common species in the NTM infection group and the NTM-PD group, followed by MAC (Table 2). In

Table 1 Baseline characteristics of the study population.

	Total (N = 215)	No-NTM (N = 201)	NTM infection (N = 14)	P-value[a]	NTM-PD (N = 9)	P-value[b]
Age at transplantation, years	56 [17–75]	57 [17–75]	49 [24–64]	0.060	47 [26–64]	0.100
Sex, male	134 (62)	124 (62)	10 (71)	0.659	6 (67)	>0.999
Body mass index, kg/m^2	21.0 [10.6–32.9]	21.1 [10.6–32.9]	19.5 [11.6–26.2]	0.090	19.3 [11.6–24.6]	0.233
Bilateral lung transplantation	204 (95)	190 (95)	14 (100)	0.786	9 (100)	>0.999
Reason for transplantation				0.424		0.276
Idiopathic pulmonary fibrosis	143 (67)	135 (67)	8 (57)	0.559	5 (56)	0.724
Lung GVHD	20 (9)	17 (9)	3 (21)	0.129	2 (22)	0.199
Bronchiectasis	18 (8)	17 (9)	1 (7)	>0.999	1 (11)	0.531
Pulmonary hypertension	12 (6)	12 (6)	0 (0)	>0.999	0 (0)	>0.999
Emphysema	5 (2)	4 (2)	1 (7)	0.289	1 (11)	0.194
Others	17 (8)	16 (8)	1 (7)	>0.999	0 (0)	>0.999
Comorbidities						
Hypertension	71 (33)	71 (35)	0 (0)	0.015	0 (0)	0.073
Diabetes mellitus	70 (33)	66 (33)	4 (29)	0.973	3 (33)	>0.999
Chronic kidney disease	23 (11)	23 (11)	0 (0)	0.372	0 (0)	0.610
Liver cirrhosis	2 (1)	2 (1)	0 (0)	>0.999	0 (0)	>0.999
Follow-up duration, months	20.0 [0.2–85.4]	17.8 [0.2–85.4]	32.0 [12.4–61.2]	0.045	31.3 [12.9–61.2]	0.105

[a] P-values for the difference between the No-NTM and NTM infection groups.
[b] P-values for the difference between the NTM-PD group and others.
Note: Data are presented as numbers (percent) or median [range].
Abbreviations: GVHD, graft-versus-host disease; NTM, nontuberculous mycobacterium; NTM-PD, NTM pulmonary disease.

Table 2 NTM species isolated after transplantation.

	NTM infection ($N = 14$)	NTM colonization ($N = 5$)	NTM-PD ($N = 9$)
MAC	6 (43)	3 (60)	3 (33)
Mycobacterium avium	2 (14)	1 (20)	1 (11)
Mycobacterium intracellulare	4 (29)	2 (40)	2 (22)
Mycobacterium abscessus	7 (50)	1 (20)	6 (66)
Mycobacterium chelonae	1 (7)	1 (20)	0 (0)
Time to the first isolation, months	11.8 [0.3–51.4]	10.1 [0.3–31.6]	15.1 [0.9–51.4]

Note: Data are presented as numbers (percent) or median [range].
Abbreviations: MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacterium; NTM-PD, nontuberculous mycobacterial pulmonary disease.

the NTM colonization group, MAC was the most common organism. The time to the first isolation of NTM was similar in both the NTM colonization and NTM-PD groups ($P = 0.518$).

Treatment of patients with NTM-PD

Table 3 shows the spectrum of patients with NTM-PD and the treatment performed. Three and six patients were infected with MAC and *M. abscessus*, respectively. Patient 1 was infected with *M. avium* and treated for co-infection with pulmonary tuberculosis for 6 months. His sputum culture was still positive for *M. avium*, but he remained under observation due to slight respiratory symptoms and minimal radiologic deterioration. Patients 4 and 5 were treated for *M. abscessus* infection after diagnosis. They reached the sputum culture conversion stage within a relatively short duration of treatment but died due to other reasons—Patient 4 owing to bacterial sepsis, and Patient 5 owing to a sudden cardiac arrest. Patients 6, 7, and 8 were cured of *M. abscessus* pulmonary disease. Patient 9 fulfilled the diagnosis criteria of *M. abscessus* pulmonary disease but was observed due to minimal disease severity. His sputum culture spontaneously converted to negative in six months.

Survival outcome

Among patients with follow-up of ≥12 months ($N = 133$), those with NTM infection had survival outcomes similar to

Table 3 Spectrum of NTM pulmonary disease and treatment.

Patient	Age, years	Sex	Reason for LTX	Type of LTX	Time to the first isolation, months	Species	DST for clarithromycin	Radiology
1	52	Male	IPF	Bilateral	15.1	*M. avium*	Susceptible	NB without cavity
2	47	Female	IPF	Bilateral	33.3	*M. intracellulare*	Susceptible	NB without cavity
3	60	Male	IPAH	Bilateral	51.4	*M. intracellulare*	Susceptible	NB without cavity
4	26	Male	BO	Bilateral	4.3	*M. abscessus*	Resistant	Lobar consolidation
5	61	Male	COPD	Bilateral	22.2	*M. abscessus*	IR	NB without cavity
6	36	Male	IPF	Bilateral	21.2	*M. abscessus*	Susceptible	NB without cavity
7	31	Female	BO	Bilateral	1.3	*M. abscessus*	Contaminated	NB without cavity
8	39	Female	IPF	Bilateral	9.2	*M. abscessus*	IR	NB without cavity
9	64	Male	IPF	Bilateral	0.9	*M. abscessus*	Susceptible	NB without cavity

Patient	Treatment regimen	Treatment duration, months	Culture conversion	Treatment result	Status	Follow-up duration after LTX, months
1	A, INH, Rfb, EMB (for co-infected M.tb)	6.2		Observation	Alive	32.8
2	A, EMB, Mfx	9.5	−	Ongoing	Alive	49.2
3	A, EMB, Cfz, Amk N	9.0	−	Ongoing	Alive	61.2
4	A, Amk, Imp, Mfx	4.7	+	Culture conversion	Dead	12.9
5	A, Amk, Imp	6.9	+	Microbiologic cure	Dead	29.7
6	C, Amk, Cefoxitin	13.5	+	Cure	Alive	41.6
7	A, Amk, Cefoxitin	24.4	+	Cure	Alive	32.8
8	A, Amk, Imp, Cfz	11.3	+	Cure	Alive	29.7
9	Observation	−		Observation	Alive	13.5

Abbreviations: A, azithromycin; Amk, amikacin; Amk N, amikacin nebulizer; BO, bronchiolitis obliterans; C, clarithromycin; Cfz, clofazimine; COPD, chronic obstructive pulmonary disease; DST, drug susceptibility test; EMB, ethambutol; Imp, imipenem; INH, isoniazid; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; IR, inducible resistance; LTX, lung transplant; Mfx, moxifloxacin; M.tb, *M. tuberculosis*; NB, nodular bronchiectatic form; NTM, nontuberculous mycobacteria; Rfb, rifabutin.

patients without NTM infection (log-rank $P = 0.816$, Fig. 1a). There was no difference in all-cause mortality between the NTM-PD and NTM colonization groups (log-rank $P = 0.350$, Fig. 1b).

Discussion

This study analyzed the epidemiology of NTM pulmonary infection after lung transplantation in a tertiary referral hospital in South Korea. On measuring the overall prevalence of NTM infection, the cumulative incidence rate of NTM-PD, and the time to the first isolation of NTM in LTX recipients, this study found that *M. abscessus* was the most common causative pathogen for NTM-PD after LTX in our institution.

Among solid organ transplant (SOT) recipients, patients with thoracic transplants have the highest rate of NTM infection.[24] The prevalence and incidence of NTM infection in LTX recipients vary among studies, the majority of which are based on single-center experience. According to the literature, the prevalence rate of NTM infection is 0.46–2.3% among LTX recipients.[25] For active pulmonary tuberculosis, the prevalence rate among SOT recipients was reported to be 1.2–6.4% in developed countries and up to 12% in highly endemic countries.[26] Yoo et al. investigated the incidence rate of both pulmonary and extrapulmonary diseases caused by *Mycobacterium tuberculosis* and NTM in recipients of liver, kidney, heart, and hematopoietic stem cell transplants in Korea.[27] The incidence rate (per 100,000 person-years) of tuberculosis was 257.4 (95% CI, 215.1–305.7), and that of NTM infection was 42.7 (95% CI, 26.8–64.7).

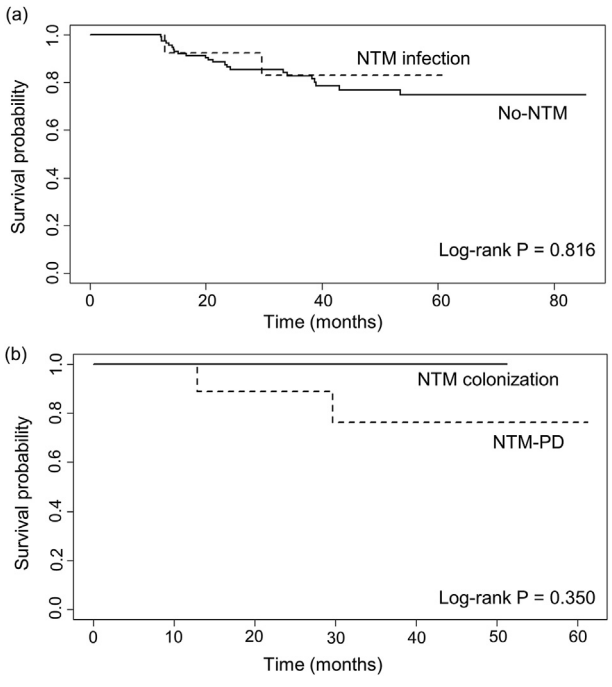

Figure 1. Kaplan–Meier survival curves. Survival curves of (a) NTM infection and no-NTM groups and (b) NTM-PD and NTM colonization groups, among those with follow-up of ≥12 months. Abbreviations: NTM, nontuberculous mycobacteria; NTM-PD, NTM pulmonary disease.

In our institution, the overall prevalence rate of NTM infection (6.5%) was higher than that reported in other studies, and the incidence rate of NTM-PD was 1980 cases per 100,000 person-years among LTX recipients. Several unique factors may have contributed to the high rate of NTM infection after lung transplantation: constant exposure to the external environment, a damaged natural defense system, including cough reflex and lymphatic drainage, and a high level of immunosuppression.[28]

The timing of NTM infection after lung transplantation varies from early to very late. Huang et al.[9] reported the median time of initial NTM isolation to be 97 days (interquartile range, 8–371 days), compared to 16 months (range, 0.5–132 months) reported by Hamad et al.[16] In our study, it was 10.1 months (range, 0.3–31.6 months) in the NTM colonization group and 15.1 months (range, 0.9–51.4 months) in the NTM-PD group. Most studies, including ours, were conducted with a small number of patients; therefore, future integrated analysis with multi-institutional data is needed to clarify this range.

There are conflicting reports regarding the impact of pulmonary NTM infection on patient survival. Huang et al.[9] stated that NTM infection was associated with an increased risk of mortality in LTX recipients. Conversely, George et al.[12] found no association between NTM infection and death. We performed a conditional survival analysis for those with follow-up of ≥12 months after LTX to adjust for the chance of acquiring an NTM infection and for high mortality during the early postoperative period in LTX recipients. In our study, NTM infection did not affect the all-cause mortality in LTX recipients. We expect the results of this study to contribute to our knowledge of the impact of NTM infection on survival.

In Korea, MAC is the most common pathogen causing NTM-PD in the general population, accounting for 45–76%, followed by *M. abscessus* complex (9–42%).[4] However, we identified *M. abscessus* in two-thirds of the NTM-PD patients in our study. One possibility for this unusually high percentage is the in-hospital transmission between recipients; they usually shared the waiting area of the outpatient department and were admitted to the same specialized clinic. However, we could not find chances of spatial or temporal relationships in a review of medical records. Whole-genome sequencing may help identify the possibility of person-to-person transmission; however, we could not perform this sequencing due to the retrospective nature of this study. Another possibility is the use of macrolides for the treatment of bronchiolitis obliterans syndrome. Bronchiolitis obliterans syndrome is a common complication in LTX recipients, for which azithromycin has been widely used.[29] In our study, seven out of nine patients with NTM-PD had been taking azithromycin before the first isolation of NTM. Since a macrolide-based regimen is the standard treatment for MAC infection, the use of macrolides could have caused the difference in the causative species.[5] Data from multi-center studies in Korea will be needed to confirm the difference in species composition between LTX recipients and the general population.

In a few studies, pre-transplant colonization was associated with an increased risk of developing post-transplant NTM infection.[9,11] In this study, two patients with post-transplant NTM-PD (Patients 5 and 7, Table 3) had positive results for a pre-transplant sputum mycobacterial culture.

Patient 5 had a positive sputum culture of *Mycobacterium fortuitum*, and Patient 7 had positive sputum cultures of *M. avium* and *Mycobacterium intracellulare*. Both patients had post-transplant *M. abscessus* pulmonary disease; therefore, we could not find a relationship between pre- and post-transplant NTM species. Besides, the culture results of the donor BAL showed a poor relationship with the post-transplant causative species of NTM-PD. Only one patient (Patient 4, Table 3) was positive for *M. abscessus* from donor BAL, which was the same causative species as that in post-transplant NTM-PD. All others had negative results for donor BAL fluid.

Treatment of *M. abscessus* infection can be challenging for respiratory and infectious disease physicians working in the area of lung transplantation. *M. abscessus* is naturally resistant to many available antimicrobial agents, and adverse drug reactions are relatively common.[30,31] The macrolide-containing regimen showed a poor sputum culture conversion rate of 35% (95% CI, 24—46%) in treatment-naïve *M. abscessus* lung disease.[32] In this study, a macrolide-containing regimen was prescribed to patients with *M. abscessus* pulmonary disease. All patients reached the sputum culture conversion stage, and three were cured of NTM-PD. We believe that routine screening resulted in the early and timely diagnosis, which may have contributed to the favorable treatment outcome. Moreover, a relatively high proportion of macrolide-susceptible species might have affected the results.[33]

There were a few limitations to this study. First, the study had a retrospective design, and we could only assume the correlation between the disease and clinical characteristics. Second, we analyzed the data from a single center. Although LTX is performed only in a few centers in Korea, the clinicodemographic characteristics of the patients visiting our hospital may have influenced the result. Third, the follow-up duration was relatively short. Therefore, we could not evaluate the long-term epidemiologic data or relapse of NTM-PD.

In conclusion, the incidence of NTM infection was considerably high among LTX recipients in a tertiary referral hospital in Korea. The incidence rate of NTM-PD was higher in LTX recipients than that in recipients of other organs. We believe that this study will contribute to our comprehension of the true nature of NTM-related infections in LTX recipients, but further research and more multicenter studies are needed.

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Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

None.

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