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# Risk factors and characteristics of post-transplant tuberculosis in an endemic area

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

## Summary

**Background:** Tuberculosis (TB) is a major post-transplant concern in endemic areas. This report summarizes the clinical characteristics, risk factors, and effects of post-transplant TB on graft and patient survival at a single center in Korea.

**Material/Methods:** We retrospectively analyzed data from 2799 kidney recipients at Yonsei University Health System between April 1979 and August 2008 to determine the incidence, outcome, and risk factors affecting the development of TB infections and the effect of TB on graft and patient survival rates.

**Results:** TB developed in 144 (109 males and 35 females; mean age, 37±12 years) out of 2799 (5.1%) recipients. Newly developed TB occurred in 116 recipients (81%) and recurrent TB occurred in 28 (19%) recipients with a pre-transplant history of a mycobacterial infection. The mean interval to TB diagnosis was 55.6±47.9 months after transplantation without a peak interval incidence for 8 years after transplantation. Based on Cox regression analysis, a history of TB was the strongest risk factor (hazard ratio [HR] =11.618) affecting the development of TB. TB negatively affected graft and patient survival after kidney transplantation. Non-pleurisy extrapulmonary and miliary TB resulted in inferior treatment results and a poor prognosis in the early treatment period.

**Conclusions:** A history of TB is the strongest predictor of post-transplant TB. Therefore, patients with a pre-transplant history of TB should be carefully monitored.

**Key words:** kidney transplantation • *Mycobacterium tuberculosis* • posttransplant infection

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## Background

Tuberculosis (TB) remains an infectious disease problem in many countries, especially in endemic areas. Although continuous efforts to prevent this disease from spreading are in progress, the prevalence of TB has not decreased in recent years. According to a 2008 WHO report, there were an estimated 9.2 million new cases of TB in 2006 (139 per 100 000 population) worldwide. This increase from 9.1 million cases in 2005 has been ascribed to population growth [1]. TB in immunocompromised transplant recipients is more complicated and has a higher incidence than in the general population, and can lead to graft loss and patient death. The reported incidence in the transplant population ranges from 0.8–13.3% [2–10]. Interactions with immunosuppressive agents and the toxicity of anti-tubercular drugs make treatment of TB an enormous challenge after transplantation. This report summarizes the clinical characteristics, risk factors, efficacy, and safety of an anti-tuberculosis protocol, and the effect on graft and patient survival of post-transplant tuberculosis infections at a single center in an endemic area.

## Material and Methods

### Patients

We conducted a retrospective study of all renal transplantation recipients between April 1979 and August 2008 at Yonsei University Health System. To find recipients with post-transplant TB, we retrospectively reviewed the medical records of the 2799 recipients in the transplant database. All of the patients who were diagnosed with post-transplant TB were reviewed for demographic features, immunosuppressive treatment, the length of time between transplantation and diagnosis of TB, involved organs, treatment protocols, adverse effects, and the effect on graft and patient survival.

### Immunosuppressive protocol

Prior to 1984, the immunosuppressive agents were azathioprine (AZA) and prednisolone; thereafter, a double regimen with cyclosporine A (CsA) and prednisolone or a triple regimen in which AZA or mycophenolate mofetil (MMF) was added was used. Since 1998, tacrolimus has been used instead of CsA. Induction immunosuppression therapy (anti-thymocyte globulin, anti-lymphocyte globulin, and muromonab-CD3) was not used; however, induction therapy with the interleukin-2 receptor antibody (basiliximab) has been used for high-risk recipients from deceased or unrelated living donors, except for zero-antigen mismatched donors, since 1999. MMF was introduced in 1997 and added for appropriate recipients as a triple regimen with a calcineurin inhibitor and steroids, which was previously used for a double regimen.

Steroid pulse therapy (methylprednisolone [500 mg/day ×4 for 5 days]) was considered the first-line therapy for acute rejection. When there was an inadequate response to steroid pulse therapy, an anti-lymphocyte antibody (ALA), such as OKT-3 or the anti-thymocyte antibody, was used. Graft loss was defined as patient death, graft removal, or conversion to regular dialysis.

### Diagnosis of tuberculosis

TB was diagnosed by 1 or more of the following methods: (1) demonstration of acid-fast bacilli (AFB) in a bronchoalveolar lavage (BAL), sputum, or pleural fluid sample, and/or *Mycobacterium tuberculosis* growth in culture media; (2) demonstration of a caseating granuloma and positive results on an AFB smear for tissue histology; (3) demonstration of TB DNA using a polymerase chain reaction (PCR); and (4) a favorable response to anti-tubercular drugs in patients with clinical symptoms and typical radiographic findings consistent with TB, or those who had a fever of unknown origin despite negative results of other extensive investigations. These diagnoses included definite, probable, or suspected cases. A pre-transplant history of tuberculosis was defined as a history of undergoing anti-tuberculosis treatment before the transplantation, with or without confirmation of post-TB inflammatory scarring on a pre-transplant chest X-ray. According to the WHO classification, we subclassified TB as follows: (1) pulmonary type of TB, including pulmonary TB and miliary TB involving lung lesion; and (2) extrapulmonary type of TB, including TB pleurisy and non-pleurisy extrapulmonary TB.

### Anti-tuberculosis protocols

The anti-tubercular regimen was comprised of multiple combinations of isoniazid (INH), ethambutol (EMB), rifampicin (RFP), streptomycin (SM), and pyrazinamide. In the pulmonary type of TB, 6–12 months of treatment was recommended and >12 months of treatment was

recommended for the extrapulmonary type of TB. The calcineurin inhibitor was adjusted by the trough level during the use of anti-tuberculosis medication because the RFP-based regimen decreased the trough level of the calcineurin inhibitor.

### Statistical analysis

The cumulative incidence of post-transplant TB was calculated by the Kaplan-Meier method. Risk factors for post-transplant TB were recipients age and sex, pre-transplant history of TB, hepatitis B virus (HBV) antigenemia (HBsAg-positive), hepatitis C virus (HCV) infection (anti-HCV antibody-positive), diabetes (including post-transplant diabetes), an acute rejection episode, and a major immunosuppressive agent. To compare the cumulative incidence for each risk factor, univariate analysis was performed with the Wilcoxon method. A Cox hazards proportional regression model, taking into account the interactions between the aforementioned factors, was used to identify the risk factors for post-transplant TB. We divided the transplant era into 3 periods (before 1984, 1984–1986, and after 1997) according to the change in the immunosuppressive regimen and prevalence of TB in the general population in Korea. Before 1984, AZA was the only major immunosuppressive agent; thereafter, CsA gradually replaced AZA. Before 1997 the prevalence of TB in the general population of Korea was about 3 times higher than after 1997 and reached a plateau until recently [11].

The results of the Cox regression test are presented as the hazard ratio (HR), the 95% confidence interval (CI), and *P*-values. The graft and patient survival rates were calculated by the Kaplan-Meier method and compared with a Wilcoxon test. Student's t-test or chi-square test was used to analyze the characteristics of each subgroup. All statistical analyses were performed using SPSS® 14.0 for Windows (SPSS, Inc., Chicago, IL, USA).

## Results

### Demographic data

Among 2799 recipients, 144 recipients were diagnosed with post-transplant TB during a mean follow-up period of 164±73.2 months (range, 2–320 months) after transplantation. The overall cumulative incidence of TB was 5.1%. The 109 male and 35 female subjects had an overall mean age at diagnosis of 41.5±12.2 years and a mean time interval between transplantation and TB diagnosis of 55.6±47.9 months (range, 0–225 months). Of the 144 post-transplant TB patients, 28 patients had a pre-transplant history of TB that was cured completely and showed no activation on the chest X-ray performed as part of the pre-transplant evaluation. All 28 patients with pre-transplant TB history had received appropriate anti-tuberculosis treatment, had been diagnosed as completely cured, and needed no more further treatment. However, there were no medical records because the treatments of pre-transplant TB were performed in other institutes many years previously in all patients.

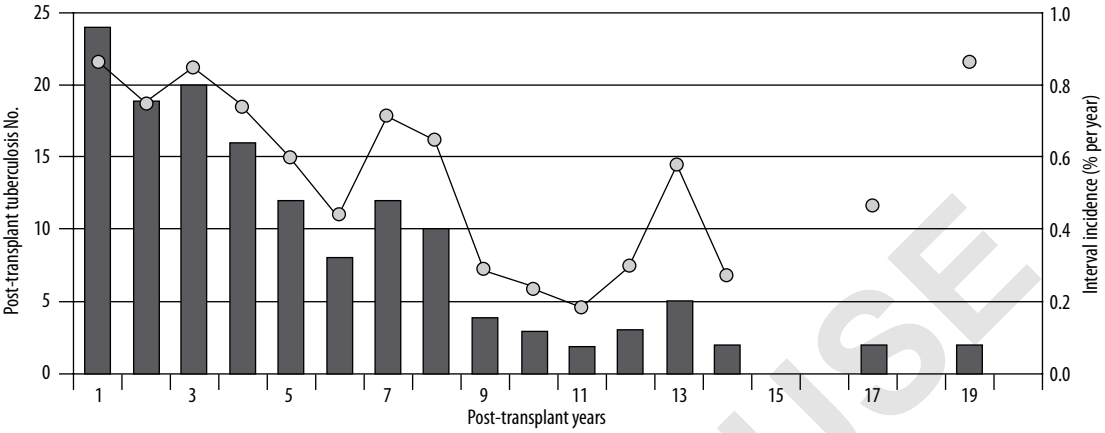
The mean interval between transplantation and TB diagnosis of the 28 patients who had a pre-transplant history of TB was 50.4±35.8 months, which was not different from the 116 patients without a pre-transplant history of TB (56.9±50.5 months; *P*=0.524).

The time table of the post-transplant TB presentation is shown in Figure 1, which includes the interval incidence by post-transplant period. There were no significant peak interval incidences in each year within the 8 years following transplantation. The overall cumulative incidence of TB 10 and 20 years after transplantation was 6.1% and 8.9%, respectively.

The most common symptom of TB in nearly all of the patients was pyrexia; however, in 25 cases there were no significant symptoms related to TB (17.4%). The most common diagnostic tool was clinical symptoms with pathologic findings on chest radiographs in 56 patients (38.9%). Thirty-nine patients (27.1%) had an AFB stain from sputum, tissues, or pleural fluid at presentation. A positive TB PCR existed in 11 patients (7.6%), a positive culture in 6 patients (4.2%), demonstration of caseating granuloma in histology in 24 patients (16.7%), and a positive adenosine deaminase (ADA) in 8 patients (5.5%).

### Risk factor analysis of post-transplant TB

Based on univariate risk factor analysis, a pre-transplant history of TB, AZA-based immunosuppression, acute rejection history, male sex, post-transplant diabetes mellitus (PTDM), HBV carrier, and transplant era before 1997 were risk factors for post-transplant TB; HCV infection was not a risk factor for TB (data not shown). Table 1 shows the differences of the clinical features between the non-TB and post-transplant TB patients.




| Post-Tx year | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 19- |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mean exposure No. | 2733 | 2547 | 2352 | 2165 | 1991 | 1834 | 1688 | 1530 | 1384 | 1249 | 1108 | 987 | 862 | 729 | 605 | 508 | 426 | 327 | 232 | 125 |
| Post-Tx TB No. | 24 | 19 | 20 | 16 | 12 | 8 | 12 | 10 | 4 | 3 | 2 | 3 | 5 | 2 | 0 | 0 | 2 | 0 | 2 | 0 |
| Interval incidence (% per year) | 0.88 | 0.75 | 0.85 | 0.74 | 0.60 | 0.44 | 0.71 | 0.65 | 0.29 | 0.24 | 0.18 | 0.30 | 0.58 | 0.27 | | | 0.47 | | 0.86 | |

**Figure 1.** Time table of tuberculosis presentation. The mean interval between transplantation and TB diagnosis was 56±47.9 months (range, 0~225 months).

**Table 1.** Clinical manifestations of post-transplant TB patients and non-TB patients.

| Variables | Post-transplant TB group (n=144) | Non-TB group (n=2,655) | p-value |
|---|---|---|---|
| Age at transplantation | 36.9±11.7 | 37.6±11.6 | 0.436 |
| Sex (male proportion;%) | 75.7 | 66.3 | **0.023** |
| Pre-transplant TB history (%) | 19.4 | 1.2 | **<0.0001** |
| Relation (LRD: LURD: Deceased) | 76: 66: 2 | 1410: 1105: 140 | 0.097 |
| Major IS agents (proportion of AZA; %) | 10.4 | 4.0 | **<0.0001** |
| AR within 1 year | 36.8 | 29.1 | 0.050 |
| PTDM (%) | 36.1 | 25.5 | **0.006** |
| HBsAg positive (%) | 11.1 | 4.5 | **0.001** |
| Anti-HCV positive (%) | 4.9 | 5.4 | 0.853 |

TB – tuberculosis; LRD – living related donor; LURD – living unrelated donor; IS – immunosuppression; AZA – azathioprine; AR – acute rejection; PTDM – post-transplant diabetes mellitus.

**Complementary Table 1.** Post-transplant TB occurrence according to the pre-transplant tuberculin skin test.

| Variables | Positive tuberculin skin test (n=185)* | Negative tuberculin skin test (n=373) | *P*-value |
|---|---|---|---|
| Post-transplant TB | 4 (2.2%) | 3 (0.8%) | 0.228 |
| Non-TB | 181 (97.8%) | 370 (99.2%) | |

* Positive tuberculin skin test ≥5 mm. TB – tuberculosis.

Based on multivariate risk factor analysis, it appears that before 1984 there were no significant risk factors for post-transplant TB. In this era, there were no HCV carriers and no recipients

**Table 2.** Risk factors affecting the development of tuberculosis by Cox regression analysis.

| Variables | 1979–1983 (n=85) | | | | 1984–1996 (n=1449) | | | | 1997–2008 (n=1265) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *P*-value | Hazard ratio | CI (95%) | | *P*-value | Hazard ratio | CI (95%) | | *P*-value | Hazard ratio | CI (95%) | |
| | | | lower | upper | | | lower | upper | | | lower | upper |
| Gender of recipient (male) | 0.892 | 1.116 | 0.229 | 5.443 | **0.037** | 1.624 | 1.029 | 2.562 | 0.776 | 0.885 | 0.383 | 2.047 |
| Age of recipient (≥35 yr) | 0.173 | 2.437 | 0.677 | 8.781 | 0.382 | 0.838 | 0.565 | 1.244 | 0.079 | 0.467 | 0.200 | 1.091 |
| AZA-based IS | – | – | – | – | **0.028** | 2.793 | 1.114 | 6.998 | – | – | – | – |
| Acute rejection within 1 yr following transplantation | 0.990 | 0.000 | 0.000 | – | 0.108 | 1.383 | 0.931 | 2.056 | **0.006** | 3.181 | 1.401 | 7.223 |
| PTDM | 0.995 | 1.005 | 0.243 | 4.156 | 0.391 | 1.199 | 0.792 | 1.815 | 0.081 | 2.206 | 0.908 | 5.361 |
| HBsAg positive | 0.360 | 2.166 | 0.415 | 11.317 | **0.001** | 2.959 | 1.593 | 5.496 | 0.261 | 2.316 | 0.536 | 10.019 |
| Anti-HCV positive | – | – | – | – | 0.343 | 0.669 | 0.292 | 1.534 | 0.639 | 1.619 | 0.217 | 12.093 |
| Pre-tx tuberculosis | – | – | – | – | **<0.0001** | 9.695 | 6.212 | 15.129 | **0.001** | 31.240 | 3.905 | 249.916 |

AZA – azathioprine; IS – immunosuppression; PTDM – post-transplant diabetes mellitus; CI – confidence interval; Pre-tx – Pre-transplant.

who had pre-transplant history of TB. However, male recipients, AZA-based immunosuppression, HBV carrier, and a pre-transplant history of TB were significantly correlated with the development of TB in the 1984–1996 era. The triple immunosuppressive regimen with MMF started in 1997, and our data showed a significant decrement in the incidence of acute rejection within 1 year post-transplant (from 35.6% to 22.1%, $P<0.0001$). Recipient sex, HBV infection, and AZA-based immunosuppression led to limited risk during the transplant era before 1997, and they were no longer risk factors in the period after 1997. On the other hand, acute rejection episodes led to a significant difference in risk according to the transplant era. Based on the incidence analysis, an acute rejection episode was a risk factor for post-transplant TB only in the transplant era after 1997. Before 1997, 78 (7.9%) of 988 recipients without acute rejection episodes had post-transplant TB, and 42 patients (7.7%) of 546 recipients with acute rejection episodes had post-transplant TB ($P=0.921$). After 1997, however, there were significantly different TB incidences from each group (1.3% in the no acute rejection episode group *vs.* 3.9% in the acute rejection episode group; $P=0.010$). As distinct from the other risk factors, pre-transplant history of TB was the sole and potent risk factor throughout the transplant era. Regardless of the transplant era, recipients with a pre-transplant history of TB had significantly higher risk for post-transplant TB (HR=11.618; $P<0.0001$) (Table 2).

### Location of TB

According to the WHO classification, TB was divided into 2 groups: 1) pulmonary TB involving miliary TB and solitary lung disease; and 2) extrapulmonary TB involving TB pleurisy and single or multiple extrapulmonary lesions. Pulmonary TB was the most common form of the disease in our series (98/144 [68.1%]). Extrapulmonary TB occurred in 46 patients (31.9%), and involved the intestines (9/144 [6.3%]), bone (2/144 [1.4%]), soft tissue (5/144 [2.8%]), central nervous system (3/144 [2.1%]), and other disseminated TB (2/144 [1.4%]). The clinical parameters of the pulmonary and extrapulmonary types of TB were not significantly different. TB pleurisy tended to occur in a younger age group than other pulmonary types of TB ($P=0.030$). TB pleurisy also had a greater proportion of males compared with other subgroups ($P=0.011$) (Table 3). Although there was no statistically significant difference, miliary TB occurred later in the post-transplant period (76.9±60.9 months) compared with the other subtypes of TB (40–50 months).

### Therapeutic results

With the exception of 2 cases of ongoing anti-tuberculosis therapy, the overall curative rate was 76.1% (108/142). Among the 108 cured patients, there were 5 reactivation cases (4.7%) that needed retreatment. All 5 reactivation cases had been completely treated with proper antituberculosis

**Table 3.** Clinical manifestations and therapeutic results of post-transplant tuberculosis according to the type of post-transplant tuberculosis.

| Clinical manifestations | Pulmonary (n=98) | | Extrapulmonary (n=46) | | *P*-value |
|---|---|---|---|---|---|
| | Lung (75) | Miliary (23) | TB pleurisy (25) | Others (21) | |
| Characteristics | | | | | |
| Gender (M: F) | 60: 15 | 14: 9 | 23: 2 | 12: 9 | **0.011** |
| Age at diagnosis | 42.5±12.9 | 45.6±9.9 | 35.7±10.5 | 40.4±11.5 | **0.030** |
| Interval between transplantation and TB diagnosis (months) | 54.5±46.5 | 76.9±60.9 | 50.4±43.7 | 42.2±36.3 | 0.087 |
| AR within 1 year | 22 (29.3%) | 12 (52.2%) | 10 (40.0%) | 9 (42.9%) | 0.205 |
| Tuberculosis history | 11 (14.7%) | 3 (13.0%) | 8 (32.0%) | 6 (28.6%) | 0.149 |
| Transplant era (before 1997) | 61 (81.3%) | 20 (87.0%) | 21 (84.0%) | 18 (85.7%) | 0.960 |
| Therapy | | | | | |
| Anti-tuberculosis regimens | | | | | |
| RFP (+) | 39 (52.0%) | 12 (52.2%) | 11 (44.0%) | 11 (52.4%) | 0.910 |
| SM (+) | 15 (20.0%) | 5 (21.7%) | 4 (16.0%) | 4 (19.0%) | 0.977 |
| Duration of therapy (months) | 10.4±5.7 | 11.0±5.4 | 11.4±4.8 | 9.9±6.5 | 0.790 |
| Therapeutic results | | | | | |
| Complete cured | 59 (78.7%) | 14 (60.9%) | 23 (92.0%) | 14 (66.7%) | |
| Incomplete cured | 0 (0.0%) | 0 (0.0%) | 1 (4.0%) | 0 (0.0%) | |
| Graft failure during medication | 11 (14.7%) | 2 (8.7%) | 1 (4.0%) | 1 (4.8%) | 0.001 |
| Patient death during medication | 3 (4.0%) | 7 (30.4%) | 0 (0.0%) | 6 (28.6%) | |
| On medication | 2 (2.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Tuberculosis-related graft failure or patient death | 9 (9/75, 12.0%) | 6 (6/23, 26.1%) | 0 (0.0%) | 5 (5/21, 23.8%) | 0.015 |

AZA – azathioprine; IS – immunosuppressive agent; RFP – rifampicin; SM – streptomycin.

regimen at the first diagnosis of post-transplant TB. The mean duration from finishing the treatment for the first TB to the second TB diagnosis was 20.0±20.3 months. In the 142 cases of TB, there were 15 graft losses (10.6%) and 16 fatalities (11.3%) during TB treatment. Among the TB-related graft losses and mortalities, there were 20 cases (64.5% [20/31]), including 4 cases of immunosuppressive agent modulation failure, 9 cases of sepsis due to primary TB, 3 cases of central nervous system TB, and 4 cases of acute deterioration of graft function. Miliary TB and non-pleurisy extrapulmonary TB had a lower complete curative rate than the other types. TB pleurisy was the most curable subtype, with a 92.0% curative rate ($P$=0.001). TB-related graft failure or patient death occurred in 26.1% and 23.8% of the miliary and non-pleurisy extrapulmonary types of TB, respectively, but occurred in 12.0% of the primary pulmonary type; no graft or patient loss occurred in the TB pleurisy type ($P$=0.015) (Table 3).

TB history did not affect the cure rate. Of the 28 recipients who had a history of TB, 20 patients were completely cured (cure rate=71.4%), which was similar to the patients without a history of TB (87/116 [27.0%]) ($P$=0.375).

### Graft and patient survival

During the mean 164±73.2 months of follow-up, 15 cases of graft loss and 16 cases of patient death occurred in the post-transplant TB group. TB negatively affected the graft, death-censored graft, and patient survival rates. There was a significant difference in the cumulative graft survival rate between the non-TB and TB groups (Figure 2). The non-TB group had 72.49% and 55.16% graft survival rates at 10 and 20 years, respectively, but the TB group had 58.31% and 29.49% graft survival rates, respectively ($P$<0.0001). The TB group had a significantly lower patient survival rate than the non-TB group ($P$=0.0003). Based on

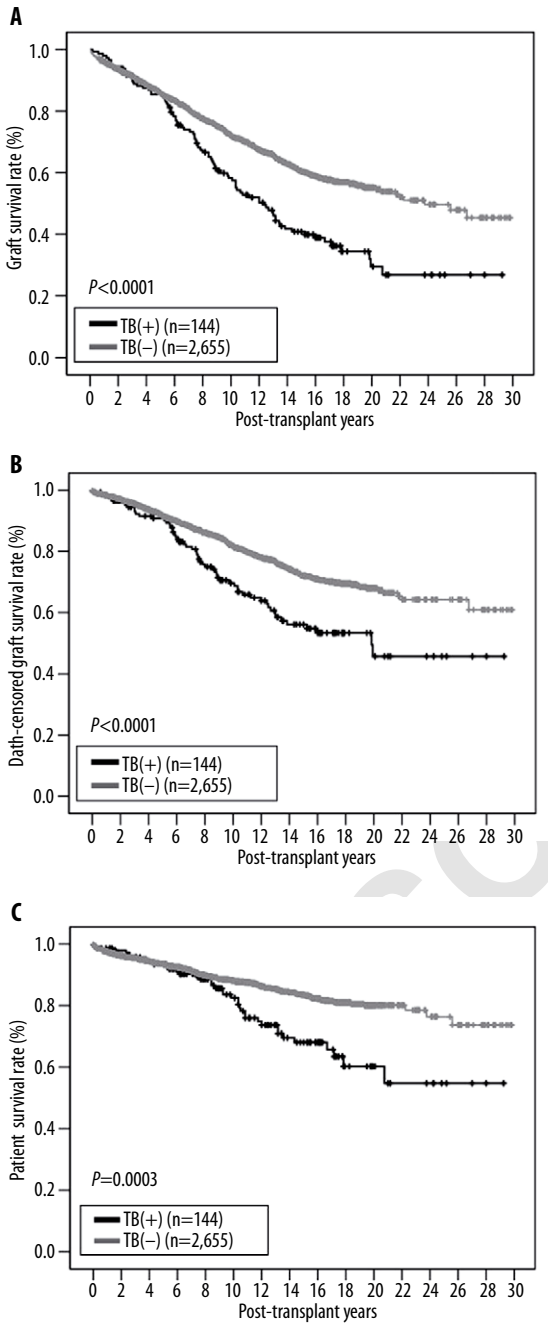



**Figure 2.** Effects of tuberculosis on graft and patient survival rates. (**A**) Graft survival rate: The non-TB group had a 72.49% and 55.16% graft survival rate at 10 and 20 years, respectively, but the TB group had a graft survival rate of 58.31% and 29.49%, respectively ($P<0.0001$). (**B**) The TB group showed a worse death-censored graft survival rate than the non-TB group ($P<0.0001$). (**C**) Patient survival rate: The non-TB group had a 88.06% and 80.09% patient survival rate of 10 and 20 years, respectively, and the TB group had a patient survival rate of 82.49% and 60.23%, respectively ($P=0.0003$). TB – tuberculosis.

multivariate survival analysis with other variables (the gender and age of the recipient, donor type,

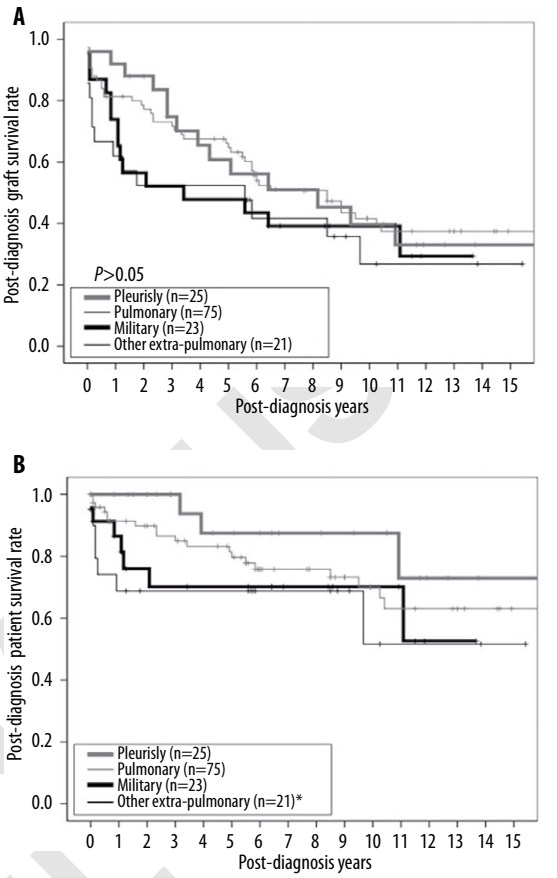



**Figure 3.** Post-tuberculosis graft survival (**A**) and patient survival rates (**B**) of each subtype of tuberculosis. TB – tuberculosis.

HLA identity, re-transplantation, pre-transplant diabetes, hepatitis B virus status, main immunosuppressive agent, and episodes of acute rejection), post-transplant TB was a significant independent variable affecting the graft and patient survival (graft survival odds ratio [OR] =1.267) ($P=0.040$; patient survival OR=1.505, $P=0.021$).

There was no significant difference in the graft survival rate between each subtype of TB. However, in the earlier post-diagnosis period, the miliary and non-pleurisy extrapulmonary types had lower graft survival rates and then exhibited a convergent survival rate to the other types of TB (Figure 3A). There was no significant difference between each group with respect to the post-diagnosis patient survival rates (Figure 3B). However, non-pleurisy extrapulmonary TB had the worst patient survival rate, especially compared with the pleurisy type of TB ($P=0.038$).

## Discussion

The incidence of post-transplant TB in renal transplantation recipients in Western countries

ranges from 0.5% to 4% [12,13]. In contrast, the incidence of TB in the endemic area is significantly greater (13.3% in India, 3.9% in Iran, 3.84% in Thailand, and 3.5% in Turkey) [2,3,6,7]. This study showed a 5.1% overall incidence of TB, which is a higher rate than the general population. In 2007, the incidence of TB in the Korean general population was reported as 71.6 per 100,000 persons by the Korean National Tuberculosis Association [11]; compared with the general population, the incidence of post-transplant TB in this study increased 70-fold.

According to the first description by Rubin et al [14], the peak incidence of TB was between 3 months and 3 years after renal transplantation. In a TB endemic area, the overall peak incidence has been reported to occur in the first post-transplant year [15]. The current study also showed the overall peak incidence of TB within 1 year following transplantation. Among all TB patients, 17.4% (25/144) of patients were diagnosed with TB within 1 year following transplantation and 45.1% (65/144) of patients were diagnosed with TB within 3 years following transplantation. However, the mean interval between transplantation and the diagnosis of TB was relatively long (55.6±47.9 months). In contrast, post-transplant TB occurred 3 years following transplantation in 54.9% of the recipients. Also, the current study showed a consistent interval incidence without a peak per every post-transplant year until 8 years after transplantation. Not only was the peak incidence within 1 year, but the consistent incidence after 1 year was a different characteristic of post-transplant TB in the current study as performed in a TB endemic area.

A pre-transplant history of TB, HBsAg, anti-HCV antibody, diabetes (including PTDM), an acute rejection episode, a major immunosuppressive agent, and use of ALA are considered to be risk factors for post-transplant TB [16–20]. The current study showed that acute rejection within 1 year following transplantation and a pre-transplant history of TB were statistical risk factors for TB infection in recent years. Among the risk factors, a pre-transplant history of TB was the strongest risk factor. Based on risk analysis, AZA-based immunosuppression was one of the risk factors for post-transplant TB in the 1984–1996 era. In our experience, the AZA-based immunosuppression group had a relatively small population (n=120, 4.29%) and was comprised of extremely early transplantation cases (before 1986). Also, in the period when AZA was used as a major immunosuppressive agent, the prevalence of TB in the general population of Korea was 3 times higher than the subsequent period [11]. Therefore, AZA-based immunosuppression is not an independent risk factor for post-transplant TB. In risk analysis only for the era between 1984 and 1986, which was the period when we used AZA or CsA as a major immunosuppressive agent, AZA was no longer a risk factor for post-transplant TB (HR, 1.272; 95% CI, 0.389–4.156, $P$=0.690; data not shown).

We identified a change in risk factors as a function of the transplant era. This change might be due to controlling some factors affecting TB. For example, an anti-hepatitis B viral agent has been used from 1999 in Korea. However, excessive immunosuppression for treatment of acute rejection and pre-transplant TB history cannot be avoided. A previous history of TB and acute rejection remains a risk factor for post-transplant occurrence. In 2,799 renal transplant recipients, there were 61 patients who had pre-transplant TB. Among them, 28 recipients (45.9%) had post-transplant TB. About one-half of the patients who had a pre-transplant history of TB acquired post-transplant TB. It is possible that latent TB was reactivated after immunosuppression. In the current study, of the 28 patients with a pre-transplant history of TB, 12 patients (42.8%) had acute rejections and treatment within 1 year post-transplant. We do not routinely use ALA as an induction therapy for living donor kidney transplantation, except for a small number of deceased donor kidney transplantations. An acute rejection episode was a risk factor for post-transplant TB in the current study. This was thought to result from the rescue therapy for acute rejection using steroid pulse therapy or ALA. As we know, severe immunosuppression during rescue therapy is related to co-infection.

The Centers for Disease Control and Prevention (CDC) guidelines recommend at least 9 months of prophylaxis with INH for high-risk transplant recipients [21]. Indications for prophylaxis also include a history of TB contact before transplantation, patients who have been newly infected with *M. tuberculosis* (ie, those with a recent PPD conversion), and recipients of transplants from donors with a history of untreated TB [22]. In the current study, 19.4% (28/144) of the recipients had a pre-transplant history of TB. We did not administer INH prophylaxis. Thus, this was a limitation of the current study. However, of the 28 patients with a previous history of TB infection,

only two patients had post-transplant TB 1 year after the post-transplant period. The median duration between transplantation and the diagnosis of TB was 38.5 months (range, 0–160 months). The mean duration between transplantation and the diagnosis of TB was not different from the group without a history of TB; there was also no significant difference in the cure rate between the patients with no TB history. TB prophylaxis for transplant recipients is controversial, especially in endemic areas [23–25]. Prophylaxis is effective among renal transplant recipients who are living in a country with a low endemicity [12]; however, no such effect was reported in a study from India involving 184 kidney transplant recipients [26]. Riska et al. suggested that patients for whom TB was completely treated in the past do not need new treatment courses or prolonged prophylaxis [27].

In the general population, a frequent TB form was pulmonary localization in Korea. The proportion of extrapulmonary TB in the endemic areas is lower; specifically, 8.3% in Poland [28] and 12.2% in Korea [11]. In other areas, however, the proportion of extrapulmonary TB in endemic areas is higher; for example, 48% in Brazil [29], 82.5% in the United States [30], and 38% in The Netherlands [31]. However, in transplant recipients it is well-known that the extrapulmonary or disseminated organ type of TB is more frequent than in the general population [24,32,33]. We showed a 31.2% extrapulmonary-type involvement among the TB patients, which is a higher proportion of extrapulmonary type of TB than 12.2% of TB patients in the general population in Korea. A predominance of extrapulmonary or disseminated-type TB is correlated with a poor prognosis in post-transplant recipients.

Our data clearly shows a negative effect of post-transplant TB on graft and patient survival rates. After solid organ transplantation, TB-related graft failure and mortality rates have been reported to be 10–25% from many countries in endemic areas [34–36]. In the current study, the TB-related graft failure and mortality rate was 13.9% (20/144), which is similar to other reports. In addition, this study also showed clear evidence of the effect of post-transplant TB on the graft and patient survival rate with a long-term follow-up period. The current study did not show a significantly different graft survival rate as a function of the TB subtype in Kaplan-Meier survival rate analysis. However, in earlier periods involving the post-diagnosis of TB, miliary TB and non-pleurisy extrapulmonary TB had worse graft survival rates than the other subgroups. Reports from endemic areas have revealed similar results [7,35]. Although the basis of this phenomenon is not fully understood, it could be related to the unusual clinical presentation of extrapulmonary TB, which can delay diagnosis and treatment [37]. The current study showed a higher TB-related graft failure and mortality rate of miliary and non-pleurisy extrapulmonary TB types than the other subtypes. However, with time, the graft survival rates of each subtype will converge. This can be attributed to the negative effect of miliary and other extrapulmonary TB on early graft survival, but in the cases in which the grafts were completely cured, the natural course of the other TB groups could be followed.

This current study is conducted by retrospective analysis. Inclusion of cases in which TB diagnosis was defined without microbiological method could be one of the limitations of the present study. In an endemic area, however, TB can be diagnosed clinically in condition of favorable response to anti-tuberculosis therapy in patients with radiologic abnormality indicating TB or fever of unknown origin when extensive investigation yielded no clues [3].

Pre-transplant TB screening is important. Our center has done tuberculin skin testing for pre-transplant TB screening since 2001 and interferon-gamma release assay since 2010. A previous report about pre-transplant TB risk factor analysis in kidney recipients revealed that positive tuberculin skin test and previously healed TB lesions visible on pre-transplant chest X-ray were significant risk factors and showed a 31.3% positivity rate in pre-transplant tuberculin skin testing [20]. False positivity in skin tests is common in endemic areas because of vaccination. In the current study, only 558 recipients were evaluated with tuberculin skin tests for pre-transplant evaluation. Among them, 185 (33.2%) recipients showed a positive (≥5mm) result. However, there was no different in TB occurrence after transplantation between the positive and negative tuberculin skin test groups (data not shown).

## Conclusions

TB is an important infectious disease for immunocompromised patients in endemic areas. In the current study, the most important risk factor for post-transplant TB was a pre-transplant history of TB. The cure rate of the group of transplant

recipients with a pre-transplant history of TB was not different from that of the group without a history of TB. Thus, we suggest that recipients with a pre-transplant TB history should be closely monitored for early detection and treatment.

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**Abbreviations**

**AFB** – acid-fast bacilli; **AR** – acute rejection; **AZA** – azathioprine; **MMF** – mycophenolate mofetil; **RFP** – rifampicin; **SM** – streptomycin; **TB** – tuberculosis.

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