Relationships between acute rejection、hemoglobin levels and BK virus infection among renal transplant recipients in China

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Abstract

This study aimed to explore the risk factors for BK virus （BKV） infection in renal transplant recipients （RTR） routinely treated with tacrolimus. Among the 93 RTRs enrolled in the study, 42 cases had BKV infections and 51 patients did not have BKV infections. A positive BKV result was detected by polymerase chain reaction （PCR） for the first time after renal transplantation. Eighty-seven healthy individuals and 77 patients undergoing dialysis were randomly included as controls during the study period. A logistic regression model was used to analyse potential variables in order to evaluate factors related to BKV infection in the RTRs. The results of a multivariate regression analysis indicated that a history of acute rejection (OR = 4.157; p = 0.031) and low hemoglobin were risk factors for BKV infection. Compared with the BKV-negative RTRs, the hemoglobin levels in the BKV-positive RTRs were significantly lower. Thus, the results of our study suggest that a history of acute rejection and low hemoglobin are risk factors for BKV infection after renal transplantation.

1. Introduction

Renal transplantation is the most effective treatment for end-stage renal disease(ESDR). Infection caused by the long-term use of immunosuppressants is a common complication after renal transplantation, and severe cases may lead to death [1]. Generally, BK virus (BKV) primary infection does not cause renal function damage. However, when the host's immunity decreases, the process of infection usually begins with BK viruria and progresses to BK viremia, which, without intervention, eventually leads to the occurrence of BKV-associated nephropathy（BKVAN), and the production of inflammatory cells that infiltrate the kidney tissue, causing renal function damage [2]. In renal transplant recipients（RTR）treated with new immunosuppressants, there has been an upward trend in BKV infection rates [3]. The gold standard for the diagnosis of BKVAN is the biopsy of a transplanted kidney, which is an invasive examination. Moreover, because some patients with BKVAN have complex conditions, its feasibility is limited. At present, there is a lack of effective antiviral drugs to treat BKV;hence, early prevention is necessary. At present, it is recommended that intervention be started at the stage of BK viremia. However, previous studies have shown that it is advantageous to start intervention at the stage of BK viruria [4, 5].

Tacrolimus is a potent immunosuppressant that is widely used to prevent organ transplant rejection in RTRs. Previous studies have shown that tacrolimus appears to be the most robust risk factor for BKV infection in RTRs [6, 7]. Tacrolimus works by binding to red blood cells in RTRs. In anaemic RTRs, it is necessary to increase the drug dose to achieve effective drug concentration, but excessive dosages of immunosuppressants lead to a decline in immunity, which leads to an increase in opportunistic infection rates, including BKV. Decreased hemoglobin in RTRs is considered associated with graft failure and mortality [8, 9]. In RTRs who regularly take tacrolimus, whether decreases in their hemoglobin levels are related to BKV infection has not been reported. Moreover, whether rejection after transplantation is a risk factor for BKV infection remains controversial. To provide a basis for early clinical intervention in RTRs, in this study, we evaluate whether acute rejection and decreased hemoglobin levels are risk factors for BK viruria.

2. Methods

2.1 Patients and Samples

We collected the clinical demographics and laboratory data on patients who underwent kidney transplantation for the first time in the Department of Organ Transplantation, Second Affiliated Hospital of Guangxi Medical University between January 2020 and July 2021. The BKV loads in the urine or plasma of RTRs were monitored by real-time fluorescent quantitative polymerase chain reaction(RT-qPCR). Positive BKV DNA in urine or plasma detected by RT-qPCR was defined as $\geq 2\times10^3$copies/mL. On the first detection, 42 patients were confirmed to have BKV infection. The control group included 51 RTRs with stable renal function. Within six months of follow-up, the fluctuations in serum creatinine in RTRs with stable renal function were within the normal range, and those with stable renal function did not have delayed recovery of graft function, infection, rejection or renal insufficiency. Immunosuppressive therapy with tacrolimus + mycophenolate mofetil + prednisone was routinely used in RTRs. Patients with leukaemia, cytomegalovirus infection, human parvovirus B19 infection, combined with other organ transplantation and cardiovascular diseases were excluded. Eighty-seven healthy individuals and 77 patients with ESRD undergoing dialysis were randomly included in the study during the same period.

2.2 Laboratory Indicators of Participants

We collected the biomarkers of patients who tested positive for BKV DNA the first time after renal transplantation. Laboratory indicators were collected from recipients with stable renal function at the sixth month after their operations. BKV DNA was detected using fluorescent quantitative PCR instruments. Hemoglobin levels were detected using an automatic hematology analyser. Serum creatinine levels were detected using a Cobas 8000 automatic biochemical analyser. Glomerular filtration rates (GFR) were calculated using the simplified Modification of Diet in Renal Disease (MDRD)formula: $186 \times (\text{serum creatinine}^{-1.154}) \times \text{age}^{-0.203} \times 1.233 \times 0.702$ (if female). A logistic regression analysis was used to analyse the independent risk factors for BKV infection after renal transplantation.

2.3 Statistical Analyses

SPSS software version 22.0 was used for the statistical analysis, and $p < 0.05$ was considered statistically significant. Normal data were expressed as mean ± standard deviation and compared using a t-test. Non-normal data were expressed as median (interquartile range) and compared using a nonparametric test. Categorical variables were expressed as frequencies or percentages. Changes in hemoglobin in the RTRs before and after renal transplant were evaluated by a paired t-test or nonparametric test. A multivariate regression analysis was used to evaluate the risk factors.

3. Results

3.1 Clinical Characteristics of RTRs, Patients Undergoing Dialysis and Healthy Subjects

The characteristics of the RTRs，the patients undergoing dialysis and the healthy controls are shown in Table 1. Among 93 RTRs, 70 received regular peritoneal dialysis or hemodialysis before the operation. Among 77 patients with ESRD undergoing dialysis, 70 received regular peritoneal dialysis or haemodialysis. The hemoglobin levels in the dialysis patients were significantly lower than those in the RTRs and the healthy controls.

3.2 Clinical Characteristics of BKV DNA-Positive and Stable Renal Function Recipients

The clinical characteristics of BKV DNA-positive and stable renal function RTRs are shown in Table 2. Among the BKV DNA-positive recipients, 41 cases had elevated BKV DNA in urine，and one case tested positive for BKV DNA in both plasma and urine. The time interval from transplantation to testing positive for BKV DNA in RTRs was 0.5-13 months. Among the 42 RTRs that were positive for BKV, 11 had a history of acute rejection. The GFR and hemoglobin levels in BKV-positive RTRs were significantly lower than those in stable renal function recipients.

3.3 Variations in Hemoglobin Levels Before and After Transplantation in Patients with and Without Infection

In the BKV-positive RTRs，compared with their pre-operative hemoglobin levels, the levels of hemoglobin were decreased significantly one week after the operation; there was no significant difference in the first and the third months after operation. Moreover, there was no significant difference between hemoglobin levels before the operation and positive for the BKV after the operation. In the BKV-negative RTRs, compared with pre-operative hemoglobin levels, the levels of hemoglobin were decreased significantly one week after operation，there was no significant difference in hemoglobin levels in the first month after operation，hemoglobin levels were significantly increased in the third and sixth months after operation. There was no significant difference in tacrolimus concentrations between the BKV- positive and BKV-negative RTRs in the first week, first month and third month after renal transplantation. The concentration of tacrolimus in the BKV-positive group was significantly lower than that in the BKV-negative group at the sixth month after operation，Table 3）.

3.4 Value of Indicators for Predicting BKV Infection

A univariate analysis showed significant differences in acute rejection and hemoglobin levels between the BKV-negative and stable renal function recipients. The results of the multivariate regression analysis showed that recipients with a history of acute rejection （OR = 4.157，p = 0.031）after renal transplantation had an increased risk for BKV infection, and reduced hemoglobin levels（OR = 0.963，p ＜ 0.001）increased the risk of BKV infection （Table 4）.

Discussion

BKV is highly prevalent in the population, but clinical symptoms occur only in immunocompromised patients, especially in RTRs. Regional differences have been found in the positive rate of BKV in the

plasma or urine of RTRs and a positive BKV in urine is more common in the Asian population [10]. Previous studies have shown that because BK viruria leads to an increase in serum creatinine the early detection of BK viruria is necessary [11, 12].

Whether a history of acute rejection is a risk factor for BKV infection after renal transplantation remains controversial. Previous studies have shown that a history of acute rejection is a cause of BKV infection [13, 14]. Shenagari et al. found that long-term dialysis before transplantation and tacrolimus treatment, rather than a history of acute rejection, were risk factors for elevated urinary BKV [6]. In our study, the number of acute rejections in RTRs who were positive for BKV was significantly higher than in RTRs who were negative for BKV. Immunosuppression plays an important role in BKV infection. Patients with acute rejection after renal transplantation might need to use higher intensity immunosuppressants, which might be a potential cause of BKV infection [15]. Although RTRs present acute rejection, different immunosuppressive regimens and/or drug doses for rejection may lead to differences in BKV infection rates.

Low hemoglobin is a predictor of decline in GFR in patients with type 2 diabetes, and the risk of ESRD increases with a decrease in hemoglobin levels [16, 17]. Anaemia could be aggravated by haemorrhage during transplantation and frequent blood drawing after transplantation in patients with ESRD. Some studies have found that the risk of graft function loss in patients with anaemia is significantly higher than that in patients without anaemia and low hemoglobin has been reported as an independent risk factor for death in transplant recipients [18, 19]. Dialysis treatment before renal transplantation is also a cause of pre-operative anaemia. In our study, the results showed that the hemoglobin levels in the dialysis patients were significantly lower than in the RTRs. However, no correlation was found between dialysis and BKV infection.

The main cause of early posttransplant anaemia in RTRs is the insufficient secretion of erythropoietin iron deficiency, or decreased erythropoiesis. Anaemia and hypoxia lead to human renal proximal tubular epithelial cell HRPTEC damage and dysfunction, resulting in pathological changes in the kidney [20, 21]. In immunosuppressed renal transplant patients, HRPTECs are the main site of virus latency and reactivation [22]. BKV infects HRPTECs and then spreads to infect urothelial cells, potentially developing into BKVAN [23, 24]. Viral infections, including BKV, could interfere with bone marrow production and lead to aplastic anaemia [25, 26] which in turn aggravates the degree of anaemia.

RTRs need to use immunosuppressive drugs regularly to avoid rejection. Therefore, the autoimmunity of the recipient is reduced, which increases the risk of BKV infection. The infection rates of BKV in tacrolimus-based immunotherapy are higher than those in cyclosporine therapy [27, 28]. Tacrolimus has a direct toxic effect on renal tubules [29]. Tacrolimus binds to red blood cells, and the toxic reaction of the drug is significantly related to its concentration in whole blood. Anaemia leads to a decrease in tacrolimus concentration in red blood cells and increases the proportion of tacrolimus into plasma; hence, it is necessary to increase the dosage of tacrolimus to ensure adequate drug concentration, which could lead to an increase in drug toxicity in renal tubules. Anaemia leads to hypoxia, forming a vicious circle

that leads to damage and dysfunction of renal tubular epithelial cells. Renal tubular epithelial cells are the main latent sites of BKV. In RTRs who receive immunosuppressive therapy, BKV can replicate in large quantities and be released into the urine.

Vanrenterghem et al. investigated 4,263 RTRs in 72 countries and showed that 38.6% of the RTRs had anaemia, including 8.5% with severe anaemia, but only 17.8% of those with severe anaemia RTRs received erythropoietin treatment [30]. Schechter et al. found that the severity of anaemia after transplantation was associated with graft loss and mortality [31]. In our study，compared with pre-operation levels, hemoglobin levels in both BKV-positive recipients and BKV-negative recipients were decreased one week after the operation and increased one month after the operation. In the BKV-positive recipients，there was no significant difference in hemoglobin levels between the RTRs at the time of operation and when BKV was positive for the first time. However, in the BKV-negative recipients，the levels of hemoglobin in the sixth month after their operations were significantly higher than the pre-operation levels. Moreover, the results showed that low hemoglobin was an independent risk factor for BKV infection.

Tacrolimus is considered a risk factor for BKV infection after renal transplantation, and anaemia may increase the risk of BKV infection. To prevent the occurrence of BKVAN at an early stage, we suggest that evaluating the hemoglobin levels in recipients after renal transplantation and the timely treatment of anaemia might help to reduce the risk of BKV infection. Because of the small sample and limited retrospective data collection in this study, further well-designed studies are needed to evaluate the relationships between acute rejection, hemoglobin and BKV infection in RTRs.

Declarations

Ethics approval

This study was approved by the ethics committee of the Second Affiliated Hospital of Guangxi Medical University.

Consent to participate

All participants signed a written informed consent according to the Declaration of Helsinki.

Consent for Publication

Not applicable.

Availability of data and materials

Not applicable.

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Authors' contributions

Study design: Qitian He, Xiaoning Wu, and Li Xie. Acquisition, analysis, or interpretation of data: Qitian He, Limin Li, and Zhengyi Liang. Drafting and revising of the manuscript: Qitian He, Limin Li, and Li Xie. Statistical analysis: Qitian He and Limin Li. All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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Tables

TABLE 1. Clinical Characteristics of Renal Transplant Recipients, Dialysis Patients and Healthy Subjects

	Renal transplant recipients		Dialysis patients		Healthy controls	
	No	Results	No	Results	No	Results
Age（years）	93	38.13±12.64	77	39.57±10.63	87	39.41±8.18
Gender（male/female）	93	60/33	77	50/27	87	57/30
Dialysis before transplantation						
Regular hemodialysis,*n* (%)		61(65.59)		32(41.56)		—
Regular peritoneal dialysis,*n* (%)		9(9.68)		38(49.35)		—
Others,*n* (%)		23(24.73)		7(9.09)		—
Creatinine (μmol/L）	91	141（107.25， 168.5）		—	87	78.21±17.35
Glomerular filtration rate (mL/min/1.73m^2)	91	46.94（37.11， 68.92）		—	87	98.07±18.7*
Hemoglobin (g/L)	91	121.13±25.79	77	92.56±20.7*	84	149.5（137， 156.75）*

* Glomerular filtration rate: Renal transplant recipients versus Healthy controls, P ＜ 0.01.

*Hemoglobin: Renal transplant recipients versus Dialysis patients, P ＜ 0.01; Renal transplant recipients versus Healthy controls, P ＜ 0.01.

TABLE 2. Clinical Characteristics of BKV DNA Positive and Stable Renal Function Recipients

	BKV positive recipients		stable renal function recipients		P value
	No	Results	No	Results	
Mean age at transplantation（years）	42	38.57±13.63	51	37.92±12.23	0.82
Gender（male/female）	42	25/17	51	35/16	0.361
BMI（kg/m^2）	38	20.23±2.93	49	21.08±3.1	0.198
Systolic (mmHg)	39	136（130，156）	49	140.35±20.54	0.817
Diastolic (mmHg)	39	85（80，96）	49	89.33±14.34	0.4
Smoking status					
Nonsmoker, *n* (%)		40（95.2）		44（86.3）	0.27
Current smoker, *n* (%)		1（2.4）		3（5.9）	0.753
Ex-smoker, *n* (%)		1（2.4）		4（7.8）	0.484
Dialysis before transplantation					
Regular hemodialysis,*n* (%)		26(61.9)		35(68.6)	0.497
Regular peritoneal dialysis,*n* (%)		2(4.8)		7(13.7)	0.27
Others,*n* (%)		14(33.3)		9(17.7)	0.08
Urine BKV DNA positive（*n*）		41		—	—
Urine+Plasma BKV DNA positive（*n*）		1		—	—
The interval from transplant to BKV DNA positive (months)	42	0.5-13		—	—
History of acute rejection, *n* (%)	42	11(26)	51	5(8)	0.037
Delayed graft function,*n* (%)	42	8(19)	51	5(8)	0.201
Creatinine (μmol/L）	41	157（120.75，176.5）	50	128.5（102.75，163.5）	0.023
Cystatin C (mg/L)	41	1.75（1.48，2.26）	51	1.55（1.31，1.89）	0.023
Glomerular filtration rate (mL/min/1.73m^2)	41	45.38±20.41	50	56.63±20.55	0.011
Haemoglobin (g/L)	40	108.71±20.55	51	130.16±26.29	0.001

Abbreviations: BKV, BK virus.

TABLE 3. Variations of Hemoglobin and Tacrolimus in BKV DNA Positive and BKV DNA Negative Recipients

	Time	Hemoglobin (g/L)	Tacrolimus（ng/ml）
BKV positive recipients	pre-operative	107.48±17.27	—
	one week after operation	87.66±16.32*	5.4（3.32～6.7）
	one month after operation	102.61±16.74	7.85±2.84
	three month after operation	112.35±13.15	7.9（6.4～10.5）
	when BKV test is positive	108.71±20.55	7.65±2.28
BKV negative recipients	pre-operative	111.11±17.87	—
	one week after operation	90.45±18.76*	5.1（3.2～6.7）
	one month after operation	104.57±15.93	8.08±2.9
	three month after operation	121.16±22.20*	9.55±3.62
	six month after operation	130.16±26.29*	7.9（6.5～11.7）

Abbreviations: BKV, BK virus.

*BKV positive recipients: pre-operative versus one week after operation, P ＜ 0.01.

*BKV negative recipients: pre-operative versus one week after operation, P ＜ 0.01; pre-operative versus three month after operation, P ＜ 0.01; pre-operative versus six month after operation, P ＜ 0.01.

TABLE 4. Independent Predictors of BKV Infection According to Multivariate Logistic Regression Analysis

	B	Standard error	Wald	Odds Ratio（95% CI)	*P*
Haemoglobin	-0.038	0.012	10.564	0.963（0.942-0.985）	＜0.001
GFR	-0.009	0.013	0.51	0.991（0.966-1.016）	0.475
History of acute rejection	1.425	0.659	4.678	4.157（1.143-15.121）	0.031

Abbreviations: BKV, BK virus; GFR, Glomerular filtration rate