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# THE INCIDENCE OF BK VIRUS INFECTION IN PATIENTS WITH DYSFUNCTION OF KIDNEY TRANSPLANT

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**Abstract.** BK virus-induced nephropathy is an important cause of renal dysfunction, leading to the loss of transplanted kidneys in up to 50% of cases. This study aimed to appraise the incidence of BKV infection among patients who have received kidney transplantation in Iran. In this retrospective cross-sectional study, recipients of kidney transplants in Mashhad Montaserieh Hospital with a rise of 25% or higher in serum creatinine after at least one month of transplantation were evaluated. Those with evidence of BKV infection, including positive serum or urine polymerase chain reaction (PCR) were included. Overall, of 471 patients, 135 cases (28.7%) were diagnosed with kidney transplant dysfunction. BKV infection was diagnosed based on positive PCR in 30 patients (22.2%) and BKV nephropathy was present in 11 patients (8.1%). The most common cause of ESRD (End Stage Renal Disease) was hypertension (33.3%) and the most common dialysis method was hemodialysis (90%). 10 patients had hematuria or pyuria. In 11 patients with pathological results, the most common finding was interstitial inflammation with tubular cytopathic changes (4 patients, 36.4%). Blood levels of cyclosporine were significantly correlated with the time from transplantation to diagnosis, and tacrolimus level was significantly correlated with creatinine level at diagnosis ($p < 0.05$). Positive urinalysis was significantly associated with the time from transplantation to the diagnosis of kidney dysfunction in the regression analysis (95%CI: –0.30 to –23.45, $p = 0.045$). The most important predictor of the occurrence of this disorder in kidney transplant patients was the presence of hematuria and pyuria in urine tests. Moreover, the frequency of BK infection was significantly higher in men than in women, while no significant difference was observed between men and women in the control group.

***Key words:*** *BKV infection, renal failure, transplant rejection, transplanted kidney.*

## ЗАБОЛЕВАЕМОСТЬ ВК-ВИРУСНОЙ ИНФЕКЦИЕЙ У ПАЦИЕНТОВ С ДИСФУНКЦИЕЙ ТРАНСПЛАНТАТА ПОЧКИ

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**Резюме.** Нефропатия, вызванная ВК-вирусом, является важной причиной почечной дисфункции, приводящей к потере трансплантированных почек в 50% случаев. Целью данного исследования была оценка частоты за-

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ражения ВК-вирусом среди пациентов после трансплантации почек в Иране. В настоящем ретроспективном поперечном исследовании реципиенты трансплантатов почек с повышением уровня креатинина сыворотки на 25% или выше по истечении как минимум одного месяца трансплантации были обследованы в больнице Мешхед Монтасериех. Были включены лица с признаками заражения ВК-вирусом, в том числе имеющих положительный результат обследования сыворотки или мочи методом полимеразной цепной реакции (ПЦР). В целом у 135 из 471 пациента (28,7%) была диагностирована дисфункция трансплантата почки. Инфекция ВК-вирусом была диагностирована на основании положительной ПЦР у 30 пациентов (22,2%), а нефропатия, вызванная ВК-вирусом, обнаружена у 11 пациентов (8,1%). Наиболее частой причиной терминальной стадии хронической почечной недостаточности (ТХПН) была гипертония (33,3%), а наиболее распространенным методом диализа был гемодиализ (90%). У 10 пациентов отмечена гематурия или пиурия. У 11 пациентов с патологическими проявлениями наиболее частой обнаружено интерстициальное воспаление с тубулярными цитопатическими изменениями (4 пациента, 36,4%). Уровень циклоспорина в крови достоверно коррелировал со сроками от проведения трансплантации до постановки диагноза, а уровень такролимуса значительно коррелировал с уровнем креатинина при постановке диагноза ($p < 0,05$). Положительная проба на ВК-вирус в моче была достоверно ассоциирована со сроками от проведения трансплантации до постановки диагноза дисфункции почек с применением регрессионного анализа (95% ДИ: от –0,30 до –23,45, $p = 0,045$). Наиболее важным предиктором возникновения указанного расстройства у пациентов после трансплантации почки было наличие гематурии и пиурии в анализах мочи. Более того, частота заражения ВК-вирусом была достоверно выше у мужчин, чем у женщин, тогда как в контрольной группе подобных межполовых различий не наблюдалось.

***Ключевые слова:*** *ВК-вирусная инфекция, почечная недостаточность, отторжение трансплантата, пересаженная почка.*

## Introduction

Most polyomaviruses are broadly distributed in nature. Of all the *Polyomaviridae* family, thirteen species are recognized to contaminate human life [26]. Polyomavirus BK is a small, non-enveloped, circular, double-stranded DNA virus that belongs to this family. BKV is omnipresent among people, and their seroprevalence in adults is from 70% to 90% [7, 22].BKV primarily infects the majority of people in the first decade of existence — the median age being 5 years — and it usually has asymptomatic or upper respiratory symptoms [22]. After subclinical primary infection, BKV remains dormant in various sites, established in the renal tubular and uroepithelial cells, where its periodical reactivation is proven by asymptomatic viruria in 7–15% of healthy individuals and does not have considerable clinical complications [21, 23]. Reactivation of BKV can cause serious clinical consequences only in people with immunodeficiency conditions such as HIV infection, cancer, pregnancy, people undergoing chemotherapy, the use of immunosuppression, and solid organ and bone marrow transplant recipients [3, 24]. BKV infection can cause hemorrhagic and non-hemorrhagic cystitis, ureteric stenosis, tubulointerstitial nephritis, transient renal dysfunction, and BKV nephropathy [24, 29, 33]. Kidney transplantation is a lifesaving operation and an alternative method to life-long dialysis for end-stage renal disease (ESRD) patients [33]. BK-associated nephropathy (BKVAN) is due to BKV reactivation in kidney transplant recipients (KTRs [6]. Studies have demonstrated that BKVAN is related to graft dysfunction in > 90% and graft loss in over 50% of the affected individuals [22]. BKV contamination progresses continuously. Due to tubular BKV replication, viremia occurs several weeks later to precede viruria. BKV replication, which mostly takes place in kidney tissue, results in viremia in 13–22% and viruria in 30–50% of individuals [24, 25, 33]. However, most infections in KTRs occur without clinical features except for a serum creatinine rise. Current recommendations suggest non-invasive screening tests in urine or plasma for early BKV contamination to avoid progression to irreversible structural damage [24, 29, 32]. As viruria precedes viremia, preventing BKAVN by using urine samples as a screening method has been shown in many researches [25]. However, a biopsy of the kidney is a definitive diagnosis of BKVAN [25]. Several studies determined using immunosuppressive regimens such as tacrolimus and cyclosporine one of the most relevant important risk factors for BKV contamination [2, 15, 28]. This study aimed to appraise the incidence of BKV infection among patients who have received kidney transplantation.

## Materials and methods

In this cross-sectional study, inclusion criteria were the records of all patients who had undergone kidney transplantation due to severe kidney diseases. The patients with an increased serum creatinine level within at least one month following kidney transplantation initially participated in the study. Transplanted kidney dysfunction was defined as an increase of more than 25% in serum creatinine compared to the previous test. Accordingly, patients diagnosed with transplanted kidney dysfunction, in terms of BKV infection were investigated. To investigate the presence of BKV infection, the results of specialized tests performed for the patient, especially the polymerase chain reaction (PCR) test for BK vi-

rus, were fully reviewed. Finally, patients whose serum PCR test was positive for the BK virus genome were included in the study.

The demographic information, including age and gender, as well as clinical data regarding the kidney disease, including the history and duration of dialysis, the type of dialysis (peritoneal or hemodialysis), the primary etiology of ESRD and dialysis, and finally, the number of transplants. Kidney transplant (unilateral or bilateral), the type of kidney transplant, and the time interval between the referral due to increased creatinine and the kidney transplant procedure of participants were extracted and recorded in the checklist. Initial paraclinical and laboratory information, including serum creatinine level, serum level of drugs, and urine test results (in terms of pyuria and hematuria) were extracted. Investigations related to BKV infection, including the polymerase chain reaction (PCR) test for BK virus, as well as the results of histological and pathological microscopic studies on the biopsy samples of all patients, were extracted as well.

The histopathological investigations encompassed a broad range of findings, including glomerular sclerosis, interstitial fibrosis, tubular atrophy, and the presence of viral inclusion bodies in tubular cells. Immunohistochemistry (IHC) was performed to detect the Simian virus 40 (SV40) antigen, which confirms BK virus infection. The sequential steps in IHC can be summarized as follows: antigen retrieval (AR), addition of primary antibody, application of a secondary antibody that binds the primary antibody, and addition of a detection reagent to localize the primary antibody.

For immunohistochemical detection strategies, antibodies are classified as primary or secondary reagents. Primary antibodies are raised against an antigen of interest and are typically unconjugated (unlabeled). Secondary antibodies are raised against immunoglobulins of the primary antibody species. The secondary antibody is usually conjugated to a linker molecule, such as biotin, that then recruits reporter molecules, or the secondary antibody itself is directly bound to the reporter molecule.

Additionally, the final diagnosis and pathology results regarding BKV infection (positive or negative) were documented.

*BK viremia monitoring.* A real-time polymerase chain reaction (PCR) test was performed at the central laboratory of the university hospital to detect the presence of the BK virus. The PCR test was made in Iran. The collected samples comprised first-morning stream urine samples or blood. Current clinical investigations define positive BK viremia as a viral load of $\geq 10^3$ copies/ml. Furthermore, histopathological assessments of kidney allograft biopsies conducted at any time post-transplant indicated the presence of BK virus-associated nephropathy (BKVAN), as evidenced by immunohistochemical staining for SV40 documented in 11 patient records. Secondary analyses employed descriptive statistics to evaluate demographic data, clinical features related to kidney disease, associated comorbidities, duration of dialysis, type of dialysis (peritoneal or hemodialysis), causes of the patient's progression to ESRD, whether the transplant was the first or second, donor type, and the time interval between kidney transplantation and the onset of renal dysfunction. Additionally, laboratory values, including hemoglobin, serum creatinine, and drug blood levels, were assessed alongside urine sample analyses (pyuria and hematuria), urine culture results, and CMV-DNA PCR among the designated kidney transplant recipients (KTRs). Serum creatinine levels were documented at baseline, one month, six months, and one-year post-transplant.

*Data analysis.* SPSS 24 was used for statistical analysis. The Kolmogorov–Smirnov test was used to check the normal distribution of the data. Repeated Measures ANOVA and Wilcoxon tests were used to compare creatinine levels between different time intervals. The Spearman Correlation test was used to check the existence of a correlation between the studied quantitative variables. Linear regression models were used to investigate the correlation between creatinine level at the time of kidney dysfunction diagnosis and the interval between the transplant procedure and the occurrence of transplant kidney dysfunction. The results of linear regression were reported using R square (R2), beta regression coefficient (Beta), standard error (SE), and 95% confidence interval (95%CI). The results of the correlation test were reported using the correlation coefficient (r). The level of significance in all tests was considered equal to 0.05.

## Results

Among these 30 patients who were evaluated, the mean age was (42.40±12.47) years old and more than half of them 22 (73.3%) were male. The most prevalent pre-transplant comorbidity among patients was hypertension (n = 15.50%). Hypertension (hypertensive nephropathy) was the most frequent cause of ESRD as an indication for transplantation (25% of cases). The mean time between transplantation and diagnosis was 15.58±15.30 months. The mean duration on dialysis before transplant was 2.85±2.30 years and the most common dialysis method was hemodialysis. 86.7% of cases were transplanted for the first time. Transplants from deceased donors were more common than living donors. All recipients had positive serum BKV PCR and 56.7% of recipients experienced CMV viremia. Tacrolimus treatments were administered more frequently than other immunosuppressive treatments.

Biopsy records of 11 patients were available. Interstitial inflammation with tubular cytopath-

**Table 1. Demographic and clinical characteristics, laboratory and histopathological findings**

| Variable | M±SD |
|---|---|
| **Mean age at diagnosis (years)±SD** | 42.40±12.47 |
| **Male** | 22 (73.3%) |
| **Female** | 8 (26.7%) |
| **Pre-transplant comorbidities** | **Frequency** |
| **Hypertension, n (%)** | 15 (50%) |
| **Diabetes, n (%)** | 9 (30%) |
| **Ischemic heart disease, n (%)** | 1 (33%) |
| **Systemic lupus erythematosus, n (%)** | 1 (33%) |
| **Hypothyroidism, n (%)** | 1 (33%) |
| **Renal agenesis, n (%)** | 1 (33%) |
| **Nephrectomy of the patient's kidney, n (%)** | 1 (33%) |
| **Liver transplant, n (%)** | 1 (33%) |
| **Hepatitis B, n (%)** | 1 (33%) |
| **Cause of ESRD** | |
| **hypertension (hypertensive nephropathy)** | 5 (25%) |
| **chronic glomerulonephritis** | 4 (20%) |
| **ADPKD** | 3 (15%) |
| **urinary reflux** | 2 (10%) |
| **antibiotic toxicity** | 1 (5%) |
| **nephrectomy due to RCC** | 1 (5%) |
| **chronic kidney disease (CKD)** | 1 (5%) |
| **lupus nephropathy** | 1 (5%) |
| **membranous glomerulonephritis (MGN)** | 1 (5%) |
| **primary hypertension** | 1 (5%) |
| **Dialysis data** | |
| **mean time between transplantation and diagnosis** | 15.58±15.30 months |
| **mean duration on dialysis prior to transplant** | 2.85±2.30 years |
| **Dialysis method** | |
| **hemodialysis** | 25 (89.3%) |
| **peritoneal dialysis** | 3 (10.7%) |
| **Transplantation** | |
| **first time** | 26 (86.7%) |
| **second time** | 4 (13.3%) |
| **Donor type** | |
| **deceased donors** | 23 (76.7%) |
| **living donors** | 7 (23.3%) |
| **Laboratory findings** | |
| **number of BKV genome in PCR (million copies)** | 3.82 ±0.18 |
| **number of CMV genome in PCR (million copies)** | 4.39 ±1.07 |
| **hematuria or pyuria in US** | 10 (33%) |

**Note.** ADPK: Autosomal dominant polycystic kidney, RCC: Renal Cell Carcinoma, US: Urine sample, ATN: Acute tubular necrosis, GN: Glomerulonephritis, MGN: membranous glomerulonephritis, TIN: tubulointerstitial nephritis.

**Table 2. Mean time until AKI diagnosis posttransplant**

| | Mean time until AKI diagnosis posttransplant |
|---|---|
| **Urinalysis (pyuria or hematuria)** | SE = 14.43, R2 = 0.0109<br>Beta = 0.376, p = 0.045<br>95%CI = –0.30 to –23.45 |

ic changes was the most common biopsy finding. Demographic and clinical characteristics and laboratory and histopathological findings are summarized in Table 1. Hematuria or pyuria was detected in 10 cases, and we developed a linear regression model among these cases ($p = 0.045$) (Table 2).

The mean average level of creatinine increase measured at baseline compared to one month, six months, and one-year posttransplant showed an increase of more than 25%. The analysis of serum creatinine levels between four different timelines showed that a rise in creatinine levels, 25% or more than the baseline, were significantly different at one month and six months post-transplant ($p < 0.05$), but its difference with one year after transplantation was not significant ($p = 0.263$) (Table 3).

The mean duration on dialysis before transplant had a significant correlation with the amount of tubular atrophy, interstitial infiltration, and blood level of cyclosporine ($p < 0.05$). we also found that the higher the cyclosporin blood level, the earlier patients with BKV infection develop renal dysfunction (rising creatinine level) ($p < 0.05$) (Table 4).

There was also a significant but inverse correlation between the blood level of cyclosporine and the time elapsed since kidney transplantation, suggesting that the higher the cyclosporin blood level, the more patients with BKV infection develop renal dysfunction and elevated serum creatinine in a shorter period than those who receive a kidney transplant (Table 4).

## Discussion

The findings of this study may not be accurately compared with similar studies. The incidence of BKV infection in the present study was 22.2%

**Table 3. The increase in serum creatinine levels (mg/dl)**

| Time after transplant | mean±sd | The amount (percentage) of the difference with the baseline | P value** |
|---|---|---|---|
| **Posttransplant** | 2.53±1.09 | | |
| **1 month** | 1.57±0.30 | 0.96 (61.1%) | < 0.001 |
| **6 months** | 1.73±0.67 | 0.80 (46.2%) | 0.004 |
| **1 year** | 1.83±0.83 | 0.70 (38.2%) | 0.263 |
| **P value*** | 0.204 | | |

**Note.** * Repeated Measures ANOVA test was used for comparison.
** Wilcoxon test was used for comparison.

**Table 4. Correlations between quantitative variables in this study**

| | Serum Tacrolimus level | Serum Cyclosporine level | Tubular atrophy | Interstitial inflammation |
|---|---|---|---|---|
| **Mean duration on dialysis prior to transplant** | | r = 0.820<br>p = 0.046 | r = 0.902<br>p < 0.001 | r = 0.951<br>p = 0.001 |
| **The time between KT and renal dysfunction** | | r = 0.764<br>p = 0.046 | | |
| **Serum creatinine level at baseline** | r = 0.465<br>p = 0.039 | | | |

**Note.** KT: Kidney transplant.

among KTRs diagnosed with AKI which is similar to a systematic review of several geographical zones in Iran that KTRs had a BKV infection rate of 23%. although Jamshidi et al.'s study was conducted in the same geographic region as our study, northeastern Iran, the prevalence of polyomavirus infection among all KTRs was 4.7% [19] in line with our study, Cobo et al. research showed 36.36% of KTRs had positive urine sampling for BKV [7] contrary to present results, some previous studies also reported a lower rate of BKV contamination among KTRs [2, 23]. The disparity between the studies can be explained by the difference in their sampled target populations. A study from Iraq published in 2016 found that only 2.8% of KTRs tested positive for BKV virus in their serum using a conventional PCR method. However, serum samples in KTRs with a rise in creatinine (AKI) were not evaluated separately [27]. Peshgagi et al. published a study in 2012 in which 31 kidney transplant recipients were tested for BKV and JC infection, two types of polyomaviruses. According to the findings, 29% of patients had positive PCR results for BKV while 16% had decoy cells. Even though the prevalence of BK virus infection was high, they did not observe changes in kidney biopsy results revealing BKVAN [30]. We found a lower PCR positivity percentage in our study, compared to this study, which can be explained by the different types of samples collected (urine and serum).

In the present study, we established that the average duration from the detection of BKV positivity to diagnosis is 16 months following transplantation. In contrast, Ghafari et al. conducted a study in Iran that indicated a longer average duration of 23 months for BKV nephropathy post-transplant. This notable difference is attributed to the variability in study methodologies; our research included all patients with positive PCR results, while Ghafari et al. focused solely on cases supported by immunohistochemical evidence. Furthermore, existing literature on adult patients consistently shows that the average time to BKV viremia detection can range from 1.5 months to one year after kidney transplantation [10, 11, 12, 14, 23, 39]. In a study conducted by Favi et al., it was found that over half of the cases were diagnosed with BKV viremia at an average of three months after transplantation. Following this, a monthly follow-up was carried out during the first six months after the transplant, according to the guidelines set by the Kidney Disease Improving Global Outcomes (KDIGO) [10]. In other studies conducted on pediatric patients, BKV infection has been detected between 3 and 11 months post-transplantation. Notably, in a prospective cohort study involving pediatric patients, Hymes et al. found that the average time until the detection of BKV viremia was 90 months [18]. In the present study, all 30 recipients had BKV viral loads exceeding 10 000 copies/mL, and all tested positive for BKV on PCR. Close monitoring of BKV viral load and creatinine levels is crucial for patients who develop BKV nephropathy (BKVN). Although no definitive cutoff for viral load has been established that is strongly associated with BKV nephropathy, some researchers suggest that BKVN may be preceded by viral loads greater than 4 log copies/mL. In the present study, all 30 recipients had BKV viral loads exceeding 10 000 copies/mL, and all tested positive for BKV on PCR. Close monitoring of BKV viral load and creatinine levels is crucial for patients who develop BKV nephropathy (BKVN). Although no definitive cut-off for viral load has been established that is strongly associated with BKV nephropathy, some researchers suggest that BKVN may be preceded by viral loads greater than 4 log copies/mL [2, 16, 23]. We also found hematuria or pyuria in the urine sample in one-third of patients, which interestingly had a significant correlation with the duration of occurrence of renal dysfunction (AKI) posttransplant. In other words, renal dysfunction was found earlier in patients who had hematuria or pyuria. CMV-DNA PCR was positive in 56.7%. Previous reports demonstrated various ranges of CMV positivity among KTRs [7, 9, 26, 38]. Several studies reported that CMV, one of the viral infections accompanying BKV infection, has been noted as a risk factor for BKV infection [2, 5, 8, 29]. According to biopsy data, the most common histopathology features were interstitial inflammation with tubular cytopathic changes in four patients. acute renal rejection was confirmed in 3 patients. Based on several studies, due to morphological similarities between early BKVAN and other diagnoses such as acute rejection, light microscopy alone cannot be used as a definite diagnosis of BKVAN. Therefore, a biopsy examination must be performed [9, 16].

In the study published by Ghafari Moghadam et al. in Urmia, northwest Iran, 160 KTRs underwent kidney biopsy examination. The average age of the patients was about 35 years, which was similar to the present study. We observed a similar ratio among our cases with positive pathology presenting BKVAN. Although considering that in this study we investigated the frequency of BKVAN among patients with AKI diagnosis after kidney transplant, not all transplant patients, it can be argued the Urmia study report appears relatively high.

Our study showed higher cyclosporin level is relatable with earlier kidney dysfunction. A few studies have demonstrated that cyclosporin may present a higher risk of BK virus infection than other immunosuppressive therapies [31, 33]. Although many studies reported tacrolimus was one of the main risk factors of post-transplant BKV infection [14, 16, 20]. The first sign of kidney damage in patients with renal dysfunction is usually an increase in serum creatinine levels change in serum creatinine value compared to previously measured values was used to select patients for this study.

## Limitations

We are aware of our study limitations, such as the lack of essential data to determine the status of BKV infection in several patients. Accordingly, an accurate estimation of the prevalence seemed difficult to achieve. Furthermore, the retrospective nature of the study, hindered the investigation of the infection amongst the study population using more specific diagnostic tests. For example, in the case of immunohistochemistry, we used a monoclonal antibody against SV40 antigen, which has a cross-reaction with SV40 and JC viruses and is not specific to BKV.

## Conclusion

In conclusion, the present findings reveal that the frequency of BKV infection among kidney transplant recipients diagnosed with acute kidney injury (AKI) at our center stands at 22%. The key predictor for this condition in kidney transplant patients is the presence of hematuria and pyuria in urine tests. Furthermore, we observed a significantly higher incidence of BK infection in men compared to women, while no significant differences were found between genders in the control group.

## Ethical approval

This research followed the tenets of the Declaration of Helsinki. The study protocols were approved by the institutional ethical committee at Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1398.481). Accordingly, all the patients were informed about the research, and consent was taken from them before any intervention.

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