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Latent Tuberculosis Infection Increases in Kidney Transplantation Recipients Compared With Transplantation Candidates: A Neglected Perspective in Tuberculosis Control

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Background. The prevalence and incidence of latent tuberculosis infection (LTBI) in patients with kidney transplantation remain unclear.

Methods. In this prospective study, we enrolled kidney transplantation candidates (KTCs) and recipients (KTRs) from 2014 to 2018. We defined LTBI as a positive result of QuantiFERON-TB Gold In-tube (QFT). We analyzed the predictors for LTBI acquisition and followed up on QFT assay test for 2 years among those initially without LTBI.

Results. Of 425 patients enrolled, 305 (71.8%) patients belonged to the KTC group and 120 (28.2%) to the KTR group. The initial QFT showed positive results in 32 (10.5%) and 24 (20.0%) patients in the KTC and KTR groups, respectively ($P = .009$). The QFT response value in patients with LTBI was higher in the KTR group than in the KTC group (1.85 vs 1.06 IU/mL, $P = .046$). Multivariate logistic regression showed that old age, absence of bacillus Calmette–Guérin (BCG) scar, presence of donor-specific antibody, and KTR group were independent factors for positive LTBI. For participants with initial negative QFT, positive QFT conversion within a 2-year follow-up was higher after kidney transplantation (20%) than in KTCs (5.5%) ($P = .034$).

Conclusions. This study is the first cohort to follow up LTBI status in patients with kidney transplantation and shows its higher prevalence and incidence in KTRs. It indicates that surveillance of LTBI after renal transplantation is important. In addition to status of kidney transplantation, old age, no BCG vaccination, and positive donor-specific antibody are also positive predictors for LTBI.

Keywords. latent tuberculosis infection; kidney transplantation; QuantiFERON-TB Gold In-tube; conversion; tuberculosis.

In 2017, an estimated 10.0 million people had active tuberculosis (TB), and 1.6 million TB-related deaths were recorded worldwide [1]. Tuberculosis remains the most common infectious disease in the world [2]. In the last decade, TB prevention has followed the Global Plan To Stop TB 2006–2015, which aims to reduce TB incidence and deaths [3]. After the goal was almost reached in 2015, the World Health Organization (WHO) suggested the END TB Strategy for the post-2015 era, including controlling latent TB infection (LTBI) towards TB elimination [4]. Among the strategies, we need to screen high-risk groups for LTBI treatment to prevent TB occurrence and transmission [5]. According to the WHO, 2 such high-risk groups are kidney transplantation candidates (KTCs) and kidney transplantation recipients (KTRs) [5].

In fact, patients with solid organ transplantation have been reported to have TB incidence as high as 506–512 per 100 000 person-years in China and Spain, respectively, which is appproximately 7–27 times higher than that of the general population [6, 7]. In particular, kidney transplantation has an odds ratio (OR) of 4.59 for developing TB [8]. In addition, preoperative LTBI has been identified as a risk factor for developing TB [8]. Once TB develops in patients with kidney transplantation, morbidity is high, approximately 6.1–8.9% [6, 7, 9, 10], and TB may cause loss of the renal allograft [11] because the manifestations of TB are atypical and delayed diagnosis ensues [9, 10]. Therefore, LTBI and TB are clinical concerns for patients belonging to the KTC and KTR groups.

Active TB can develop in patients after kidney transplantation from different pathogenesis, including reactivation from LTBI before or a new infection after transplantation

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[12], which increases due to immunosuppressive therapy. The WHO suggests that clinicians screen and manage LTBI before transplantation to reduce the possibility of reactivation [13]. Under the LTBI intervention strategy, the problem that remains after we have treated pre-existing LTBI is new infection or the reactivation of immune-unrecognized *Mycobacterium tuberculosis* after kidney transplantation. However, the prevalence of LTBI and its incidence trend after kidney transplantation remain unclear. Only a few cross-sectional studies have evaluated LTBI prevalence in KTRs [14, 15], and we have limited knowledge of new *M. tuberculosis* infection in this targeted population. Therefore, we conducted this study to evaluate the status of LTBI in patients after kidney transplantation in order to provide information for future TB-control consensus.

METHODS

Participant Enrollment

This prospective study was conducted in a tertiary referral medical center in northern Taiwan. Under the approval of the Research Ethics Committee of the study hospital (no. 201309056RINC), we recruited patients aged 20 years or older who were KTCs or KTRs in transplantation clinics from January 2014 to December 2018. All of the final enrolled participants provided signed informed-consent forms. We excluded patients with active TB, prior history of TB, liver cirrhosis, active cancer, and human immunodeficiency virus infection (Figure 1).

Tuberculosis and Latent Tuberculosis Infection Definitions

Each participant's clinical history, symptoms, and chest radiograph were reviewed to exclude active TB disease [16]. Mycobacterial study of 3 sputum samples and computerized tomography were arranged if active TB was suspected [17]. Active TB was defined as microbiology positive for *M. tuberculosis* or typical pathology or radiographic findings if available. After excluding cases of active TB, we sampled each participant's peripheral blood and examined a QuantiFERON-TB Gold In-Tube assay (QFT) (Cellestis, Australia) using a 3-tube kit [18]. Interferon-γ level was measured in the reaction supernatants, and the results were interpreted as positive, negative, or indeterminate according to the manufacturer's recommendation [19, 20]. In this study, LTBI was defined as a positive QFT result. We then compared the prevalence of LTBI status between the KTR and KTC groups.

For patients with initial negative QFT, we followed up the QFT status every 6 months for 2 years. We categorized the positive conversion of QFT as new LTBI and stopped further follow-up. If a KTC with negative QFT received transplantation, he or she was transferred from the KTC group to the new KTR group for follow-up. For those without a pretransplantation test of QFT, we tested their LTBI status within 3 months after kidney transplantation and followed up with them if the QFT result was negative. The overall incidence rates of new LTBI were calculated for the KTC group, overall KTR group, and new KTR group.

For patients with positive QFT, we suggested preventive therapy if there were no contraindications. The acceptance rate

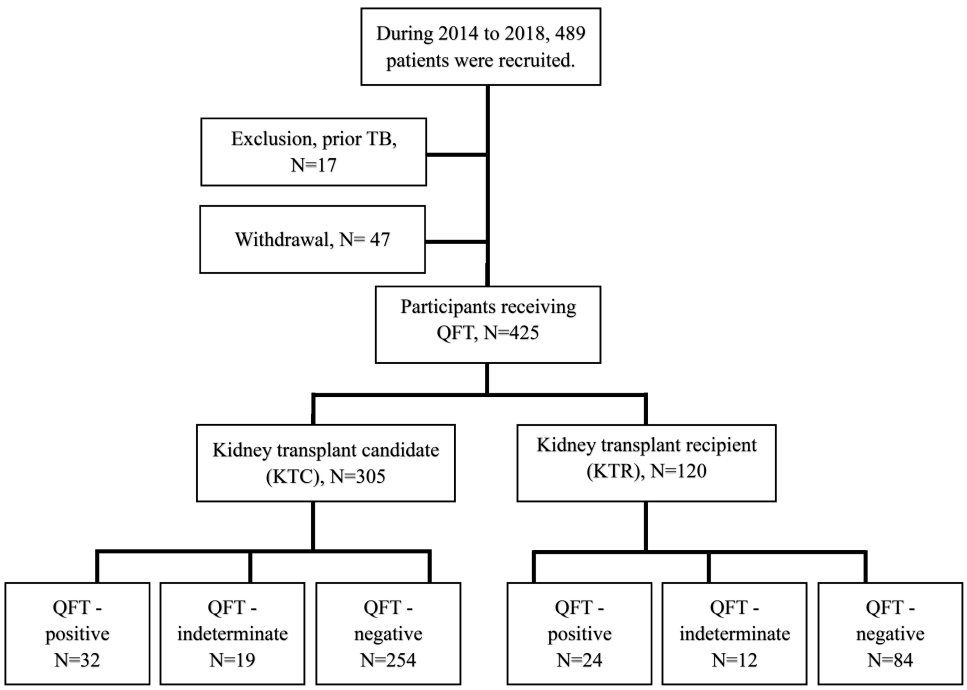

Figure 1. Flow chart of participant enrollment. Abbreviations: QFT, QuantiFERON-TB Gold In-tube; TB, tuberculosis.

of the therapy was not 100% because it was not a mandatory component of standard care in Taiwan. We followed up all participants for 2 years and checked for the occurrence of active TB in the Taiwan TB Registry.

Data Collection

The demographic and clinical data, including age, gender, underlying comorbidities, details of dialysis or transplantation, prior TB history, laboratory results, and immunosuppressants, were reviewed from the hospital's electronic records. Trained assistants and investigators interviewed the participants for respiratory and constitutional symptoms, smoking status, and history of TB exposure with a questionnaire. Body mass index (BMI) and scar number for bacillus Calmette–Guérin (BCG) vaccination were checked by trained assistants.

For the KTR group, we recorded the data of the transplants, including living or deceased donor, the presence of donor-specific antibody (DSA), ABO blood type-incompatible (ABO incompatible) status of the donor, usage of induction therapy, and maintenance immunosuppressant drugs. We recorded induction therapy and the kinds of maintenance immunosuppressant drugs, especially during the examination of baseline QFT. The usual maintenance immunosuppressive regimen comprised tacrolimus with mycophenolate mofetil and steroids. We used rituximab plus plasmapheresis as the induction therapy for kidney transplantation with positive DSA (DSA+) [21] or ABO-incompatible donors [22]. For recipients with positive DSA, intravenous immunoglobulin (IVIG) infusion after plasmapheresis was given for desensitization [21].

Chest radiography and computerized tomography were interpreted independently by a pulmonologist and a radiologist [23]. If the interpretations by the 2 readers differed, we consulted a senior pulmonologist to discuss the final coding. The classifications of radiographic findings are detailed in the Supplementary File.

Statistical Analysis

Intergroup differences were analyzed using the Student's *t* test for numerical variables, as appropriate, and chi-square test for categorical variables. Multivariate logistic regression analysis was used to identify factors associated with baseline LTBI using the stepwise method. (The details of factor selection are provided in the Supplementary File). A 2-sided $P < .05$ was considered significant. All analyses were performed in SPSS (version 19.0; IBM Corporation).

RESULTS

Participant Recruitment and Demographics

During the study period, 489 participants were recruited. Among them, 17 were excluded due to prior TB and 47 withdrew their consent. Finally, 425 patients received QFT examinations. Among them, 305 patients belonged to the KTC group and the other 120 patients were in the KTR group (Figure 1).

Table 1. Baseline Clinical Characteristics of the Kidney Transplantation Candidates and Kidney Transplantation Recipients

	KTCs (n = 305)	KTRs (n = 120)	*P*
Age, year	47.5 ± 10.9	48.9 ± 11.9	.217
Male gender	182 (60)	58 (48)	.034
Smoking			.320
Current	24 (8)	5 (4)	
Former	48 (16)	18 (15)	
BMI, kg/m^2	23.4 ± 4.4	23.1 ± 3.6	.473
BCG scar[a]			.900
0	11 (4)	4 (3)	
1	220 (73)	85 (71)	
≥2	72 (24)	31 (26)	
History of TB exposure	22 (7)	4 (3)	.133
Dialysis[b]			
Dialysis duration, years	4.3 ± 5.2	4.1 ± 4.3	.745
Mode: HD	175 (57)	…	
Mode: PD	123 (40)	…	
Diabetes mellitus, presence			.043
Diet control	6 (2)	0	
OAD use	36 (12)	6 (5)	
Insulin use	12 (4)	8 (7)	
Cardiovascular disease			
CAD	31 (10)	6 (5)	.089
CHF	22 (7)	1 (1)	.009
Liver disorder			
HBV	17 (6)	14 (12)	.030
HCV	7 (2)	1 (1)	.318
Autoimmune disease			
RA	0	2 (2)	.024
SLE	13 (4)	6 (5)	.740
Previous kidney transplantation	11 (4)	2 (2)	.296
COPD	2 (1)	2 (2)	.331
Any radiological lesion			.337
Not compatible with TB	68 (22)	31 (26)	
Compatible with prior TB	10 (3)	3 (3)	
Presence of symptoms[c]	84 (28)	25 (21)	.154
Leukocytes, cells/mm^3	7086 ± 2341	6590 ± 1931	.026
Hemoglobin, g/dL	10.8 ± 1.8	12.9 ± 2.3	<.001
Albumin,[a] g/dL	4.2 ± 0.5	4.3 ± 0.4	.072
Total bilirubin,[a] mg/dL	0.45 ± 0.15	0.59 ± 0.22	<.001
First QFT response, /mL			
TB tube–Nil tube	0.21 ± 0.87	0.21 ± 0.58	.887
Mitogen tube	6.66 ± 3.64	6.03 ± 4.01	.138

Data are presented as no. (%) or mean ± standard deviation.

Abbreviations: BCG, bacillus Calmette–Guérin vaccination; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HD, hemodialysis; KTC, kidney transplantation candidate; KTR, kidney transplantation recipient; Nil tube, negative control tube or NC tube; OAD, oral antidiabetic agent; PD, peritoneal dialysis; QFT, QuantiFERON-TB Gold In-tube; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]Data missing in 2 for BCG, 11 for albumin, and 26 for total bilirubin.

[b]Dialysis indicates current dialysis status of the KTC group but pretransplantation status of the KTR group. There were 7 KTCs who did not receive dialysis.

[c]Indicates chronic cough, dyspnea, and other constitutional symptoms.

With regard to demographic characteristics (Table 1), the average age between the 2 groups was similar (47.5 vs 48.9 years, $P = .217$), but the proportion of males was higher (60% vs 48%, $P = .034$) in the KTC group than in the KTR group. In addition,

the presence of underlying diabetes mellitus and congestive heart failure was higher in the KTC group, whereas hepatitis B virus infection and rheumatoid arthritis were higher in the KTR group. Laboratory data showed lower blood hemoglobin and total bilirubin but higher blood leukocyte counts in the KTC group than in the KTR group. There were no differences regarding other TB-associated clinical factors, such as smoking, scar of BCG vaccination, BMI, TB exposure, and dialysis history. The presence of any respiratory symptoms and radiographic lesions as well as the values of the initial QFT response were similar between the 2 groups.

Details of Initial Latent Tuberculosis Infection Status

In the initial QFT examination, positive results were reported in 32 (10.5%) patients in the KTC group and 24 (20.0%) patients in the KTR group (Figure 1). The positive rate of QFT was significantly higher in the KTR group ($P = .009$ by chi-square test) than in the KTC group. Among the patients with positive initial QFT, 13 (54%) in the KTR group and 20 (63%) in the KTC group received preventive therapy for LTBI ($P = .530$). The remaining patients with LTBI requested observation and declined preventive LTBI treatment. The QFT response value in LTBI treatment recipients was 1.20 ± 1.10 IU/mL, which was similar to the response value of 1.89 ± 2.19 in those without treatment ($P = .174$). Although indeterminate results were also higher in the KTR group than in the KTC group, the difference was not significant (10% vs 5.9%, $P = .138$). With regard to the QFT response value, the response was higher in the KTR group with positive initial QFT results than in the KTC group (1.85 ± 2.01 vs 1.06 ± 0.82, $P = .046$). For those with initial negative or indeterminate results, the values were similar in the 2 groups.

Factors Associated With Baseline Latent Tuberculosis Infection

To further differentiate factors associated with baseline LTBI in all of the study participants, we performed logistic regression. Increasing age, coronary artery disease (CAD), hepatitis B virus infection, scar of BCG vaccination, positive DSA, induction therapy, and kidney transplantation were significant factors in the univariate analysis (Table 2). Multivariate logistic regression by a stepwise method was performed by using all significant factors in univariate analysis and other relevant factors, such as gender and TB exposure. The results showed that the positive independent factors for LTBI included increasing age (OR, 1.027; 95% confidence interval [CI], 1.000–1.055, per 1-year increment; $P = .050$), positive DSA (OR, 8.242; 95% CI, 1.249–54.399; $P = .028$), and receiving kidney transplantation (OR, 1.904; 95% CI, 1.031–3.516; $P = .040$), whereas the negative factor was BCG vaccination (OR [95% CI], 0.199 [.065–.608] [$P = .005$] for 1 scar and 0.175 [.051–.598] [$P = .005$] for 2 scars compared with no vaccination scar).

Within the KTR group (Table 3), positive DSA was also significantly associated with LTBI status. Underlying CAD, autoimmune disease, hepatitis C virus infection, prior kidney transplantation history, and presence of respiratory symptoms were associated with LTBI status. Immunosuppressants were not significantly associated with LTBI status.

Details of Latent Tuberculosis Infection in the Follow-up Course

The participants with initial negative QFT status were invited to be followed up for QFT every 6 months. There were 161 in the KTC group, 51 in the overall KTR group, and 15 in the new KTR group (Table 4). The demographic characteristics among those with initial negative LTBI and follow-up were similar, except that the blood hemoglobin and total bilirubin levels were higher but leukocyte counts were lower in the overall KTR group than in the KTC group. With regard to induction therapy, 3 patients received induction therapy before kidney transplantation with incompatible ABO status in the KTR group. Among them, all 3 patients had no LTBI conversion (6.8% vs 0, $P = .476$). All of the cohort reported no TB exposure during the follow-up. The new positive QFT numbers in the 3 groups are shown in Figure 2A. Within the 2-year follow-up, 9 (5.6%), 7 (13.7%), and 3 (20%) patients had QFT positive conversion in the KTC, overall KTR, and new KTR groups, respectively. The positive conversion rate was higher in the new and overall KTR groups than in the KTC group ($P = .034$ and .055, respectively) (Figure 2B).

Among those who underwent kidney transplantation, 2 cases had active TB development. The first patient received kidney transplantation from a deceased donor. His maintenance immunosuppressants included tacrolimus, mycophenolate mofetil, and prednisolone. His initial QFT was positive, but no preventive therapy was given because the patient refused it. Active pulmonary TB was diagnosed by suspicious findings on radiography plus treatment response at approximately 11.5 months after kidney transplantation. He was treated with an anti-TB regimen with good graft function. The other patient, who had hepatitis C virus infection, had received a deceased-donor kidney transplantation 27 years before the initial negative QFT. The maintenance immunosuppressants were cyclosporine, mycophenolate mofetil, and prednisolone. During our follow-up, his kidney function declined, and he received a second renal transplantation from a deceased donor at the 22nd month of follow-up. He had chronic cough and QFT at the 24th month, indicating positive conversion. Pulmonary TB was diagnosed by positive sputum acid-fast smear and mycobacterial culture for *M. tuberculosis*. The treatment course for TB was uneventful, without major drug adverse effects. The incidence of TB was approximately 833 per 100 000 person-years (2 in 120 cases with kidney transplantation in 2 years). In contrast, no active TB cases developed in the KTC group during the 2-year follow-up.

DISCUSSION

In the present study, we report that KTRs had a higher LTBI prevalence and incidence than KTCs in a cross-sectional and

Table 2. Univariate and Multivariate Logistic Regression for Predicting Positive Interferon-γ Release Assay Among Patients

	Univariate		Multivariate	
Characteristics	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years	1.028 (1.001–1.055)	.046	1.027 (1.000–1.055)	.050
Gender, male vs female	1.333 (.748–2.378)	.330	…	
Current smoker vs others	1.805 (.701–4.650)	.221	…	
Diabetes mellitus				
Absence	Reference		…	
Diet control	1.387 (.158–12.141)	.221	…	
OAD use	1.156 (.461–2.879)	.221	…	
Insulin use	1.733 (.555–5.416)	.221	…	
Cardiovascular disease				
CAD	2.332 (1.037–5.245)	.041	…	
CHF	0.287 (.038–2.171)	.226	…	
Liver disorder				
HBV	2.507 (1.062–5.921)	.036	…	
HCV	2.241 (.441–11.387)	.331	…	
Autoimmune disease				
RA	N/A	.999	…	
SLE	1.249 (.352–4.431)	.731	…	
Previous kidney transplantation	1.205 (.260–5.587)	.811	…	
COPD	N/A	.999	…	
TB exposure	0.852 (.247–2.952)	.799	…	
BMI, kg/m^2	0.996 (.931–1.065)	.900	…	
BCG scar[a]				
0	Reference		Reference	
1	0.213 (.072–.633)	.005	0.199 (.065–.608)	.005
≥2	0.198 (.060–.654)	.008	0.175 (.051–.598)	.005
Current dialysis mode				
No dialysis	Reference		…	
Peritoneal dialysis	0.637 (.290–1.398)	.260	…	
Hemodialysis	1.028 (.533–1.982)	.934	…	
KTR compared with KTC group	2.133 (1.196–3.802)	.010	1.904 (1.031–3.516)	.040
KTR, liver donor vs deceased donor	0.986 (.425–2.284)	.973	…	
Donor, ABO, incompatible vs compatible	3.060 (.910–10.294)	.071	…	
DSA, presence vs absence	3.214 (1.299–7.954)	.012	8.242 (1.249–54.399)	.028
Induction therapy, presence vs absence	3.900 (1.257–12.095)	.018	…	
Symptoms,[b] presence vs none	1.447 (.787–2.660)	.234	…	
Radiologic lesion, any vs none	0.807 (.417–1.564)	.526	…	
Leukocyte count, cells/mm^3	1.000 (1.000–1.000)	.870	…	
Hemoglobin, g/dL	1.088 (.966–1.225)	.165	…	
Albumin,[a] g/dL	1.268 (.709–2.268)	.423	…	
Total bilirubin,[a] mg/dL	2.212 (.480–9.380)	.321	…	

Abbreviations: ABO, ABO blood types; BCG, bacillus Calmette–Guérin vaccination; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DSA, donor-specific antibody; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; KTC, kidney transplantation candidate; KTR, kidney transplantation recipient; N/A, not applicable, meaning the results were very low; OAD, oral antidiabetic agent; OR, odds ratio; QFT, QuantiFERON-TB Gold In-tube; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]Data missing in 2 for BCG, 11 for albumin, and 26 for total bilirubin.

[b]Indicates chronic cough, dyspnea, and other constitutional symptoms.

cohort study design, respectively. For this population, old age, absence of BCG vaccination scar, and positive DSA, in addition to receiving a kidney transplantation, were significant factors associated with positive QFT-defined LTBI.

In the post-2015 era, the WHO aims to eliminate TB worldwide and has established many frameworks [4]. Among them, LTBI screening and treatment are vitally important issues [5] and have been recommended in high- or intermediate-income countries with a TB incidence of less than 100 per 100 000 person-years [13]. Of the LTBI-risk population, patients with kidney transplantation account for a major proportion of transplantation patients [24] and need to be targeted because of their immunocompromised status and high mortality once active TB develops. Under contemporary recommendations,

Table 3. Details of Status and Immunosuppressants Among Kidney Transplantation Recipients According to Status of Latent Tuberculosis Infection

	All (N = 120)	LTBI (n = 24)	No LTBI (n = 96)	*P*
Age, years	48.9 ± 11.9	51.6 ± 10.7	48.3 ± 12.2	.233
Male gender	58 (48)	14 (58)	44 (46)	.273
Smoking				.668
Current	5 (4)	1 (4)	4 (4)	
Former	18 (15)	5 (21)	13 (14)	
BMI, kg/m^2	23.1 ± 3.6	23.4 ± 3.4	23.1 ± 3.7	.711
BCG scar				.281
0	4 (3)	2 (8)	2 (2)	
1	85 (71)	17 (71)	68 (71)	
≥2	31 (26)	5 (21)	26 (27)	
Time after transplantation, years	6.3 ± 5.6	5.0 ± 5.6	6.7 ± 5.6	.177
Donor				
Living donor	61 (51)	12 (50)	49 (51)	.927
DSA[a]	5 (4)	3 (13)	2 (2)	.024
ABOi[a]	11 (9)	3 (11)	8 (9)	.549
Induction therapy	14 (12)	5 (21)	9 (10)	.128
Immunosuppressants, at QFT test				
Mycophenolate mofetil	64 (53)	14 (58)	50 (52)	.583
Tacrolimus	111 (93)	21 (88)	90 (94)	.298
Everolimus	11 (9)	0	11 (12)	.082
Sirolimus	48 (40)	9 (38)	39 (41)	.780
Azathioprine	14 (12)	3 (13)	11 (12)	.887
Mycophenolic acid	38 (32)	8 (33)	30 (31)	.844
Cyclosporine	2 (2)	0	2 (2)	.476
Prednisolone	96 (80)	17 (71)	79 (82)	.209
History of TB exposure	4 (3)	0	4 (4)	.309
Diabetes mellitus, presence				.289
Diet control	0	0	0	
OAD use	6 (5)	2 (8)	4 (4)	
Insulin use	8 (7)	3 (13)	5 (5)	
Cardiovascular disease				
CAD	6 (5)	4 (17)	2 (2)	.003
CHF	1 (1)	0	1 (1)	.616
Liver disorder				
HBV	14 (12)	5 (21)	9 (9)	.118
HCV	1 (1)	1 (4)	0	.045
Autoimmune disease				
Total	10 (8)	5 (21)	5 (5)	.013
RA	2 (2)	2 (8)	0	.004
SLE	6 (5)	3 (13)	3 (3)	.059
Kidney transplantation before	2 (2)	2 (8)	0	.004
COPD	2 (2)	0	2 (2)	.476
Any radiological lesion				.337
Not compatible with TB	31 (26)	5 (21)	26 (27)	
Compatible with prior TB	3 (3)	1 (4)	2 (2)	
Presence of symptoms[b]	25 (21)	9 (38)	16 (17)	.025
Leukocytes, cells/mm^3	6590 ± 1931	6524 ± 1779	6606 ± 1975	.853
Hemoglobin, g/dL	12.9 ± 2.3	12.5 ± 2.6	13.0 ± 2.4	.404
Albumin, g/dL	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	.584
Total bilirubin, mg/dL	0.59 ± 0.22	0.61 ± 0.20	0.59 ± 0.22	.713

Data are presented as no. (%) or mean ± standard deviation.

Abbreviations: ABOi, ABO blood type-incompatible; BCG, bacillus Calmette–Guérin vaccination; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DSA, donor-specific antibody; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; LTBI, latent tuberculosis infection; OAD, oral antidiabetic agent; QFT, QuantiFERON-TB Gold In-tube; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]There were 2 cases with ABOi and DSA together.

[b]Indicated chronic cough, dyspnea, and other constitutional symptoms.

Table 4. Demographic Characteristics of Participants With Initial Negative Result of QuantiFERON-TB Gold In-tube and Receiving Follow-up Using QuantiFERON-TB Gold In-tube

	KTCs (n = 161)	All KTRs (n = 51)	*P*1	New KTRs (n = 15)	*P*2
Age, years	47.8 ± 10.9	49.3 ± 10.6	.396	43.9 ± 13.0	.323
Male gender	89 (55)	27 (53)	.830	11 (73)	.175
Smoking			.965		.944
Current	11 (8)	3 (6)		1 (7)	
Former	27 (17)	9 (18)		2 (13)	
BMI, kg/m^2	23.5 ± 4.7	23.4 ± 4.0	.991	23.4 ± 4.8	.926
BCG scar			.324		.635
0	4 (2)	2 (4)		1 (7)	
1	116 (72)	31 (61)		10 (67)	
≥2	41 (26)	18 (35)		4 (27)	
History of TB exposure	11 (7)	3 (6)	.812	1 (7)	.985
Dialysis duration,[a] years	4.3 ± 4.5	4.5 ± 3.8	.473	4.2 ± 3.8	.953
Living donor (otherwise deceased)	…	18 (35)		7 (47)	
DSA positive	…	0		0	
ABOi	…	3 (6)		1 (7)	
Induction therapy	…	3 (6)		1 (7)	
Immunosuppressants, after kidney transplantation					
Mycophenolate mofetil	…	37 (73)		13 (87)	
Tacrolimus	…	45 (88)		15 (100)	
Everolimus	…	0		0	
Sirolimus	…	3 (6)		1 (7)	
Azathioprine	…	0		0	
Mycophenolic acid	…	8 (16)		2 (13)	
Cyclosporine	…	5 (10)		0	
Prednisolone	…	50 (98)		15 (100)	
Diabetes mellitus			.457		.944
Diet control	1 (1)	0		0	
OAD use	20 (12)	5 (10)		2 (13)	
Insulin use	5 (3)	4 (8)		1 (7)	
Cardiovascular disease					
CAD	12 (7)	3 (6)	.703	2 (13)	.416
CHF	13 (8)	1 (2)	.126	1 (8)	.852
Liver disorder					
HBV	7 (4)	4 (8)	.327	1 (7)	.676
HCV	2 (1)	0	.424	0	.665
Autoimmune disease					
Total	12 (7)	3 (6)	.703	1 (7)	.916
SLE	11 (7)	2 (4)	.450	1 (7)	.985
Kidney transplantation before	8 (5)	0	.105	0	.378
COPD	1 (1)	1 (2)	.388	0	.760
Any radiological lesion			.840		.526
Not compatible with TB	38 (24)	13 (26)		2 (14)	
Compatible with prior TB	6 (4)	1 (2)		0	
Presence of symptoms[b]	57 (35)	11 (22)	.065	3 (20)	.224
Leukocytes, cells/mm^3	7139 ± 2399	6026 ± 1739	.002	6255 ± 2062	.165
Hemoglobin, g/dL	10.9 ± 1.7	12.8 ± 2.4	<.001	12.0 ± 2.4	.148
Albumin, g/dL	4.2 ± 0.5	4.2 ± 0.5	.764	4.1 ± 0.7	.227
Total bilirubin, mg/dL	0.44 ± 0.12	0.58 ± 0.20	<.001	0.49 ± 0.17	.520

Data are presented as no. (%) or mean ± standard deviation. Patients are classified by transplantation status. *P*1 and *P*2 values are compared between all patients with kidney transplantation vs waiting group and patients with new kidney transplantation vs waiting group, respectively.

Abbreviations: ABOi, ABO blood type-incompatible; BCG, bacillus Calmette–Guérin vaccination; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DSA, donor-specific antibody; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; KTC, kidney transplantation candidate; KTR, kidney transplantation recipient; OAD, oral antidiabetic agent; QFT, QuantiFERON-TB Gold In-tube; SLE, systemic lupus erythematosus; TB, tuberculosis.

[a]Dialysis indicates current dialysis status of KTC group but pretransplantation status of KTR group.

[b]Indicates chronic cough, dyspnea, and other constitutional symptoms.

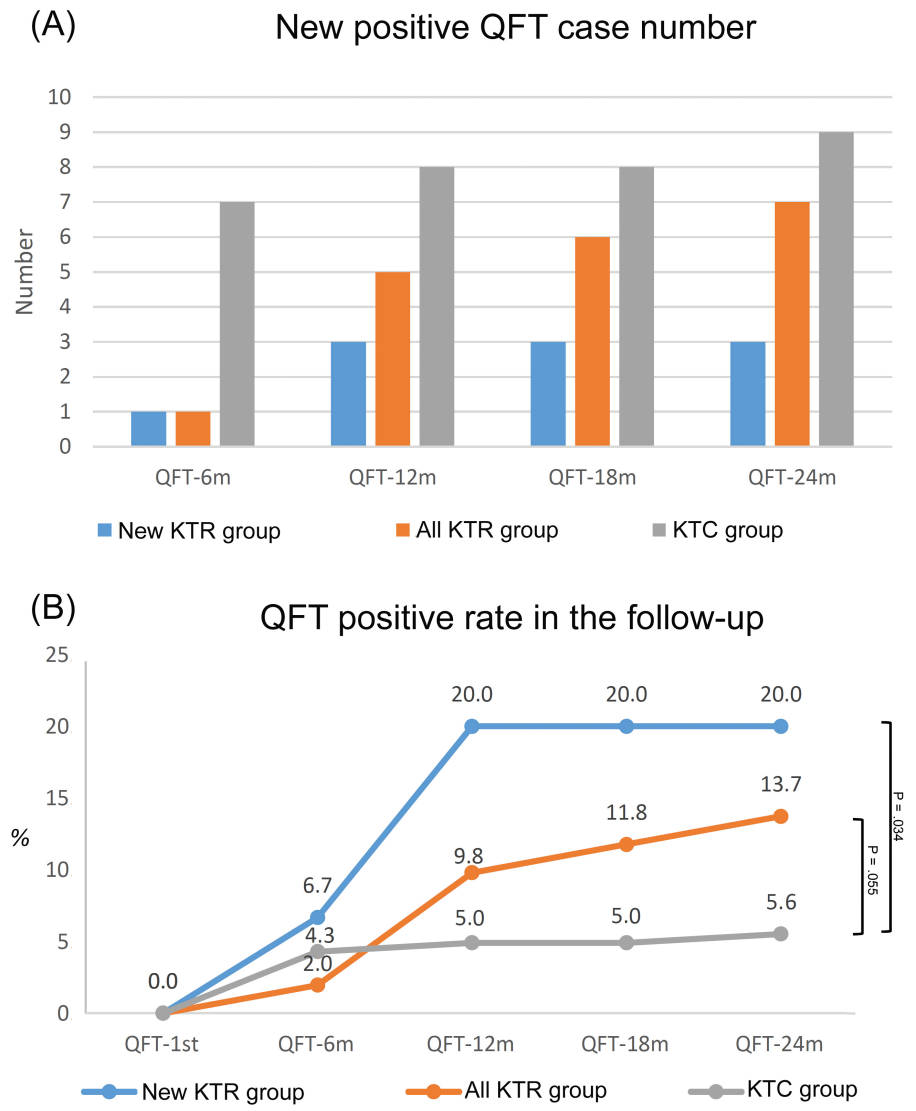

Figure 2. The follow-up results of QFT for participants with initial negative QFT according to kidney transplantation status. *A*, The new positive QFT number. *B*, The percentage of positive conversion. Abbreviations: KTC, kidney transplantation candidate; KTR, kidney transplantation recipient; m, months; QFT, QuantiFERON-TB Gold In-tube.

pretransplantation LTBI screening has been implemented worldwide [7, 25]; however, no evidence of LTBI survey after transplantation has been reported before this prospective study.

The present cross-sectional study found a higher LTBI prevalence in the KTR group than in the KTC group, which was supported by adjustment of the multivariate analysis. In addition, the occurrence of new LTBI infection and active TB development within 2 years was also higher in the KTR group than in the KTC group. These facts emphasize the importance of LTBI/TB control after kidney transplantation. Among the factors associated with LTBI status after kidney transplantation, positive DSA was an independent factor. The process and medication given before transplantation with positive DSA included induction with rituximab and IVIG infusion after plasmapheresis for desensitization [21]. In comparison with incompatible ABO status, IVIG was the only additional medication in recipients with positive DSA. Therefore, we suggest that IVIG-related suppression of T cells [26] and innate immune cells [27] might be an important factor that leads to susceptibility to *M. tuberculosis* infection. In addition, the status of kidney transplantation was still one of the independent predictors for LTBI (Table 2). Kidney transplantation status might be a surrogate of many complex factors after transplantation, one which cannot be dissected with the scale of the current study and the collinearity between transplantation status and immunosuppressant medications. Although the procedure of induction therapy and the immunosuppressants might be important concerns related to LTBI status, no statistical significance was found in this study. Further large-scale studies focusing on the effects of medication are required.

The higher rate of positive conversion among the new KTR group might have arisen because some of them had false-negative QFT prior to transplantation due to dormant status or a long interval since *M. tuberculosis* infection [28]. This kind of activation of dormant or immune-unrecognized *M. tuberculosis* might be the pathogenesis of positive conversion of LTBI soon after recent kidney transplantation with the use of immunosuppressants. On the other hand, a new *M. tuberculosis* infection could exist among the KTR or KTC group [29]. However, the susceptibility to new *M. tuberculosis* infection might be higher in the KTR group than in the KTC population (Figure 2B), possibly due to the process and immunosuppression therapy used for the transplantation [30, 31]. The QFT conversion rates in the KTR groups were similar, with 7–8.5% conversion at the 12-month follow-up [32, 33] and 13.6% conversion at the 24-month follow-up [34] among patients with rheumatoid disease receiving biologic agents. Therefore, this result indicates that, in addition to pretransplantation screening, surveillance of LTBI is also needed after transplantation. Although the duration of follow-up remains unclear and requires further investigation, we propose LTBI checks at least twice annually after transplantation because the highest risk of LTBI conversion occurs approximately 6–12 months after kidney transplantation, and active TB occurs more frequently within the first 2 years, according to the literature and our report [6, 35]. We have no suggestions for periods exceeding 2 years due to limited data. In addition, data may need to be collected in an area with less TB prevalence.

On the other hand, many clinical factors in addition to kidney transplantation favored positive LTBI status. Among them, age is a well-known factor that is positively correlated with the QFT-positive rate [36]. In contrast, a present BCG vaccination scar shows a negative correlation with LTBI, which is consistent with investigations in children [37] and adult prisoners [38]. With regard to TB exposure, the association with positive QFT is not significant and may be related to the information not being recent and having been collected by questionnaire. Therefore, the effect and significance might be less correlated than in a previous report on TB contact [39].

There are several limitations to the present study. First, the participants were voluntarily enrolled, so selection bias might exist. Second, the use of questionnaires for some data collection, such as TB exposure and smoking, might have incurred recall bias. Third, the case number for the 2-year follow-up was small. A validation study is needed. Fourth, the QFT statuses of the living donors were not checked. Last, the participants were enrolled in Taiwan, so generalization to other areas or ethnicities may not be applicable and will require further study.

In conclusion, LTBI was higher in the KTR group than in the KTC group. Old age, absent BCG scar, positive DSA, and status of kidney transplantation were LTBI-associated factors. In particular, the prevalence of positive LTBI conversion was approximately 20% within 2 years in the new KTR group. This finding indicated that a strategy for posttransplantation LTBI surveillance is needed, despite this not being included in current LTBI recommendations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. C-C. S., C-Y. L., and M-K. T. designed and performed the study. C-C. S., C-Y. L., S-W. L., J-Y. W., C-J. Y., and M-K. T. were involved in data interpretation, analysis, critique, and manuscript preparation. C-Y. L. was responsible for coordinating the study.

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References

1. World Health Organization. Global Tuberculosis Report 2018. Geneva, Switzerland: World Health Organization, **2018**.
2. World Health Organization. Group at risk: WHO report on the tuberculosis epidemic. Geneva, Switzerland: World Health Organization, **1996**.
3. Wejse C. Tuberculosis elimination in the post Millennium Development Goals era. Int J Infect Dis **2015**; 32:152–5.
4. Lönnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J **2015**; 45:928–52.
5. Rose DN. Benefits of screening for latent *Mycobacterium tuberculosis* infection. Arch Intern Med **2000**; 160:1513–21.
6. Liu J, Yan J, Wan Q, Ye Q, Huang Y. The risk factors for tuberculosis in liver or kidney transplant recipients. BMC Infect Dis **2014**; 14:387.
7. Torre-Cisneros J, Doblas A, Aguado JM, et al; Spanish Network for Research in Infectious Diseases. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis **2009**; 48:1657–65.
8. Lopez de Castilla D, Schluger NW. Tuberculosis following solid organ transplantation. Transpl Infect Dis **2010**; 12:106–12.
9. Canet E, Dantal J, Blancho G, Hourmant M, Coupel S. Tuberculosis following kidney transplantation: clinical features and outcome: a French multicentre experience in the last 20 years. Nephrol Dial Transplant **2011**; 26:3773–8.
10. Gras J, De Castro N, Montlahuc C, et al. Clinical characteristics, risk factors, and outcome of tuberculosis in kidney transplant recipients: a multicentric case-control study in a low-endemic area. Transpl Infect Dis **2018**; 20:e12943.
11. Krishnamoorthy S, Kumaresan N, Zumla A. Latent tuberculosis infection and renal transplantation—diagnosis and management. Int J Infect Dis **2019**; 80S:73–6.
12. Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. Eur Respir J **2012**; 40:990–1013.
13. Getahun H, Matteelli A, Abubakar I, et al. Management of latent *Mycobacterium tuberculosis* infection: WHO guidelines for low tuberculosis burden countries. Eur Respir J **2015**; 46:1563–76.

14. Sester M, van Leth F, Bruchfeld J, et al; Tuberculosis Network European Trials group (TBNET). Risk assessment of tuberculosis in immunocompromised patients: a TBNET study. Am J Respir Crit Care Med **2014**; 190:1168–76.
15. Hadaya K, Bridevaux PO, Roux-Lombard P, et al. Contribution of interferon-gamma release assays (IGRAs) to the diagnosis of latent tuberculosis infection after renal transplantation. Transplantation **2013**; 95:1485–90.
16. Chiang CY, Wang JY, Yu MC, et al. Taiwan guidelines for TB diangosis and treatment. 5th ed. Taipei, Taiwan: Center for Disease Control, Executive Yuan, Taiwan, **2017**.
17. Shu CC, Wang JT, Lee CH, Wang JY, Lee LN, Yu CJ. Predicting results of mycobacterial culture on sputum smear reversion after anti-tuberculous treatment: a case control study. BMC Infect Dis **2010**; 10:48.
18. Lalvani A, Pathan AA, McShane H, et al. Rapid detection of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. Am J Respir Crit Care Med **2001**; 163:824–8.
19. Dyrhol-Riise AM, Gran G, Wentzel-Larsen T, Blomberg B, Haanshuus CG, Morkve O. Diagnosis and follow-up of treatment of latent tuberculosis; the utility of the QuantiFERON-TB Gold In-tube assay in outpatients from a tuberculosis low-endemic country. BMC Infect Dis **2010**; 10:57.
20. Banach DB, Harris TG. Indeterminate QuantiFERON®-TB Gold results in a public health clinic setting. Int J Tuberc Lung Dis **2011**; 15:1623–30.
21. Lee CY, Lin WC, Wu MS, Yang CY, Yeh CC, Tsai MK. Repeated cycles of high-dose intravenous immunoglobulin and plasmapheresis for treatment of late antibody-mediated rejection of renal transplants. J Formos Med Assoc **2016**; 115:845–52.
22. Tsai MK, Wu MS, Yang CY, et al. B cells and immunoglobulin in ABO-incompatible renal transplant patients receiving rituximab and double filtration plasmapheresis. J Formos Med Assoc **2015**; 114:353–8.
23. Wang JY, Hsueh PR, Jan IS, et al. Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas. Thorax **2006**; 61:903–8.
24. Grim SA, Layden JE, Roth P, Gallitano S, Adams W, Clark NM. Latent tuberculosis in kidney and liver transplant patients: a review of treatment practices and outcomes. Transpl Infect Dis **2015**; 17:768–77.
25. Sidhu A, Verma G, Humar A, Kumar D. Outcome of latent tuberculosis infection in solid organ transplant recipients over a 10-year period. Transplantation **2014**; 98:671–5.
26. Trépanier P, Bazin R. Intravenous immunoglobulin (IVIg) inhibits CD8 cytotoxic T-cell activation. Blood **2012**; 120:2769–70.
27. Tjon AS, van Gent R, Jaadar H, et al. Intravenous immunoglobulin treatment in humans suppresses dendritic cell function via stimulation of IL-4 and IL-13 production. J Immunol **2014**; 192:5625–34.
28. Shu CC, Wu VC, Yang FJ, et al. Dynamic changes in positive interferon-gamma release assay in a dialysis population: an observational cohort study. J Infect **2013**; 67:529–35.
29. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP. The immune response in tuberculosis. Annu Rev Immunol **2013**; 31:475–527.
30. Simmons JD, Stein CM, Seshadri C, et al. Immunological mechanisms of human resistance to persistent *Mycobacterium tuberculosis* infection. Nat Rev Immunol **2018**; 18:575–89.
31. Esmail H, Barry CE III, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philos Trans R Soc Lond B Biol Sci **2014**; 369:20130437.
32. Hatzara C, Hadziyannis E, Kandili A, et al. Frequent conversion of tuberculosis screening tests during anti-tumour necrosis factor therapy in patients with rheumatic diseases. Ann Rheum Dis **2015**; 74:1848–53.
33. Taxonera C, Ponferrada Á, Riestra S, et al; CONVERT Study Group from Grupo Español de Trabajo de Crohn y Colitis Ulcerosa. Serial tuberculin skin tests improve the detection of latent tuberculosis infection in patients with inflammatory bowel disease. J Crohns Colitis **2018**; 12:1270–9.
34. Cuomo G, D'Abrosca V, Iacono D, Pantano I. The conversion rate of tuberculosis screening tests during biological therapies in patients with rheumatoid arthritis. Clin Rheumatol **2017**; 36:457–61.
35. Ulubay G, Kupeli E, Duvenci Birben O, et al. A 10-year experience of tuberculosis in solid-organ transplant recipients. Exp Clin Transplant **2015**; 13(Suppl 1):214–8.
36. Shu CC, Wu VC, Yang FJ, et al. Predictors and prevalence of latent tuberculosis infection in patients receiving long-term hemodialysis and peritoneal dialysis. PLoS One **2012**; 7:e42592.
37. Basu Roy R, Sotgiu G, Altet-Gómez N, et al. Identifying predictors of interferon-γ release assay results in pediatric latent tuberculosis: a protective role of bacillus Calmette-Guerin? A pTB-NET collaborative study. Am J Respir Crit Care Med **2012**; 186:378–84.
38. Chan PC, Yang CH, Chang LY, et al. Lower prevalence of tuberculosis infection in BCG vaccinees: a cross-sectional study in adult prison inmates. Thorax **2013**; 68:263–8.
39. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. Am J Respir Crit Care Med **2008**; 177:1164–70.