Study title:

Treatment of BK Virus with a Stepwise Immunosuppression Reduction and Intravenous Immunoglobulin in Pediatric Kidney Transplant

Short title:

BK Treatment in Pediatric Kidney Transplant

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Abbreviations:

BK virus: BK

BKV: BK Viremia

BKVN: BK Virus Nephropathy

CERTAIN: The Cooperative European Pediatric Renal Transplant Initiative

DNA: Deoxyribonucleic Acid

eGFR: Estimated Glomerular Filtration Rate

HLA: Human Leukocyte Antigen

IVIG: Intravenous Immunoglobulin

MMF: Mycophenolate Mofetil

MDRD: Modification of Diet in Renal Disease

NAPRTCS: The North American Pediatric Renal Trials and Collaborative Studies

qPCR: Quantitative Real-Time Polymerase Chain Reaction

SV40T: Simian Virus 40 Large T antigen

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Key words: Pediatric, kidney transplant, immunosuppression, BK virus and IVIG

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Abstract:

Background: BK viremia (BKV) and BK virus nephropathy (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 quantitative real-time polymerase chain reaction (qPCR) and report treatment outcomes with stepwise immunosuppression reduction (IR) and intravenous immunoglobulin (IVIG).

Methods: A retrospective study of all pediatric kidney transplants from 2013-2020. Excluded patients>21 years at transplant and immediate graft failure. Surveillance was conducted using only

plasma BK qPCR at 1,3,6,9,12,18,24 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=0.004). 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=0.438). There were no rejection episodes and graft survival was 100% over median follow up of 3 years.

Conclusion: 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.

Introduction:

BK virus (BK) is a deoxyribonucleic acid (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 BK viremia (BKV), which in turn may progress to BK virus nephropathy (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 20-37%, while BKVN rates are 1-16%.[7-10] These pediatric rates have shown an increase in the last decade compared to reported incidence of 10-20% and 2-8%, for BKV and BKVN respectively, in adult transplant population.[11-13]

Quantitative real-time polymerase chain reaction (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 simian virus 40 large T antigen (SV40T) of kidney biopsy remains the gold standard test for diagnosis of BKVN.[14,18] Most adult and pediatric studies report 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 two years post-transplant has been recommended by the American Society of Transplantation Infectious Diseases Community.[15]

Treatment strategies including 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 immunosuppression reduction (IR) as the most effective first line treatment.[6-7] In adult literature, mechanistic target of rapamycin (mTOR) inhibitors-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 intravenous immunoglobulin (IVIG) as a mediator of humoral immunity and specifically a BK neutralizing effect has been reported in adult studies; however, there is 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.

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 one 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) (1.5mg/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 mycophenolate mofetil (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 0.05mg/kg/dose orally every 12 hours. The dose was gradually increased to achieve a target 12-hour trough levels (measured with microparticle enzyme immunoassay) of 10-12 ng/ml for the first 3 months, 8-10 ng/ml from 4-6 months, 6-8 ng/ml from 7-9 months, 5-7 ng/ml from 10-12 months and 4-6 ng/ml thereafter. MMF started at 1200mg/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 800mg/m^2/day (maximum dose of 1000 mg twice daily) once the tacrolimus target 12 hour 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 lab, Detroit Medical Center with reporting range of 250-250,000,000 copies/ml) at 1 month, 3 month, 6 month, 9 month, 12 month, 18 month, 24 month 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 lab), the screening frequency was increased to every 2 weeks.

Patients were divided in to 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 two 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 (eg, if target trough level is 8-10 ng/ml from 4-6 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 modification of diet in renal disease (MDRD) equation for patients ≥ 18 years.[30-32] Baseline eGFR was defined as the lowest eGFR in the first four weeks post-transplant.

Statistical analysis

Statistical analysis was done using SPSS version 27.0 (Armonk, NY: IBM Corp). Categorical variables were analyzed using Chi-Square test or Fisher 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 vs. Non-BKV group. A p-value of < 0.05 was considered statistically significant.

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 (Figure1). 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, panel reactive antibody (PRA), donor source (living vs. cadaver), EBV and CMV of donor/recipient status, primary vs. re-transplantation status, Human leukocyte antigen (HLA) mismatches, median cold ischemia time, median total thymoglobulin dosing (mg/kg), delay graft function (DGF) and median duration of follow up were not statistically significant (Table 1). Univariate analysis showed a statistically significant difference between the BKV group vs. Non-BKV group for the duration of stent placement of 40 vs. 33.5 days respectively (p=0.004).

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 rage, 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 group and 3 in the BKV group (p=0.209). 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/1.73m^2) for BKV group at baseline vs. at the last follow up was 75 (IQR; 58-94) vs. 67 (IQR; 59-84), respectively (p=0.888) (Figure 3). The median eGFR (ml/min/1.73m^2) at the last follow up in BKV vs. Non-BKV group was 67 (IQR; 59-84) vs. 64 (IQR; 43-80), respectively (p=0.764) (Figure 4). Both, the BKV and Non-BKV group had 100% graft survival after a median duration of follow of 34 months and 36.5 months, respectively.

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 three years without acute rejection episodes after treatment of BKV and BKVN with a stepwise IR and IVIG.

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry in 2007 showed that 84% of the pediatric transplant centers were 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, 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 the Cooperative European Pediatric Renal Transplant Initiative (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's 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 of calcineurin inhibitor→50% MMF reduction→discontinuation of MMF and b. 50% MMF reduction→25-50% reduction of 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 were 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 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 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 2g/kg given over 24-48hrs. 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 to 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 three 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.

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.

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Figure Legends:

Figure 1. Flow chart of the study population

Figure 2. Immunosuppression reduction and intravenous immunoglobulin (IVIG) treatment for presumed/confirmed BK virus nephropathy patients (n=4)

Figure 3. Box-plot of BK viremia (BKV) group estimated glomerular filtration (eGFR) rate in relation to BK viremia timeline during the study period

Figure 4. Box-plot comparison between BK viremia group (BKV) and Non-BK viremia (Non-BKV) group for the median estimated glomerular filtration (eGFR) rate at baseline and last follow up

Table 1: A comparison of demographic and transplant variables between BK Viremia (BKV) and Non-BK Viremia (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)	0.262
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)	0.394
Race				0.876
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*	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)	0.121
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)	0.753

CMV IgG D+/R-	24 (42.8)	10 (50)	14 (38.9)	0.256
First kidney transplantation	51 (81)	19 (95)	32 (88.8)	0.541
Mismatches (Mode, range) <4 mismatches ≥4 mismatches	5 (0-6) 9 (16) 47 (84)	5 (3-6) 3 (15) 17 (85)	5 (0-6) 6 (17) 30 (83)	0.870
Median cold ischemia time in minutes Living donor Cadaver donor	74 (62-111) 788 (669-926)	 70 (59-97) 720 (660-874)	 90 (59-128) 795 (669-938)	 0.638 0.373
Median duration of ureteral stent in days	36 (31-43)	40 (37-44)	33.5 (29.5-38.5)	**0.004**
Cumulative thymoglobulin dose in mg/kg	4.6 (4.3-5)	4.9 (4.4-5.2)	4.5 (4.3-4.9)	0.254
Delay graft function (DGF)	4 (7.1)	1 (5)	3 (8.3)	0.642
Median baseline eGFR in ml/min/1.73m^2	76 (64-92)	75 (58-94)	76 (70-88)	0.764
Acute rejection Humoral rejection Cellular rejection Mixed rejection	15 (26.8) 6 (10.7) 7 (12.5) 2 (3.6)	3 (15) 2 (10) 1 (5) 0	12 (33.3) 4 (11.1) 6 (16.7) 2 (5.5)	0.209
Median last follow up eGFR in ml/min/1.73m^2	67 (45-80)	67 (59-84)	64 (43-80)	0.438

Median duration of follow up in months	36 (26-58)	34 (18-61)	36.5 (26-56.5)	0.603

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

*Structural= renal hypoplasia, renal dysplasia, reflux nephropathy, and obstructive uropathy.

EBV: Epstein Barr Virus, CMV: Cytomegalovirus.

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 3month follow up	5 (25)
At 6month follow up	9 (45)
At 12month follow up	17 (85)
Peak	6.75 (5.75-10.5)
At 3month follow up	0 (0)
At 6month follow up	9 (45)
At 12month follow up	17 (85)
Resolution	15 (8-17)
At 6month follow up	3 (15)
At 12month follow up	7 (35)
At 18month follow up	17 (85)
Persistent BK Viremia	6 (30)

Values are expressed as numbers (%) and median (inter quartile1- inter quartile3)

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

	Age (yrs)	Gender	Race*	Primary diagnosis	Donor source	Number of transplants	Baseline eGFR (ml/min/1.73m^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/1.73m^2)
1	3	Female	C	Renal Dysplasia	Cadaver donor	2	76	3.5	5000000	Confirmed	8	<250	31	58
2	14	Male	AA	Glomerulonephritis	Cadaver donor	1	52	20	1510000	Presumed	22	5200	12	50
3	17	Male	C	Renal Dysplasia	Cadaver donor	1	56	7	724500	Confirmed	12	<250	13	68
4	3	Male	AA	Renal Dysplasia	Living donor	1	130	7	84300	Presumed	10	<250	12	97

Figure1: Flow chart of the study population

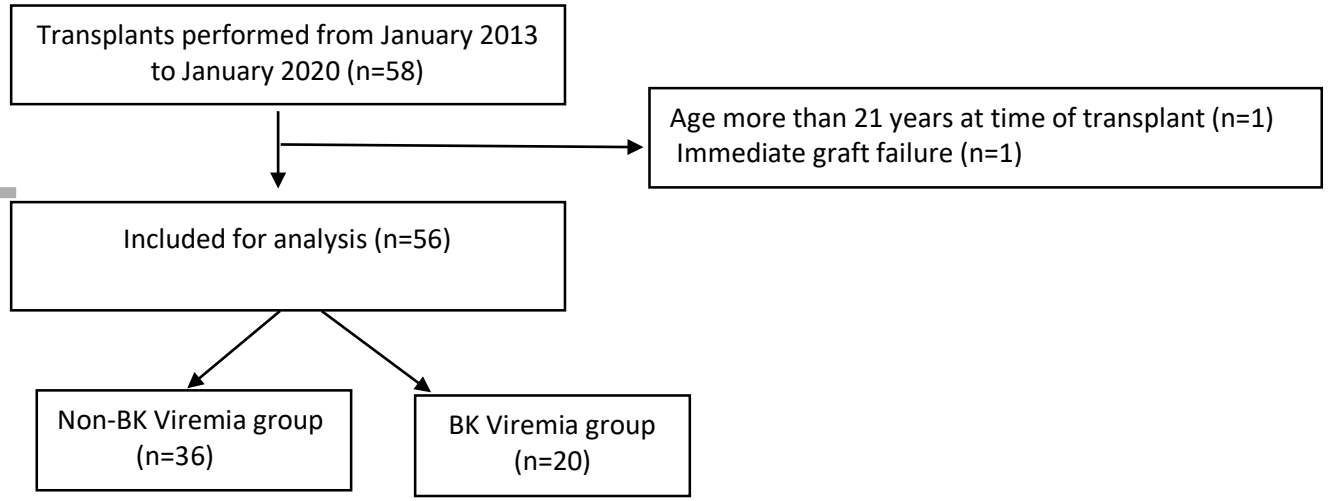

Figure 2: Immunosuppression reduction and intravenous immunoglobulin (IVIG) treatment for presumed/confirmed BK virus nephropathy patients (n=4)

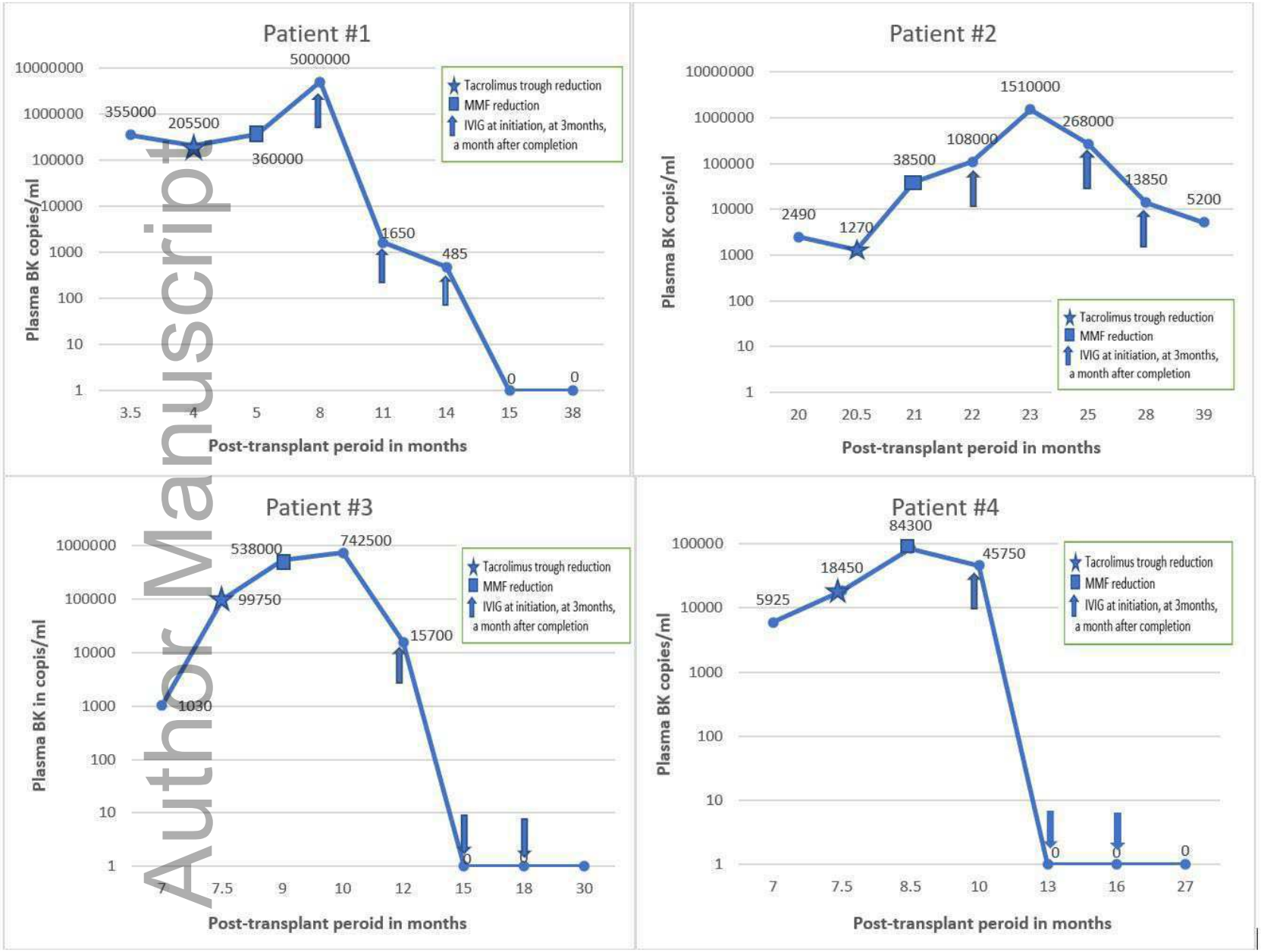

Figure 3: **Box-plot of BK viremia (BKV) group estimated glomerular filtration (eGFR) rate in relation to BK viremia timeline during the study period**

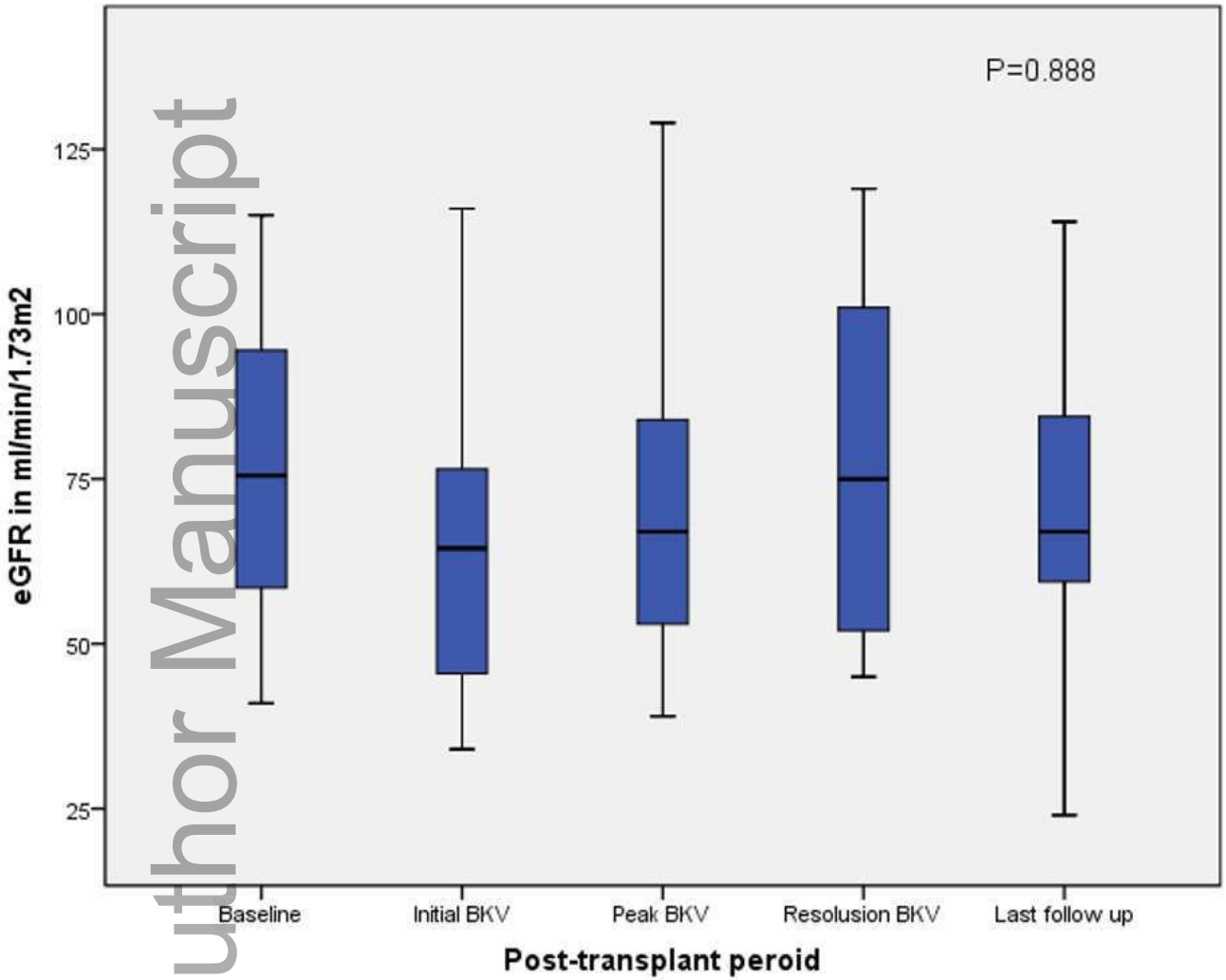

Figure 4: Box-plot comparison between BK viremia group (BKV) and Non-BK viremia (Non-BKV) group for the median estimated glomerular filtration (eGFR) rate at baseline and last follow up