Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2022;47(4):1477-1484
DOI: 10.17826/cumj.1133550

ARAŞTIRMA / RESEARCH

Biopsy-proven BK virus nephropathy in kidney transplant patients: risk factors, prevalence and treatment approach

Böbrek nakli hastalarında biyopsi ile kanıtlanmış BK virüs nefropatisi: risk faktörleri, sıklığı ve tedavi yaklaşımı

Eda Altun[1], Sena Ulu[1], Süheyla Apaydın[2], Bahtışen Güven[2]

[1]Bahcesehir University Faculty of Medicine, Department of Nephrology, Istanbul, Turkey.
[2]Göztepe Medikalpark Hastanesi Nefroloji Bölümü, Istanbul, Turkey

Cukurova Medical Journal 2022;47(4):1477-1484

Abstract

Purpose: BK virus nephropathy (BKVN) is a latent infection and it is closely associated with immunsuppressive therapy. We aimed in this study to evaluate biopsy-proven BKVN and investigate frequency, risk factors and treatment management.

Materials and Methods: In this study, 422 kidney transplant recipients were analysed retrospectively between April 2014 and April 2020 for biopsy-proven BK virus nephropathy. Group I included 16 kidney transplant patients with biopsy-proven BK nephropathy and group II included 36 kidney transplant patients with negative BK virus nephropathy. We aimed demographic, clinical features of kidney transplant recipients with BKVN (group I, n: 16) and non-BKVN (group II, n:36) were compared and the factors affecting of BKVN.

Results: The mean age of grup I and group II were were 41±14.8 years and 39±15.2 respectively. The patients mean follow-up period of 43±11.2 months. Serum creatinine and proteinuria degree were significantly higher in the group with BKVN. In order to reduce the dose of immunosuppression in patients with BKVN, tacrolimus treatment was discontinued in 8 patients, and they were switched to everolimus + MMF + prednisone treatment, leflunamide + MMF + prednisone treatment in 4 patients, and sirolimus + MMF + prednisone treatment in 4 patients. The mean serum creatinine level of the patients who were followed up were observed as 1.78±0.98 mg/dl in group I.

Conclusion: In our center, the prevalance of BKVN was found 3.92% during the study period. Reduction of dose immunosuppressive therapy is the most effective treatment. It is thought that there was no differences between Leflunamide and other approaches for treatment.

Öz

Amaç: BK virüs nefropatisi (BKVN) böbrek nakli sonrasında immunsupresif tedavi dozu ile yakından ilişkili, latent enfeksiyonun reaktivasyonudur. Bu çalışmada kliniğimizde takipli hastalarda BKVN sıklığını ve olası risk faktörlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Nisan 2014- Nisan 2020 tarihleri arasında kliniğimizden takipli olan 422 böbrek nakil hastası BK virus nefropati açısından geriye dönük oalrak analiz edildi. Gruo I'e biyopsi ile kanıtlanmış BK virus nefroatili 16 hasta, grup II'ye ise BK virus negatif olan 36 hasta dahil edildi. BKVN saptanan 16 hastanın (grup I) ve BKVN negatif olan 36 hastanın (grup II) demografik, klinik ve laboratuar özellikleri özellikleri ile BKVN ilişkili faktörler karşılaştırıldı.

Bulgular: Grup I'deki hastaların yaş ortalaması 41±14.8 yıl, grup II'deki hastaların yaş ortalaması ise 39±15.2 yıl olarak saptandı. Hastaların böbrek nakli sonrasında ortalama takip süreleri 43±11.2 ay idi. BKVN olan grupta serum kreatinin ve proteinüri düzeyinin istatistiksel anlamlı olarak daha yüksek olduğu saptandı. BKVN saptanan hastalarda immunsupresyon dozunu azaltmak amacı ile 8 hastada kullanmakta oldukları takrolimus tedavisi kesilerek everolimus +MMF+ prednisone tedavisine, 4 hastada leflunamid+ MMF+ prednisone tedavisine, 4 hastada ise sirolimus +MMF+ prednisone tedavisine geçiş yapıldı. BKVN tanısı sonrasında hastaların ortalama 58.9±34.2 ay takip edildiği, 1 hastada NODAT geliştiği, 2 hastanın kardiyovasküler nedenlerle kaybedildiği, 2 hastanın ise greft kaybı nedeni ile hemodiyaliz tedavisine döndüğü gözlendi. Takibe devam eden hastaların ortalama serum kreatinin değerlerinin 1.78±0.98 mg/dl olarak gözlendi.

Sonuç: Kliniğimizde çalışmanın yapıldığı dönemde BKVN sıklığı %4.86 olarak gözlendi. İmmunsupresif

Yazışma Adresi/Address for Correspondence: Dr. Eda Altun, Bahcesehir University Faculty of Medicine, Department of Nephrology, Istanbul, Turkey. E-mail: dredaaltun@gmail.com
Geliş tarihi/Received: 2106.2022 Kabul tarihi/Accepted: 23.09.2022

Early diagnosis and screening (frequently intervals) seems to be most effective way for BKVN.

Keywords: BK virus, nepropathy, kidney transplantation

tedavi dozunun azaltılması hala en etkin tedavi yöntemidir. Leflunamid tedavisi ile diğer tedavi yaklaşımları arasında fark olmadığı saptandı. Sık aralıklarla tarama ve erken tanının BKVN takibinde daha etkili olduğu gözlenmiştir.

Anahtar kelimeler: BK virüs, nefropati, böbrek nakli

INTRODUCTION

BK virus (Polyama hominis I, BKV) was first described in 1971, isolated in the urine and urinary epithelium of a kidney transplant recipient with renal failure and ureteral stenosis[1]. BKV is a non-enveloped, 42 nm virus with a double-stranded circular DNA containing 5000 bases and an icosahedral capsid from the Papoavirus group in the Polyomaviridae family[1].

The prevalence of BK virus (BK) in the adult population is approximately up to 90%[1,2]. BKV is reactivated in patients who is receiving immuno-suppressive treatment[3]. Kidney transplant patients is receiving immunosuppressive medication for preventing to acut rejection and allograft dysfunction[4]. In kidney transplantation patients; BKV is activated and manifests as tubulointerstitial nephritis. BKVN directly related with the intensity of immunosuppressive medications[5,6].

There are many risk factors for BKVN (BK virus nephropathy); donor, recipient and transplant related risk factors. These risk factors include; total HLA antigen mismatch, immunsuppressive regimen (tacrolimus (Tac) or mycophenolate mofetil (MMF)), a deceased donor, older and younger age transplantation, a male patient, a history of diabetes mellitus, and previous transplant, ureteral trauma, cytomegalovirus infection, delayed graft function, and treatment for acute rejection episodes[7,8,9].

Maintenance immunosuppression in kidney transplant recipients include of three immunosuppressive madications: firstly calcineurin inhibitors (CNI); tacrolimus or ciclosporin, secondly antiproliferative agent mycophenolate mophetil/sodium or azathioprine, and thirdly corticosteroids. In large studies have showned that high serum levels of CNI suppressed responce to anti-BK vırus T-antigen. And some of the studies documented that higher risk for BK virus nephropathy in patients treated with CNI[10,11].

The early diagnosis and monitoring of BKVN in kidney transplant patients are most important both preventing and teratment [5,6]. Viruria or viremia may be detected weeks to months before there is a detectable allograft dysfunction. Viruria and viremia ocur before nephritis, which can occur as early as 6 days and up to 5 years posttransplant (mean of 10-13 months)[5,6].

Until today there is no specific immunosuppressive therapy has been definitively related with clinically BKVN[12]. Data from large studies are suggesting that prevention and treatment for BKVN in kidney transplant patients are firstly routine screeining for viremia and preemptive strategy that include to started early medication. Secondly aimed to eveluate modification of immunsuppressive therapy when proven by kidney biopsy or after a presumptive diagnosis[7,8,13]. In addition, cidofovir, intravenous immunoglobulin (IVIG), quinolones, and leflunomide therapy may be applied, but none of these treatments have strong evidence to be recommended[6].

There is a limited data in the literature for prevention, treatment and long-term findings of BKVN. We thought that it is important to research the prevalance and clinical findings of BKVN at transplant center to determine BKVN screning, prevention and treatment protocols spesific to each transplant center. In this study we aimed to determinated our transplant centers'outcomes, frequency and risk factors with biopsy-proven BKVN.

MATERIALS AND METHODS

Sample

We retrospectively analyzed 422 kidney transplant recipients from deceased donor or living related donors at Bahcesehir University faculty of Medicine, Goztepe Medicalpark Hospital Transplant Center during a six year period (April 2014 to April 2020).

Patients who were included in this study were categorized according to positive biopsy-proven BKVN and negative biopsy-proven BKVN or negative BKV viremia. Patients in group I were positive biopsy-proven BKVN (n:16). Recipients in group II (n:36) biopsy-proven BKVN or negative

negative BK virus in blood and urine; those with underwent kidney transplantation in same period, same surgical procedure, used same immunsuppressive therapy and had same immunological risk with group I.

The patients' demographic, laboratory and follow-up data were obtained from their hospital records. Data for analysis were obtained at routine controls; these variebles involved blood pressure level, blood analysis (hemogram, urea, creatinin, electrolytes, urinalysis, proteinuria), and kidney transplant ultrasound. Patients without an allograft kidney biopsy or missing data were excluded from the study. This study was approved by the Bahcesehir University Faculty of Medicine Ethical Commite (2022-06/01). The study is compliant with the guidelines of the Declaration of Helsinki.

Procedure

After transplantation, a screening for BKV DNA in blood samples was performed every months in the first six months, then for every three months and when the unexplained elevation serum creatinine level was detected. The diagnosis and screening of presumptive BKVN in patients are dependent on real-time polymerase chain reactin (PCR) analysis for BKV DNA of blood sample. Diagnosis of BKV infection was defined if the number of viral copies detected 10^4 copies/mL in blood sample. BKVN is diagnosed by histological evaluation after performing a fine-needle biopsy of the allograft. Also kidney transplant receivers (KTRs) had rising creatinine level were evaluated for the indication kidney biopsy. Biopsies were evaluated according to Banff calssification for the presence of BKVN[12].

Patients were divided into 2 groups according to BKV positivity in blood and BKVN in kidney biopsy. Group 1 included 16 (KTRs) with biopsy-proven BKVN, Group 2 included 36 KTRs with (who underwent kidney transplant in the same period with group I) negative BK viremia and no biopsy-proven BKVN. We compared in these patients with in terms of demographic features, clinical signs and biochemical parameters.

Immunsuppression therapy and follow-up

Methylprednisolone (MP) was given (1000 mg/day) starting on the transplantation day and progressively tapered to 64 mg/day at the one week of transplantaion. Doses of calcineurin inhibitor (CsA or Tac) were adjusted to maintain morning trough serum levels (150-250 ng/ml and 7-10 ng/ml for CsA and Tac retrospectively). Anti-metabolite agents (mycophenolate sodium (MPA, 1140 mg/da or MMF, 2 g/day) and azotioprine (AZA, 1-2 mg/kg/day) were also used. Our study population were followed-up considering to the transplantation guidelines.

Statistical analysis

Statistical analyses was conducted with SPSS version 20.0 (IBM Co., Armonk, NY, USA). Qualitative variables are presented as number and percentage, whereas quantitative variables are presented as means and standard deviation. Demographic and clinical variables between recipients with and without BKVN were compared by use Fisher exact or chi-square tests. *P* values $\leq .05$ was considered significant.

RESULTS

A total of 402 kidney transplant patients were analyzed between April 2014 and April 2020, retrospectively. Sixteen patients (Group I: 9 male, 7 female) diagnosed with BKVN and 36 patients (Group II: 21 male, 15 female) who underwent simultaneous transplantation with patients who developed BKVN were included in the study. The incidence of BKVN was detected as 3.92% in our clinic. Mean age of the patients in group I was 41±14.8 years, mean age of patients in group II was 39±15.2 years, the mean follow-up period after kidney transplantation was 43±11.2 months. The laboratory and demographic features of the patients are summarized in Table 1.

In the group I patients, 13 patients were transplanted from a living donor and 3 patients from a cadaveric donor, while in the other group, 28 patients were transplanted from a living donor and 8 patients were transplanted from a cadaveric donor. The mean time of diagnosis of BKVN was found to be 8.2±5.8 months. It was observed that 12 patients in the BKVN group received anti-thymocyte globulin+ steroid treatment as induction treatment before transplantation, 4 patients received only steroid treatment, 32 patients in the BKVN negative group received Anti-T lymphocyte globuline (ATLG) + steroid treatment and 4 patients did not receive induction treatment. Patients immunosuppressive treatment regimens included prednisolone, anti-metabolite agents (MMF, MPA), and calcineurin

inhibitor (cyclosporine A (CsA), Tac). All patients were given fluconazole, valganciclovir, and trimethoprim-sulfamethoxazole prophylaxis for possible fungal, viral, or pneumocystis jiroveci infection prophylaxis in the post-transplant period.

Table 1. Clinical and Laboratory Characteristics of Patients with BKVN

	N (%) or mean±SD
Gender	
Female	7 (%43.75)
Male	9 (%56.25)
Age (years)	39±13.8
Transplantation Time (months)	39±12.2
Donor Type	
Living	13 (%81.25)
Cadaveric	3 (%18.75)
Mean time to diagnosis of BKVN (month)	8.2±5.8
Mean serum creatinine at diagnosis BKVN (mg/dl)	2.84±1.1
Induction Treatment	
ATLG+ Steroid	12 (%33.3)
Steroid	4 (%66.6)
Primary Disease	
Diabetes Mellitus	4 (%25)
Hypertension	6 (%37.5)
Chronic Glomerulonephritis	4 (%25)
Others (VUR, PCKD…)	2 (%12.5)
İmmunsuppresive regime	
Tac+ MMF+ PRD	15 (%93.75)
CsA+ MMF+ PRD	1 (%6.25)
Donor Type	
Living	13 (%81.25)
Cadaveric	3 (%18.75)
Mean time to diagnosis of BKVN (month)	8.2±5.8
Mean serum creatinine at diagnosis BKVN (mg/dl)	2.84±1.1

ATLG: Anti-T lymphocyte globuline, Tac: Tacrolimus, MMF: Mycophenolate mofetil, MFA: Mycophenolic acid, CsA: Cyclosporine-A, VUR: Vesicoretheral reflux, PCKD: polycystic kidney disease, BKVN: BK virüs nephropathy

When the average serum creatine levels of both groups before BKVN diagnosis was compared, there was no found statistical significantly difference between the two group (0.98±0.32 mg/dl, respectively, (min: 0.58 mg/dl- max: 1.86 mg/dl), 0.87±0.29 mg/dl, (min: 0.62 mg/dl- max: 1.78 mg/dl) p=0.06). However, when the mean serum creatinine values of the patients with BKVN at the time of diagnosis (2.84±1.1 mg/dl) were compared with the serum creatinine values at the time of diagnosis (0.84±0.38 mg/dl) of the patients without BKVN, the mean serum creatinine values of the group diagnosed with BKVN were found to be statistically significantly higher. (p=0.01). Both groups were found to have no difference when the groups were compared to age and gender (Table 2).

When the immunosuppressive treatment regimens used by the patients in the BKVN group at the time of diagnosis were viewed, it was observed that 1 patient received CsA+ MMF+ Prednisone treatment, and the other patients received Tac + MMF + prednisone treatment. In the group without BKVN, it was determined that 8 patients received CsA + MMF + Prednisone treatment, and 28 patients received Tac + MMF + prednisone treatment.

Table 2. Analysis of demographic, clinical and laboratory characteristics of patients with and without BKVN

	BKVN (+)	BKVN (-)	p
Gender (n , %)			
Female	7 (43.75%)	15(41.6%)	0.1
Male	9 (%56.25)	21 (58.4%)	
Age (years)	41±14.8	39±15.2	0.07
Diabetes Mellitus (n , %)	4 (25%)	8(22.2%)	0.2
NODAT (n , %)	1 (6.25%)	3(8.3%)	0.1
Creatinine, time to diagnosis (mg/dl)	2.84±1.1	0.84±0.38	0.01
Proteinuria, time to diagnosis (mg/day)	0.98±0.24	0.42±0.18	0.02
Immunosuppressive regimen time to diagnosis (n , %)			
Tac+ MMF+ PRD	13(81.25%)	28(77.7%)	0.04
CsA+ MMF+ PRD	3(18.75%)	8(22.3%)	
Induction Treatment			
ATLG+ Steroid	13(81.25%)	29(80.5%)	0.3
Steroid	3(18.75%)	7(19.5%)	
Delayed graft function (n , %)	1 (6.25%)	3 (8.33%)	0.1
Acute rejection (n , %)	2 (12.5%)	3 (8.33%)	0.00

ATLG: Anti-T lymphocyte globuline, Tac: Tacrolimus, MMF: Mycophenolate mofetil, CsA: Cyclosporine-A, NODAT: New onset Diabetes Mellitus after Transplantation, BKVN: BK virüs nephropathy

It was detected that, in order to reduce the immunosuppression dose of the patients after the diagnosis, Tac treatment was discontinued and 8 patients switched to everolimus + MMF + prednisone treatment, 4 patients switched to leflunomide + MMF + prednisone treatment, and 4 patients switched to sirolimus + MMF + prednisone treatment. While intravenous immunoglobulin was given to 6 patients with BKVN diagnosis, pulse steroid + ATLG treatment was given to 3 patients with simultaneous acute rejection diagnosis. It was observed that graft functions regressed to basal values in all 3 patients who developed acute rejection.

It was found that, the mean proteinuria levels of the patients at the time of diagnosis of BKVN were 0.98±0.24 mg/day, and the difference was statistically significant when compared with the mean proteinuria (0.42±0.18 mg/day) 1 month prior the diagnosis of disease (p=0.01). It was observed that the mean serum creatinine value of the patients who were followed up was 1.78±0.98 mg/dl. In table 3 summerized that serum creatinine and proteinuria level, during the follow-up time in BKVN group. It was detected that the mean follow-up period of the patients after the diagnosis of BKVN was 58.9±34.2 months, 2 patients died due to cardiovascular reasons, and 2 returned to hemodialysis treatment due to graft loss.

When patients with BKVN were analysed in terms of new onset diagnosed diabetes mellitus after transplantation (NODAT), it was observed that NODAT developed in only 1 (6.25%) patient in Group I at the 11th month of follow-up. Whereas, in Group II, NODAT development was detected in 3 patients (8.3%).

Table 3. Serum creatinine and proteinuria level, following time in BKVN

	Time to diagnosis	3. month	6. month	12. month	Last
Creatinine(mg/dl)	2.84±1.1	2.19±0.58	1,79±0,88	2.4±3.7	2.8±1.9
eGFR(ml/min, MDRD)	38.6±21.2	41.4±18.6	48.7±19.2	45.9±36.7	38.9±27.6
Proteinuria(gr/day)	0.98±0.24	0.68±0.72	0.53±0.73	0.99±0.82	1.11±0.86

eGFR: Glomerular Filtration Rate, MDRD: Modification of Diet in Renal Diseas, BKVN: BK virüs nephropathy

Again, when the patients were evaluated in terms of urinary tract infection after transplantation, it was detected that oral or IV antibiotic treatment was given due to urinary tract infection in 4 (25%)

patients in Group I and 10 patients (7.27%) in Group II during the period until the diagnosis of BKVN after transplantation. It was observed that all patients who developed UTI had a double J catheter. A double J catheter was observed to be applied to 13 patients in the post-transplant period in the BKVN group, and the mean catheter stay time was 34.2±10.8 days. In the BKVN negative group, double J catheter was applied to 28 patients, in these patients the mean catheter stay time was 31±11.4 days, and no statistically significant difference was detected (p=0.07).

DISCUSSION

The fact that effective immunosuppressive treatments applied to reduce the risk of acute rejection and enhance graft survival rate after kidney transplantation can lead to latent BKV reactivation is known. According to the literature, the incidence of BKVN in transplantation centers around the world was observed to be between 2-9.3%, whereas in our study, the incidence of BKVN was found to be 4.8%[13,15]. The mean time of BKVN diagnosis in our patients was observed to be 6.8 ± 2.4 months after transplantation, while the graft loss rate was 12.5%. In different studies, graft loss rates have been reported as 40-80%[7-16].

In our study, when immunosuppressive treatment drugs used by patients who developed BKVN were examined, it was observed that 15 patients received Tac + MMF + prednisolone treatment. In many studies, BKVN incidence was reported higher for patients using immunosuppressive treatment including Tac + MMF + prednisolone[17-19].

In a study in which 56 kidney transplant patients were examined, it was shown that the frequency of BKVN was higher in patients with serum tacrolimus level >10 ng/ml[20,21]. In our study group, while the serum tacrolimus level of 4 patients was >10 ng/ml, the mean tacrolimus level was 8.1±2.11 ng/ml.

Although it is known that the most important factor among the risk factors for BKVN is the drugs used for immunosuppressive therapy, it is also known that there are risk factors such as changes in the humoral and cellular immune system of the recipient, advanced age, and male gender[21,22]. In our study group, the male sex ratio was 62.5% and the mean age was 41.2±13.2 years. In the study of Hirsch et al., advanced age was defined as an independent risk factor for the development of BKVN[18]. In addition, the time of diagnosis after transplantation and the serum creatinine level at the time of diagnosis are also extremely crucial for graft survival[19]. Graft survival rates were observed to be higher in patients with low serum creatinine values and in patients who were diagnosed in the first month[22]. In our study group, the mean time of diagnosis was detected as 6.8±2.4 months after transplantation, and the mean serum creatinine value was 2.84±1.1 mg/dl (min: 0.96 mg/dl-max: 4.2).

Among patients treated with Tacrolimus; 8 patients were switched to everolimus+MMF+ prednisolone, 5 were switched to leflunomide + MMF + prednisolon theraphy. Among patients treated with CsA; in 1 patient, the dose of CsA was reduced and the treatment was continued as MMF + prednisone, in 2 patients MMF treatment was discontinued and low-dose CsA + azathioprine + prednisolone treatment was started.

In the treatment of BKVN, the replacement or dose reduction of immunosuppressive drugs can be effective in the treatment of infection but can increase the risk of acute and chronic rejections[17-23]. While there are publications reporting that the viral load is reduced by 58-60% when the tacrolimus level is kept between 3-5 ng/ml and the MMF treatment is completely discontinued, there are also publications reporting that the graft loss is reduced by 20% when the MMF dose is reduced by 40-60%[24]. In our study group, the MMF treatment dose was reduced by 50% in all patients. It was observed that at the time of BKVN diagnosis, the serum creatinine levels were higher in the patients whose MMF treatment was ceased than in the other patients. While the graft loss was not observed in the patient group treated with Leflunamide, both other graft losses were found to be in the group treated with MMF + everolimus + prednisolone.

There was no difference detected in the rate of regression of serum creatinine value to basal values between the patients treated with leflunomide and the other patients. Although there are publications reporting that leflunomide treatment is more effective in reducing viral clearance, the need for dose follow-up and the immunosuppressive efficacy of the drug should still be discussed[24].

Publications reporting that quinolone antibiotics are successful in the treatment of BKVN are present[25]. In the study of Gabardi et al., it was shown that the risk of BKVN was lower in the group of patients who

received levofloxacin treatment for approximately 1 month in the post-transplant period[24]. In our study, quinolone prophylaxis was not given in the post-transplant period.

When the patients were analysed in terms of double J stenting after transplantation, it was found that only 3 patients were not stented, and the mean catheter stay was 34.2±10.8 days in the stented patients. There are studies in the literature showing that double j stenting increases the risk of BKVN[27]. It is thought that with stenting superficial epithelial cells get eroded, ureters get destracted, ulceration and reactive changes in the transitional epithelium ocur[28-30]. Standard double-J stent was applied in our patients.

In our results, acute rejection was observed in 2 patients at the time of diagnosis of BKVN, and these patients were given pulse steroid therapy followed by a reduction in the doses of the immunosuppression therapy. The limitations of our study are primarily its retrospective design and power analysis was not performed in the statistical method. In addition, while all patients had kidney biopsy at the time of diagnosis, only 9 patients had a control biopsy.

In conclusion, the frequency of BKVN in kidney transplant patients followed up in our clinic was consistent with data of the literature. It was observed that BKVN continued to be an important risk factor for acute rejection and graft loss, and there was no difference in graft survival between the groups receiving leflunomide therapy and mTOR inhibitor therapy. In recent years, with the development of technological methods, easier access of patients to hospitals and doctors, routine application of screening tests, and close monitoring of immunosuppressive therapy dose setting, we believe that the frequency of BKVN incidence can be further reduced. It was established again that the prognosis was more favorable in patients who were diagnosed early in the post-transplant period, and it was important to perform a screening test every month for the first 3 months and then every 2-3 months among first years of transplantation.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EA, SU, AA; Veri toplama: EA, BG; Veri analizi ve yorumlama: EA, SA; Yazı taslağı: EA; İçeriğin eleştirel incelenmesi: SU, SA; Son onay ve sorumluluk: EA, SU, SA, BG; Teknik ve malzeme desteği: EA, BG; Süpervizyon: EA, SA; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için BAhçeşehir Üniversitesi Klink Araştırmalar Etik Kurulundan 02.03.22 tarih ve 2022-06/01 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan ederler.
Finansal Destek: Bu araştırma için, kamu, ticari veya kar amacı gütmeyen sektörlerdeki finansman kuruluşlarından herhangi bir hibe alınmadı
Author Contributions: Concept/Design : EA, SU, AA; Data acquisition: EA, BG; Data analysis and interpretation: EA, SA; Drafting manuscript: EA; Critical revision of manuscript: SU, SA; Final approval and accountability: : EA, SU, SA, BG; Technical or material support: EA, BG; Supervision: EA, SA; Securing funding (if available): n/a.
Ethical Approval: For this study, ethical approval was obtained from Bahcesehir University Klink Research Ethics Committee with the decision dated 02.03.22 and numbered 202-06/01.
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Kotla SK, Kadambi PV, Hendricks AR, Rojas R. BK polyomavirus-pathogen, paradigm and puzzle. Nephrol Dial Transplant. 2021;36:587-93.
2. White LH, Casian A, Hilton R, MacPhee IA, Marsh J, Sweny P et al. BK virus nephropathy in renal transplant patients in London. Transplantation. 2008;85:1008-15.
3. Tan CS, Koralnik JC. BK, and other polyomaviruses: progressive multifocal leukoencephalopathy. In textbook of Principles and practices of infectious diseases (Ed GL Mandell): 10th ed. Philadelphia, Churchill Livingstone, 2009.
4. Demir E, Turkmen A, Sever MS. Risk factors, pathogenesis, presentation and management of BK virus infection in kidney transplantation. Nephrol Dial Transplant. 2021;27:985-87.
5. Mengel M, Marwedel M, Radhermacher J. Incidence of polyomavirus nephropathy in renal allografts: influence of modern immunosupressive drugs. Nephrol Dial Transplant 2003;18:1190-6.
6. Sawinski D, Goral S.BK virus infection: an update on diagnosis and treatment. Nephrol Dial Transplant. 2015;30:209-17.
7. Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP et al. Polyomavirus associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. Transplantation. 2005;79:1277.
8. Favi E, Puliatti C, Sivaprakasam R, Ferraresso M, Ambrogi F, Delbue S et al. Incidence, risk factors, and outcome of BK polyomavirus infection after kidney transplantation. World J Clin Cases. 2019;6:270-90.
9. Funahashi, Y. BK Virus-associated nephropathy after renal transplantation. Pathogens. 2021;10:150-55.
10. Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A et al. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. Am J Transplant. 2013;13:136-45.
11. Doesum WB, Gard L, Bemelman FJ, Fijter JW, Homan Heide JJ, Niesters HG et al. Incidence and

outcome of BK polyomavirus infection in a multicenter randomized controlled trial with renal transplant patients receiving cyclosporine-, mycophenolate sodium-, or everolimus-based low-dose immunosuppressive therapy. Transpl Infect Dis. 2017;19:1-10.
12. Turgut D, Sayin B, Soy EA, Topcu DI., Ozdemir BH, Haberal, M. Tacrolimus intrapatient variability in BK virus nephropathy and chronic calcineurin toxicity in kidney transplantation. Saudi J Kidney Dis Transpl. 2021;32:348-54.
13. Sachdeva MS, Nada R, Jha V, Sakhuja V, Joshi K. The high incidence of BK polyoma virus infection among renal transplant recipient in India. Transplantation. Transplantation. 2004;77:429-31.
14. Nickeleit V, Singh HK, Randhawa P, Drachenberg CB, Bhatnagar R, Bracamonte E et al. The Banff Working Group classification of definitive polyomavirus nephropathy: morphologic definitions and clinical correlations. J Am Soc Nephrol. 2018;29:680–93.
15. Awadalla Y, Randhawa P, Ruppert K, Zeevi A, Duquesnoy RJ. HLA mismatching increases the risk of BK virus nephropathy in renal transplant recipients. Am J Transplant. 2004;4:1691-6.
16. Herrera S, Bernal-Maurandi J, Cofan F, Ventura P, Marcos MA, Linares L et al. BK virus and cytomegalovirus coinfections in kidney transplantation and their impact on allograft loss. J Clin Med. 2021;10:3779.
17. Brennan DC, Agha I, Bohl DL. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant. 2005;5:582-94.
18. Hirsch HH, Vincenti F, Friman S. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. Am J Transplant. 2013;13:136-45.
19. Sánchez DM, García LJ, Jiménez IL, Luján IS, Soriano MG, Viñas SL et al. Renal function impairment in kidney transplantation: importance of early BK virus detection. Transplant Proc. 2019;51:350-52.
20. Steubl D, Baumann M, Schuster T. Risk factors and interventional strategies for BK polyomavirus infection after renal transplantation. Scand J Urol Nephrol. 2012;46:466-74.
21. Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. Am J Transplant. 2006;6:2000-5.
22. Shen CL, Wu BS, Lien TJ, Yang AH, Yang, CY et al. BK polyomavirus nephropathy in kidney transplantation: balancing rejection and infection. Viruses. 2021;13:487.
23. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplant. 2006;81:704-10.
24. Johnston O, Jaswal D, Gill JS. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation. 2010;89:1057–70.
25. Lee BT, Gabardi S, Grafals M. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebocontrolled trial. Clin J Am Soc Nephrol. 2014;9:583–89.
26. Gabardi S, Waikar SS, Martin S. Evaluation of fluoroquinolones for the prevention of BK viremia after renal transplantation. Clin J Am Soc Nephrol. 2010;5: 1298-304.
27. Hashim F, Rehman S, Gregg JA, Dharnidharka VR. Ureteral stent placement increases the risk for developing bk viremia after kidney transplantation. J Transplant. 2014;2014:459747.
28. Atencio IA, Shadan FF, Zhou XJ, Vaziri ND, Villarreal LP. Adult mouse kidneys become permissive to acute polyomavirus infection and reactivate persistent infections in response to cellular damage and regeneration. J Virol. 1993;67:1424–32.
29. Atencio IA, Villarreal LP. Polyomavirus replicates in differentiating but not in proliferating tubules of adult mouse polycystic kidneys. Virology. 1994;201:26–35.
30. Kayler L, Zendejas I, Schain D, Magliocca J. Ureteral stent placement and BK viremia in kidney transplant recipients. Transpl Infect Dis. 2013;15:202–07.