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Risk factors and etiology of repeat infection in kidney transplant recipients

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Abstract

Kidney transplantation (KT) is the best therapy available for patients with end-stage renal disease, but postoperative infections are a significant cause of mortality.

In this retrospective study the frequency, risk factors, causative pathogens, and clinical manifestations of infection in KT recipients from Beijing Chao-Yang Hospital, Capital Medical University were investigated. Ninety-seven KT recipients who were hospitalized with infection between January 2010 and December 2016 were included. Clinical characteristics, surgery details, laboratory results, and etiology were compared in patients who developed single infection and patients who developed repeated infection (2 or more) after KT.

A total of 161 infections were adequately documented in a total of 97 patients, of which 57 patients (58.8%) had 1 infection, 24 (24.7%) had 2, 11 (11.3%) had 3; 3 (3.1%) had 4, and 2 (2.1%) had 5 or more. The most common infection site was the urinary tract (90 infections; 56%), both overall and in the repeated infection group. The most frequently isolated pathogen was *Pseudomonas aeruginosa*. In the repeated infection patients, in most cases of *P. aeruginosa* infection (54%) it was cultured from urine. For first infections, a time between KT and infection of $\leq$ 21 days (area under receiver operating characteristic curve [AUC] 0.636) and a tacrolimus level $\geq$ 8 ng/mL (AUC 0.663) independently predicted repeat infection. The combination of these two predictive factors yielded an AUC of 0.716, which did not differ statistically significantly from either predictor alone.

With regard to first infections after KT, a time between KT and infection of $\leq$ 21 days, and a tacrolimus level $\geq$ 8 ng/mL each independently predicted repeated infection in KT recipients.

Abbreviations: A. baumannii = Acinetobacter baumannii, AUC = area under receiver operating characteristic curve, B. cepacia = Burkholderia cepacia, BALF = bronchoalveolar lavage fluid, C. albicans = Candida albicans, C. difficile = Clostridium difficile, C. glabrata = Candida glabrata, C. hellenical = Candida hellenical, C. lusitaniae = Candida lusitaniae, C. parapsilosis = Candida parapsilosis, C. tropicalis = Canadida tropicalis, DNA = deoxyribonucleic acid, E. aerogenes = Enterobacter aerogenes, E. avium = Enterococcus avium, E. cloacae = Enterobacter cloacae, E. coli = Escherichia coli, E. faecalis = Enterococcus faecalis, E. faecium = Enterococcus faecium, E. gallinarum = Enterococcus gallinarum, K. pneumoniae = Klebsiella pneumonia, KT = kidney transplantation, KTR = kidney transplant recipient, LKTFI = length of time from kidney transplantation to first infection, MDR = multi-drug resistant, P. aeruginosa = Pseudomonas aeruginosa, P. jiroveci = Pneumocystis jiroveci, P. mirabilis = Proteus mirabilis, RI = repeat-infection, RNA = ribonucleic acid, S. aureus = Staphylococcus aureus, SI = single-infection, TAC = tacrolimus, UTI = urinary tract infection.

Keywords: etiology, infection, kidney transplantation, risk factor

1. Introduction

Kidney transplantation (KT) is currently the best method for extending the lives of patients with end-stage renal disease. In reports that span the globe, patient and graft survival rates are > 90% at 1 year and > 80% at 5 years after KT.[1–4] Infectious complications remain a common cause of mortality however, especially during the first year after KT.[5,6] In a recent study, 8.6% of kidney transplant recipients (KTRs) died within 5 years of transplantation and 53% of those deaths were due to infection, a rate that is twice that of the second most common cause of death.[7] Infections were also the main cause of death in another study that was conducted over 15 years, in which 10,400 KTRs were enrolled.[8] In that study, there were 404 cases of complications associated with infection, and in 34% of those cases the patient died. Most deaths were due to infection that occurred within the first year after transplantation (157 deaths, 38.9%). In another study, even among KTRs exhibiting long-term survival (> 25 years post-KT), infection was reportedly still the most prevalent complication (86/112, 77%), and most patients experienced more than one infection.[9] In a study focused on older adults, 92.3% of patients aged $\geq$ 65 years developed at least one infection within the first year after KT.[10]

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Y-XC and RL contributed to the work equally and should be regarded as co-first authors.

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Therefore, vigilant prevention and treatment of infections are crucial components of successful KT.

Different studies have identified a variety of risk factors for infection.[11] The risk of infection for a transplant recipient is a function of 2 factors: 1) the epidemiologic exposures of the patient and the organ donor including recent, nosocomial, and remote exposures; and 2) the patient's state of immunosuppression.[12] Few studies have investigated the risk factors for repeat infection (RI), defined as 2 or more infections post-transplant at the same site or different sites. In the present study, the risk factors and etiology of RI in KTRs were investigated.

2. Materials and methods

2.1. Study design

The present investigation was a retrospective observational study conducted at Beijing Chao-Yang Hospital, Capital Medical University from November 2018 to March 2019. The study was approved by the Beijing Chao-Yang Hospital ethics committee (reference ID: 2018-ke-301).

2.2. Patients and grouping

The electronic medical records of hospitalized KTRs who were treated for post-transplantation infection between January 2010 and December 2016 were reviewed. Patients who developed one infection during the study period were assigned to a single-infection (SI) group, and those who experienced two or more infections were assigned to an RI group.

2.3. Definitions of infection

An infectious episode was defined as a clinical and/or laboratory diagnosis of infection. The sites of infection were recorded as urinary, pulmonary, bloodstream, intra-abdominal, gastrointestinal, or "other" (e.g., surgical wound, skin). Urinary tract infection (UTI) was diagnosed clinically based on fever, dysuria, frequency, suprapubic tenderness, and/or isolation of an infectious agent in urine culture. Pneumonia was diagnosed on a clinical and/or laboratory basis. *Pneumocystis jiroveci* pneumonia was diagnosed clinically with or without a positive test for *P. jiroveci* DNA in any respiratory samples, including sputum and bronchoalveolar lavage fluid (BALF). Bloodstream infection was defined as at least one positive blood culture in conjunction with clinical symptoms of infection. Contamination was excluded. Cytomegalovirus infection was defined as isolation of cytomegalovirus DNA in a blood and/or respiratory sample (BALF) and a viral load of $> 1.0 \times 10^3$. Multi-drug-resistant (MDR) pathogens were defined as those that were not susceptible to at least one agent in three or more antimicrobial categories, as proposed by an international expert group.[13]

2.4. Data collection

The baseline information collected included age at the time of the first KT, sex, primary disease associated with end-stage renal disease, time between primary disease onset and KT, frequency of KT, pre-transplant dialysis modality, immunosuppression regimen, and KT surgical information. Clinical and laboratory data pertaining to infections were recorded, and from these data the highest serum creatinine level during an infection was used to assess the influence of the infection on graft function. Etiologic findings within 7 days after an infectious episode were reviewed and recorded.

2.5. Etiologic examination methods

Etiologic samples including blood, urine, sputum, and others (catheter tip, swab, BALF, purulence, stool, drainage fluid, and infected tissue) were taken and sent to the clinical microbiology laboratory for routine microscopy and culture examination in accordance with standard operation procedures described in the Manual of Clinical Microbiology, 11th edition. DNA or RNA were directly extracted from clinical samples (blood, sputum, or BALF) for examination of cytomegalovirus in blood and BALF, *P. jiroveci* pneumonia in sputum or BALF, and respiratory tract virus in sputum, BALF, or nasopharyngeal swab, then tested via commercial real-time PCR kits (Liferiver, Shanghai, China).

2.6. Statistical analyses

Statistical analyses were performed with SPSS software 18.0 (IBM Corporation, Armonk, NY). Normally distributed data were compared via a *t* test and the results are expressed as mean ± standard deviation. Non-normally distributed data were analyzed using the Mann–Whitney *U* test and the results are expressed as median and quartiles. Frequencies were analyzed using the Chi-square test. Binary logistic regression was performed to identify independent predictors of RI. Receiver operating characteristic curves were generated to assess predictive performance. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were also calculated. A 2-sided *P* value of $< .05$ was considered statistically significant.

3. Results

During the study period, 671 KTs were conducted at the study hospital, and 206 infections were documented in 125 hospitalized KTRs. Forty-five infections in 28 KTRs were excluded because of a lack of relevant information, resulting in 161 infections in 97 KTRs being included in the final analysis (Fig. 1).

3.1. Baseline characteristics

Baseline patient characteristics are shown in Table 1. The SI group contained 57 patients (58.8%), and the RI group contained 40 patients (41.2%); 24 (24.7%) with 2 infections, 11 (11.3%) with 3, 3 (3.1%) with 4, and 2 (2.1%) with ≥ 5. RI patients were more likely to have received pre-transplant hemodialysis than SI patients (Fig. 2). Cyclosporin-A was used more frequently in the RI group than in the SI group (20% vs 5%, $P = .047$). The prevalence of RI was higher in those who received cyclosporin-A-based vs tacrolimus (TAC)-based immunosuppression (75.0% vs 36.5%, $P = .025$) (Fig. 2). Other baseline parameters did not differ significantly, including primary disease preceding end-stage renal disease, time from primary disease onset to KT, frequency of KT, renal function after KT, and surgery complications. The in-hospital mortality rate was 5% in the entire study cohort, and mortality did not differ significantly in the 2 groups (7% in the SI group vs 3% in the RI, group, $P = .646$) (Table 1).

3.2. Clinical characteristics of first infections

The clinical characteristics of first infections are shown in Table 2. Compared with the SI group, RI patients had a shorter mean length of time from KT to first infection (LKTFI) (22 vs

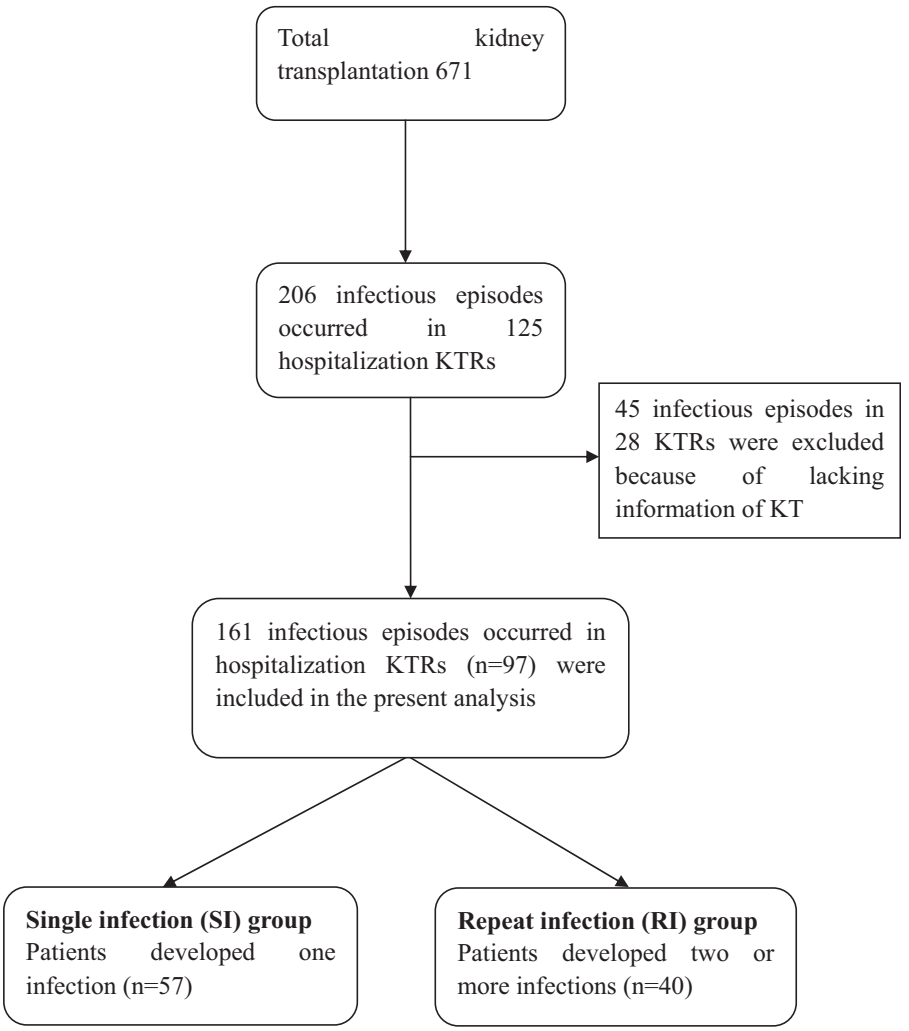

Figure 1. Flowchart of patient enrolment.

44 days, $P=.003$). All 40 of the first infections in the RI group and 42/57 of the infections in the SI group occurred within 180 days after KT. There was a higher prevalence of UTI in the RI group (70% vs 42%, $P=.007$). Despite the frequency of infection, the mean TAC levels around the time of the first infection were 9.3 ± 3.6 ng/mL within 180 days after KT ($n=68$), 8.2 ± 3.6 ng/mL between 181 and 365 days after KT ($n=9$), and 6.6 ± 4.9 ng/mL $>$ 365 days after KT ($n=6$). The mean TAC level was much higher in the RI group (10.4 ± 3.5 vs 8.2 ± 3.5 ng/mL, $P=.005$). The prevalence of RI is shown in Figure 2. The median level of procalcitonin was higher in RI KTRs, but the difference was not significant (6.83 vs 0.81 ng/mL, $P=.288$). Complications occurred in 4 patients, all of whom were in the SI group, and of these 2/4 progressed to multiple organ dysfunction syndrome and the other 2/4 developed septic shock.

3.3. Sites of infection

The most common site of infection was the urinary tract, and the second most common was the lung (Fig. 3). Bloodstream, urinary tract, and pulmonary infections were most common in the first 180 days after KT, and cases of *P. jiroveci* pneumonia became more frequent after 180 days.

3.4. Pathogens

The most commonly isolated pathogen was *Pseudomonas aeruginosa* (24 times), followed by *Escherichia coli* (23 times) and *P. jiroveci* (21 times) (Table 3). Most bacterial and fungal infections occurred within 180 days after KT, and 72% (33/46) of the infections caused by MDR pathogens were detected in the early phase. Approximately 54% *P. aeruginosa* were isolated from urine, and 92% *P. aeruginosa* were isolated from RI group. No MDR *P. aeruginosa* was isolated. *E. coli* was detected in similar proportions in urine (48%) and blood (43%). The numbers of MDR pathogens were higher in the RI group than in the SI group, but the MDR-positive ratio (MDR number/number of infections) did not differ significantly between the groups (12/57 vs 34/104, $P=.118$). Approximately 96% of *E. coli*, 91% of *Klebsiella pneumoniae*, and 100% of *Proteus mirabilis* infections were MDR (Table 3).

3.5. Clinical characteristics and etiology of RI in KTRs

In RI patients, the median number of days between KT and their first infection was 22 (12–56; $n=40$). The median numbers of days associated with subsequent infections were 116 (51–218) for second infections ($n=40$), 205 (74–286) for third infections

Table 1

Baseline characteristics of the study cohort.

	All patients (n = 97)	Single-infection (n = 57)	Repeat-infection (n = 40)	*P*
Recipient age (yr)	41.7 ± 12.6	42.4 ± 12.4	40.5 ± 13.0	.465
Male, n (%)	60 (62%)	34 (60%)	26 (65%)	.593
Etiology of underlying ESRD n(%)				
Unknown	48 (50%)	25 (44%)	23 (58%)	.186
IgA nephropathy	12 (12%)	7 (12%)	5 (13%)	1.000
Polycystic kidney disease	8 (8%)	4 (7%)	4 (10%)	.714
Glomerulonephritis	9 (9%)	6 (11%)	3 (8%)	.732
Diabetes	7 (7%)	5 (9%)	2 (5%)	.696
Hypertension	6 (6%)	4 (7%)	2 (5%)	1.000
Others	7 (7%)	6 (11%)	1 (3%)	.234
Time from primary disease to kidney transplantation (months)	84 (36–156)	66 (36–192)	96 (30–144)	1.000
Twice or more kidney transplantation n(%)	9 (9%)	5 (9%)	4 (10%)	1.000
Dialysis before kidney transplantation				
Blood dialysis n(%)	78 (80%)	41 (72%)	37 (93%)	.012
Duration of blood dialysis (months)	15 (6–28)	12 (3–24)	18 (7–36)	.091
Peritoneal dialysis n(%)	13 (13%)	9 (16%)	4 (10%)	.410
Duration of peritoneal dialysis (months)	27 ± 21 (n = 11)	27 ± 15 (n = 7)	27 ± 31 (n = 4)	1.000
Immunological induction				
ATG usage during surgery n(%)	65 (67%)	38 (67%)	27 (68%)	.932
ATG dosage during surgery (mg)	255 ± 175	255 ± 167	255 ± 189	.991
Basiliximab usage during surgery n (%)	34 (35%)	21 (37%)	13 (33%)	.659
Basiliximab dosage during surgery (mg)	29 ± 11	29 ± 10	29 ± 13	.871
Immunosuppression				
Tacrolimus + Mycophenolic acid n(%)	83 (86%)	52 (91%)	31 (78%)	.058
Tacrolimus + Mizoribine n(%)	2 (2%)	2 (4%)	0 (0)	.510
Cyclosporin-A+ Mycophenolic acid n(%)	11 (11%)	3 (5%)	8 (20%)	.047
Cyclosporin-A + Everolimus n(%)	1 (1%)	0 (0)	1 (3%)	.412
Length of dwelling urethral catheter (days)	14 (13–17) (n = 95)	14 (13–18) (n = 55)	14 (12–17) (n = 40)	.900
Length of ureteric stent (days)	36 (28–50) (n = 65)	35 (28–50) (n = 36)	36 (28–51) (n = 29)	.787
Renal function after transplantation				
The lowest serum creatinine level (umol/L)	104.8 (88.5–154.6)	105.1 (93.9–162.8)	104.0 (78.2–133.0)	.242
Delayed graft function n (%)	21 (22%)	11 (19%)	10 (25%)	.502
Surgery complications				
Infection	45 (46%)	23 (40%)	22 (55%)	.154
Acute rejection	7 (7%)	3 (5%)	4 (10%)	.442
Urinary fistula	6 (6%)	3 (5%)	3 (8%)	.688
Others	7 (7%)	4 (7%)	3 (8%)	1.000
Mortality	5 (5%)	4 (7%)	1 (3%)	.646

Skew-distributed data are expressed as median and quartiles.
ATG = anti-human thymocyte globulin, ESRD = end-stage renal disease.

($n = 16$), 398 ± 228 for fourth infections ($n = 5$), and 964 ± 726 for fifth infections ($n = 2$). One patient had 6 infections, and the sixth was documented 1512 days after KT (Table 4).

In 40 RI patients, the first infection site was the urinary tract in 28, and a pulmonary site in 11. Fourteen had urinary tract involvement in all of their infections, and 8 had pulmonary site involvement in all of their infections. In the RI group 18 patients had 2 or more infections with positive etiologic findings (Table 4). The same pathogen was isolated in at least 2 different episodes in 12 patients. The most common pathogen was *P. aeruginosa*, followed by extended-spectrum beta-lactamase-producing *E. coli* and non-extended-spectrum beta-lactamase-producing *K. pneumoniae*.

3.6. Performance of independent predictors of RI

Two significant independent predictors of RI were identified, LKTFI and TAC level around the time of the first infection (Table 5). The area under the receiver operating characteristic curve (AUC) values were 0.636 for LKTFI and 0.663 for TAC level, and the difference between them was not significant (Fig. 4). We assigned 1 point to LKTFI $\leq$ 21 days and 0 points to any other number of days, and we assigned 1 point to TAC $\geq$ 8 ng/mL and 0 points to TAC $<$ 8 ng/mL. A combination score consisting of the sum of these LKTFI and TAC-derived values was calculated. The AUC of this combination score was 0.716 with regard to predicting RI, which was slightly better but did not differ significantly from the individual AUCs for LKTFI or TAC level. Notably however, the specificity of the combination score (90.4%) was improved.

4. Discussion

In the present study, infection soon after KT ($\leq$ 21 days) and a high TAC level ($\geq$8 ng/mL) predisposed KTRs to RI.

How pre-transplant hemodialysis influences the outcomes of KT remains controversial. Some studies suggest that hemodialysis is a risk factor for mortality and graft function loss, while others have shown no such association.[14–16] Few studies have investigated infection as an outcome of KT and analyzed the

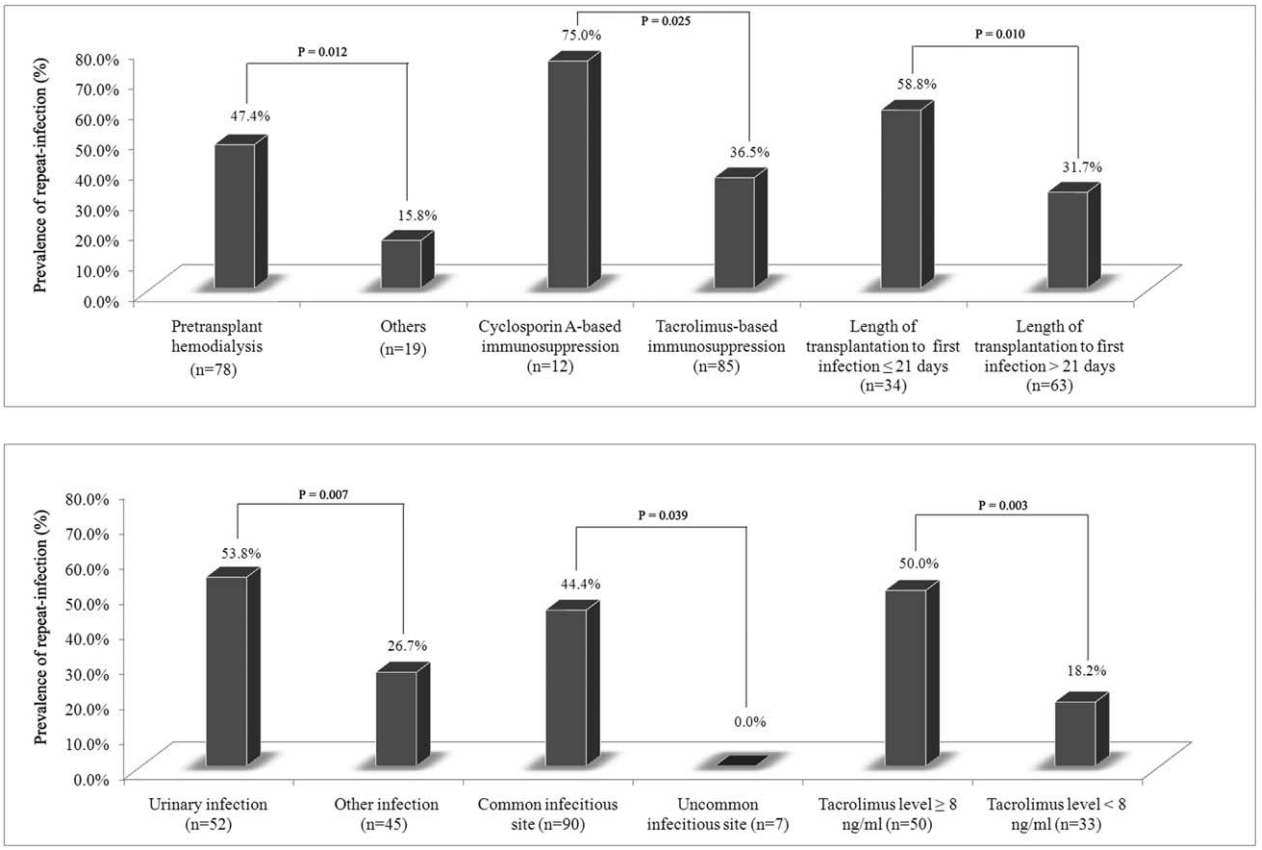

Figure 2. Effects of different risk factors on the prevalence of repeat infection in kidney transplant recipients.

Table 2

Clinical characteristics of the first infectious episode.

	All patients (n = 97)	Single-infection (n = 57)	Repeat-infection (n = 40)	*P*
Length of transplantation to the first infection (days)	37(14–103)	44(21–189)	22 (12–56)	.003
Infection and KT in the same hospitalization	45 (46%)	23 (40%)	22 (55%)	.154
Site of infection n (%)				
Blood stream	22 (23%)	9 (16%)	13 (33%)	.053
Urinary	52 (54%)	24 (42%)	28 (70%)	.007
Pulmonary	42 (43%)	28 (49%)	14 (35%)	.167
Intra-abdominal	4 (4%)	4 (7%)	0 (0)	.140
Gastrointestinal	3 (3%)	2 (4%)	1 (3%)	1.000
Others	7 (7%)	7 (12%)	0 (0)	.039
Complications after infection episode n (%)	4 (4%)	4 (7%)	0 (0)	.140
The highest creatinine during infection (umol/L)	160.5 (110.4–266.7)	170.8 (121.7–266.7)	157.2 (96.4–273.3)	.337
Renal function exacerbation n (%)	20 (21%)	15 (26%)	5 (13%)	.098
Procacitonin (ng/mL)				
Infection episode	0.14 (0.06–0.79)(n = 75)	0.21 (0.06–0.77)(n = 43)	0.11 (0.06–2.86)(n = 32)	.804
The highest	1.49 (0.26–15.44) (n = 42)	0.81 (0.25–8.85) (n = 26)	6.83 (0.35–28.71) (n = 16)	.288
The lowest	0.11 (0.05–0.31)(n = 42)	0.14 (0.05–0.40)(n = 26)	0.08 (0.05–0.28)(n = 16)	.625
Etiology positive (≥once)	57 (59%)	31 (54%)	26 (65%)	.296
Tacrolimus level around infection (ng/ml)	9.0 ± 3.7 (n = 83)	8.2 ± 3.5 (n = 52)	10.4 ± 3.5 (n = 31)	.005
Respiration support (NPPV and/or IPPV) n (%)	14 (14%)	9 (16%)	5 (13%)	.650
Length of respiration support (hours)	81 ± 69 (n = 13)	93 ± 84 (n = 8)	62 ± 37	.457
ICU admission n (%)	20 (21%)	10 (18%)	10 (25%)	.372
Length of ICU stay (days)	16 ± 13	18 ± 16	14 ± 9	.532
Length of hospitalization (days)	26 (13–38)	26 (12–36)	25 (17–48)	.695

ICU = intensive care unit, IPPV = invasive positive pressure ventilation, KT = kidney transplantation, NPPV = noninvasive positive pressure ventilation.

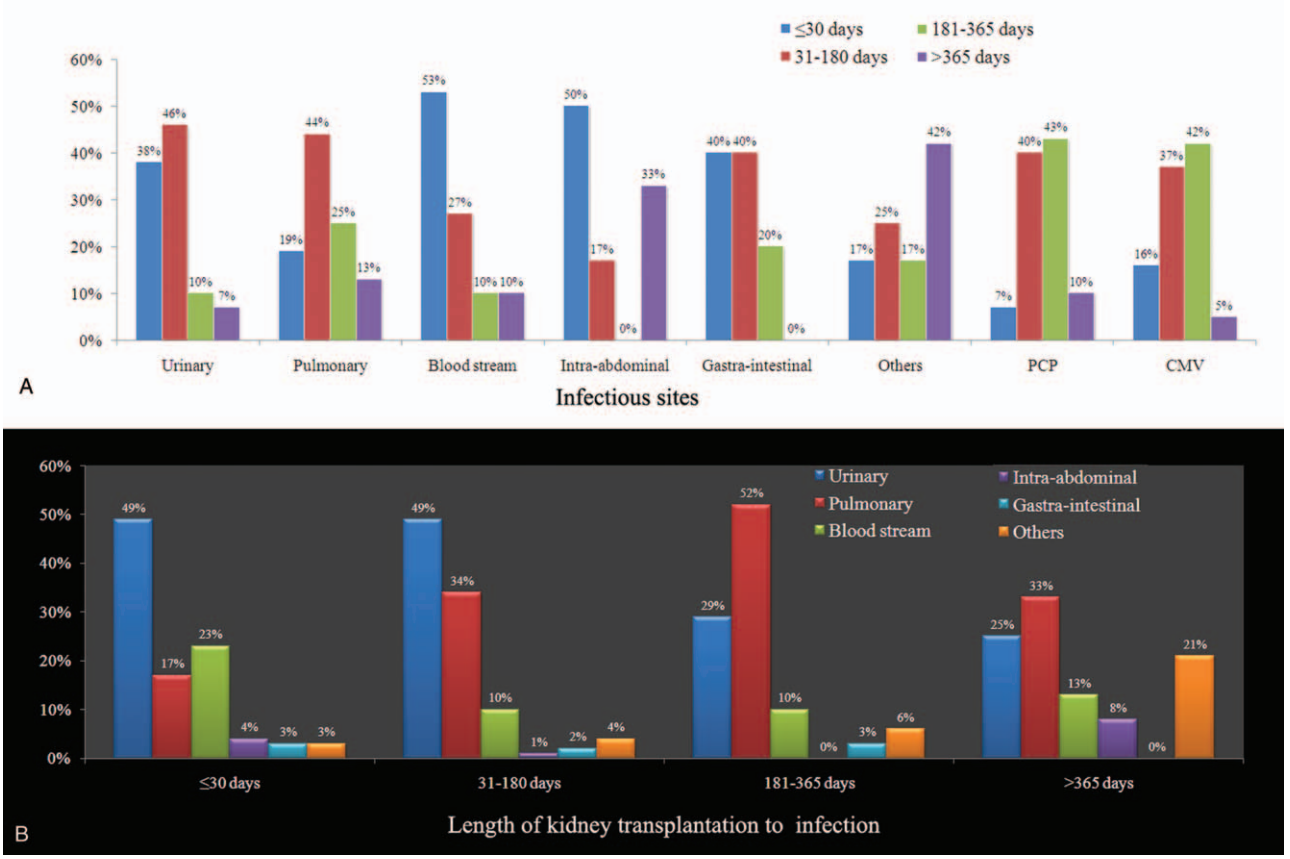

Figure 3. Infection sites and times from kidney transplantation to infection.

risk factors of RI. In the current study a high proportion of RI patients had pre-transplant hemodialysis, and they tended to have had it for longer than SI patients. Although the difference was not statistically significant, the finding warrants greater caution in transplant recipients who undergo extensive pre-transplant hemodialysis. Because the sample size of the present study was small, the results need to be verified in a larger cohort.

Cyclosporin-A was used more frequently in RI recipients in the current study, suggesting that cyclosporin-A-based immunosuppression may be associated with increased RI. Notably however, this finding is not concordant with the results of some previous studies. A meta-analysis reported by Webster et al in 2005 suggested that primary immunosuppression did not affect infection after KT irrespective of the time-frame considered (follow-up period) or the type of infection (bacterial, viral, fungal, protozoan), and a more recent meta-analysis reported in 2018 supported those results.[17,18] Notably however, neither of those two meta-analyses collated and examined a collectively derived RI subgroup. With regard to the results pertaining to cyclosporin-A in the present study, because the study sample was small and only 12 KTRs had taken cyclosporin-A, the results suggesting potential associations between cyclosporin-A and RI require verification in future studies.

It has been suggested in previous reports that the TAC trough level should be maintained at ≥ 8 ng/mL to protect KTRs from acute rejection, especially during the early period after KT, and that this level does not significantly increase the risk of infection.[19,20] In the present study, however, the TAC level around the time of the first infection independently predicted RI. The median LKTFI was 22 days in the RI group. While a target TAC trough level of ≥ 8 ng/mL during the first month after KT has been recommended, in the current study TAC was ≥ 8 ng/mL in 50% of the patients who experienced RI during the follow-up period. (Fig. 2). Although RI is a result of complex causes, immunosuppression status should always be of initial concern.

As well as high TAC level, LKTFI was identified as an independent predictor of RI in the present study in which 58.8% of infected KTRs with a LKTFI of < 21 days subsequently developed RI (Fig. 2). The risk of infection in a KTR at any point after KT is a function of two main factors, one being the collective exposures of the patient and the organ donor (including recent, nosocomial, and remote exposures) and the other being the patient's state of immunosuppression.[12] In the early phase after KT, surgery stress, intravenous lines, high-density immunosuppressive regimens, and prophylactic antibiotics render KTRs more susceptible to infection. It is also worth considering that KTRs who are not infected in the early period may have a superior capacity to avoid infection. The LKTFI is undoubtedly influenced by interactions between many complex factors of potential relevance in KT, but the results of the current study suggest that it may be an informative indicator of subsequent RI.

The durations of time between KT and initial infections in the current study are concordant with previous reports.[12] The mean procalcitonin level associated with the first infection was higher in RI patients than in SI patients, but the difference was not significant. This finding should be further investigated in a larger

Table 3

Timeline and antibiotic resistance of the pathogens isolated in kidney transplantation recipients.

	Number of positive pathogen test results					Specimen type					SI group	RI group
	≤30days	31–180 days	181–365 days	>365 days	Total	Blood	Sputum	Urine	Others (n)		Number (MDR number)	
S. aureus	1 (MRSA)		3		4		3		Wound secretion (1MRSA)		1 (1MRSA)	3
MRSCoN	3	2			5	3			Drainage fluid (1)	Catheter tip (1)	4	1
A. baumannii		2 (2MDR)		2	4		3	1			1 (MDR)	3 (1MDR)
B. cepacia	1				1		1					1
P. aeruginosa	15	9			24	4	5	13	Drainage fluid (1)	BALF (1)	2	22
E. coli	5 (5E+)	9 (9E+)	3 (3E+)	6 (5E+)	23	11		10	Ascitic fluid (1)	Purulence (1)	6 (5E+)	17 (17E+)
E. aerogenes	3	1			4	1		2	Purulence (1)		2	2
E. cloacae	10 (2E+)		1		11	4	2	5			4	7 (2E+)
K. pneumoniae		6 (5E+)	4 (4E+)	1 (1E+)	11	3	1	6	Drainage fluid (1)		2 (1E+)	9 (9E+)
P. mirablis		3 (3E+)			3			3				3 (3E+)
E. avium				1	1				Purulence (1)		1	
E. faecalis	1	7	1		9	2		6	Catheter tip (1)		1	8
E. faecium	6	6			12			7	Drainage fluid (3)	Wound secretion (1) Catheter tip (1)	6	6
E. gallinarum		1 (VRE)			1			1				1 (VRE)
C. albicans	3	2			5			5			3	2
C. glabrata	1	5			6	1		4	Drainage fluid (1)		1	5
C. parapsilosis	2				2			2			2	
C. lusitaniae		1			1				Drainage fluid (1)			1

	Number of positive pathogen test results					Specimen type					SI group	RI group
	≤30days	31–180 days	181–365 days	>365 days	total	Blood	Sputum	Urine	Others (n)			
C. tropicalis	2				2			2			2	
C. hellenical	3	2			5			5				5
C. difficile		1			1				Stool (1)		1	
Nocardia			1		1				BALF (1)			1
CMV DNA	1	10	3	1	15		10		BALF (2)	Throat swab (3)	6	9
Mycoplasma RNA	1	1		1	3				Throat swab (3)		2	1
Flu A RNA			1		1				Throat swab (1)			1
CMV PP50			1		1				Serum (1)			1
P. jiroveci DNA		8	13		21		17		BALF (4)		9	12
Total times	58	76	31	12	177	29	41	72	35		56	121
Total MDR	11	22	7	6	46						12	34

A. baumannii = *Acinetobacter baumannii*, *B. cepacia* = *Burkholderia cepacia*, BALF = bronchoalveolar lavage fluid, *C. albicans* = *Candida albicans*, *C. glabrata* = *Candida glabrata*, *C. parapsilosis* = *Candida parapsilosis*, *C. lusitaniae* = *Candida lusitaniae*, *C. tropicalis* = *Candida tropicalis*, *C. hellenical* = *Candida hellenical*, *C. difficile* = *Clostridium difficile*, CMV = cytomegalovirus, *E. coli* = *Escherichia coli*, *E. aerogenes* = *Enterobacter aerogenes*, *E. cloacae* = *Enterobacter cloacae*, *E. avium* = *Enterococcus avium*, *E. faecalis* = *Enterococcus faecalis*, *E. faecium* = *Enterococcus faecium*, *E. gallinarum* = *Enterococcus gallinarum*, E+ = extended spectrum beta-lactamase-producing, *K. pneumoniae* = *Klebsiella pneumoniae*, MDR = multi-drug resistant strains, MRSA = methicillin-resistant *S. aureus*, MRSCoN = methicillin-resistant coagulase-negative staphylococcus, *P. aeruginosa* = *Pseudomonas aeruginosa*, *P. mirablis* = *Proteus mirabilis*, *P. jiroveci* = *Pneumocystis jiroveci*, RI = repeat-infection, *S. aureus* = *Staphylococcus aureus*, SI = single-infection, VRE = vancomycin-resistant Enterococcus.

cohort, and notably in a previous study procalcitonin was reportedly an informative predictor of infection after solid organ transplantation.[21]

Because of the present study's small sample size, no statistical analysis assessing the significance of differences between the pathogens afflicting the RI and SI groups was conducted. *P. aeruginosa* was the most frequently detected pathogen overall, and it was isolated from blood, sputum, urine, drainage fluid, and BALF. *P. aeruginosa* was also the most commonly detected pathogen in RI patients. *E. coli* was reportedly the most commonly isolated pathogen in KTRs in multiple previous studies,[22–24] but the etiology of RI was not evaluated in these studies. In a study investigating potential therapeutic targets, *P. aeruginosa* was the sixth most common repeat-occurrence pathogen.[25] *P. aeruginosa* infection is very difficult to treat due to the associated development of a biofilm that promotes bacterial persistence.[25] Interestingly no MDR *P. aeruginosa* was cultured in the present study, whereas more than 90% of the *Enterobacteriaceae* isolates cultured were MDR. This result provided an empirical basis for an antibiotic strategy to cover both *P. aeruginosa* and extended-spectrum beta-lactamase-producing bacteria that has been implemented in our hospital.

Most research investigating RI in KTRs has focused on recurrent UTIs, and several risk factors have been identified including being female, advanced age, diabetes mellitus, nosocomial infection, infection with MDR bacteria, reoperation, and renal calculi, among others.[26–29] Few studies have investigated repeated infections in KT patients. In the present study, LKTFI and TAC level independently predicted RI regardless of the site of infection, and UTI constituted the majority of RI cases. For clinical convenience we utilized a simple potentially predictive model in which 1 point was assigned to LKTFI $\leq$ 21 days and to TAC $\geq$ 8 ng/mL, and 0 points were assigned to LKTFI $>$ 21 days and to TAC $<$ 8 ng/mL. Patients with 1 point for either one of the 2 predictive factors had a 2-fold risk of developing RI, and patients with 2 points had a 4.7-fold risk of developing RI.

The current study had several limitations. It was a retrospective study involving patients with incomplete medical records, and

Table 4

Characteristics of repeat-infection patients with two or more positive etiologies.

Patients	Duration from kidney transplantation to infection (days)						Infection sites					
	1st	2nd	3rd	4th	5th	6th	1st	2nd	3rd	4th	5th	6th
1	10	40					Urinary; Blood stream	Urinary				
2	12	146					Urinary; Blood stream	Pulmonary				
3	12	25	208				Urinary	Urinary	Pulmonary			
4	19	35	72				Pulmonary	Urinary; Pulmonary	Urinary			
5	1	267	433				Gastrointestinal	Pulmonary	Urinary (BKV)			
6	19	55	232				Urinary	Urinary	Pulmonary			
7	9	151					Urinary	Urinary				
8	6	52					Urinary; Blood stream	Urinary; Blood stream				
9	39	142					Urinary; Pulmonary; Blood stream	Urinary; Blood stream				
10	20	64	128				Urinary; Pulmonary	Urinary; Pulmonary	Urinary			
11	10	90	185	243			Urinary; Blood stream	Urinary; Blood stream	Urinary	Urinary		
12	12	51	80				Urinary; Blood stream	Urinary	Urinary			
13	97	221	288				Urinary	Urinary	Urinary			
14	51	448	1326				Pulmonary	Pulmonary	Pulmonary			
15	6	48	69				Pulmonary	Pulmonary	Pulmonary			
16	13	32	53	234			Urinary	Urinary	Urinary	Pulmonary		
17	10	34	233	274	450		Urinary; Blood stream	Urinary	Pulmonary	Urinary	Pulmonary	
18	31	168	201	767	1477	1512	Urinary; Pulmonary; Blood stream	Pulmonary	Blood stream; Gastrointestinal	Pulmonary	Nasal sinuses	Urinary; Blood stream

Patients	Same pathogens	Pathogens					
		First infection	Second infection	Third infection	Fourth infection	Fifth infection	Sixth infection
1	No	Blood and urine culture: *E. cloacae (E+)*	Urine culture: *P. aeruginosa*				
2	No	Drainage culture: *E. faecium*	Sputum and BALF: PJ DNA				
3	No	Urine culture: *E. cloacae*		Sputum: PJ DNA			
4	No	Throat swab: mycoplasma RNA		Urine culture: *K. pneumoniae* (E+)			
5	No	Sputum: *B. cepacia*	Serum: CMV-PP65				
6	No	Urine culture: *P. aeruginosa*		Sputum: PJ DNA			
7	Yes	Purulence culture: *E. aerogenes*	Urine culture: *E. aerogenes*; *E.faecium*				
8	Yes	Blood and urine culture: *E.coli (E+)*	Blood culture: *E.coli (E+)*				
9	Yes	Urine culture: *E. faecalis*; *C. albicans*	Blood culture: *E. faecalis*; urine culture: *E. faecalis+C. albicans*				
10	Yes		Urine culture: *K. pneumoniae (E+)*; *C. glabrata*	Urine culture: *Candida*			
11	Yes	Blood and urine culture: *E.coli (E+)*	Blood and peritoneal fluid culture: *E.coli (E+)*				
12	Yes	Urine culture: *P. aeruginosa*; *C. guilliermondii*	Urine culture: *P. mirabilis*; *E. faecium*; *C. guilliermondii*	Urine culture: *P. mirabilis (E+)* *E. gallinarum (VRE)*			
13	Yes	Urine culture: *K. pneumoniae (E+)*	Blood and urine culture: *K. pneumoniae (E+)*	Urine culture: *E. cloacae*; catheter tip: *E. faecalis*			
14	Yes	Throat swab: CMV DNA	Sputum: CMV DNA	Sputum: *A. baumanii*			
15	Yes	Sputum: *E. cloacae*; *P. aeruginosa*; CMV-DNA	Sputum: *P. aeruginosa*; CMV-DNA; BALF: *P. aeruginosa*	Sputum: *P. aeruginosa*; CMV DNA			
16	Yes	Urine culture: *P. aeruginosa*	Urine culture: *P. aeruginosa*		Sputum: PJ DNA; flu A RNA		
17	Yes	Blood and urine culture: *P. aeruginosa*	Urine culture: *P. aeruginosa*				
18	Yes	Drainage culture: *E. faecium*; *Candida lusitaniae*	Urine culture: *C. glabrata*; Drainage culture: *K. pneumoniae (E+) + C. glabrata*;	Blood culture: *K. pneumoniae (E+)*	Urine culture: *K. pneumoniae (E+)*	Urine culture: *E. coli (E+)*	Urine culture: *E. coli (E+)*

A. baumanii = *Acinetobacter baumanii*, *B. cepacia* = *Burkholderia cepacia*, BALF = bronchoalveolar lavage fluid, *C. albicans* = *Candida albicans*, *C. glabrata* = *Candida glabrata*, *C. guilliermondii* = *Candida guilliermondii*, CMV = cytomegalovirus, *E. cloacae* = *Enterobacter cloacae*, *E. coli (E+)* = *Escherichia coli (ESBL+)*, *E. faecium* = *Enterococcus faecium*, *E. aerogenes* = *Enterobacter aerogenes*, *E. gallinarum* = *Enterococcus gallinarum*, E+ = extended spectrum beta-lactamase-producing, K. pneumoniae = Klebsiella pneumoniae, P. aeruginosa = Pseudomonas aeruginosa, P. mirabilis = Proteus mirabilis, PJ = pneumocystis jiroveci, VRE = vancomycin-resistant Enterococcus.

Table 5

Independent predictors of repeat infection after kidney transplantation (n = 83).

Variables	B	SE	Wals	P	OR	95% CI of OR	Sensitivity	Specificity	PPV	NPV	LR+	LR−
Length of transplantation to first infection ≤ 21days	1.109	0.518	1.492	.032	3.032	1.099–8.363	48.4%	78.8%	57.7%	71.9%	2.28	0.65
Tacrolimus level ≥ 8 ng/ml	1.39	0.546	6.473	.011	4.016	1.376–11.72	80.6%	51.9%	50.0%	81.8%	1.68	0.37
Combination							45.2%	90.4%	73.7%	73.4%	4.71	0.61
Constant	−1.805	0.492	13.487	<.001	0.164							

CI = confidence interval, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, NPV = negative predictive value, OR = odds ratio, PPV = positive predictive value, SE = standard error.

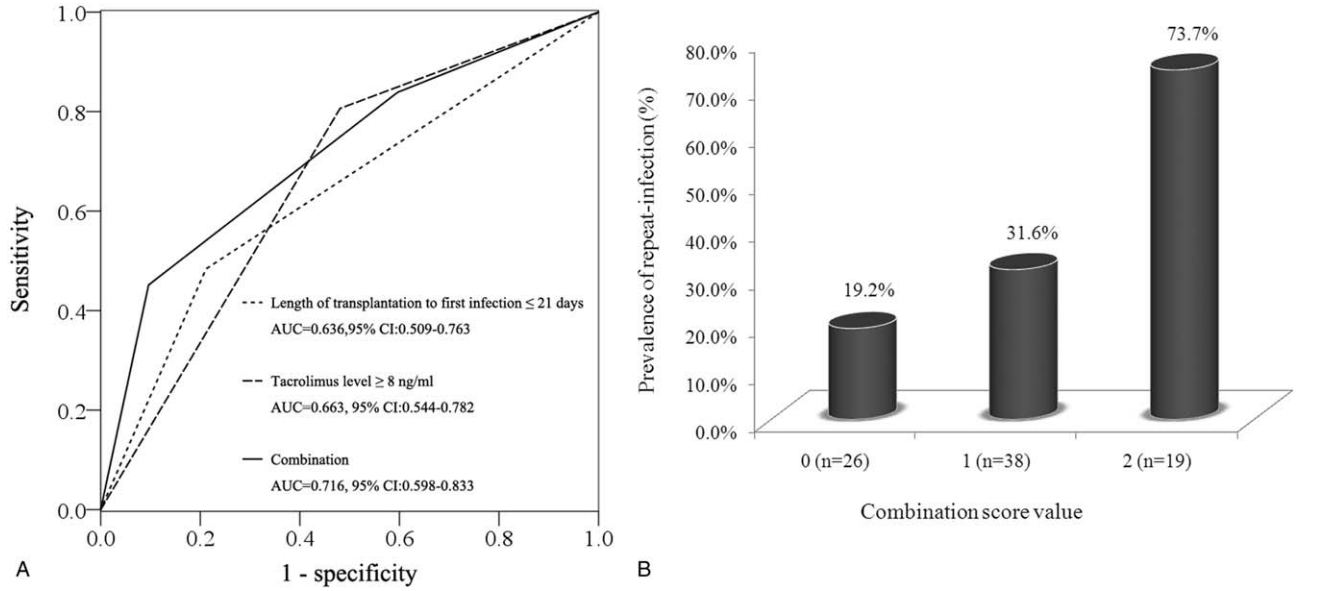

Figure 4. Receiver operating characteristic curves of independent predictors of repeat infection: 1) length of time from kidney transplantation to first infection; 2) tacrolimus level ≥ 8 ng/mL; and 3) the combination of the two. The prevalence of repeat infection in relation to the combined score is also shown.

some kidney donor information was not available for inclusion in the study due to complexities involved in the organ donation process. Thus, many potentially important and informative factors were not included. The sample size was small and outpatients were not included in the study, thus we presume that some mild infections were missed. Last, we did not include an uninfected KTR cohort, which might have facilitated the identification of more risk factors. With these limitations in mind, we have designed a prospective study that is currently underway, in an effort to investigate risk factors associated with RI more thoroughly.

5. Conclusion

In the current study, at the time of the first post-transplant infection in KTRs a duration of ≤21 days between KT and infection, and TAC ≥8 ng/mL were independent predictors of subsequent RI.

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