**European Journal of Clinical Pharmacy**
**Print ISSN:** 2385-409X **Online ISSN**: Applied Website:
https://farmclin.com/

# Prevalence and Risk Factors of BK Virus In Renal Transplant Patients In A Tertiary Care Hospital

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## ABSTRACT

**Purpose**- BKV (BK, Polyomavirus hominis 1), a human polyomavirus virus remains dormant in the kidney and bladder urothelium, lymphoid tissues, and leukocytes in the peripheral blood.Viral reactivation can occur in the general population but is much more frequent during intensive immunosuppression.

**Method**- This is a hospital-based cross-sectional study on post-renal transplant patients, who were inpatients or attending the outpatient unit of a tertiary care hospital in northern India. This study included clinical and laboratory data from patients tested for the BK virus over a 1-year period, from January to December 2022. DNA extraction: DNA was extracted from both plasma and whole urine using the QIAmp® Viral RNA minikit(QIAGEN) according to the manufacturer's instructions. RT-PCR was done using the Artus® BK Virus RG PCR Kit as per the manufacturer's instructions.

**Results**- During the study period, 165 renal transplant recipients were tested for the BK virus in both plasma and urine. Among all samples tested, 45 patients tested positive for the BK viremia.Out Of these 45 patients positive for BK virus viremia, 7 hadviruriain urine samples; all other samples were negative for viruria. Significant viruria was seen in 4 patients with >=107 copies/ml in urine,and 3 patients had non-significant viruria with <107 copies/ml. All 4 patients with significant viruria had significant viremia, whereas 3 patients with non-significant viruria had non-significant viremia. The median time to positivity in urine was 18 months (5–108). The median number of copies of the BK virus in urine was 4.7 × 107 (8032–4.5×109).

**Conclusions**: The role of screening methods in testing samples with a significant BK virus load is toexclude BK virus nephropathy and identify other causes. Samples with significant viral copies alert clinicians to investigate for BK virus nephropathy using immunofluorescence or immunohistochemistry and to start antivirals early.

**KEYWORDS**: BK virus, renal transplant, immunocompromised

**Highlights**: There is a clear need for appropriate recommendations for simultaneous urine and plasma testing in the suspicion of BK virus nephropathy. The clinicians should strictly investigate for BK virus nephropathy for the timely start of antivirals

**How to Cite:** Dr. Romya Singh, Dr. Pratima Rawat, Dr. Atul Garg*, Dr. Rungmei SK Marak (2026) Prevalence and Risk Factors of BK Virus In Renal Transplant Patients In A Tertiary Care Hospital, European Journal of Clinical Pharmacy, Vol.8, No.1, pp. 2375-2379

## INTRODUCTION

BKV (BK, Polyomavirus hominis 1), a human polyomavirus, is a member of the polyomavirus family, which is an unenveloped DNA virus containing circular double-stranded DNA of about 5 kb in size. It was first identified in 1970 in the urine of a renal allograft recipient who developed ureteric stenosis and was named BKV, using the first letters of the patient's name and surname [1, 2]. The virus remains dormant in the kidney and bladder urothelium, lymphoid tissues, and leukocytes in the peripheral blood [2]. Asymptomatic urinary shedding is observed in 5%–10% of healthy blood donors. Viral reactivation can occur in the general population but is much more frequent during intensive immunosuppression. Viral reactivation can occur in the general population but is much more frequent during intensive immunosuppression. After kidney transplantation and allogenic hematopoietic stem cell transplantation (AHSCT), BKV replication can cause nephropathy and hemorrhagic cystitis (HC), respectively [3, 4]. Its seroprevalence in the human population is over 80% among adults and 73% among paediatric patients [5, 6].

Among renal transplant patients, BK virus-related nephropathy may occur in 1–10% of renal transplant recipients due to virus reactivation [7]. The major complications of BK virus nephropathy include graft failure and rejection, occurring in

approximately 10–100% of cases [7]. Among post-transplant infections, the BK virus is most commonly detected within the first year of transplantation, although it can occur after one transplant in about 25% of cases [7]. It is difficult to diagnose BK virus-associated nephropathy because it lacks specific clinical features. It is mainly characterised by rising serum creatinine levels and the presence of obstructive uropathies such as hydronephrosis or hydroureter in the absence of any histological evidence of graft rejection. Allograft biopsy for histopathological evaluation and immunohistochemistry is used for the definitive diagnosis of BK virus nephropathy. Unexplained increase in serum creatinine levels in post-transplant patients raise suspicion for BK virus nephropathy, and early screening for BK virus in blood and urine samples may play a crucial role in its prevention [8]. For screening of the BK virus in urine and blood, a quantitative real-time polymerase chain reaction (PCR) assay is done. There are no established universal cutoff points; however, a urine BK virus load $>10^{7}$ copies/ml or a plasma BK virus load $>10^{4}$ copies/ml is considered a significant load for BK virus nephropathy. More studies are needed to investigate BK virus nephropathy in post-transplant patients and its significant levels in urine and blood. There is not much data on BK virus nephropathy in post-renal transplant patients from India. This study aims to study the prevalence and associated factors of BK virus nephropathy.

## METHODOLOGY

This hospital-based cross-sectional study focused on post-renal transplant patients who were either inpatients or attending the outpatient clinic at a tertiary care hospital in northern India. The study collected clinical and laboratory data from patients tested for the BK virus over a one-year period, from January to December 2022. DNA extraction was performed on both plasma and whole urine samples using the QIAamp® Viral RNA Mini Kit (QIAGEN), following the manufacturer's instructions. RT-PCR was conducted using the Artus® BK Virus RG PCR Kit in accordance with the manufacturer's guidelines.

**Data collection**

Data analysis: Clinical, demographic, and laboratory data were gathered from the hospital information system and patient records. Clinical data, including transplant duration, immunosuppressive treatment, serum creatinine levels, and patient outcomes, were included. Viruria and viraemia were defined as the detection of viruses in urine and plasma, respectively.

**Statistical analysis**

Patients with varying degrees of viruria and viremia were compared using nonparametric tests. Categorical variables were analysed using the chi-square test with analysis of adjusted residual values. SPSS 21.0 (Illinois, USA) was used for statistical analysis.

## RESULT

During the study period, 165 renal transplant recipients were screened for BK virus in both plasma and urine. Among all,45 patients were screened positive for the BK viremia. Out of the total patients, 149 were male, and 16 were female. The mean age of the study participants was 37.36 years (S.D. =11.86). Most of the patients (n = 158) were on triple immunosuppression with tacrolimus, mycophenolate mofetil, and prednisolone. In this study, the median duration of plasma BK virus positivity after renal transplantation was 48 months (IQR 8.75–72 months).

Viremia was detected in 45 (27.3%) patients. Among them, 12 (8%) had significant viremia with $>=10^{4}$ copies/ml in plasma, while 33 patients had non-significant viremia with $<10^{4}$ copies/ml. The median plasma viral load among viraemic patients was 3765 copies/ml (IQR 1795–14340).

Out of the 45 patients positive for BK virus viremia, 7 had viruria in urine samples; all other samples were negative for viruria. Significantviruria was seen in 4 patients with $>=10^{7}$ copies/ml in urine,and 3 patients had non-significant viruria with $<10^{7}$ copies/ml. All 4 patients with significant viruria had significant viremia, whereas 3 patients with non-significant viruria had non-significant viremia. The median time to positivity in urine was 18 months (5–108). The median number of copies of the BK virus in urine was $4.7 \times 10^{7}$ (8032–$4.5\times10^{9}$).

In this study, thymoglobulin was used most commonly as induction therapy (68.8% in the BK virus group and 83.3% in the non-BK virus group); the remaining patients were given basiliximab (31.1%) in the BK virus-positive group and 16.7% in the non-BK virus group. A total of 100% received steroids, 96.9% MMF, 95% tacrolimus, 2.42% azathioprine, 4.24% cyclosporine, and 0.6% everolimus. Only a significant difference was observed in induction therapy, specifically thymoglobulin and basiliximab. No statistically significant differences were found for gender, age group, steroids, tacrolimus, cyclosporine, mycophenolate mofetil, or azathioprine, as shown in Table 1.

**Association between creatinine levels and viral loads in urine and plasma**

Among patients positive for the BK virus, 36 had elevated serum creatinine, while 9 had normal creatinine. Mean creatinine levels according to levels of viremia and viruria shown in Table 2

**Table1. Patients' Demographics, Clinical Parameters, and Laboratory Parameters**

| | BK VIRUS n=45 | NON BKVIRUS n=120 | P value |
|---|---|---|---|
| **Gender** | | | |
| Male | 44(97.8) | 105 (87.5) | 0.072 |
| Female | 1 (2.2) | 15 (12.5) | 0.85 |

| **Age** | | | |
|---|---|---|---|
| **0-30** | 14(31.1) | 42(35) | 0.958 |
| **31-60** | 29(64.4) | 72 60 | 0.958 |
| **61-90** | 2(4.4) | 6(5) | 0.864 |
| **Induction therapy** | | | |
| Thymoglobulin | 31(68.8) | 100(83.3) | 0.049 |
| Basiliximab | 14(31.1) | 20(16.6) | 0.049 |
| **Maintenance therapy** | | | |
| Steroid | 45(100) | 120(100) | NS |
| **Antimetabolite** | | | |
| Mycophenolate | 43(95.5) | 117(97.5) | 1.00 |
| Azothioprine | 2(4.44) | 2(1.66) | 0.174 |
| **Calcineurin inhibitor** | | | |
| Tacrolimus | 44(97.7) | 113(94.2) | 0.343 |
| Cyclosporine | 1(2.22) | 6(5) | 1.00 |
| **CMV Coinfection** | 3 | 9 | 0.578 |
| **Lab Parameter** | | | |
| S.creatinine Mean(Range) | 1.89(1.64-2.72) | 1.05(0.89-1.45) | 0.038 |

**Table 2. Mean creatinine levels according to levels of viremia and viruria**

| Sample | Mean creatinine levels (S.D.) |
|---|---|
| **Urine** | |
| Aviruria | 1.12(1.7) |
| Non significantviruria | 1.62(0.309) |
| Significant viruria | 1.79(0.197) |
| **Plasma** | |
| Aviremia | 1.05(0.89) |
| NonSignificant viremia | 2.08(1.04) |
| Significant viremia | 2.335(1.02) |

The survival rate was higher in the non-BK virus group than in the BK virus group, at 99.15% and 91.1%, respectively, as shown in Figure 1.

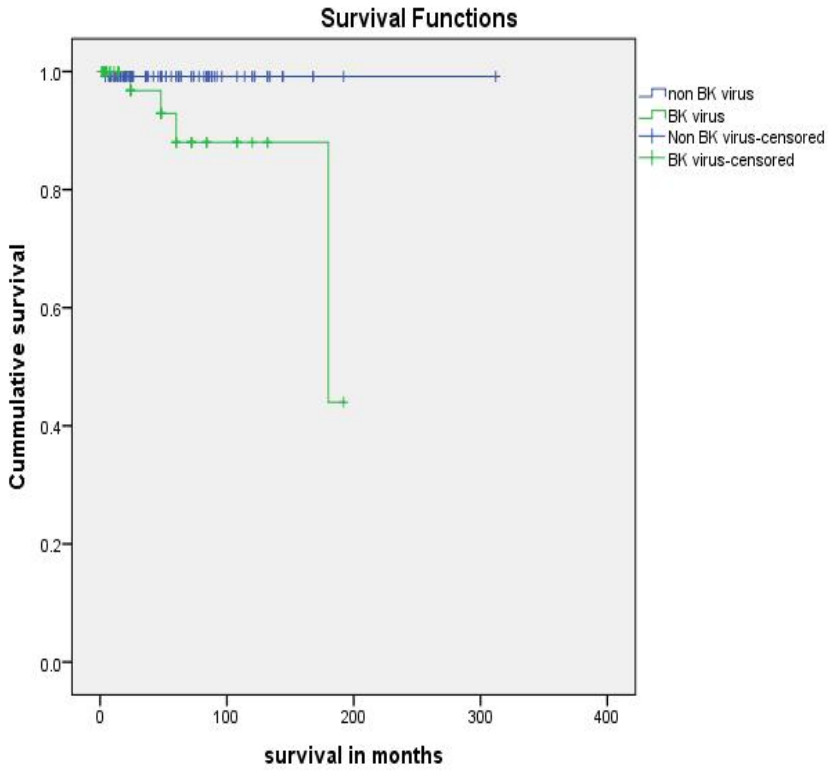


**Figure 1 Kaplan-Meier analysis of cumulative patient survival in BKV vs non-BKV patients.**

## DISCUSSION

This study was done to study the prevalence of BK virus in renal transplant patients in screening methods by PCR in plasma and urine samples in the microbiology department of a tertiary care hospital in northern India. We detected an overall prevalence of 27.3%. In our study, we found significant viremia in 8% of patients, indicating further testing to confirm polyoma virus-associated nephropathy (PVAN). As per the international data, BK virus infection ranges from 10-45%; however, the prevalence rates of PVAN range from 2.5–7.1% [9–11]. There is a scarcity of data from India; one study showed a BK virus incidence of 9.3% [12]. Another study showed a prevalence of 19% [13].

The screening method used in this study was real-time PCR by the Artus kit, which has a sensitivity of 95% and specificity of 100%. Significant urinary viral loads indicate a higher probability of viremia.
Several studies have identified various clinical features associated with BK virus infection, including immunosuppressive therapy, rejection episodes, male gender, age, and HLA mismatch [14–16].Inour study, gender and age were not associated with BK virus prevalence. In accordance with this study, Brennan et al. [15] and Yeo et al. [17] determined that neither sex nor age was a significant risk factor. In contrast to other studies, steroids were not associated with BK virus infection. In our study, the use of thymoglobulin was a significant risk factor, consistent with other studies [18–20]. In addition,basiliximab was also found to be a significant risk factor in this study.

In this study, patients with viremia or viruriahad elevated creatinine levels which is consistent with other studies [21, 22]. However, studies have also observed no association between viruria or viremia and abnormal serum creatinine [23].

The role of screening methods insamples with a significant BK virus load helps exclude BK virus nephropathy and identify other causes. Samples with significant viral copies alert clinicians to investigate for BK virus nephropathy using immunofluorescence or immunohistochemistry and to start antivirals early.

The study's limitation is that it lacks recommendations for PCR testing using urine samples, whether to use pelleted urine or whole urine, which may influence viral load measurements. There is a clear need for proper guidelines on conducting simultaneous urine and plasma tests for suspected BK virus nephropathy.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Funding sources**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Acknowledgements**

Nil

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