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Tacrolimus Trough Level at the First Month May Predict Renal Transplantation Outcomes Among Living Chinese Kidney Transplant Patients: A Propensity Score–Matched Analysis

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Background: Monitoring and maintaining a stable tacrolimus trough level is essential because of its narrow therapeutic window and considerable fluctuation in the early phase after kidney transplantation. However, optimal tacrolimus exposure early after transplantation remains unclear among Chinese patients.

Methods: In this propensity score–matched cohort study, we thoroughly investigated the association between tacrolimus trough level at the first month and acute rejection (AR) as well as infection within the first year after kidney transplantation.

Results: In a first step, a total of 1415 patients were divided into 3 groups according to the receiver operating characteristic curve: low-level group (410 patients with a tacrolimus trough level <5.35 ng/mL at the first month), median-level group (466 patients with a tacrolimus trough level from 5.35 to 7.15 ng/mL), and high-level group (539 patients with a tacrolimus trough level >7.15 ng/mL). Ultimately, 363 and 459 pairs of cases were enrolled by using 2 propensity score matches between low- and median-level groups and between high- and median-level groups, respectively. Compared with patients in the low-level group, patients in the median-level group had lower risk of AR without increased incidence of infection (AR, 12.4% versus 5.7%, $P = 0.02$; infection, 13.2% versus 13.2%, $P = 1.00$ for low- and median-level groups, respectively) within the first year. Compared with patients in the high-level group, patients in the median-level group had lower incidence of infection without the growing risk of AR (infection, 17.6% versus 12.2%, $P = 0.021$; AR, 4.6% versus 5.4%, $P = 0.545$ for high- and median-level groups, respectively) within the first year. Multilogistic analysis showed that tacrolimus trough levels were an independent factor for AR (odds ratio, 0.749, 95% confidence interval, 0.632–0.888, $P = 0.001$). Tacrolimus trough levels were also associated with infection (odds ratio 1.110, 95% confidence interval, 1.013–1.218, $P = 0.001$). Serum creatinine levels were similar among groups. No difference was found in 1-, 3-, and 5-year graft survival and patient survival among groups.

Conclusions: The tacrolimus trough level maintained between 5.35 and 7.15 ng/mL at the first posttransplant month may prevent AR without increasing the incidence of infection within the first year after living kidney transplantation among Chinese patients.

Key Words: tacrolimus, AR, infection, kidney transplantation, Chinese

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INTRODUCTION

As a preferred treatment for end-stage renal diseases, kidney transplantation is more effective in prolonging the life span and improving the quality of life compared with dialysis.[1,2] Lifelong immunosuppressive therapy is indispensable to ensure a higher survival rate of grafts and patients after kidney transplantation.[3] Tacrolimus, combined with mycophenolate mofetil (MMF)/EC-MPS and steroid, has been accepted as the standardized immunosuppressive regimen and is now adopted in over 90% of the kidney transplantation recipients.[4]

However, considerable fluctuation of tacrolimus trough levels early after transplantation may cause poor clinical outcome due to the narrow therapeutic window.[5] Moreover, low tacrolimus trough levels may not prevent acute rejection

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(AR) effectively, whereas high levels are associated with increased infection and toxicity.[6] Appropriate tacrolimus concentration early after kidney transplantation remains unreported in the Chinese population.

The Kidney Disease Improving Global Outcomes has recommended 5–15 ng/mL of tacrolimus at the early post-transplant stage.[7] However, recent studies have challenged previous results. Richards et al[8] reported that tacrolimus concentrations of >8 ng/mL are needed to reduce the incidence of early AR. By contrast, Bouamar et al[9] showed that the tacrolimus trough level has no impact on AR early after transplantation. Furthermore, a number of studies indicated that various infections, partially resulting from intense immunosuppression, caused early-stage recipient death as the primary complication.[10–12]

We hypothesize that tacrolimus trough levels during the first month are associated with AR and infection within the first year after kidney transplantation. The aim of this propensity score–matched cohort study is to explore the optimal tacrolimus trough level among the Chinese population.

MATERIAL AND METHODS

Patients and Data Collection

The clinical data of patients who received kidney transplantation from a living relative donor in West China Hospital between 2007 and 2017 were reviewed. The Ethical Committee of West China Hospital approved this study. Patients were excluded if they conformed to any one of the following criteria: (1) younger than 18 years; (2) initial calcineurin inhibitor was not tacrolimus; (3) ABO-incompatible renal transplantation; (4) organ transplantation history; (5) lost in the first-year follow-up; and (6) follow-up less than 1 year.

Tacrolimus trough levels were measured using the enzyme multiplied immunoassay technique (Dade-Behring, NY) via collecting whole blood samples every week in the first 3 months, every 2 weeks in 4–6 months, every month after 6 months, and every 3–6 months after 12 months. Any tacrolimus trough level that was lower than 3 ng/mL or higher than 15 ng/mL was individually reviewed and was excluded if not valid. Any undetectable tacrolimus trough level was regarded as 0.0 ng/mL. AR and infection episodes were investigated and recorded. AR was suspected if serum creatinine increased rapidly and empirical treatment with a bolus dose of methylprednisolone was needed and was confirmed by biopsy when necessary. Infection was defined as patients having any infectious symptom and needing medication intervention. Re-establishment of long-term dialysis therapy was considered as graft loss. Serum creatinine was collected for assessing kidney function. Age, sex, and body mass index (BMI) variables were extracted from donors and recipients. The following variables were also collected: duration of pretransplantation dialysis, ABO blood type mismatch, organ transplant history, panel reactive antibody (PRA), human leukocyte antigen (HLA) mismatch, induction therapy, delayed graft function (DGF), and cold ischemic time.

Immunosuppression Regimen

Our hospital adopted rabbit antihuman thymocyte immunoglobulin (ATG, Novartis, Switzerland, 1 mg/kg for 3–7 days after transplantation) or anti-CD25 monoclonal antibody (IL-2R antibody, Astellas, Japan, 20 mg at day 0 and day 4 after transplant) as the induction therapy. Maintenance immunosuppressive therapy consisted of triple immunosuppression regimens: tacrolimus, MMF/EC-MPS (MMF/enteric-coated mycophenolate sodium), and corticosteroid. Tacrolimus was initiated on the second day after transplantation at a dosage of 1.5 mg bid and maintained at 5–10 ng/mL. MMF was given once the night before transplant surgery at a dose of 1000 and 1000 mg bid thereafter. Methylprednisolone was intravenously administered in 500 mg during surgery and 300 mg for the next 3 days. It was then replaced with 60 mg of prednisone, which was tapered by 10 mg/d until a maintenance dose of 5–10 mg/d was reached.[13]

Propensity Score Match Procedure

We used propensity score match (PSM) to increase comparability among groups.[14,15] First, all patients were divided into 3 groups in accordance with the 2 cutoff points of tacrolimus trough levels as determined using receiver operating characteristic (ROC) curves: low-level group, median-level group, and high-level group. ROC analysis is an effective tool to select the optimal threshold by balancing between sensitivity and specificity under various clinical circumstances. As described by Zou and O'Malley,[16] the cutoff point with maximum sum of sensitivity and specificity was considered as the optimal threshold of a test. We conducted 2 ROC analyses to evaluate the optimal lower limit and upper limit of the tacrolimus trough level based on AR and infection separately.

Second, we performed 2 PSMs, creating well-balanced groups, to compare the incidence of AR and infection between the median-level group and the low- or high-level groups, respectively. The propensity score is defined as the probability of being exposed, given the values of measured covariant variables.[14] First, PSM was conducted between the median- and high-level groups. For this process, covariant factors were first selected for the next propensity score calculation from the following variables: (1) age, sex, and BMI of donors and recipients; and (2) DGF, induction therapy, PRA, HLA mismatch, and cold ischemic time. Variables that were not comparable ($P > 0.1$) between the median- and high-level groups were selected as covariant factors. These covariant factors were used to calculate the propensity score of each individual in both groups by using a logistic regression analysis.[17] Then, based on the propensity score, patients were matched 1:1 with a predefined caliper of 0.01 to try to select a single match in the high-level group for each individual in the median-level group. Those patients in the median group who can be matched with patients in the high-level group were eligible for ultimate statistical analysis. Second, similar processes were conducted to try to select the corresponding single patient in the low-level group for each individual in the median-level group, and matched patients were eligible for ultimate statistical analysis. All procedures

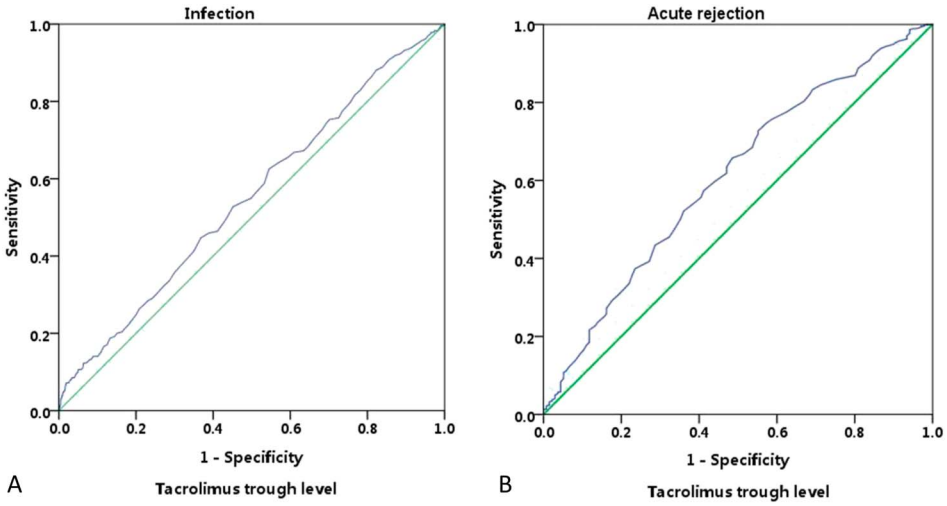

FIGURE 1. ROC curve for the tacrolimus trough level at the first posttransplant month based on infection (A) and AR (B) in kidney transplantation recipients.

were performed using the IBM SPSS Statistics software package, version 24.0 (IBM, Armonk, NY).

Statistical Analyses

Descriptive statistics were used to describe the baseline characteristics of donors and recipients exposed to different tacrolimus trough levels after PSM. Continuous variables were compared using the Student *t* test. Categorical variables were compared using the χ^2 test or Fisher exact test (if the expected number was less than 5). ROC curves were generated to determine whether any tacrolimus trough level measured at the first month can discriminate between patients with and without AR and between patients with and without infection. The tacrolimus trough level with the maximum sum of sensitivity and specificity under the ROC curve was selected for further analysis.

Time to AR, infection, graft loss, and recipient death were analyzed by the Kaplan–Meier method, and differences between groups were assessed by the Breslow test for a short period and the log-rank test for a long period. Logistic regression analysis was used to investigate the predictors for AR and infection episodes within the first year. Variables with $P < 0.2$ in the univariate analysis were included in the multilogistic analysis. Statistical analysis was conducted using SPSS 24.0, and $P < 0.05$ was considered statistically significant.

RESULTS

From August 2007 to April 2017, 2048 patients received kidney transplantation from living relative donors in West China Hospital. A total of 633 patients were excluded: (1) follow-up time was less than 1 year (N = 203); (2) calcineurin inhibitor was not tacrolimus (N = 269); (3) lost in the follow-up (N = 77); (4) younger than 18 years (N = 39); (5) organ transplantation history (N = 13); and 6) ABO-incompatible kidney transplantation (N = 32). Ultimately, 1415 patients were included in our study with a median follow-up time of 44 months. The median time to the first AR was 142 days (interquartile range, 64–238 days). A total of 239 (16.4%) patients developed an infection at least once during the first 12 months with a median time to the first infection of 167 days (interquartile range, 87–258 days). Of all infections, 67%, 19%, and 6% were pulmonary, urinary tract, and herpes zoster infections, respectively. A total of 21 (1.4%) patients developed DGF. The optimal cutoff value for the tacrolimus trough level was determined to be 5.35 and 7.15 ng/mL, as assessed by the ROC curves based on the AR (sensitivity, 72.5%; specificity, 54.0%) and infection (sensitivity, 55.6%; specificity, 63.4%) within the first year (Fig. 1). Hence, 1415 patients were divided into 3 groups: 410 in the low-level group (tacrolimus < 5.35 ng/mL), 466 in the median-level group, and 539 in the high-level group (tacrolimus > 7.15 ng/mL). Figure 2 presents the detailed selection process.

Before PSM, significant differences were observed in cold ischemic time ($P = 0.05$) and DGF ($P = 0.03$) between median- and low-level groups. After PSM, each group consisted of 363 patients. Similarly, significant differences were observed in DGF ($P = 0.04$) and induced therapy ($P = 0.04$) between median- and high-level groups. After PSM, 459 cases were analyzed in each group. The clinical features were comparable among groups after matching (Table 1).

Distribution of tacrolimus trough levels at different time points (first, third, sixth, 12th, 18th, 24th, 30th, 36th, 42th, 48th, 54th, and 60th month after transplantation) is shown in Figure 3. After PSM, mean tacrolimus trough levels at the first posttransplantation month were 4.23 ± 0.86 and 6.32 ± 0.50 ng/mL in the low- and median-level groups, respectively. Notably, the mean tacrolimus trough level was also 6.32 ± 0.50 ng/mL for the median-level group and 8.94 ± 1.62 ng/mL for the high-level group after matching. Statistical significance was found only at the first and third month between the low- and the median-level groups and at the first and 60th month between the median- and the high-level groups. The mean tacrolimus trough level of patients with AR at the first month was 5.96 ng/mL compared with 6.80 ng/mL of patients without AR ($P < 0.001$). The mean tacrolimus trough level of patients without infection at the first month was 6.63 ng/mL compared with 7.13 ng/mL of patients with infection ($P = 0.002$).

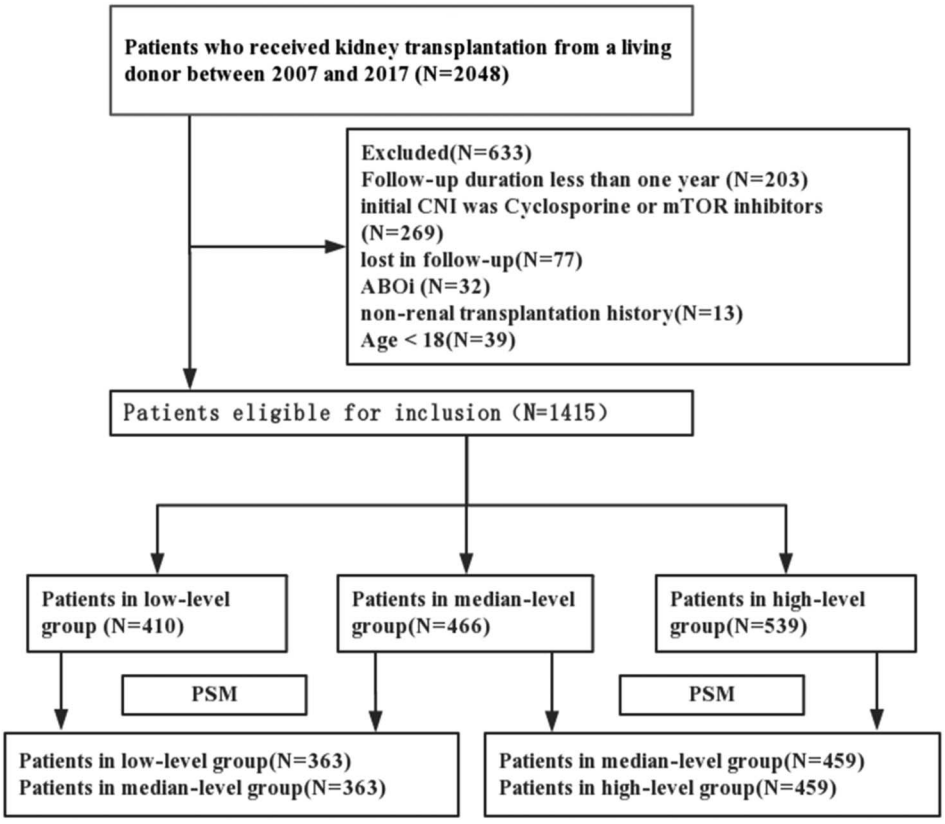

FIGURE 2. Flow chart of the selection process.

Clinical Outcomes After Matching Between Median- and Low-Level Groups

Within the first year after transplantation, 21 (5.7%) of 363 patients had AR in the median-level group compared with 45 (12.4%) in the low-level group (P = 0.02). The incidence of infection episodes was comparable in 2 groups [48 (13.2%) versus 48 (13.2%), P = 1.00]. Kaplan–Meier estimation of rejection-free survival was significantly higher in the median-level group (P = 0.002 in the log-rank test and P = 0.002 in the Breslow test) (Fig. 4). However, no statistical significance was noted in the incidence of infection between low- and median-level groups (P = 0.79 in the log-rank test, P = 0.74 in the Breslow test) (Fig. 4).

Furthermore, univariate logistic analysis was first used to assess the influence of different factors on AR when the tacrolimus trough level was below 7.15 ng/m. The tacrolimus trough level was associated with AR [odds ratio (OR), 0.756, 95% confidence interval (CI), 0.638–0.895]. Based on the selection criterion of $P < 0.20$, 4 baseline variables possibly associated with AR were selected into the multilogistic analysis: DGF (P = 0.158), recipient BMI (P = 0.160), induction therapy (P = 0.083), and tacrolimus trough level (P = 0.001). According to multilogistic analysis, the tacrolimus trough level was associated with AR (OR, 0.749, 95% CI, 0.632–0.888) as an independent factor, which showed an estimated 25.1% lower AR rate for every 1 ng/mL increase when the tacrolimus trough level was below 7.15 ng/mL. However, the tacrolimus trough level was not associated with infection in univariate logistic analysis (P = 0.301). After adjustment, multilogistic analysis showed that recipient age and induction therapy (P = 0.042) were associated with the risk of infection (P = 0.05) (Table 2).

Clinical Outcomes After Matching Between Median- and High-Level Groups

We used the same method to explore the association after matching the median with high-level groups. Within the first year after transplantation, 25 (5.4%) of 459 patients had AR in the median-level group compared with 21 (4.6%) in the high-level group (P = 0.545). However, the incidence of infection episodes was higher in the high-level group (12.2% versus 17.6%, P = 0.021). Kaplan–Meier estimation of infection-free survival was higher in the median-level group in a short period (P = 0.040 in the Breslow test and P = 0.089 in the log-rank test). However, no statistical significance was observed in the incidence of AR between the median- and high-level groups (P = 0.760 in the log-rank test and P = 0.696 in the Breslow test) (Fig. 5).

Similarly, univariate logistic analysis was first used to assess the impact of clinical factors on AR and infection when the tacrolimus trough level was above 5.35 ng/mL. Based on the selection criterion of $P < 0.20$, 3 baseline variables were selected into the multilogistic analysis: PRA >20% (P = 0.101), induction therapy (P = 0.122), and tacrolimus trough level (P = 0.022). Multilogistic analysis showed that the tacrolimus trough level was associated with infection (OR, 1.110, 95% CI, 1.013–1.218) as an independent factor, which showed an estimated 11% higher infection rate for every 1 ng/mL increase when the tacrolimus trough level was above

TABLE 1. Baseline Clinical and Demographic Characteristics of Donors and Recipients After PSM

	After Propensity Score Matching					
Characteristics*	**Low-Level Group (N = 363)**	**Median-Level Group (N = 363)**	***P***	**Median-Level Group (N = 459)**	**High-Level Group (N = 459)**	***P***
Donor age (yrs)	47.02 (±9.48)	47.06 (±8.81)	0.962	47.38 (±9.09)	46.61 (±9.82)	0.218†
Donor sex			0.342			0.945‡
Male	112 (30.9%)	124 (34.2%)		159 (34.6%)	160 (34.9%)	
Female	251 (69.1%)	239 (65.8%)		300 (65.4%)	299 (65.1%)	
Recipient age (yrs)	33.10 (±8.84)	32.98 (±8.29)	0.856	32.79 (±8.31)	32.83 (±8.54)	0.931†
Recipient sex			0.364			0.338‡
Male	255 (70.2%)	266 (73.3%)		325 (70.8%)	338 (73.6%)	
Female	108 (29.8%)	97 (26.7%)		134 (29.2%)	121 (26.4%)	
Recipient BMI, Kg/m^2	21.16 (±3.13)	21.25 (±3.34)	0.728	21.30 (±3.39)	21.38 (±3.32)	0.290†
Allograft cold ischemic time, hours	2.51 (±0.88)	2.51 (±0.88)	1.000	2.56 (±0.89)	2.51 (±0.85)	
DGF	1 (0.3%)	1 (0.3%)	1.000	5 (1.1%)	5 (1.1%)	1.000‡
Induction therapy			0.487			1.000‡
No	138 (38.0%)	139 (38.3%)		153 (33.3%)	153 (33.3%)	
ATG	30 (8.3%)	39 (10.7%)		54 (11.8%)	54 (11.8%)	
IL-2R antibody	195 (53.7%)	185 (51.0%)		252 (54.9%)	252 (54.9%)	
HLA mismatches			0.128			0.432‡
0 mismatch	23 (6.3%)	28 (7.7%)		37 (8.1%)	27 (5.9%)	
1 mismatch	13 (3.6%)	16 (4.4%)		22 (4.8%)	21 (4.6%)	
2 mismatches	74 (20.4%)	58 (16.0%)		73 (15.9%)	91 (19.8%)	
3 mismatches	182 (50.1%)	209 (57.6%)		257 (56.0%)	228 (49.7%)	
4 mismatches	16 (4.4%)	18 (5.0%)		26 (5.7%)	28 (6.1%)	
5 mismatches	26 (7.2%)	18 (5.0%)		25 (5.4%)	49 (10.7%)	
6 mismatches	29 (8.0%)	16 (4.4%)		19 (4.1%)	15 (3.3%)	
Pretransplant PRA >20%	12 (3.3%)	13 (3.6%)	0.839	16 (3.5%)	11 (2.4%)	0.329‡
Duration of dialysis (SD), mo	12.89 (±14.12)	12.96 (±13.73)	0.946	13.70 (±16.47)	12.28 (±14.67)	0.168†

*Continuous data are presented as mean ± SD and categorical data as number (percentage of the total), unless otherwise noted.
†The Student *t* test.
‡The χ^2 test.
ATG, anti-CD25 monoclonal antibody; IL-2R antibody, rabbit antihuman thymocyte immunoglobulin.

5.35 ng/mL. However, the tacrolimus trough level was not associated with AR in univariate logistic analysis ($P = 0.687$). After adjustment, multilogistic analysis showed induction therapy was associated with the risk of AR ($P = 0.009$) (Table 3).

RENAL FUNCTION

Changes in serum creatinine over time are shown in **Supplemental Digital Content 1**, (see **Figure 1**, http://links.lww.com/TDM/A298). Serum creatinine levels only differed at the 30th and 54th month between patients in the median- and low-level groups ($P < 0.05$) after transplantation. Similarly, no statistical difference was found in serum creatinine except at the 30th and 48th months between median- and high-level groups ($P < 0.05$).

Patient and Graft Survival

During the median of 44-month follow-up, graft loss developed in 25 of 726 patients, including 9 (2.5%) in the median-level group and 16 (4.4%) in the low-level group. Graft-free survival did not differ between median- and low-level groups ($P = 0.144$ in the log-rank test and $P = 0.113$ in the Breslow test). Fourteen deaths occurred: 7 in the low-level group and 7 in the median-level group. Overall, patient survival between the median- and low-level groups was also comparable ($P = 0.957$ in the log-rank test and $P = 0.944$ in the Breslow test) (see **Figure 2**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A299).

When comparing between median- and high-level groups, similar results in graft and patient survival were found. In total, 12 graft losses (2.6%) occurred in the median-level group compared with 15 (3.3%) in the high-level group. Kaplan–Meier analysis showed no statistical significance in graft survival between both groups ($P = 0.656$ in the log-rank test and $P = 0.606$ in the Breslow test). In addition, 8 deaths were observed in both groups, and no statistical significance was observed ($P = 0.785$ in the log-rank test and $P = 0.868$ in the Breslow test) (see **Figure 2**, **Supplemental Digital Content 2**, http://links.lww.com/TDM/A299).

DISCUSSION

This is the first study to use the PSM method to investigate the optimal tacrolimus trough level in the early

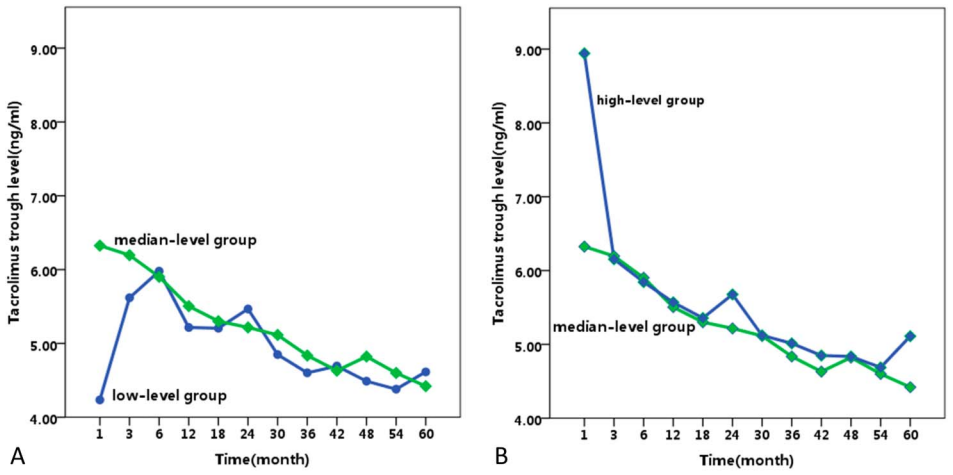

FIGURE 3. Tacrolimus trough level distribution at the different time points after PSM. A, Tacrolimus trough level between low- and median-level groups. B, Tacrolimus trough level between high- and median-level groups.

posttransplant phase in the Chinese population. We found that the tacrolimus trough level at the first month was associated with AR and infection within the first year after kidney transplantation. We further found that the tacrolimus trough level of 5.35–7.15 ng/mL may be appropriate in controlling AR without increasing the risk of infection among the Chinese population.

Because of CYP3A5 polymorphisms and changes in concomitant medications, the tacrolimus trough level varies considerably within the early weeks,[18,19] which can cause subsequent complications. Few studies have explored the minimum level of tacrolimus in the control of AR. Gaynor suggested that the tacrolimus trough level of <4.0 ng/mL should be avoided within the first 12 months after transplantation to control AR despite the fact that a cutoff point, tacrolimus level <5.0 versus >5.0 ng/mL, is greatly associated with the AR rate ($P = 0.003$).[20] Similar to our results, Israni showed an additional AR risk of 23% resulting from each 1 ng/mL reduction in the tacrolimus trough level in the early phase [Hazard ratio (HR) = 1.23, 95% CI, 1.06–1.43, $P = 0.008$].[21] Our findings were also supported by additional evidence indirectly. Studies have reported that high tacrolimus clearance (defined as daily tacrolimus dose (mg)/tacrolimus tough concentration (ng/mL) > 1.5 units) had an adjusted HR of 2.25 (95% CI, 1.70–2.99) for AR within the first 90 days after transplantation.[22] High clearance of tacrolimus causes a tacrolimus trough level lower than the target concentration when patients are given a standard dosage, achieving target trough levels more slowly. Other studies showed that high variability of the tacrolimus trough level contributes to an increased risk of AR in recipients at the early postoperative period.[23–25] As described by David et al, a 10% increase in the coefficient of variation of tacrolimus concentrations increases the adjusted risk of AR by 20% (HR, 1.20, 95% HR, 1.13–1.28; $P < 0.001$). High variability means that the tacrolimus trough level fluctuates considerably in patients who may show low tacrolimus blood concentrations.

A new finding in our study is that higher tacrolimus trough levels during the first month were associated with increased incidence of infection within the first year. Therefore, we set the upper limit of tacrolimus concentration based on the analysis of infection, which was lower than the recommended concentration by other studies[8,26] but has been supported by clinical experience in our hospital. However, the difference was only found in a short period but disappeared in the long term. Two reasons may explain these changes. First, we only took the first infection into account despite subsequent infection episodes. Second, tacrolimus trough levels of patients have

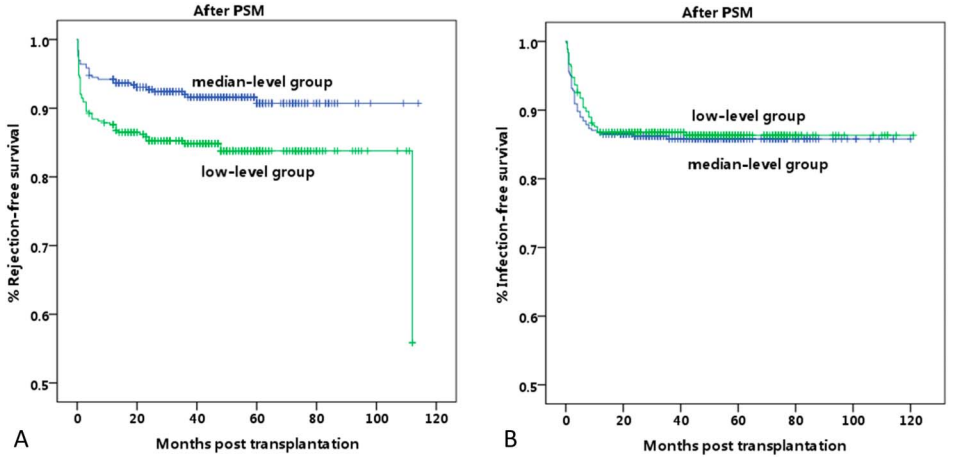

FIGURE 4. Kaplan–Meier curves of the AR (A) and infection (B) according to different tacrolimus trough levels in median- and low-level groups.

TABLE 2. Factors Associated With AR and Infection by Logistic Analysis After PSM Between Median- and Low-Level Groups

	AR				Infection			
Variable Domains	**Unadjusted OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	***P***	**Unadjusted OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	***P***
Donor age	1.005 (0.980–1.030)	0.701			1.622 (0.996–2.641)	0.052	1.010 (0.986–1.034)	0.418
Donor sex	1.303 (0.792–2.145)	0.297			1.007 (0.984–1.031)	0.554		
Recipient age	1.003 (0.977–1.029)	0.84			0.981 (0.956–1.006)	0.134	0.973 (0.947–1.000)	0.05
Recipient sex	0.733 (0.432–1.242)	0.248			0.639 (0.383–1.064)	0.085	0.698 (0.411–1.185)	0.183
Duration of dialysis	0.997 (0.980–1.014)	0.697			1.005 (0.990–1.019)	0.523		
DGF	7.419 (0.460–119.693)	0.158	9.584 (0.571–160.800)	0.116	6.313 (0.392–101.752)	0.194	4.663 (0.284–76.436)	0.281
Recipient BMI	1.050 (0.981–1.124)	0.16	1.052 (0.982–1.127)	0.15	1.054 (0.989–1.124)	0.107	1.064 (0.992–1.140)	0.083
HLA mismatch	1.039 (0.880–1.227)	0.652			1.025 (0.876–1.199)	0.758		
PRA	0.630 (0.146–2.721)	0.536			0.535 (0.124–2.305)	0.401		
Induction therapy	0.811 (0.641–1.027)	0.083	0.801 (0.630–1.018)	0.069	1.273 (1.008–1.608)	0.043	1.276 (1.009–1.613)	0.042
Cold ischemic time	0.935 (0.724–1.208)	0.608			0.996 (0.783–1.267)	0.975		
TAC trough level	0.756 (0.638–0.895)	0.001	0.749 (0.632–0.888)	0.001	1.095 (0.922–1.301)	0.301		

TAC, tacrolimus.

been maintained in the recommended standard range during 3, 6, 9, and 12 months after kidney transplantation. Notably, although incidence of AR and infection was lower in the median group compared with that in the low- and high-level groups, no difference was found in 1-, 3-, and 5-year grafts and patient survival among groups, which was similar to previous results.[8] In fact, studies have reported that the achievement of lower AR rates in the early phase does not necessarily translate into improved graft survival after kidney transplantation.[27,28] Generally, overall immunosuppression included tacrolimus, MMF, and steroids. In our study, we maintained the MMF area under the curve at the range of 30–60, which was measured by HPLC. The dosage of MMF was gradually tapered to 500 mg bid for most patients after 3 months. Hence, we did not take the impact of MMF on AR into consideration.

Our study adopted PSM, which is an appropriate method to reduce bias in the estimations of the effect of an exposure due to confounding by indication. After PSM, some confounding factors possibly influencing the outcomes of kidney transplantation, including DGF, induction therapy, and other factors, were balanced among groups, which makes our results more reliable. Induction therapy was found to be associated with AR both in univariate and multilogistic analysis. Previous studies have also indicated that ATG is better than IL-2R antibody induction therapy in preventing AR.[29] Another new finding in our study was that induction therapy was also associated with infection, which remains to be further explored because induction therapy has been balanced as a matching variable between groups. A meta-analysis of 34 studies concluded that patients with DGF had a 49% pooled incidence of AR compared with 35% incidence in non-DGF patients (risk ratio, 1.38 95% CI 1.29–1.47).[30,31] Previous study also showed that the risk of DGF increases by 23% by every 6 hours of cold ischemia.[32] However, incidence

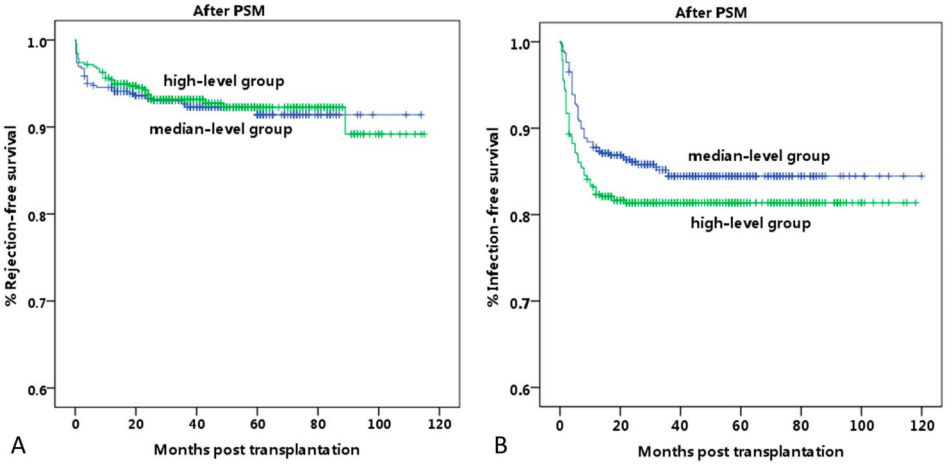

FIGURE 5. Kaplan–Meier curves of the AR (A) and infection (B) according to different tacrolimus trough levels in median- and high-level groups.

TABLE 3. Factors Associated With AR and Infection by Logistic Analysis After PSM Between Median- and High-Level Groups

	AR				Infection			
Variable Domains	**Unadjusted OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	***P***	**Unadjusted OR (95% CI)**	***P***	**Adjusted OR (95% CI)**	***P***
Donor age	1.000 (0.974–1.027)	0.973			1.007 (0.989–1.026)	0.448		
Donor sex	0.774 (0.466–1.286)	0.323			1.244 (0.856–1.809)	0.252		
Recipient age	0.996 (0.967–1.026)	0.804			1.003 (0.982–1.023)	0.812		
Recipient sex	0.734 (0.406–1.329)	0.308			0.906 (0.611–1.342)	0.621		
Duration of dialysis	0.984 (0.963–1.006)	0.151	0.986 (0.965–1.007)	0.198	1.000 (0.989–1.011)	0.976		
DGF	3.242 (0.675–15.583)	0.142	3.775 (0.746–19.091)	0.108	1.253 (0.264–5.960)	0.777		
Recipient BMI	1.000 (0.982–1.017)	0.965			1.000 (0.989–1.011)	0.985		
HLA mismatch	1.090 (0.900–1.320)	0.375			1.082 (0.947–1.237)	0.246		
PRA	1.017 (0.236–4.387)	0.982			0.187 (0.025–1.389)	0.101	0.193 (0.026–1.437)	0.108
Induction therapy	0.683 (0.523–0.893)	0.005	0.700 (0.535–0.916)	0.009	1.166 (0.960–1.417)	0.122	1.166 (0.959–1.417)	0.123
Cold ischemic time	1.028 (0.772–1.368)	0.853			1.032 (0.845–1.260)	0.761		
TAC trough level	0.970 (0.838–1.124)	0.687			1.114 (1.106–1.222)	0.022	1.110 (1.013–1.218)	0.026

TAC, tacrolimus.

of DGF was low in our hospital in the condition that cold ischemic time was usually less than 4 hours, and conservative living donor selection criteria were adopted in our hospital. This may explain why DGF was not associated with AR in univariate logistic analysis in our study. A previous study has also shown that patients with PRA >20% often present with AR.[33] Lim et al[34] reported that recipients with peak PRA levels greater than 80% are at an increased risk of AR (OR 1.81, 95% CI, 1.30–2.35; $P < 0.001$). However, patients with PRA >20% in our study were less than 4%, and a good balance among groups was also reached.

Our study has several limitations compared with previous studies. First, 2 PSMs were adopted in 1:1 proportion but not multigroup matching. Second, our results were generated from a retrospective cohort study in a single center, which may cause selection bias. A prospective study is warranted to demonstrate whether the target tacrolimus trough level can bring the same benefits in practice. Third, part of AR episodes was not proven by biopsy, and we only considered the infection excluding other side effects, including neurotoxicity and nephrotoxicity. Finally, the optimal cutoff points of the tacrolimus trough level for AR and infection may be less convincing because the corresponding sensitivity and specificity are not high enough, indicating that the predictive power of a single measurement of tacrolimus is limited and that regular therapeutic drug monitoring of tacrolimus should be conducted.

CONCLUSIONS

In this study, we found that tacrolimus trough levels during the first month were associated with AR and infection after kidney transplantation. We observed that patients with tacrolimus trough levels of 5.35–7.15 ng/mL developed less AR episodes without increasing the infection within the first year. Generally, the tacrolimus trough level maintained between 5.35 and 7.15 ng/mL may be optimal during the first month after living relative kidney transplantation among the Chinese.

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