ORIGINAL ARTICLE

# Incidence, characteristics, and treatment outcomes of mycobacterial diseases in transplant recipients

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## SUMMARY

The incidence, clinical characteristics, and treatment outcomes of tuberculosis (TB) and nontuberculous mycobacterial (NTM) disease developed after transplantation (TPL) in transplant recipients were investigated retrospectively. Between 1996 and 2013, 7342 solid-organ transplantation and 1266 hematopoietic stem cell transplantation were performed at a tertiary referral center in South Korea. Among them, TB and NTM disease developed in 130 and 22 patients, respectively. The overall incidence of TB was 257.4 cases/100 000 patient-years (95% confidence interval [CI], 215.1–305.7) and that of NTM disease was 42.7 cases/100 000 patient-years (95% CI, 26.8–64.7). The median interval from organ TPL to the development of mycobacterial disease was 8.5 months (95% CI, 6.3–11.4) in recipients with TB patients and 24.2 months (95% CI, 13.5–55.7) in those with NTM, respectively. Among NTM patients, *Mycobacterium avium–intracellulare* complex was the most common causative organism, and nodular bronchiectatic type (77.8%) was the most frequent radiologic feature. Favorable treatment outcome was achieved in 83.7% (95% CI, 76.4–89.1) and 68.8% (95% CI, 44.4–85.8) of TB and NTM patients, respectively ($P = 0.166$). In conclusion, the overall incidence of TB was higher than that of NTM disease in transplant recipients and treatment outcomes were favorable in both drug-susceptible TB and NTM patients.

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**Key words**
incidence, nontuberculous mycobacteria, transplantation, treatment outcomes, tuberculosis

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## Introduction

Transplantation (TPL) is a therapeutic option for end-stage organ disease. After TPL, recipients receive immunosuppressive agents to prevent rejection, which results in impairment of their immune status and thus an increased risk for infectious complications. Traditionally, tuberculosis (TB) is known to be associated with poor clinical outcomes in transplant recipients [1–4]. In addition, nontuberculous mycobacteria (NTM), ubiquitously found in soil or water, can cause various types of diseases in humans [5]. The incidence of NTM disease has been increasing worldwide including South Korea [6–10]. Nontuberculous mycobacteria have also been reported to cause diseases involving the lung, skin, bone and joint, and other organs in several organ transplant recipients [11–13]. Although some studies reported the clinical characteristics and outcomes of TB or NTM diseases in transplant recipients [4,12–17], direct comparison of clinical parameters between TB and NTM disease


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in transplant recipients has been rarely shown, especially in a TB-endemic area such as South Korea.

The aim of this study was to investigate and compare the clinical characteristics, microbiologic and radiologic features, and treatment outcomes of TB and NTM disease developed after organ TPL.

## Patients and methods

### Study design and patients

This study was conducted retrospectively at the Asan Medical Center in Seoul, South Korea, which is an intermediate TB-burden country. Between January 1996 and December 2013, all transplant recipients with ≥15 years old of age were evaluated, including 3726 liver, 3253 kidney, 363 heart TPL recipients, and 1266 allogenic hematopoietic stem cell transplantation (HSCT) recipients. Among them, patients in whom TB or NTM diseases developed after TPL were enrolled. TB was diagnosed if *Mycobacterium tuberculosis* was identified from any clinical specimen or if polymerase chain reaction (PCR) for *M. tuberculosis* was positive (bacteriologically confirmed TB) [18]. Patients with clinical suspected active TB but negative mycobacterial culture finding and a good therapeutic response to anti-TB treatment were also considered as TB patients (clinical TB). NTM disease was defined according to the 2007 diagnostic criteria proposed by the American Thoracic Society/Infectious Disease Society of America [5]. Clinical data were collected, including information on TPL (type and time), baseline and clinical characteristics, microbiologic data [acid-fast bacilli (AFB) smear and culture], radiologic features (fibrocavitary, nodular bronchiectatic, and others), drug susceptibility test (DST) results, treatment outcomes, and adverse effects of antimycobacterial drugs.

### Microbiologic examination

Acid-fast bacilli smears were examined by Ziehl–Neelsen staining [19]. AFB culture was carried out using solid media alone until July 2007 and then using both solid Ogawa medium (Korean Institute of Tuberculosis, Osong, Korea) and liquid MGIT (BACTEC 960 Mycobacterial Growth Indicator Tube; Becton Dickinson, Sparks, MD, USA) thereafter [20]. Cultured isolates were identified as *M. tuberculosis* or NTM using the Duplex PCR test (Seegene Inc., Seoul, Korea). NTM species were identified using a PCR-restriction fragment length polymorphism method, based on the *rpoB* gene [21]. Conventional DST for *M. tuberculosis* was performed using the absolute concentration method with Lowenstein–Jensen media at the Korean Institute of Tuberculosis (Osong, South Korea), a supranational TB reference laboratory. Pyrazinamide susceptibility was determined using the pyrazinamidase test (Korean Institute of Tuberculosis, Osong, South Korea). The DST for NTM was tested using a commercial kit (Sensititre; TREK Diagnostic Systems, Cleveland, OH, USA) and interpreted according to tentative guidelines established by the National Committee for Clinical Laboratory Standards [22].

### Pretransplantation screening for latent tuberculosis infection

In heart TPL, LTBI screening and prophylaxis had introduced since 2009 using TST or QuantiFERON-TB Gold In-Tube (QFT-GIT; Cellestis, Carnegie, Vic., Australia). If LTBI test result was positive, there was two prophylaxis strategies: isoniazid (INH) prophylaxis for 1 year or a combination of INH and rifampicin for 3 months. In kidney TPL, there was no screening and prophylaxis until 2000. All patients received 3 month of INH from 2001 to May 2008 without LTBI screening. From June 2008 to December 2009, LTBI screening was performed using TST and T-SPOT.TB assay (T-SPOT; Oxford Immunotec, Abingdon, UK). At that time, INH was given to patients with positive TST or clinical risk factors for LTBI. From June 2010 to May 2013, LTBI screening was performed using T-SPOT assay. INH was administered to those with clinical risk factors for LTBI during 9 months. Patients with positive T-SPOT results who had no clinical risk factors for LTBI were randomly assigned to INH treatment or no treatment on a research basis. Since 2013, LTBI screening has performed using QFT-GIT. In HSCT, pretransplantation screening for LTBI has been conducted since 2004. From 2004 to 2013, 9-month INH prophylaxis was administered to recipient with clinical risk factor for LTBI. Since 2014, QFT-GIT has been used as a screening tool and if QFT-GIT was positive, 9-month INH was administered. In liver TPL, LTBI screening has not been performed systematically yet.

### Assessment of annual incidence and treatment outcomes

Incidences of TB and NTM were calculated as cases per 100 000 patient-years. Follow-up period was until death or censored at July 31, 2014. Median intervals from TPL



Transplant International 2016; 29: 549–558

to diagnosis of mycobacterial disease were calculated just from the patients with mycobacterial disease. Treatment outcomes were evaluated until July 31, 2014. Treatment outcomes of TB were classified according to the WHO criteria [23]. Treatment outcomes for NTM disease were classified as treatment success, failure, or default [24]. 'Treatment success' was defined if all of the following criteria were satisfied: (i) culture conversion, (ii) clinical improvement, (iii) minimum duration of medication at least 6 months, and (iv) treatment completion to the satisfaction of the attending physician. 'Failure' was defined as no conversion to negative sputum culture after treatment for 6 months or more and absence of clinical improvement. 'Default' was defined as interruption of treatment for more than 2 consecutive months. Favorable response included cure or treatment completion for TB and treatment success for NTM disease.

Sputum conversion was defined as three consecutive negative cultures within 6 months. If the patient could not expectorate sputum during the treatment duration, the sputum was considered to have be negative conversion [25].

The study protocol was approved by the Institutional Review Board of the Asan Medical Center (number: 2013-0932) and conducted according to the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the analysis.

### Statistical analysis

The incidence rates of TB and NTM disease were calculated using the number of incident cases divided by the person-time of follow-up and an exact confidence interval (CI) was calculated based on the Poisson distribution. Categorical variables are expressed as the number (%) and noncategorical variables as the median (range). The chi-squared test or Fisher's exact test was used to compare categorical variables, while noncategorical variables were compared using the unpaired *t*-test. Two-tailed *P* values were used for all *t*-tests, and a *P* value $<0.05$ was considered statistically significant. All analyses were performed using SPSS software (version 18; SPSS Inc., Chicago, IL, USA).

## Results

### Annual incidence of TB and NTM

A total of 152 patients were enrolled: 130 TB and 22 NTM patients. The annual incidences of TB and NTM disease developed after TPL according to transplanted organs are shown in Table 1. Regarding the incidence of TB and NTM diseases, the 95% CIs do not overlap, giving rise to the conclusion that the overall annual incidence of TB and NTM disease was different in solid-organ transplantation (SOT) recipients. The overall annual incidence of TB was six times higher than that of NTM disease. The incidence of NTM disease in HSCT recipients was higher than that of those receiving SOT. Figure 1 depicts the overall annual prevalence of TB and NTM diseases during the time frame. In general, the annual prevalence of TB was higher than that of NTM diseases during study period. The prevalence of TB before and after LTBI screening was evaluated. In case of kidney TPL, the prevalence of TB was 1.8% (13/711) [95% CI, 1.1–3.1] in 1996–2000 year period, 1.6% (16/1000) [95% CI, 1–2.6] in 2001–2007 year period, and 0.5% (8/1420) [95% CI, 0.3–1.1] in 2008–2013 year period. The prevalence of TB in recipients with heart TPL was 4.7% (9/192) [95%, CI, 2.5–8.7] until 2009 year and after that, 1.9% (3/154) [95% CI, 0.7–5.6]. The prevalence in HSCT was 1.3% (4/315) [95% CI, 0.5–3.2] until 2004 and after 2004, 0.9% (9/951) [95% CI, 0.5–1.8]. The median interval from TPL to the diagnosis of mycobacterial disease was 24.2 months (95% CI, 13.5–55.7) in recipients with NTM and 8.5 months (95% CI, 6.3–11.4) in those with TB, respectively.

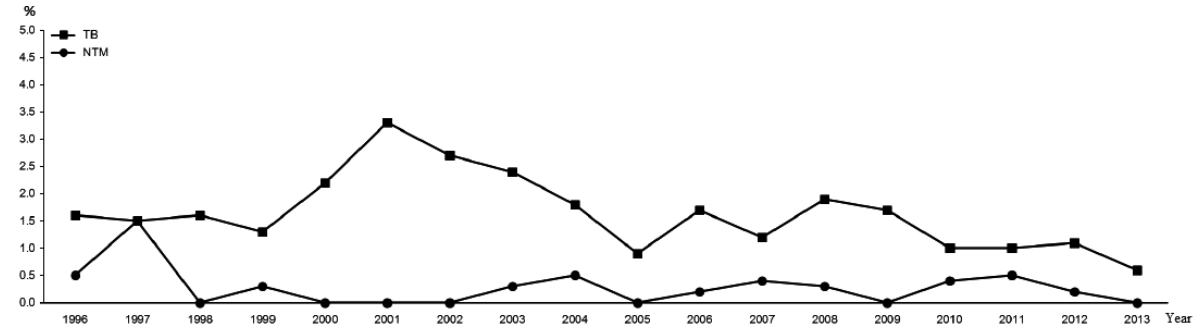
### Clinical characteristics of transplant recipients at diagnosis of mycobacterial infection

A comparison of clinical characteristics between NTM and TB transplant recipients at the time of diagnosis of mycobacterial infection is shown in Table 2. There were more cases of chronic lung disease and graft-versus-host disease in transplant recipients with NTM disease than in those with TB. Steroid had been used more frequently in NTM patients, while tacrolimus had been used more frequently in patients with TB. Cough and sputum were more common symptoms in recipients with NTM disease, while fever was more frequent in those with TB. Pulmonary involvement was more common in patients with NTM disease (81.8%) than in those with TB disease (69.2%), but the difference was not statistically significant. Bronchiolitis obliterans developed at the diagnosis of NTM lung disease in about 33.3% (3/9) HSCT recipients. Fourteen (9.2%) patients had disseminated TB. Extrapulmonary TB sites were as follows: lymph node ($n = 12$, 29.3%), pleura ($n = 10$, 24.3%), intestine ($n = 5$, 12.2%), central nervous system ($n = 4$, 9.8%), peritoneum ($n = 4$, 9.8%), pericardium ($n = 2$, 4.9%), kidney ($n = 3$, 7.3%), and soft tissue ($n = 1$, 2.4%). In cases of NTM diseases,

**Table 1.** Annual incidence of TB and NTM according to transplanted organs.

| TPL organs | Disease | Incidence* | 95% CI |
|---|---|---|---|
| SOT ($n$ = 7395) | Mycobacterial ($n$ = 130) | 276.7 | 231.2–328.5 |
| | TB ($n$ = 117) | 248.7 | 205.7–298.1 |
| | NTM ($n$ = 13) | 27.1 | 14.4–46.3 |
| Liver ($n$ = 3796) | Mycobacterial ($n$ = 71) | 353.9 | 276.4–446.4 |
| | TB ($n$ = 68) | 338.8 | 263.1–429.6 |
| | NTM ($n$ = 3) | 14.7 | 3.04–43.1 |
| Kidney ($n$ = 3253) | Mycobacterial ($n$ = 44) | 177.7 | 129.1–238.5 |
| | TB ($n$ = 37) | 149.3 | 105.1–205.7 |
| | NTM ($n$ = 7) | 28.0 | 11.3–57.6 |
| Heart ($n$ = 346) | Mycobacterial ($n$ = 15) | 694 | 388.4–1144.6 |
| | TB ($n$ = 12) | 549.9 | 284.2–960.6 |
| | NTM ($n$ = 3) | 114.9 | 23.7–335.7 |
| HSCT ($n$ = 1266) | Mycobacterial ($n$ = 22) | 638.1 | 399.9–966.1 |
| | TB ($n$ = 13) | 376.1 | 200.3–643.2 |
| | NTM ($n$ = 9) | 258.7 | 118.3–491.1 |
| Total ($n$ = 8661) | Mycobacterial ($n$ = 152) | 301.4 | 255.4–353.3 |
| | TB ($n$ = 130) | 257.4 | 215.1–305.7 |
| | NTM ($n$ = 22) | 42.7 | 26.8–64.7 |

*Incidences are expressed as cases per 100 000 patient-years. TPL, transplantation; SOT, solid-organ transplantation; HSCT, hematopoietic stem cell transplantation; TB, tuberculosis; NTM, nontuberculous mycobacterial disease.




| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of TPL | 186 | 196 | 246 | 319 | 272 | 337 | 331 | 340 | 437 | 433 | 482 | 562 | 622 | 688 | 718 | 799 | 885 | 808 |
| TB | 3 (1.6) | 3 (1.5) | 4 (1.6) | 4 (1.3) | 6 (2.2) | 11 (3.3) | 9 (2.7) | 8 (2.4) | 8(1.8) | 4 (0.9) | 8 (1.7) | 7 (1.2) | 12 (1.9) | 12 (1.7) | 7 (1) | 8 (1) | 10 (1.1) | 5 (0.6) |
| NTM | 1 (0.5) | 3 (1.5) | 0 (0) | 1 (0.3) | 0 (0) | 0 (0) | 0 (0) | 1 (0.3) | 2 (0.5) | 0 (0) | 1 (0.2) | 2 (0.4) | 2 (0.3) | 0 (0) | 3 (0.4) | 4 (0.5) | 2 (0.2) | 0 (0) |

Data are expressed as number (%). No, number; TPL, transplantation; TB, tuberculosis; NTM, nontuberculous mycobacteria

**Figure 1** The annual prevalence of tuberculosis and nontuberculous mycobacterial disease.

three patients with skin and soft tissue infection and one with musculoskeletal infection were identified.

### Microbiologic, radiologic features, and DST of mycobacterial infection

There was no difference in the proportion of positive AFB smears in cases of pulmonary involvement between TB and NTM groups (50% (9/18) in NTM vs. 42.2% (38/90) in TB, $P$ = 0.543). MAC (59.1%) was the most common causative organism, and nodular bronchiectatic type (77.8%) was the most frequent radiologic feature in patients with NTM disease. The percentage of patients with a cavitary lung lesion did not differ between the two groups (5.6% in NTM vs. 11.1% in TB, $P$ = 0.687).

Drug susceptibility test results are summarized in Table 3. DST was performed in 59.1% (13/22) of recipients with NTM disease, of whom seven had MAC, three had *Mycobacterium abscessus* complex, and three had *Mycobacterium kansasii*. All MAC and *M. abscessus* complex isolates were susceptible to clarithromycin. DST was performed in 74% (74/100) of TB patients, of whom 61

**Table 2.** Comparison of clinical characteristics between transplant recipients with NTM and those with TB at the diagnosis of mycobacterial diseases.

| Clinical characteristics | NTM ($n$ = 22) | TB ($n$ = 130) | $P$ value |
|---|---|---|---|
| Median age, years (range) | 53.5 (24–77) | 52.1 (19–71) | 0.441 |
| Male gender | 9 (40.9) | 96 (73.8) | 0.002 |
| Comorbidities | | | |
| Diabetes mellitus | 5 (22.7) | 43 (33.1) | 0.334 |
| Chronic liver disease | 1 (4.5) | 4 (3.1) | 0.548 |
| Chronic renal disease | 3 (13.6) | 8 (6.2) | 0.2 |
| Chronic lung disease | 7 (31.8) | 44 (3.1) | <0.001 |
| Solid-organ malignancy | 2 (9.1) | 3 (2.3) | 0.153 |
| Hematologic malignancy | 2 (9.1) | 1 (0.8) | 0.055 |
| Acute rejection | 4 (18.2) | 14 (10.8) | 0.299 |
| Chronic rejection | 1 (4.5) | 4 (3.1) | 0.548 |
| GVHD | 6 (27.3) | 6 (4.3) | 0.002 |
| Concomitant medication | | | |
| Steroid | 17 (77.3) | 67 (51.5) | 0.025 |
| Tacrolimus | 7 (31.8) | 84 (64.6) | 0.004 |
| Cyclosporin | 8 (36.4) | 33 (25.4) | 0.283 |
| Azathioprine | 2 (9.1) | 4 (3.1) | 0.209 |
| Mycophenolate mofetil | 9 (40.9) | 61 (46.9) | 0.601 |
| Symptoms | | | |
| Fever | 5 (22.7) | 62 (47.7) | 0.029 |
| Cough | 12 (54.5) | 40 (30.8) | 0.03 |
| Sputum | 13 (59.1) | 23 (17.7) | <0.001 |
| Dyspnea | 4 (18.2) | 18 (13.8) | 0.528 |
| Hemoptysis | 1 (4.5) | 4 (3.1) | 0.548 |
| Chest pain | 1 (4.5) | 16 (12.3) | 0.469 |
| Site of disease | | | 0.229 |
| Pulmonary | 18 (81.8) | 90 (69.2) | |
| Extrapulmonary | 4 (18.2) | 40 (30.8) | |

Data are presented as $n$ (%) unless otherwise stated. TPL, transplantation; NTM, nontuberculous mycobacterial disease; TB, tuberculosis; GVHD, graft-versus-host disease.

(82.4%) were pan-susceptible to first-line drugs, while 11 (14.9%) had mono-resistant (five isoniazid, one ethambutol, three streptomycin, and two moxifloxacin) and two (2.7%) had multidrug-resistant TB.

### Comparison of treatment outcomes and adverse drug reactions in recipients with TB or NTM disease developed after TPL

All patients with TB received anti-TB medication, while anti-NTM medication was initiated in 77.3% (17 of 22) of NTM patients. Four (23.5%) of 17 NTM patients underwent surgical resection in addition to medical therapy. Five NTM patients were observed without antimycobacterial treatment. Combined isoniazid and rifamycin (rifampicin or rifabutin) were initiated in 75.4% (98/130), either isoniazid or rifamycin was initiated in 17.6% (23/130), and neither isoniazid nor rifamycin was initiated in 7% (9/130) of patients with TB. The ratio of rifampicin to rifabutin use was 63.3%: 36.7%. Excluding two MDR-TB patients (all received first-line drugs as initial therapy and then regimens were changed after recognizing DST results), 128 patients received first-line drugs alone in 72 (56.3%), first-line drugs plus quinolone in 47 (36.7%), or second-line drugs in 9 (5.9%). Fifty-one (70.8%) of 72 patients completed treatment with first-line drugs alone (three experienced hepatotoxicity but anti-TB drugs were not changed). In 12 patients (16.7%), first-line TB drugs were changed to second-line drugs: 10 of 12 patients experienced hepatotoxicity and regimens were changed. In the remaining 9 patients (12.5%), quinolone was added to the first-line drugs.

A macrolide (clarithromycin or azithromycin) was included in the regimens of all treated NTM patients caused by MAC or *M. abscessus* complex. The median duration of medical therapy was 396 days (95% CI, 191–487) in recipients with NTM disease and

**Table 3.** Results of drug susceptibility test in mycobacterial species.

| Drug (S/I/R) | *Mycobacterium tuberculosis* | *Mycobacterium avium–intracellulare complex* | *Mycobacterium abscessus complex* | *Mycobacterium kansasii* |
|---|---|---|---|---|
| Isoniazid | 67 (90.5)/0/7 (9.5) | | | |
| Rifampin | 71 (97.3)/0/2 (2.7) | | | 1 (33.3)/0/2 (66.7) |
| Rifabutin | 62 (100)/0/0 | | | |
| Ethambutol | 69 (95.8)/0/3 (4.2) | | | |
| Pyrazinamide | 71 (98.6)/0/1 (1.4) | | | |
| Streptomycin | 67 (93.1)/0/5 (6.9) | | | |
| Kanamycin | 72 (100)/0/0 | | | |
| Cycloserine | 72 (100)/0/0 | | | |
| PAS | 69 (97.2)/0/2 (2.8) | | | |
| Ofloxacin | 69 (97.2)/0/2 (2.8) | | | |
| Moxifloxacin | 57 (96.6)/0/2 (3.4) | 2 (28.6)/3 (42.9)/2 (28.6) | | |
| Clarithromycin | | 7/7 (100) | 3 (100)/0/0 | 2 (100)/0/0 |
| Linezolid | | 3 (42.9)/1 (14.3)/3 (42.9) | 2 (66.7)/0/1 (33.3) | 2 (100)/0/0 |
| Amikacin | | | 3 (100)/0/0 | |
| Cefoxitin | | | 3 (100)/0/0 | |

Data are expressed as number (%). S, susceptible; I, intermediate; R, resistant. PAS, Para aminosalicylic acid.

274.5 days (95% CI, 270–281) in those with TB ($P = 0.212$).

Treatment outcomes of the 129 TB and 16 NTM patients are described in Table 4. One TB and one NTM patient remained on antimycobacterial treatment and were thus excluded from the outcome analyses. The treatment success rate was higher in recipients with TB [83.7% (95% CI, 76.4–89.1)] than in those with NTM disease [68.8% (95% CI, 44.4–85.8)], but there was no significant difference ($P = 0.166$). Excluding 13 patients with drug-resistant TB including MDR-TB, a higher favorable response rate was seen in SOT recipients initially treated with both isoniazid and rifamycin than in other patients [90.8% (69/76); 95% CI, 82.2–95.5 vs. 75.9% (22/29); 95% CI, 57.9–87.8, $P = 0.057$]. Eleven (8.5%) TB patients died during anti-TB treatment [6% (7/116); 95% CI, 2.9–11.9 in SOT vs. 30.8% (4/13); 95% CI 12.7–57.6 in HSCT, $P = 0.014$], eight of whom died due to TB itself [4.3% (5/116); 95% CI, 1.9–9.7 in SOT vs. 23.1% (3/13); 95% CI, 8.2–50.3 in HSCT, $P = 0.034$]. Both MDR-TB patients died due to TB. No NTM patients died during anti-NTM treatment. Five cases were observed without treatment. All five cases were infected with MAC (three with *Mycobacterium avium* and two with *M. intracellulare*). Two cases were followed up without clinical aggravation but minimal radiologic progression. The remaining three had no clinical and radiologic aggravation, so no treatments were required. Adverse drug reactions were noted in 47.1% (8/17) [95% CI, 26.2–69] of patients with NTM disease, and gastrointestinal trouble (60%) was the most common. Among TB patients, 33.8% (44/130) [95% CI, 26.3–42.3] experienced 61 episodes of adverse drug reactions; hepatotoxicity (31.1%, 19/61 episodes) was the most common event followed by leukopenia (19.7%, 12/61). Drug-induced hepatotoxicity developed in 19 of 44 patients (43.2%). Thirteen of 72 patients receiving first-line drugs experienced hepatotoxicity: TB

**Table 4.** Comparison of treatment outcomes of mycobacterial disease between transplant recipients with NTM and those with TB.

| No. of patients | NTM ($n = 16$) | TB ($n = 129$) | *P* value |
|---|---|---|---|
| Favorable response (treatment success) | 11 (68.8) | 108 (83.7) | 0.166 |
| Unfavorable response | 5 (31.2) | 21 (16.3) | |
| Treatment failure | 1 (6.3) | 0 (0) | |
| Death | 0 (0) | 11 (8.5) | |
| Default | 4 (25) | 10 (7.8) | |
| Cause of death | 0 | 11 | |
| TB related | 0 | 8 (72.7) | |
| TB unrelated | 0 | 3 (27.3) | |

Patients still receiving treatment (NTM = 1; TB = 1) were excluded to assess treatment outcomes. NTM, nontuberculous mycobacteria; TB, tuberculosis.

medication was changed in 10 (76.9%) and no change was made in 3 (23.1%). Three patients who did not receive first-line drugs experienced hepatotoxicity: two of them changed anti-TB medication due to hepatotoxicity. The remaining three patients receiving first-line drugs plus quinolone experienced hepatotoxicity and two of them changed anti-TB medication due to hepatotoxicity. Resultantly, anti-TB medication was changed to another regimens in 14 of 19 patients and was maintained in the remaining five patients.

## Discussion

To our knowledge, this is the first study that directly compared clinical characteristics, microbiologic and radiologic features, and treatment outcomes between transplant recipients who developed TB or NTM disease. Our study was conducted in an intermediate TB-burden area where the incidence of NTM is continuously increasing. The results showed that the overall annual incidence of TB was about six times that of NTM disease in transplant recipients. Incidences of both TB and NTM disease were higher in patients receiving heart transplant than any other types of solid-organ transplants. The incidence of NTM disease was higher in HSCT recipients than that of total SOT recipients. Our data also revealed that the clinical characteristics differed between the two groups. However, treatment outcomes were favorable in both diseases and compatible with those in immunocompetent patients.

The development of TB is a well-known infectious complication in transplant recipients. The risk of active TB in both SOT and HSCT recipients is higher than in the general population depending on the type of TPL and the local epidemiology of TB [26,27]. One study in South Korea reported that the incidence density of TB in SOT was 372 cases per 100 000 patient-years, which is 4 times higher than that for the general Korean population (90 cases per 100 000 person-years) and the overall frequency of TB was 1.67% (40/2144 SOT recipients) [17]. In our data, the frequency of TB in SOT recipients was 1.59% (117/8458 SOT recipients), which is higher than that reported for the RESITRA cohort in Spain [4]. However, the incidence of TB was lower in the current study than that in RESITRA cohort in Spain. One of the reasons may be that lung transplant recipients were not included in the current study. Higher incidence of TB was observed in lung transplant recipient [4]. The frequency of TB occurrence in our data was lower than previous reports in Korea (0.96% vs. 3.0%) [28,29], but incidence of TB was four times higher than that of general Korean population. In the current study, incidences of both TB and NTM disease were significantly the highest in heart transplant recipients among SOT recipients. The range of incidence of TB in HSCT recipients varies from country to country [1].

Determining the appropriate treatment regimen for transplant recipients with TB is especially challenging due to drug toxicity to the transplanted organ or drug–drug interaction between the immunosuppressive agents and rifamycin. In our study, both isoniazid and rifamycin (rifampicin or rifabutin) were administered in 75.4% of recipients with TB with a close monitoring of drug level of the immunosuppressive agents. Our data showed that an overall favorable response was 83.7% of TB patients. In the present study, both isoniazid and rifamycin (rifampicin or rifabutin) were administered in about three-fourths recipients with TB with a close monitoring of drug level of the immunosuppressive agents. Favorable treatment outcome suggests that the combination of both isoniazid and rifamycin is an optimal regimen even in organ transplant recipients.

The overall mortality rate of SOT recipients with TB ranges from 19% to 29% [3,4] and that of allogenic HSCT recipients is reported to be about 18% [30]. In the present study, mortality rates were higher than those of previous reports of general TB patients in South Korea showing from 1.9% to 5.6% mortality [31,32].

The incidence range of NTM disease in transplant recipients varies widely depending on the geographical region and type of TPL. In the present study, the prevalence of NTM disease in SOT recipients and in HSCT recipients was similar to those in previous reports [13,16]. The overall incidence of NTM disease for transplant recipient in the present study was higher than that of general population [33,34]. The incidence of NTM disease in HSCT recipients was higher than that of overall SOT recipients. The incidence of NTM disease is not yet well defined in liver transplant recipients, with one study reporting an incidence of 0.04% [13]. In the present study, the frequency of NTM disease in liver transplant recipients was 0.08% and incidence was 14.7 cases/100 000 patient-years (CI, 3.04–43.1 cases/100 000 patient-years), which is lower than the rates reported for other types of TPL.

Several factors affecting treatment outcome should be considered when determining treatment for NTM disease. Even in the face of adverse effects of macrolide or rifamycin [35], we achieved a favorable response in 68.8% of patients; treatment outcome was better in

patients with MAC disease than in those with disease caused by other organisms. The current data suggest that treatment outcome of NTM disease in transplant recipients be similar to those of NTM disease in the general population if early diagnosis, timely and appropriate treatment with an anti-NTM regimen, and close monitoring of drug–drug interactions and adverse effects are carried out.

Our study compared the characteristics between TB and NTM disease in transplant recipients. The incidence of TB was higher than that of NTM disease, which may reflect that, despite the increasing incidence of NTM disease, TB is a dominant mycobacterial infection in South Korea, an intermediate TB country. The main symptom of TB was fever, while cough and sputum were most common in NTM disease. The frequency of extrapulmonary involvement was higher in TB patient than in NTM patients. These findings are in agreement with those reported in patients treated with a TNF-α antagonist [36]. Among patients with mycobacterial disease, more HSCT recipients had NTM disease (compared with TB) significantly than that in SOT recipients. This phenomenon may be due to the development of bronchiolitis obliterans (BO) in HSCT recipients as a manifestation of graft-versus-host disease and, resultantly, higher incidence of NTM lung disease in patients with structural lung disease such as BO [37,38]. Au *et al.* [39] addressed that the existence of BO was a risk factor for NTM infection. The interval from TPL to the development of disease was longer in patients with NTM than in those with TB in our cases, which is consistent with other studies showing that TB developed within 1 year of TPL [4,17]. More favorable treatment response was shown in patients with TB than in those with NTM disease, but the difference was not significant. These findings imply that treatment of NTM disease is more challenging than that of TB in transplant recipients as well as in the general population.

Although many transplant recipients were enrolled in this study, this is a retrospective study conducted in a single center during long period, which will always limit generalizability, and selection bias cannot be avoided. All outcomes were assessed by review of records at the same institution where TPL was performed. Therefore, patients who received follow-up care at other institutions would not have outcomes captured.

Another concerned potential bias in this study is survival bias in transplant recipients. Given that the median time of developing active TB and NTM is 8.5 months and 24.4 months, only transplantation recipients who survived more than 8.5–24.4 months can have the possibilities to get active TB and NTM disease. Transplant patients with worse prognosis and early mortality will not live long enough to get TB/NTM disease. Therefore, the patients who affected with TB and NTM are those with better prognosis and longer survival. In addition, a small number of cases of NTM disease were included and it would be difficult to make any firm conclusion regarding NTM diseases in such a low case numbers. Generalization of the characteristics of NTM disease in transplant recipients should made with caution. The definition of treatment outcomes of NTM disease was arbitrarily chosen due to the lack of standardized definitions. Despite these limitations, our data are valuable with respect to the comparison of characteristics between TB and NTM disease in transplant recipients.

In summary, the incidence of mycobacterial infection in transplant recipients was higher than that of general population. However, treatment outcomes were favorable in both drug-susceptible TB and NTM patients.

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## Authorship

JWY: participated in data collection and analysis and wrote the manuscript. KWJ, SHK, and SOL: assisted in patient data assessment. JJK, SKP, JHL, DJH, and SHSGL: provided patient data and assisted in data collection. TSS: performed study conception and designed and revised the manuscript.

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## Conflicts of interest

The authors report no financial or other conflict of interest relevant to the subject of this article.

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