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# Treatment of BK virus with a stepwise immunosuppression reduction and intravenous immunoglobulin in pediatric kidney transplant

**Dunya Mohammad**[1] | **Dean Y. Kim**[2] | **Rossana Baracco**[3] | **Gaurav Kapur**[3] | **Amrish Jain**[3]

[1]Division of Pediatrics, Children's and Women's Hospital, University of South Alabama, Mobile, Alabama, USA

[2]Division of Kidney Transplant Surgery, Department of Transplant Services, Children's Hospital of Michigan, Detroit, Michigan, USA

[3]Division of Pediatric Nephrology and Hypertension, Department of Pediatrics, Children's Hospital of Michigan, Central Michigan University, Detroit, Michigan, USA

**Correspondence**
Amrish Jain, Division of Pediatric Nephrology and Hypertension, Department of Pediatrics, Central Michigan University, Children's Hospital of Michigan, Detroit, MI, USA.
Email: jain1a@cmich.edu

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## Abstract

**Background:** BKV and BKVN are common in pediatric kidney transplant, but there is limited data on treatment approaches. Our objective was to study the prevalence of BKV and BKVN utilizing only plasma qPCR and report treatment outcomes with stepwise IR and IVIG.

**Methods:** A retrospective study of all pediatric kidney transplants from 2013 to 2020. Excluded patients >21 years at transplant and immediate graft failure. Surveillance was conducted using only plasma BK qPCR at 1, 3, 6, 9, 12, 18, and 24 months and annually. BKV defined as ≥250 copies/ml and resolution as <250 copies/ml. Presumed BKVN as >10 000 copies/ml despite IR; and BKVN if confirmed on histology.

**Results:** Fifty-six patients were included in the study; 20 (35.7%) had BKV. BKV was associated with longer duration of stent, 40 vs. 33.5 days ($p$ = .004). Two patients (3.5%) had confirmed, and 2(3.5%) had presumed BKVN. The first-line treatment was IR in 100% of patients. BKVN confirmed and presumed received IVIG every month for six doses. Viral resolution was achieved in 70%, and no difference was noted in estimated glomerular filtration rate between BKV and non-BKV group ($p$ = .438). There were no rejection episodes, and graft survival was 100% over median follow-up of 3 years.

**Conclusions:** Plasma qPCR alone is adequate for screening and monitoring treatment of BKV and BKVN. A stepwise IR and IVIG resulted in BKV resolution in the majority of patients. Larger studies are required to study the role of IVIG in the treatment of BKVN.

**KEYWORDS**
BK virus and IVIG, immunosuppression, kidney transplant, pediatric

**Abbreviations:** BK, BK virus; BKV, BK viremia; BKVN, BK virus nephropathy; CERTAIN, The Cooperative European Pediatric Renal Transplant Initiative; DGF, delay graft function; DNA, Deoxyribonucleic acid; eGFR, Estimated glomerular filtration rate; HLA, Human leukocyte antigen; IR, immunosuppression reduction; IVIG, Intravenous immunoglobulin; MDRD, Modification of Diet in Renal Disease; MMF, Mycophenolate mofetil; mTOR, mechanistic target of rapamycin; NAPRTCS, The North American Pediatric Renal Trials and Collaborative Studies; PRA, panel reactive antibody; qPCR, Quantitative real-time polymerase chain reaction; SV40T, Simian virus 40 large T antigen.

  

## 1 | INTRODUCTION

BK is a DNA virus which belongs to a family of polyomaviruses with fourteen identified species that are known to infect humans.[1] The virus has a high affinity for the uroepithelium, in particular tubular epithelial cells, and has a tendency to remain latent after a primary infection. Hosts with intact immune systems are either asymptomatic with BK infection or may have mild cystitis.[1] However, immunosuppression promotes viral reactivation and multiplication in kidney transplant recipients.[2] Typically, viruria is followed by BKV, which in turn may progress to BKVN and graft failure.[3,4] Infection with BK in pediatric kidney transplants is associated with cystitis (hemorrhagic or non-hemorrhagic), BKVN (asymptomatic or with slowly increasing creatinine), and rarely ureteral stricture.[5,6] The incidence of BKV in the pediatric population ranges from 20 to 37%, while BKVN rates are 1–16%.[7–10] These pediatric rates have shown an increase in the last decade compared with reported incidence of 10–20% and 2–8%, for BKV and BKVN, respectively, in adult transplant population.[11–13]

qPCR assay in urine or plasma is commonly used screening test for diagnosis of BK infection.[14–16] Plasma qPCR has a higher specificity and negative predictive value, 97.4% and 54.5%, respectively, as compared to urine qPCR values of 91.7% and 27.3%, respectively.[17] Urine BK of $>10^7$ copies/ml and plasma BK of $>10^4$ copies/ml have been suggested as a surrogate marker of BKVN, but a positive immunohistochemistry for SV40T of kidney biopsy remains the gold standard test for diagnosis of BKVN.[14,18] Most adult and pediatric studies report the use of both urine and plasma qPCR for diagnosis and monitoring of BK infection.[10,19] Recently, routine screening of all kidney transplant recipients with plasma BK qPCR for the initial 2 years post-transplant has been recommended by the American Society of Transplantation Infectious Diseases Community.[15]

Treatment strategies including the use of cidofovir, leflunomide, and fluoroquinolones have been used in controlling BKV and preventing renal injury, but have been shown to be not as beneficial.[20–23] In the absence of effective antiviral therapy, adult and pediatric studies support IR as the most effective first-line treatment.[6,7] In adult literature, mTOR inhibitor-based immunosuppression has been suggested to reduce the risk of BKV because of their in vitro antiviral properties, but this has not been addressed in children.[24] The role of IVIG as a mediator of humoral immunity and specifically a BK neutralizing effect has been reported in adult studies; however, there are limited data on use of IVIG for treatment of children with BKV and BKVN.[25–29]

The aim of our study was to evaluate the prevalence of BKV and BKVN in our pediatric transplant cohort utilizing plasma BK qPCR for surveillance and identify potential risk factors for BKV. We report our treatment outcomes of BKV and BKVN using a stepwise IR and IVIG. Here, we also report our approach with early initiation of IVIG treatment in presumed and confirmed BKVN.

## 2 | MATERIALS AND METHODS

We conducted a retrospective chart review of all (58) pediatric kidney transplant recipients followed in the renal transplant clinic at Children's Hospital of Michigan after obtaining Institutional Review Board approval. Patients transplanted from January 2013 to January 2020 with a minimum follow-up of 1 year were included in the study. Exclusion criteria were age >21 years at transplant and immediate graft failure.

All patients received induction immunosuppression with intravenous anti-thymocyte globulin (rabbit) (1.5 mg/kg/dose, 3 doses for 1st transplant and 5 doses for repeat transplant) and a single dose of intravenous methylprednisolone (10 mg/kg; maximum 250 mg) in the operating room. Methylprednisolone dose was tapered to 2 mg/kg/day (maximum of 80 mg) by postoperative day 3. Maintenance immunosuppression was prednisone, tacrolimus, and MMF in all patients. Prednisone was started on postoperative day 4 (1.5 mg/kg/day; maximum 60 mg) and tapered to 1 mg/kg/day (maximum 40 mg) by day 7. The dose of prednisone was further tapered to 0.15 mg/kg/day (maximum 5 mg) by 3 months. Tacrolimus was started at 0.05 mg/kg/dose orally every 12 h. The dose was gradually increased to achieve a target 12-h trough levels (measured with microparticle enzyme immunoassay) of 10–12 ng/ml for the first 3 months, 8–10 ng/ml from 4 to 6 months, 6–8 ng/ml from 7 to 9 months, 5–7 ng/ml from 10 to 12 months, and 4–6 ng/ml thereafter. MMF started at 1200 mg/m$^2$/day in two divided doses (maximum dose of 1000 mg twice daily), with the first dose being given pre-operatively. MMF dose was decreased to 800 mg/m$^2$/day (maximum dose of 1000 mg twice daily) once the tacrolimus target 12-h trough levels were achieved. All patients received prophylaxis with co-trimoxazole, nystatin, and valganciclovir (irrespective of donor/recipient CMV serostatus) for at least 6 months following transplantation.

BK surveillance was performed using plasma BK qPCR (measured with Light Cycler 1536 real-time PCR and TaqMan assay at clinical virology laboratory, Detroit Medical Center with reporting range of 250–250 000 000 copies/ml) at 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, and then annually post-transplant. BK qPCR was also performed after treatment of rejection episode with anti-thymocyte globulin. Once BK qPCR was positive (≥250 copies/ml as per the reference laboratory), the screening frequency was increased to every 2 weeks.

Patients were divided into two groups: those with BKV (BKV group) and those without BKV (non-BKV group). In our study, BKV was defined as a plasma BK ≥250 copies/ml on two consecutive blood draws 2 weeks apart. BKV resolution defined as a plasma BK undetected or <250 copies/ml on two consecutive blood draws. Persistent BKV defined as a plasma BK ≥250 copies/ml at last follow-up. BKVN defined as confirmed positive SV40T staining on transplant kidney biopsy. Presumed BKVN defined as a BKV >10 000 copies/ml for more than 3 weeks despite immunosuppression reduction.[15]

BKV and BKVN were managed using a stepwise approach. On detection of BKV on two consecutive blood draws, the initial step in treatment was to reduce immunosuppressive medications.

1. If tacrolimus trough level was higher than the target range for the post-transplant period per above immunosuppression protocol, then tacrolimus dose was decreased.

2. If tacrolimus trough level was within the target range, MMF dose was reduced by 25–50% of the dose.
3. If no improvement in BKV was noticed with above intervention after 2–4 weeks, target tacrolimus trough level was reduced to the next expected target trough level (e.g., if target trough level is 8–10 ng/ml from 4 to 6 months post-transplant, it is reduced to 6–8 ng/ml on detection of BKV) by reducing the dose of tacrolimus by 20%.
4. If no further improvement in BKV was noticed in 2–4 weeks, MMF dose was reduced by >50% of the dose or discontinued.
5. If elevation in serum creatinine was noticed with BKV, biopsy was performed to confirm BKVN or acute rejection.
6. If presumed or confirmed BKVN, IVIG was used as second-line treatment.

Glomerular filtration rate was estimated (eGFR) using modified Schwartz formula for children <18 years and MDRD equation for patients ≥18 years.[30–32] Baseline eGFR was defined as the lowest eGFR in the first four weeks post-transplant.

### 2.1 | Statistical analysis

Statistical analysis was done using SPSS version 27.0 (Armonk, NY: IBM Corp). Categorical variables were analyzed using Chi-Squared test or Fisher's exact test as appropriate. Mann–Whitney *U* test was used to compare medians of two groups. Box-plot analysis was used to compare BKV group eGFR at different time line during the study period and compare median eGFR between BKV group and non-BKV group. A *p*-value of <.05 was considered statistically significant.

## 3 | RESULTS

Fifty-six children met the inclusion criteria. One patient more than 21 years of age and 1 with immediate graft failure were excluded from the study (Figure 1). Median age at the time of transplant was 14 years (interquartile range {IQR}; 6.5–17) (Table 1). Median duration of follow-up was 36 months (IQR; 26–58). Twenty (35.7%) of 56 transplants had BKV, with initial median BKV load of 2632 copies/ml (IQR; 800–8803). Of the 20 patients with BKV, 19 had BKV load of >1000 copies/ml. The median time to initial detection of BKV was 5.5 months (IQR; 3.25–9.5). The timelines for development of BKV in relation to the post-transplant period is shown in Table 2.

A comparison of the BKV group vs. non-BKV group for median age at transplant, gender, race, primary diagnosis, PRA, donor source (living vs. cadaver), EBV and CMV of donor/recipient status, primary vs. re-transplantation status, HLA mismatches, median cold ischemia time, median total thymoglobulin dosing (mg/kg), DGF, and median duration of follow-up were not statistically significant (Table 1). Univariate analysis showed a statistically significant difference between the BKV group and non-BKV group for the duration of stent placement of 40 vs. 33.5 days, respectively ($p = .004$).

The first line of therapy for BKV was IR in all patients. At initial detection of BKV, 8 (40%) patients had tacrolimus trough level higher than the target range for the post-transplant period, and their tacrolimus dose was decreased to achieve the expected target range. Twelve (60%) patients, with tacrolimus trough level within the target range, had 25–50% reduction in the MMF dose. After 2–4 weeks of initial IR, 3 (15%) had reduction in tacrolimus trough level to below the expected target range, and 7 (35%) had >50% reduction in MMF dose. Three (15%) had MMF dose discontinued. One (5%) had tacrolimus switched over to cyclosporine. IR achieved BKV resolution in 11 (55%) patients over a median duration of 15 months. At the last follow-up, 18 (90%) patients were at the expected tacrolimus target trough range for the post-transplant period and 8 (40%) were on full-dose MMF post-BKV resolution.

Four (7%) of the 56 transplant patients had BKVN. Three out of 4 patients underwent biopsy; two had histological evidence of BKVN. Two were classified as biopsy-proven BKVN and two as presumed BKVN (Table 3). All 4 patients with BKVN were treated with a combination of IR and IVIG (500–620 mg/kg/dose) given once per month for a total of six doses (Figure 2). BKV resolution was achieved in three (#1, #3, and #4) out of four patients over a median duration of 4 months (range 2–7 months) from the start of IVIG treatment. Overall, treatment with IR and IVIG resulted in BKV resolution in 70% (14/20) of the patients.

Other opportunistic infections, besides BK, were diagnosed in 5 (8.9%) patients. Two in the BKV group, one patient had pneumocystis pneumonia and one had disseminated bartonella infection prior to detection of BK. Three patients in the non-BKV group were diagnosed with opportunistic infections (trichodysplasia spinulosa, cytomegalovirus colitis, and cryptosporidiosis). Acute rejection was diagnosed in 15 (26.8%) of the study patients; 12 in the non-BKV

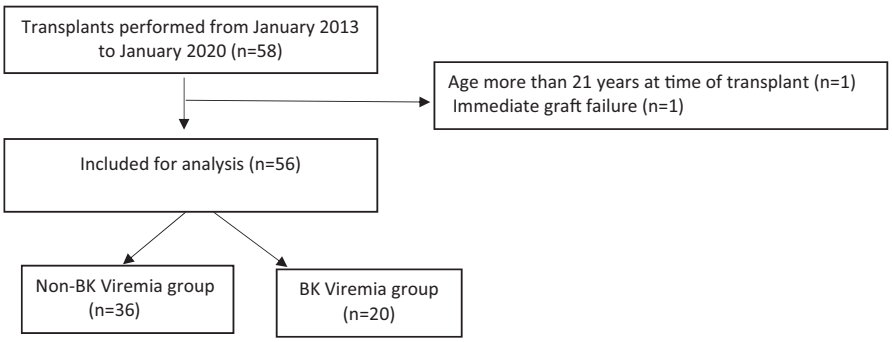


**FIGURE 1** Flow chart of the study population

**TABLE 1** A comparison of demographic and transplant variables between BKV and Non-BKV group

| Study variables | Total ($n = 56$) | BKV ($n = 20$) | Non-BKV ($n = 36$) | $p$-value |
|---|---|---|---|---|
| Median age at transplant in years | 14 (6.5–17) | 12.5 (4–15.5) | 14 (7.5–17) | .262 |
| 2–5 years | 10 (17.8) | 6 (30) | 4 (11) | |
| 6–9 years | 10 (17.8) | 3 (15) | 7 (19.5) | |
| 10–13 years | 7 (12.6) | 1 (5) | 6 (16.5) | |
| >13 years | 29 (51.8) | 10 (50) | 19 (53) | |
| Gender | | | | |
| Male | 38 (67.9) | 15 (75) | 23 (61) | .394 |
| Race | | | | .876 |
| African American | 31 (55.4) | 11 (55) | 20 (55.5) | |
| Caucasian | 21 (37.5) | 8 (40) | 13 (36.2) | |
| Other | 4 (7.1) | 1(5) | 3 (8.3) | |
| Primary diagnosis | | | | 1 |
| Structural[a] | 28 (50) | 10 (50) | 18 (50) | |
| Non-structural | 28 (50) | 10 (50) | 18 (50) | |
| Panel reactive antibody (PRA) | | | | |
| <40% | 52 (92.8) | 19 (95) | 33 (91.6) | |
| ≥40% | 4 (7.2) | 1 (5) | 3 (8.4) | .121 |
| Donor source | | | | 1 |
| Living donor | 14 (25) | 5 (25) | 9 (25) | |
| Cadaver donor | 42 (75) | 15 (75) | 27 (75) | |
| EBV and CMV status of donor/recipient | | | | |
| EBV IgG D+/R− | 26 (46.4) | 9 (45) | 17 (47.2) | .753 |
| CMV IgG D+/R− | 24 (42.8) | 10 (50) | 14 (38.9) | .256 |
| First kidney transplantation | 51 (81) | 19 (95) | 32 (88.8) | .541 |
| Mismatches (mode, range) | 5 (0–6) | 5 (3–6) | 5 (0–6) | .870 |
| <4 mismatches | 9 (16) | 3 (15) | 6 (17) | |
| ≥4 mismatches | 47 (84) | 17 (85) | 30 (83) | |
| Median cold ischemia time in minutes | | | | |
| Living donor | 74 (62–111) | 70 (59–97) | 90 (59–128) | .638 |
| Cadaver donor | 788 (669–926) | 720 (660–874) | 795 (669–938) | .373 |
| Median duration of ureteral stent in days | 36 (31–43) | 40 (37–44) | 33.5 (29.5–38.5) | **.004** |
| Cumulative thymoglobulin dose in mg/kg | 4.6 (4.3–5) | 4.9 (4.4–5.2) | 4.5 (4.3–4.9) | .254 |
| Delay graft function (DGF) | 4 (7.1) | 1 (5) | 3 (8.3) | .642 |
| Median baseline eGFR in ml/min/1.73m$^2$ | 76 (64–92) | 75 (58–94) | 76 (70–88) | .764 |
| Acute rejection | 15 (26.8) | 3 (15) | 12 (33.3) | .209 |
| Humoral rejection | 6 (10.7) | 2 (10) | 4 (11.1) | |
| Cellular rejection | 7 (12.5) | 1 (5) | 6 (16.7) | |
| Mixed rejection | 2 (3.6) | 0 | 2 (5.5) | |
| Median last follow up eGFR in ml/min/1.73 m$^2$ | 67 (45–80) | 67 (59–84) | 64 (43–80) | .438 |
| Median duration of follow up in months | 36 (26–58) | 34 (18–61) | 36.5 (26–56.5) | .603 |

*Note:* Values are expressed as numbers (%) and median (inter quartile1- inter quartile3).

Abbreviations: CMV, Cytomegalovirus; EBV, Epstein Barr Virus.

[a]Structural = renal hypoplasia, renal dysplasia, reflux nephropathy, and obstructive uropathy.

Bold value indicating a statistical significance.

**TABLE 2** Time lines of BK viremia in relation to the post-transplant time period

| Time lines of BK viremia in months | BK viremia group ($n = 20$) |
|---|---|
| Initial detection | 5.5 (3.25–9.5) |
| At 3 months follow up | 5 (25) |
| At 6 months follow up | 9 (45) |
| At 12 months follow up | 17 (85) |
| Peak | 6.75 (5.75–10.5) |
| At 3 months follow up | 0 (0) |
| At 6 months follow up | 9 (45) |
| At 12 months follow up | 17 (85) |
| Resolution | 15 (8–17) |
| At 6 months follow up | 3 (15) |
| At 12 months follow up | 7 (35) |
| At 18 months follow up | 17 (85) |
| Persistent BK viremia | 6 (30) |

*Note:* Values are expressed as numbers (%) and median (inter quartile1-inter quartile3).

group and 3 in the BKV group ($p = .209$). All 3 rejections in the BKV group were diagnosed and treated prior to BKV diagnosis; no rejection episode was reported after treatment of BKV and BKVN.

The median eGFR (ml/min/1.73 $m^2$) for BKV group at baseline vs. at the last follow-up was 75 (IQR; 58–94) vs. 67 (IQR; 59–84), respectively ($p = .888$) (Figure 3). The median eGFR (ml/min/1.73 $m^2$) at the last follow-up in BKV vs. non-BKV group was 67 (IQR; 59–84) vs. 64 (IQR; 43–80), respectively ($p = .764$) (Figure 4). Both, the BKV and non-BKV group had 100% graft survival after a median duration of follow-up of 34 months and 36.5 months, respectively.

## 4 | DISCUSSION

Our single-center study highlights a systematic approach of using plasma qPCR alone for diagnosis of BKV in pediatric kidney transplants. We report a 100% graft survival over a median duration of 3 years without acute rejection episodes after treatment of BKV and BKVN with a stepwise IR and IVIG.

NAPRTCS registry in 2007 showed that 84% of the pediatric transplant centers was using both urine (either cytology or qPCR) and plasma qPCR for BK screening.[9] At our center, since 2013 we performed only plasma qPCR for screening of BK because of the higher specificity and negative predictive value as compared to urine qPCR. The American Society of Transplantation Infectious Diseases Community guidelines at that time recommended either plasma or urine qPCR for screening of BK. However, the recent 2019 update of the guidelines recommend monitoring plasma qPCR only, which is consistent with the screening methodology in our study.[14,15]

The prevalence of BKV for our cohort was 35.7%, of which 85% occurred within the first 12 months post-transplant. Our results are comparable to reports of 20–37% BKV in children[7–10]; however,

**TABLE 3** Demographic and BK viremia variables of presumed/confirmed BK virus nephropathy patients treated with intravenous immunoglobulin ($n = 4$)

| | Age (yrs) | Gender | Race[a] | Primary diagnosis | Donor source | Number of transplants | Baseline eGFR (ml/min/1.73 $m^2$) | Initial detection of BK viremia (post-transplant month) | Peak BKV (copies/ml) | BK virus nephropathy | Initiation of IVIG treatment (post-transplant month) | BKV at last follow up (copies/ml) | Follow up post IVIG-completion (months) | Last follow up eGFR (ml/min/1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3 | Female | C | Renal dysplasia | Cadaver donor | 2 | 76 | 3.5 | 5 000 000 | Confirmed | 8 | <250 | 31 | 58 |
| 2 | 14 | Male | AA | Glomerulonephritis | Cadaver donor | 1 | 52 | 20 | 1 510 000 | Presumed | 22 | 5200 | 12 | 50 |
| 3 | 17 | Male | C | Renal dysplasia | Cadaver donor | 1 | 56 | 7 | 724 500 | Confirmed | 12 | <250 | 13 | 68 |
| 4 | 3 | Male | AA | Renal dysplasia | Living donor | 1 | 130 | 7 | 84 300 | Presumed | 10 | <250 | 12 | 97 |

*Note:* [a]Used as a reference to the race AA: African American and C: Caucasian.

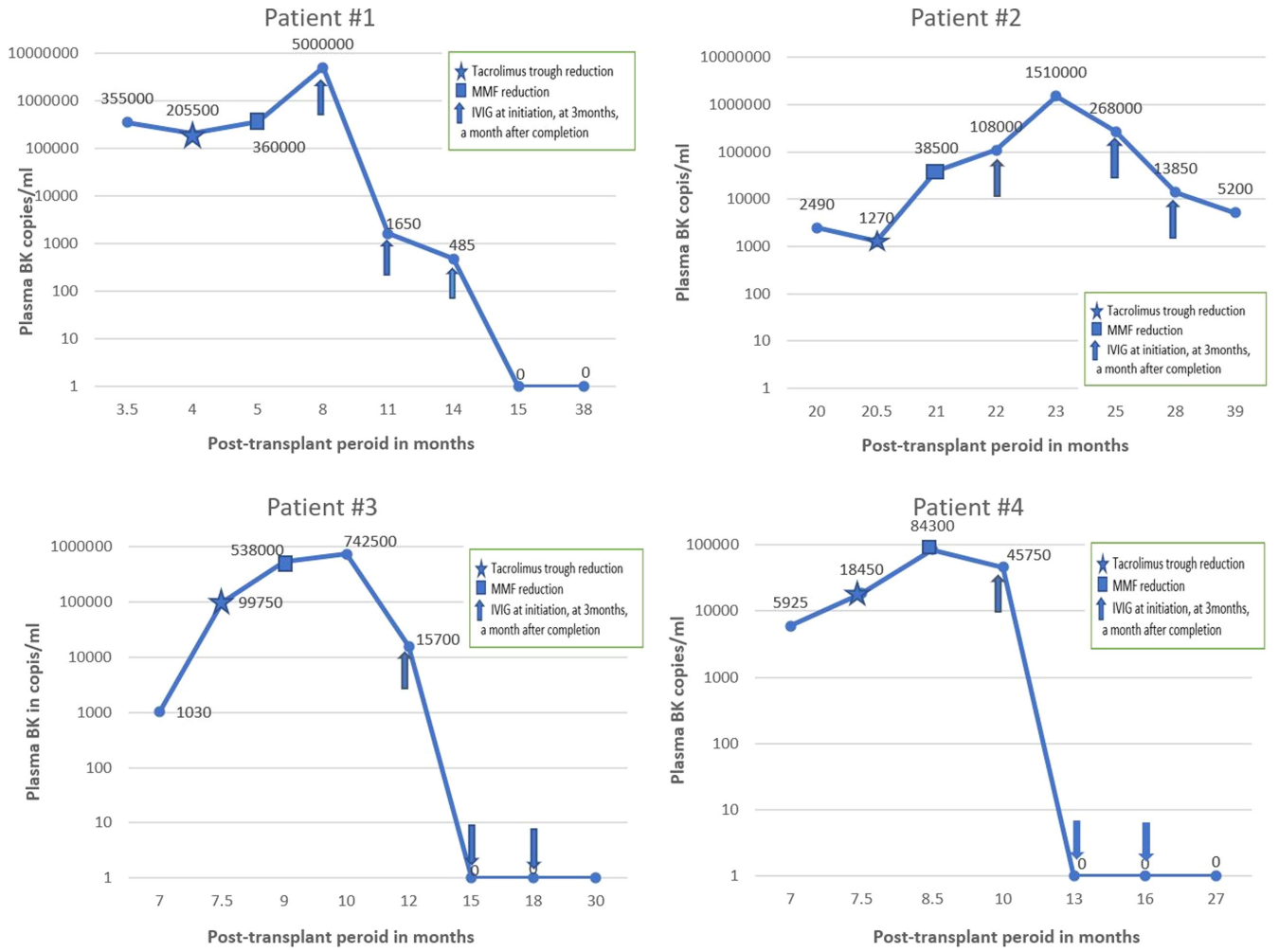


**FIGURE 2** Immunosuppression reduction and IVIG treatment for presumed/confirmed BK virus nephropathy patients ($n = 4$)

adult studies have lower reports of 10–20%.[11,12] A 7% prevalence of BKVN (presumed and confirmed) in our cohort is similar to other pediatric studies,[7,9,33,34] but lower as compared to 20.3% in CERTAIN Registry research network.[8] The age at transplant, duration of follow-up, and immunosuppression used in the CERTAIN registry were similar, but the prevalence of presumed BKVN was 15.8% as compared to 3.5% in our study. A higher presumed BKVN rate in the registry could be a result of variability in diagnosis and treatment approach at different study sites.

Ureteral stent post-transplant is suggested as a risk factor for BKV in few previous studies.[35,36] The proposed hypothesis is mechanical uroepithelial trauma and inflammation leading to viral reactivation and replication and thus resulting in viruria.[36] However, it is unclear whether it is the presence of the stent that increases the risk of BK infection or it's the long duration of the stent. Wingate et al reported ureteral stent duration of >21 days as a risk factor for development of BKV.[37] In our study, duration of ureteral stent (40 vs. 33.5 days) was a risk factor for BKV. Thus, our study implies a shorter duration of stent placement to decrease risk for BKV.

BK viremia and BKVN are treated with IR in 80–85%.[9] However, different approaches have been reported: a. 25–50% reduction in calcineurin inhibitor→50% MMF reduction→discontinuation of MMF and b. 50% MMF reduction→25–50% reduction in calcineurin inhibitor→discontinuation of MMF.[15] We followed a stepwise IR which takes into consideration the expected target trough levels of tacrolimus. Also, a smaller reduction in dose of tacrolimus (20%) and MMF (25–50%) was performed. IR was done in multiple steps with periodic plasma qPCR monitoring. Deviation from protocol by switching to cyclosporine was done in one patient only. Patient #1 developed BKV, after a repeat kidney transplant, which was treated with IR as per stepwise approach. MMF was reduced by ≥50%, but was not discontinued in view of history of antibody mediated rejection in this patient. Once diagnosis of BKVN was confirmed, IVIG administration was started and additional IR was done by switching from tacrolimus to cyclosporine. In our study, 80% of patients with BKV was treated with only IR. Also, patients with decreasing BKV (<10 000 copies/ml) and without increase in serum creatinine were continued on IR.

Leflunomide (8–46%), cidofovir (21–24%), quinolone (10–15%), and IVIG (8–20%) have been used for treating BKV and BKVN.[9,23] However, cidofovir and leflunomide are nephrotoxic and quinolones are reported to have lower efficacy.[20–22] Use of IVIG in BKV and BKVN has been rationalized based on its general anti-inflammatory

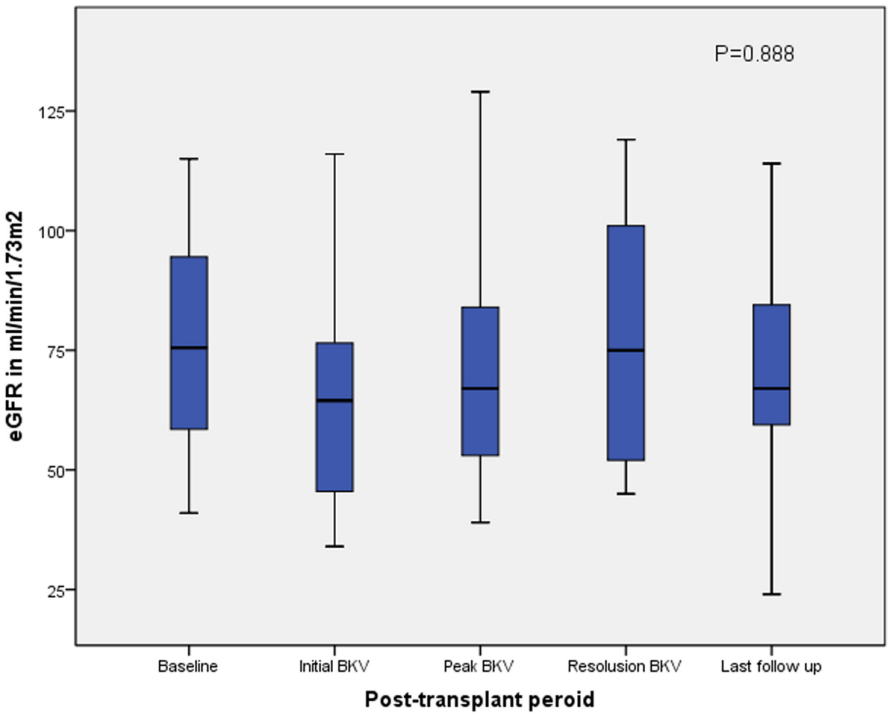


**FIGURE 3** Box-plot of BKV group eGFR in relation to BK viremia timeline during the study period

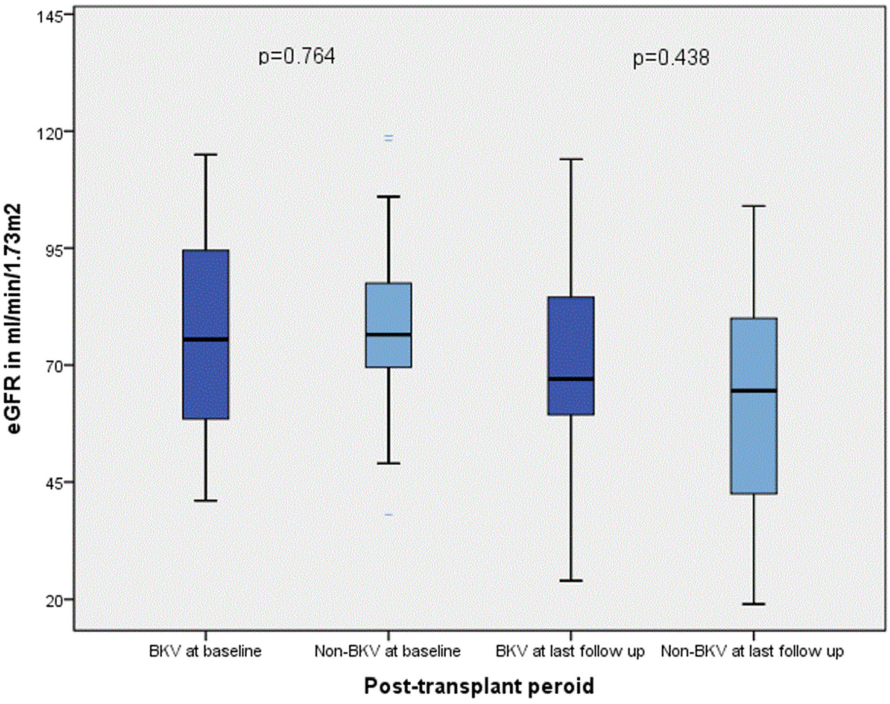


**FIGURE 4** Box-plot comparison between BKV group and non-BKV group for the median eGFR at baseline and last follow-up

properties and the presence of specific anti-BK neutralizing factors in commercially available preparations.[38]

IVIG use has been reported to have 90% BKV resolution and 96.7% graft survival in an adult study ($n$ = 30) with biopsy-proven BKVN who failed treatment with IR and leflunomide.[39] Anyaegbu et al reported the use of IVIG in treatment of BKV and BKVN in two pediatric case series.[28,40] First study reported BKV resolution and stable graft function in the four patients who received IVIG as a single dose of 2 g/kg given over 24–48 h. Three patients had persistent BK viruria and viremia with a peak viral load of 400–5200 copies/ml despite low-dose tacrolimus monotherapy, and one patient had no BKV but was diagnosed with BKVN on protocol biopsy. However, compared with our study, the patients in this report are considered low risk for BKVN based on their low viral load, normal eGFR, and negative surveillance allograft biopsies. In our study, IVIG was indicated only in cases of presumed BKVN (BKV >10 000 copies/ml despite IR) and confirmed BKVN. The second pediatric study by Anyaegbu et al included three patients who presented with elevation in serum creatinine and had biopsy-proven BKVN; however, unlike our study patients were not periodically screened using either

urine or plasma qPCR.[40] Similar to our study, these patients were treated with 500 mg/kg/dose IVIG once a month for 5–6 doses. In various studies, a wide variability in IVIG dosing (150 mg/kg to 2 g/kg) and frequency (single dose to monthly for 3–6 doses) has been reported.[27,38,41,42] We used a moderate dose (500 mg/kg) every month to avoid the side effects of high-dose IVIG.[43,44]

Our overall BKV resolution of 70% is comparable to outcomes of 75–83% in pediatric studies and 70–95% in adult studies.[9,14,33,34] Our cohort had an overall acute rejection of 26.8% (15% of BKV group and 33.3% of non-BKV group), which is similar to the reported pediatric rejection rates in a high-risk cohort.[8,9,45] All acute rejection episodes were diagnosed prior to detection of BKV, suggesting that increased immunosuppression for treatment of acute rejection likely contributed to BKV. On the contrary, IR for treatment of opportunistic infections/BKV can be associated with increased risk for rejection (8–25%).[14,33] No episode of acute rejection occurred after BKV treatment during our study. This underscores the advantage of our stepwise IR and likely benefit of IVIG treatment in prevention of rejection.

A graft failure rate of 7–24% is reported when MMF and tacrolimus were reduced or stopped in patients with BKV and BKVN.[9,14,33,46] In contrast, our study cohort had 100% graft survival, a similar median eGFR between BKV and non-BKV groups, and no significant difference in baseline and follow-up eGFR in the BKV group after median follow-up of 3 years. In our opinion, the improved graft survival in our study highlights the importance of a stepwise approach to IR followed by IVIG treatment in selected cases of BKV and BKVN.

Our study is limited by its retrospective design and analysis of a small group of predominantly African American pediatric transplant recipients, which affects the generalizability of the results. We did not have data on donor BK status to address BK donor–recipient mismatch. Since BKVN may be diagnosed on protocol biopsies in the absence of BKV,[47] lack of protocol biopsies at our center could potentially contribute to a lower rate of biopsy-proven BKVN in our cohort.

## 5 | CONCLUSION

Our study highlights the role of plasma qPCR alone for active surveillance of BK infection in pediatric kidney transplants. A stepwise IR protocol and monitoring of treatment response with plasma qPCR at regular interval is helpful in achieving BKV resolution in majority of patients and preserving renal allograft function. IVIG is effective in treating persistent BKV despite IR and BKVN. Larger studies are required to further validate the role of IVIG treatment in pediatric transplants with BKV and BKVN.

### CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this study to disclose.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

### ORCID

*Dunya Mohammad* https://orcid.org/0000-0002-8445-5808

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