Risk Factors for Polyomavirus, Cytomegalovirus, and Viruria Co-Infection for Follow-Up of Renal Transplant Patients

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Background: The interaction of viral infection may be associated with increased morbidity after renal transplantation. This study aimed to identify the incidence and risk factors of viruria infections in renal transplant recipients.

Material/Methods: In this longitudinal study, 502 episodes recorded in 81 kidney transplant patients from 1/2019 to 12/2021 in a hospital in Vietnam were included. BK, JC polyomaviruses, CMV, EBV, and HSV were detected. Multivariable Cox regression analysis was performed to evaluate risk factors for the viruria infection.

Results: Fifty-six patients (69.1%) had viruria co-infection. The incidence of JC, CMV, and BK infection was the most common viruria, with 67.9%, 61.7%, and 56.8%, respectively. Cox regression revealed that the risk factors for JC were single infection, dose of MMF (HR 1.002), corticoid (HR 1.02), hypertension (HR 1.65), and hematuria (HR 2.03); risk factors for CMV infection were male sex (HR 1.92) and eGFR (HR 0.98); risk factors for BK single infection were hypertension (HR 1.67), proteinuria (HR 3.80), higher tacrolimus trough level (HR 1.17), and dose of MMF (HR 1.002). Hypertension (HR 1.68), fasting plasma glucose (HR 1.13), proteinuria (HR 6.01), tacrolimus trough level (HR 1.12), and dose of MMF (HR 1.004) were independent risk factors for the viruria co-infection.

Conclusions: Kidney function was associated with the incidence of viruria. Higher tacrolimus trough level and dose of MMF were associated with higher risk of BK, JC, and co-infection.

Keywords: BK Virus • Cytomegalovirus • JC Virus • Kidney Transplantation • Urinary Tract Infections • Vietnam

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Background

Urinary tract infections are a major cause of graft dysfunction or failure in renal transplant patients [1]. The mortality and graft survival prevalence in post-transplant patients have remarkably improved with the development of immunosuppressive agents [2]. However, the renal recipients faced a greater risk for infections owing to sufficient immunosuppression. Immunosuppression therapy is a notable factor leading to an increased incidence of polyomavirus-associated diseases [3]. A low dose of anti-thymocyte globulin (ATG) (1 mg/kg/day for 4 days) lowers survival free of CMV than basiliximab at a dose of 20 mg on day -0 and day -4 post-transplant.

Viruria usually results in an asymptomatic infection that hides in the urinary tract [4]. JCV and BKV are 2 of 5 human polyomaviruses associated with clinical disease [3,5]. BKV in urine is one of the early markers of risk for BK viremia and nephropathy [6]. BKV is a polyomavirus associated with nephropathy in early post-renal transplant (RTx) [7]. The impact of JCV on nephropathy was shown in a few cases [8]. However, there is evidence showing that JCV nephropathy occurs at both early and late after renal transplantation [3,4]. The interaction of viral infection may be associated with increased post-RTx morbidity [9]. BKV and CMV co-infection have significantly lower eGFR after RTx than a single BK or CMV infection [9,10].

The treatment for post-transplantation viral infections is not straightforward due to difficulties in identifying potential pathogens [2]. Therefore, identifying active viral infections is vital in therapy decisions and monitoring transplant recipients [11]. There is limited information on the incidence of viral infections in Vietnamese kidney recipients. Therefore, the present study was conducted to assess the incidence of common viral infections in the urine of RTx recipients and to identify the risk factors for viruria infection after renal transplantation.

Material and Methods

Subjects

From 1/2019 to 12/2021, we enrolled 101 patients with first-time renal transplants and underwent treatment therapy after transplantation in the Department of Nephrology and Transplantation, 108 Military Central Hospital, Vietnam. Eighty-nine patients who had at least 6 months of follow-up were included. In 3 years, 501 urine samples were collected, and at least 1 virus was detected in 369 samples of 81 patients (Figure 1).

This study complied with the principles of the Declaration of Helsinki. The study proposal, related appendix, participant information sheet, and written informed consent were reviewed and approved by the Institutional Review Board in Biomedical Research of 108 MCH (approval ID: 2021-1539/HDDD).

Study Design

We conducted a longitudinal study to follow up renal transplant patients with repeated monitoring of health status and relevant infections every 3 months. Patients’ age, sex, etiology of renal failure, and donor-related factors were also collected.

Detecting Infection Pathogens

Physicians diagnosed all clinically pertinent infections. Clinically relevant infections included probable and proven viral infections and viral syndromes. To detect opportunistic pathogens in patients’ urine specimens, we performed real-time PCR using TaqMan probes (Bio-Rad, USA) for various types of viral infection (CMV, BK, JC, EBV, and HSV).

Figure 1. Flowchart of patient inclusion.

The figure was created using Microsoft® Word for Microsoft Office 2019 MSO (Version 2208 Build 16.0.15601.20072).
Table 1. Characteristics of renal transplant recipients.

| Characteristic                        | Total patients (n=81) | Patients in VS groups (n=25) | Patients in VC groups (n=56) | p-value |
|---------------------------------------|-----------------------|-----------------------------|------------------------------|---------|
| Gender, male (%)                      | 62 (76.54)            | 18 (72.0)                   | 44 (78.57)                   |         |
| Age (years), mean±SD                  | 40.91±12.02           | 38.42±12.58                 | 41.84±12.18                 |         |
| Etiology of End-Stage Renal Disease (%) |                       |                             |                              |         |
| Glomerulonephritis                    | 58 (71.6)             | 17 (68.0)                   | 41 (73.21)                   |         |
| Diabetes                              | 6 (7.41)              | 2 (8.0)                     | 4 (7.14)                     |         |
| Hypertension                          | 10 (12.35)            | 4 (16.0)                    | 6 (10.71)                    |         |
| Others                                | 6 (7.41)              | 1 (1.12)                    | 5 (5.62)                     |         |
| Type of renal replacement therapy (%) |                       |                             |                              |         |
| No renal replacement therapy          | 10 (12.34)            | 3 (12.0)                    | 7 (12.5)                     |         |
| Hemodialysis                          | 69 (85.19)            | 20 (80.0)                   | 49 (87.5)                    |         |
| Peritoneal dialysis                   | 2 (2.47)              | 2 (8.0)                     | 4 (7.14)                     |         |
| Time of RRT (months), mean±SD         | 45.76±5.18            | 39.87±58.37                 | 21.47±27.55                  | <0.05*  |
| Time of follow up after RTx           | 28.84±19.78           | 20.57±12.45                 | 33.27±21.38                  | <0.05*  |
| Donor source, Deceased (%)            | 3 (3.7)               |                             | 3 (5.4)                      | <0.05** |
| Frequency in charge due to clinical manifestations |                 |                             |                              |         |
| No in-charge                          | 60 (74.07)            | 18 (72.0)                   | 42 (75.0)                    |         |
| 1 time                                | 11 (13.58)            | 4 (16.0)                    | 7 (12.5)                     |         |
| 2 times and above                     | 10 (12.35)            | 3 (12.0)                    | 7 (12.5)                     |         |
| Creatine                              |                       |                             |                              |         |
| Baseline                              | 113.10±44.89          | 107.08±36.72                | 115.36±50.11                 |         |
| End-line                              | 106.70±76.89          | 95.58±22.73                 | 109.97±94.93                 |         |
| Estimated glomerular filtration rate  |                       |                             |                              | <0.05***|
| Baseline                              | 75.56±22.43           | 81.82±19.84                 | 75.18±23.09                  |         |
| Immunosuppressive therapy             |                       |                             |                              |         |
| Tacrolimus (n, %)                     | 79 (97.53)            | 24 (96.0)                   | 55 (98.21)                   |         |
| Tacrolimus dose (mg/day), mean±SD     | 5.48±3.47             | 5.25±3.50                   | 5.08±3.17                    | <0.05*  |
| Tacrolimus trough level (ng/mL), mean±SD | 7.36±2.92            | 7.19±2.84                   | 7.02±2.88                    | <0.05*  |
| MMF, (n, %)                           | 74 (91.36)            | 23 (92.0)                   | 51 (91.07)                   | <0.05** |
| MMF dose (mg/day), mean±SD            | 1430.66±264.83        | 1409.84±260.71              | 1370.19±208.96               | <0.05*  |
| Prednisolone (mg/day), mean±SD        | 9.37±42.80            | 9±0.58                      | 6±2.37                       |         |
| Myfortics (n, %)                      | 6 (7.41)              | 1 (4.0)                     | 5 (8.93)                     | <0.05** |
| Cyclosporine (n, %)                   | 1 (1.23)              |                             | 1 (1.79)                     |         |
| Combine tacrolimus+MMF+prednisolone   | 73 (90.12)            | 23 (92.0)                   | 50 (89.29)                   |         |
Table 1 continued. Characteristics of renal transplant recipients.

| Characteristic                  | Total patients (n=81) | Patients in VS groups (n=25) | Patients in VC groups (n=56) | p-value |
|---------------------------------|-----------------------|-------------------------------|-----------------------------|---------|
| Induction therapy               |                       |                               |                             |         |
| ATG (n, %)                      | 8 (9.88)              | 1 (4.0)                       | 7 (12.5)                    |         |
| Basiliximab (n, %)              | 64 (79.01)            | 22 (88.0)                     | 42 (75.0)                   |         |
| Time until viremia, mean±SD     | 9.47±15.28            | 7.07±7.48                     | 10.49±17.55                 | >0.05   |

* p-value of T-test; ** p-value of Chi-square test; *** p-value of Pair T-test. ATG – anti-human thymocyte globulin; MMF – mycophenolate mofetil; RTx – renal transplantation.

Table 2. Characteristics of viruria infection in renal transplant recipients (n, %).

| Characteristic          | Total patients (n=81) | Patients in VS groups (n=25) | Patients in VC groups (n=56) | p-value |
|-------------------------|-----------------------|-------------------------------|-----------------------------|---------|
| BK infection            | 50 (61.73)            | 10 (40.0)                     | 40 (71.43)                  | <0.05   |
| 1 time                  | 12 (24.0)             | 2 (20.0)                      | 10 (25.0)                   |         |
| Repeated                | 38 (76.0)             | 8 (80.0)                      | 30 (75.0)                   |         |
| JC infection            | 46 (56.79)            | 8 (32.0)                      | 38 (67.86)                  | <0.05   |
| 1 time                  | 14 (30.43)            | 2 (25.0)                      | 12 (31.58)                  |         |
| Repeated                | 32 (69.57)            | 6 (75.0)                      | 26 (68.42)                  |         |
| CMV infection           | 55 (67.9)             | 7 (28.0)                      | 48 (85.71)                  | <0.05   |
| 1 time                  | 20 (36.36)            | 3 (42.86)                     | 17 (35.42)                  |         |
| Repeated                | 35 (63.64)            | 4 (57.14)                     | 31 (64.58)                  |         |
| EBV infection           | 7 (8.64)              |                               | 7 (12.5)                    |         |
| 1 time                  | 6 (85.71)             |                               | 6 (85.71)                   |         |
| Repeated                | 1 (14.29)             |                               | 1 (14.29)                   |         |
| HSV infection           | 2 (2.47)              |                               | 2 (3.57)                    |         |
| 1 time                  | 2 (100.0)             |                               | 2 (100.0)                   |         |
| Repeated                | –                     |                               | –                           |         |
| Time until viruria, mean±SD | 9.47±15.28         | 7.07±7.48                     | 10.49±17.55                 | >0.05   |

BK – BK polyomavirus; CMV – cytomegalovirus; EBV – Human Epstein-Barr virus; HSV – Herpes Simplex Virus; JC – JC polyomavirus.

Data Analysis

Statistical analysis was conducted using SPSS software version 21. Categorical variables were presented as frequency (n) and percentage (%). Continuous variables (age, months in renal replacement therapy, time of follow-up, eGFR, dose, and blood level of drugs) were presented as means and standard deviations. Multivariable Cox regression analysis was performed to evaluate risk factors for viruria infection.

Results

Characteristics of Renal Transplant Patients

Clinical characteristics and transplant-related data are illustrated in Table 1. Among 81 renal transplant patients included in the study (mean age 40.9±12.0 years, 76.5% male), 25 (30.9%) patients had only 1 type of viruria infection (viruria single group, VS), and 56 (69.1%) had at least 2 viruses (viruria co-infection group, VC). The leading cause of end-stage renal disease was glomerulonephritis (71.6%); 88% of patients...
had used renal replacement therapy. The mean follow-up duration after RTx was 28.8 months. Deceased donor and time of dialysis were significantly different between groups. The mean eGFR at baseline and at the end-point showed a significant improvement in kidney graft (paired t test, \( P < 0.05 \)), but there was no association with creatinine values.

Antibiotic prophylaxis and immunosuppressive therapy, which included calcineurin inhibitor (tacrolimus), antimetabolite (mycophenolate mofetil [MMF]) and prednisone, were administered for 73 (90.1%) RTx patients. Myfortics were replaced by MMF in 6 (7.4%) patients; 1 (1.2%) patient used cyclosporin instead of tacrolimus. The number of patients and dose of mycophenolate mofetil, and the amount and blood level of tacrolimus were significantly greater in the single viruria groups. There was no significant difference in the type of induction therapy, either ATG or basiliximab, and the prednisolone dose.

Characteristics of Viruria Infection in Renal Transplantation

Overall, CMV and polyomaviruses (BK and JC) infection were the most common viruria in the current study. The mean time until viruria in the co-infection group was not significantly different from that of the single-infection group (Table 2). Human Epstein-Barr virus and Herpes Simplex Virus were rare.

Figures 2 and 3 showed the frequency of viruria infection by the number of episodes. It is clear that the number of BKV infection episodes was highest, but the incidence of BK co-infection was lower than CMV and JCV. In contrast, the frequency of CMV detected was lower, but there were 89 episodes (80%) of CMV co-infection (Figure 3), and the number of patients who had CMV was highest, at 55 (67.9%) (Table 2). Table 2 shows that among 50 patients with BK infection, three-quarters of them had recurrent BK infection. There were 32/46 (69.6%) recurrent JC infections, and 35/55 (63.6%) patients had CMV, but no significant difference was recorded.

Risk Factors For Viral Infection in Renal Transplantation

Potential risk factors were age of recipients at renal transplantation time, sex, renal function (eGFR, hematuria, and proteinuria), donor-related factors (sex, age, deceased donor), immunosuppressive therapy, hypertension, blood glucose, and time until detection of the first viruria. In the last step, the fitting Cox multiple regression only showed significant variables.

Age (HR 0.97, \( P < 0.01 \)) and the first time BK was detected (HR 0.91, \( P < 0.001 \)) were associated with lower risk of BK infection. Renal recipients who had hypertension (HR 1.67, \( P < 0.01 \)), proteinuria (HR 3.80, \( P < 0.001 \)), higher tacrolimus trough levels (HR 1.17, \( P < 0.001 \)), and dose of MMF (HR 1.002, \( P < 0.001 \)) had a greater risk of a single BK infection (Table 3).
Cox regression analysis revealed that the dose of MMF (HR 1.002, \( p < 0.001 \)) and corticoid (HR 1.02, \( p < 0.01 \)), hypertension (HR 1.65, \( p < 0.05 \)), and hematuria (HR 2.03, \( p < 0.001 \)) were associated with a higher risk of single JC infection. Improved eGFR (HR 0.99, \( p < 0.05 \)) and late detection of JC (HR 0.88, \( p < 0.001 \)) were associated with lower risk of JC infection (Table 4). In patients with single CMV infection, eGFR (HR 0.98, \( p < 0.01 \)) and time until the first CMV (HR 0.91, \( p < 0.001 \)) were protective factors (Table 5). Males had a higher risk of CMV infection (HR 1.92, \( p < 0.01 \)).

### Table 3. Cox-regression for the development of BK polyomavirus only.

|                      | HR     | (95% CI)          | p     |
|----------------------|--------|-------------------|-------|
| Age (year)           | 0.97   | (0.954-0.987)     | <0.01 |
| Tacrolimus trough level (ng/mL) | 1.171  | (1.089-1.259)     | <0.001|
| MMF dose (mg/day)    | 1.002  | (1.001-1.003)     | <0.001|
| Hypertension         | 1.674  | (1.158-2.421)     | <0.01 |
| Proteinuria          | 3.802  | (2.356-6.135)     | <0.001|
| Time until 1st BK detected (months) | 0.912  | (0.892-0.933)     | <0.001|

### Table 4. Cox-regression for the development of JC polyomavirus only.

|                      | HR     | (95% CI)          | p     |
|----------------------|--------|-------------------|-------|
| Hypertension         | 1.653  | (1.053-2.596)     | <0.05 |
| MMF dose (mg/day)    | 1.002  | (1.001-1.003)     | <0.001|
| Corticoid dose (mg/day) | 1.070  | (1.005-1.034)     | <0.01 |
| eGFR                 | 0.988  | (0.978-0.998)     | <0.05 |
| Hematuria            | 2.032  | (1.399-2.956)     | <0.001|
| Time until 1st JC detected (months) | 0.884  | (0.862-0.907)     | <0.001|

### Table 5. Cox-regression for the development of CMV only.

|                      | HR     | (95% CI)          | p     |
|----------------------|--------|-------------------|-------|
| Male                 | 1.918  | (1.257-2.925)     | <0.01 |
| eGFR                 | 0.985  | (0.975-0.995)     | <0.01 |
| Time until 1st CMV detected (months) | 0.909  | (0.885-0.933)     | <0.001|

### Table 6. Cox-regression for the development of viruria co-infection.

|                      | HR     | (95% CI)          | p     |
|----------------------|--------|-------------------|-------|
| Age                  | 0.953  | (0.935-0.971)     | <0.001|
| Hypertension         | 1.680  | (1.035-2.727)     | <0.05 |
| Fasting plasma glucose level | 1.129  | (1.004-1.270)     | <0.05 |
| Tacrolimus trough level | 1.118  | (1.035-1.207)     | <0.01 |
| MMF dose (mg/day)    | 1.004  | (1.002-1.005)     | <0.001|
| eGFR                 | 0.984  | (0.971-0.997)     | <0.05 |
| Proteinuria          | 6.099  | (3.248-11.451)    | <0.001|

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Cox regression analysis showed age (HR 0.95, P<0.001), hypertension (HR 1.68, P<0.05), fasting plasma glucose (HR 1.13, P<0.05), eGFR (HR 0.98, P<0.05), proteinuria (HR 6.01, P<0.001), tacrolimus trough level (HR 1.12, P<0.01), and dose of MMF (HR 1.004, P<0.001) were independent risk factors for the occurrence of co-infection (Table 6).

**Discussion**

The study is the first to investigate these 5 common viruses that cause asymptomatic urinary tract infection in RTx patients who were screened in Vietnam. The results showed that CMV and polyomaviruses were the most common viruria infections.

The viruria infection rate of cytomegalovirus (CMV) in our study was 67.9%, which is higher than in other studies [12-16]. The difference may be due to the price of antiviral prophylaxis drugs, and we used acyclovir as a pre-emptive treatment. Valacyclovir had greater efficacy than acyclovir in preventing CMV infection [17]. Although there was evidence that a low dose of ATG was associated with lower CMV-free survival than basiliximab [18], there was no significant difference in the infection rate between the 2 groups in our study. This could be because in our study only 8 patients received ATG as induction therapy, while 64 patients received basiliximab.

Our study’s rate of polyomavirus infection in urine was 61.73 for BK infection and 56.79 for JC infection. These results were higher than in the studies by Eidgahi et al [16] and Babazadeh et al [19]. The different outcomes may be due to the use of cyclosporin in other studies and use of tacrolimus in our research. Regarding the maintenance of immunosuppression therapy, we followed the guideline of tacrolimus blood level 7-10 ng/mL and a 1.5-2 g/day dose of MMF [18]. A higher tacrolimus trough level was reported to be an independent risk factor for BK infection in Chinese and Tunisian renal transplant recipients [20]. Our study also found that tacrolimus and MMF were associated with BK, JC, and co-infection in the urine. In immunocompetent patients, polyomavirus infection was asymptomatic; however, sufficient triple-drug immunosuppressive in RTx patients can reactivate polyomavirus in the urine [21]. On average, it would take a few months for BK viruria to cause BK viremia in 10-15% of kidney recipients [7,22]. BK viruria was an important marker indicating when to start therapeutic intervention to reduce the risk of developing BK viremia and nephropathy [6].

We also showed the connection between viruria infection and renal function, including eGFR and proteinuria status. Excess proteins in the urine caused a greater risk of kidney damage; therefore, the damaged glomerular basement membrane created a suitable environment for the development of infection [23]. The current evidence identified risk factors for each single viruria or co-infection. Potential risk factors of viral infection included the age of recipients at renal transplantation time, sex, renal function, donor age, deceased donor, immunosuppressive therapy, and co-morbidities [10,14-16,19]. Our study showed a negative association between age and risk of viruria infection. In contrast, studies by Eidgahi et al and Babazadeh et al found the age of RTx patients was associated with increasing risk of BKV infection [16] and CMV infection [15,19]. A study from Argentina also reported that older patients, deceased donors, and length of hospital stay after transplantation were risk factors for CMV infection [15]. It could be explained that although immunosuppressive agents may predispose elderly patients to the risk of over-immunosuppression [24], older people theoretically had a slower immune response than younger people [25]. In addition, our patients were younger than in these other studies. As a result, the incidence of infection was lower as age increased in our study.

The current study showed that more than 40% of viruria co-infection episodes were related to CMV and BK, which contrasted with Jehn et al, who showed that although CMV and BK accounted for most RTx patients, the CMV and BK co-infection were rare [10]. Our study illustrated that in RTx patients who were routinely screened for viruria, those with late detection had lower risk of repeated BKV, JCV, and CMV viruria infection than those with early detection. We found that the degree of immunosuppression at 1-6 months after transplant was the leading cause of opportunistic infections or pathogens reactivation in recipients with latent infection [7,13]. After 6 months post-transplant, the patient’s dose of immunosuppressive agents was adjusted and reduced, making it a protective factor against viruria infection. These findings highlighted the need for post-transplant routine screening of viruses in blood and urine for all kidney transplant recipients until the end of the first post-transplant year [7,19,26].

**Conclusions**

In conclusion, renal function, including eGFR, proteinuria, and hematuria, were associated with the incidence of viruria. Late detection of viruria significantly reduced the risk of repeated single viruria infection. Higher tacrolimus trough level and dose of MMF increased the risk of single BK, JC, and co-infection. In addition, age, hypertension, and fasting plasma glucose level were independent risk factors for the occurrence of co-infection. The study suggests the need for routine screening of viruses in blood and urine for all kidney transplant recipients in the first post-transplant year.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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