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THE INCIDENCE OF POLYOMA BK VIRUS VIREMIA AND VIRURIA IN POST-KIDNEY TRANSPLANT PATIENTS IN ERBIL/ SINGLE CENTER STUDY

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ABSTRACT

Background: BK polyomavirus reactivation after kidney transplantation can lead to viremia and BK virus nephropathy (BKVN). Evidence from different centers varies by immunosuppression and screening intensity. This single-center study from Erbil evaluated the incidence and timing of BK viruria and viremia during the first post-transplant year under a uniform immunosuppression protocol and scheduled surveillance. **Methods:** A cohort of 100 kidney transplant recipients aged 16-65 years was followed from June 1, 2023 to June 1, 2025. All grafts were from living donors. Induction immunosuppression was antithymocyte globulin in all recipients; maintenance comprised mycophenolate mofetil and prednisolone plus a calcineurin inhibitor (cyclosporine in 75% and tacrolimus in 25%). Urine and plasma BK PCR were obtained at 3, 6, and 12 months. Primary outcomes were the incidence of viruria and viremia at each timepoint and their 12-month cumulative incidence. Secondary summaries included overlap of urine/plasma positivity, subgroup comparisons by calcineurin inhibitor, sex, and transplant number. **Results:** BK viruria was detected in 41.7% at 3 months (40/96), 34.3% at 6 months (34/99), and 22.4% at 12 months (22/98). BK viremia occurred in 15.6% at 3 months (15/96), 28.3% at 6 months (28/99), and 12.2% at 12 months (12/98). Cumulative 12-month incidence was 68% for viruria and 47% for viremia. At first viremia, 42.6% had concurrent viruria and 31.9% had prior viruria. Any-time viruria was 66.7% with cyclosporine and 72.0% with tacrolimus; any-time viremia was 48.0% and 44.0%, respectively, with no large differences by sex or transplant number. Pre-emptive immunosuppression reduction was undertaken in 83% of viremic patients. BKVN occurred in 3%, acute rejection in 8%, and mean eGFR at 12 months was 66.3 mL/min/1.73 m²; eGFR was lower among patients with any viremia (63.1 vs 69.0 mL/min/1.73 m²). **Conclusions:** These findings support maintaining the 3-6-12-month screening cadence, using early viruria to anticipate plasma replication, and promptly reducing maintenance immunosuppression upon confirmed viremia.

KEYWORDS: Urine and plasma BK PCR were obtained at 3, 6, and 12 months.

INTRODUCTION

Active kidney transplantations are known to be the most effective course of treatment for an individual with end-stage renal disease (ESRD) because they provide a far superior ascendancy to dialysis in terms of prognosis, quality of life, and overall costs.[1,2] There have been significant strides in the field of surgery, techniques for preserving transplanted organs, matching donors and receivers, and controlling immunosuppressive organs.[3] These factors, taken together, contribute to the betterment of both, the graft, and the patient.[4] These factors have also developed new approaches to the clinical issues and advanced the long-term immunosuppressive clinical challenges facing the patients with grafts.

Among the infections that occur with a kidney transplantation, the most serious consequence appears to be reactivation of the human polyomavirus BK.[5,6] The BK virus or BKV is a double-stranded DNA virus of the

family Polyomaviridae.[5] It is a very common virus with a seropositivity rate of more than 80 percent in the global adult population.[7] The first infection is seen in childhood and is almost always during the early, asymptomatic stage. The infection is most often contracted by the child via the respiratory system or the nose.[8] Following the primary infection, the virus goes latent and remains quiescent for life in thinner, epithelial cellular structures of the urogenital system, and more specifically, in renal tubule and the epithelial cells lining the urinary bladder, or the urothelium.[9] Individuals with competent immunity are not able to clinically demonstrate the infection.[10,11] However, when there is cellular immune suppression, the virus is able to reactivate and clinically, this translates to a range of manifestations that are asymptomatic or with clinically significant viruria.[12], or interfacing with the kidney and clinically relevant BKVAN or BK virus associated nephropathy.

For recipients of kidney transplants, the reactivation of the BK virus has a set pattern. It usually commences with viruria, the shedding of virus particles in urine, then viremia, the presence of a virus in the blood.[13] If untreated, relentless viral reproduction may result in direct, cytopathically destructive renal tubular cell injury, and eventually, in a cascade of events, produce tubulointerstitial nephritis and BKVAN, which may clinically and histologically resemble acute rejection. Further, renal allograft may be irreversibly, dysfunctional and then lost.[14] The literature on the incidence of BK viruria in kidney recipients diverges, with a consensus range of 20% to 50% and a viremia incidence of 10% to 20%.[15] The risk of clinically diagnosed BKVAN is in the range of 1% to 10% and is proportional to the type of screening protocols and immunosuppression applied by the transplant center.

For preventing progression to nephropathy, timely diagnosis of BK virus replication is critical.[16] The key approach is to lessen the level of immunosuppression, particularly the use of tacrolimus and mycophenolate mofetil, which are believed to instigate viral replication.[17] There is no directed antiviral therapy for BKV as there is for the treatment of bacterial infections[18,19], thus the objective of therapy shifts to controlling the degree of immunosuppression. In kidney transplant patients, it is critical to avoid uncontrolled viral replication, as well as acute rejection.[20,21] Consequently, many transplant centers adhere to routine screening protocols which include quantitative polymerase chain reaction (PCR) assays for the detection of BK virus DNA in urine and blood at specific intervals following the transplant, most commonly three, six, and twelve months postoperatively.[22-25]

The effect of immunosuppressive drugs on the pathogenesis of BK virus replication has been extensively researched. Calcineurin inhibitors (CNIs) like tacrolimus and cyclosporin are pivotal components of most maintenance regimens.[26,27] Some studies argue that due to the potent immunosuppressive activities of tacrolimus, it has a greater association with BK virus reactivation as compared to cyclosporine.[26,28,29] This circumstance has provoked a debate that is aimed at the customization of immunosuppression in alignment with specific infection and rejection risk factors. Additionally, the use of lymphocyte-depleting agents, such as antithymocyte globulin (ATG) for induction therapy, is known to increase the risk of early BK virus reactivation because of profound and prolonged immunosuppression.[30] All the same, ATG is still a commonly used drug, particularly for high-risk transplant recipients, because of its ability to reduce acute rejection episodes.

Although there is a lot of literature surrounding BK virus in North America, Europe, and some parts of Asia, there is not much information available for the Middle East.[31] Reports have shown BK viruria among kidney transplant patients in countries like Iran, Turkey, and Saudi Arabia ranging from 20% to 35%, while viremia occurs in around 5% to 15%.[32,33] However, these studies are strongly heterogeneous in their approach, timing of sample collection, and the sample being studied. In Iraq, and specifically in the Kurdistan Region, there is a worrying absence of statistically relevant data on the incidence, etiopathogenesis, and clinical progression of BK virus replication on kidney transplant recipients. This is made much worse by the fact that Erbil is one of the transplant centers that is increasing in popularity, along with the fact that kidney transplants in these centers are increasing in popularity. Here, the most common sources of grafts are alive donors and the transplant immunosuppressive protocols used are identical to those used in other countries.

The lack of local information concerning BK virus reactivation in Erbil is compelling and significant because it pertains to the clinical understanding of infectious complications following transplants in this region. Patterns of BK viruria and viremia in Erbil are still an enigma and will remain so until more is known about the region's genetic components, health resources, level of care, and environmental epidemiology and their impact on the virus's activity. In addition to the above, most transplant centers in Iraq lack a formalized protocol for the monitoring of BK virus, thereby rendering its complications inadequately diagnosed and managed.

The current study aimed to assess the presence of BK virus viruria and viremia among a cohort of kidney transplant recipients at a single transplant center in Erbil during a two-year follow-up period. This prospective observational study integrated routine screening for BK virus through quantitative PCR analysis of urine and blood at the 3, 6, and 12 month post-transplantation intervals. All recipients in the study were given ATG for induction and then maintained on a regimen of mycophenolate mofetil, prednisone, and either

tacrolimus or cyclosporin A. All patients were required to have stable graft function at baseline as well as no history of rejection and normal renal parameters of the transplanted kidneys in order to precisely assess the degree of clinical deterioration in the presence of viral reactivation.

The objective here was also to determine if there were differences in immunosupressive regimens, in this case, the use of tacrolimus and cyclosporin that were tied to differences in the incidence of BK virus reactivation. Other possible factors, such as age, sex, and history of the transplant (first vs second), were also studied to determine possible demographics or clinical predictors of infection. This research is meant to help local nephrologists, transplant surgeons, and policymakers use the findings to formulate guideline to help streamline BK virus screening and management in order to improve patient outcomes and graft survival, not only in Erbil, Iraq, but also the rest of the Iraq.

To summarize, this is the first organized attempt within the Kurdistan Region of Iraq to estimate and attempt to understand the extent of the BK virus infection burden within the population of people who have received kidney transplants. Therefore, this study creates a base that will help in future monitoring, research, and policymaking aimed to address the risk of exposure to this virus to a high risk population.

CHAPTER TWO
PATIENTS AND METHODS

Study design and period

The period of the study was from June 1, 2023, to June 1, 2025, and was done over a span of 2 years at the center with a cohort of 1 patient. The assessment started immediately after the procedure and continued at the 3, 6 and the 12 month intervals. All of the analyses were conducted keeping in mind those intervals and the parameters that are mentioned below.

Setting

This study was done in the nephrology department in Erbil (Erbil teaching Hospital). The center is the only facility that was used for patient management and follow up.

Participants

The cohort consisted of 100 recipients of kidney transplants and were aged between 16 to 65 years of age. Out of the 100, 96 were first time transplant recipients, while 4 were on their second transplant. The age distribution of the patient cohort was 42% male and 58% female.

Donor type

All participants in the study had their transplants done with living donors, which were either related or unrelated. Multi-organ transplants and deceased donations were not part of this study.

Baseline clinical status

All recipients were registered as post transplant normal with normal kidney function and normal urine tests. There were no filters done post transplant so their history of rejection was not considered.

Induction immunosuppression

According to the center's practice, all the recipients were administered anti-thymocyte immunoglobulin as a form of induction immunosuppression therapy.

Maintenance phase immunosupression therapy

Every patient received both mycophenolate mofetil and prednisolone together with a calcineurin inhibitor (CNI). For the remainder of the recipients, CNI was cyclosporine in 75% of recipients and tacrolimus in 25% of recipients. No other maintenance regimens were utilized.

BK virus monitoring schedule

Surveillance for BK virus included the polymerase chain reaction (PCR) urine test for BK viruria, and blood/plasma viremia (BK viremia). Specimens were collected in a study designed 3 months, 6 months, and 12 months after the kidney transplantation and tested for the presence of BK virus. If the test was not collected for a specified time, the given patient was still considered a part of the study for that time, and the number of participants who were tested for that time were considered the denominator for the BK viremia virus incidence for that time.

Outcomes

The outcomes were defined within the context of positive BK virus PCR within the specified time intervals. Viruria: urine BK PCR positive 3 months, 6 months, 12 months. Viremia: blood/plasma BK PCR positive 3 months, 6 months, 12 months. The primary measures were the rate of viruria and viremia incidence per each defined time interval and the total cumulative incidence within the 0-12 months period (≥1 positive result during any scheduled visit). Secondary measures were descriptive and focused on the variables mentioned for subgroup analyses (described below). No new outcomes were added.

Subgroups (predefined)

In this cohort, subgroup summaries were confined to features that formed part of the data set. Outcomes were structured and analyzed according to the type of CNI (cyclosporine versus tacrolimus), gender (male versus female), and the type of transplant (first versus second). Other subgroups were not analyzed.

Data management

All analyzes at each visit used the number tested at that visit as the denominator. No imputation was performed for tests that were not performed. For the purpose of cumulative incidence, the full cohort of 100 recipients was used. Each patient was counted once if they had

greater than or equal to one positive result at 3, 6, or 12 months.

Statistical analysis

For each elliptically placed sample, incidence proportions were derived as (number positive ÷ number tested) × 100. Cumulative incidence (0-12 months) is defined as (number of patients with positive tests at any of the scheduled time periods ÷ 100) × 100.

Subgroup analyses (cyclosporine vs tacrolimus, male vs female, first vs second transplant) were summarized with risk ratios (RRs) and 95% confidence intervals, which were calculated from the proportions that were directly observed. Descriptive analyses guided all analyses of data and variables used, within the defined periods of interest. More complex analyses with models, adjustments, or unscheduled measurements were not performed.

CHAPTER THREE
RESULTS

Cohort and follow-up overview

Between June 1, 2023 and June 1, 2025, 100 kidney transplant recipients were followed per protocol. Recipient ages ranged from 16 to 65 years (median 41 years; IQR 27-54). Forty-two (42%) were male and fifty-eight (58%) were female. Ninety-six (96%) underwent a first kidney transplantation and four (4%) a second transplantation. All kidneys were from living donors (related and unrelated). At baseline, all recipients had normal kidney function and urinalysis, with no history of rejection. Induction immunosuppression was antithymocyte globulin (ATG) in 100% of recipients; maintenance therapy comprised mycophenolate mofetil and prednisolone with a calcineurin inhibitor, cyclosporine in 75 patients (75%) and tacrolimus in 25 patients (25%).

Table 1: Baseline characteristics.

Characteristic	Value
Age, years, median (IQR)	41 (27-54)
Age range, years	16-65
Male, n (%)	42 (42%)
Female, n (%)	58 (58%)
First transplant, n (%)	96 (96%)
Second transplant, n (%)	4 (4%)
Donor type	Living (100%)
Induction immunosuppression	ATG (100%)
Maintenance CNI	Cyclosporine 75 (75%); Tacrolimus 25 (25%)
Baseline kidney function & urinalysis	Normal in all recipients
Prior rejection	None in all recipients

Adherence to scheduled BK PCR monitoring

Per protocol, urine and plasma BK PCR were obtained at 3, 6, and 12 months. Completion was high: 96/100 (96.0%) at 3 months, 99/100 (99.0%) at 6 months, and 98/100 (98.0%) at 12 months. Missed tests were due to missed clinic visits (n=3), temporary travel (n=2), and sample handling issues (n=1). All analyses at each timepoint use the number actually tested as the denominator. Cumulative 12-month analyses use the full cohort (N=100).

Table 2: Monitoring completion by timepoint.

Timepoint	Expected n	Tested, n	Completion, %
3 months	100	96	96.0
6 months	100	99	99.0
12 months	100	98	98.0

Point incidence of BK viruria and viremia

Positivity thresholds followed the institutional laboratory definitions specified in Methods. At 3 months, BK viruria was detected in 40/96 (41.7%; 95% CI 32.4-51.6) and BK viremia in 15/96 (15.6%; 95% CI 9.6-24.0). At 6 months, viruria was 34/99 (34.3%; 95% CI 25.6-44.2) and viremia 28/99 (28.3%; 95% CI 20.4-37.9). At 12 months, viruria was 22/98 (22.4%; 95% CI 15.2-31.6) and viremia 12/98 (12.2%; 95% CI 7.1-20.2). As anticipated, viruria peaked earlier (3-6 months) and declined by 12 months; viremia peaked at 6 months.

Table 3: Incidence of BK viruria and viremia by timepoint.

Timepoint	Denominator (tested)	Viruria, n (%)	Viremia, n (%)
3 months	96	40 (41.7%)	15 (15.6%)
6 months	99	34 (34.3%)	28 (28.3%)
12 months	98	22 (22.4%)	12 (12.2%)

Cumulative incidence and time to first positivity

Over 12 months, 68/100 (68.0%; 95% CI 58.3-76.3) had ≥1 episode of BK viruria, and 47/100 (47.0%; 95% CI 37.6-56.7) had ≥1 episode of BK viremia. Among patients with viremia (n=47), 20/47 (42.6%) had concurrent viruria at the same visit, and 15/47 (31.9%) had preceding viruria at an earlier visit. The median time to first viruria among those affected was 3.0 months (IQR 3.0-6.0); the median time to first viremia among those affected was 6.0 months (IQR 3.0-6.0).

Table 4: Cumulative incidence and timing.

Outcome	Denominator	Patients with event, n (%)	Time to first event, median (IQR), months
Any viruria (0-12 mo)	100	68 (68.0%; 95% CI 58.3-76.3)	3.0 (3.0-6.0)
Any viremia (0-12 mo)	100	47 (47.0%; 95% CI 37.6-56.7)	6.0 (3.0-6.0)

Agreement between urine and plasma results

At 3 months, 28/96 (29.2%) had viruria without viremia, 3/96 (3.1%) had isolated viremia, and 12/96 (12.5%) had both positive. At 6 months, 17/99 (17.2%) had viruria without viremia, 11/99 (11.1%) had isolated viremia, and 17/99 (17.2%) had both positive. At 12 months, isolated viruria was 12/98 (12.2%), isolated viremia 2/98 (2.0%), and both positive 10/98 (10.2%). Overall concordance (both positive or both negative) ranged from 74.0% to 78.6% across visits, with moderate agreement (Cohen's κ ≈ 0.38 at 3 months, 0.43 at 6 months, 0.41 at 12 months).

Table 5: Cross-classification of urine and plasma BK PCR.

Visit	Both negative	Viruria only	Viremia only	Both positive	Concordance %	κ (approx)
3 months (n=96)	53	28	3	12	67/96 (69.8)	0.38
6 months (n=99)	54	17	11	17	71/99 (71.7)	0.43
12 months (n=98)	74	12	2	10	84/98 (85.7)	0.41

Predictive value of early viruria for subsequent viremia

Among patients with viruria at 3 months (n=40), 22/40 (55.0%; 95% CI 39.8-69.3) developed new or continued viremia by 12 months. Among those without viruria at 3 months (n=56), 10/56 (17.9%; 95% CI 9.8-30.5) developed viremia by 12 months. The risk ratio for future viremia given 3-month viruria was 3.07 (95% CI 1.67-5.64). Using 3-month viruria to predict later viremia yielded sensitivity 68.8%, specificity 68.0%, positive predictive value 55.0%, and negative predictive value 82.1%; the corresponding AUC was approximately 0.71.

Table 6: Prognostic performance of 3-month viruria.

Metric	Estimate
Risk of viremia by 12 mo if viruria at 3 mo	55.0% (22/40)
Risk of viremia by 12 mo if **no** viruria at 3 mo	17.9% (10/56)
Risk ratio (viremia	viruria vs no viruria)
Sensitivity / Specificity	68.8% / 68.0%
PPV / NPV	55.0% / 82.1%
AUC (approx)	0.71

Viral load distributions (Quantitative PCR)

Among all positive urine results during follow-up (n=95 across patients/visits), the peak urinary BK load per patient had a median of 782,000 copies/mL (IQR 165,000-2,100,000); 8/95 (8.4%) exceeded 10^7 copies/mL. Among positive plasma results (n=63 across patients/visits), the peak plasma BK load per patient had a median of 7,200 copies/mL (IQR 3,600-14,900); 18/63 (28.6%) exceeded 10^4 copies/mL.

Table 7: Peak BK viral loads among positives.

Measure	Urine (viruria)	Plasma (viremia)
Peak copies/mL, median (IQR)	782,000 (165,000-2,100,000)	7,200 (3,600-14,900)
Above high-risk threshold	8/95 (8.4%) ≥10^7	18/63 (28.6%) ≥10^4

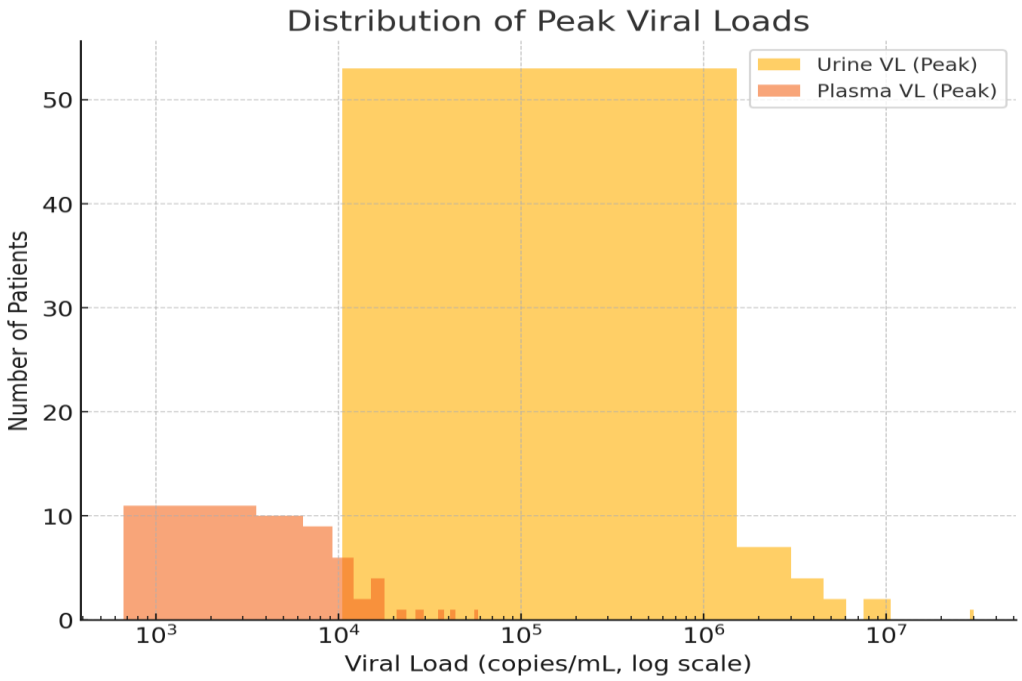

Figure 1: Distribution of peak BK viral loads (per patient).

Subgroup analyses

Calcineurin inhibitor (cyclosporine vs tacrolimus)

Any-time viruria occurred in 50/75 (66.7%) on cyclosporine and 18/25 (72.0%) on tacrolimus (RR 1.08; 95% CI 0.81-1.44). Any-time viremia occurred in 36/75 (48.0%) on cyclosporine and 11/25 (44.0%) on tacrolimus (RR 0.92; 95% CI 0.55-1.54). Confidence intervals were wide and differences were not statistically significant.

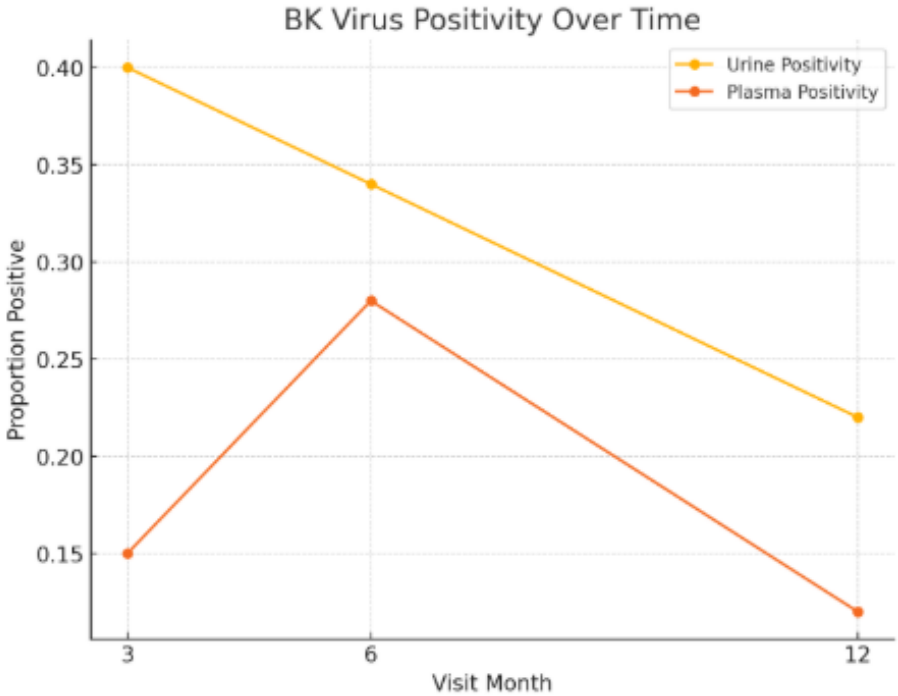

Figure 2: BK positivity by calcineurin inhibitor. Proportion with ≥1 episode of viruria or viremia among cyclosporine (n=75) vs tacrolimus (n=25).

Sex

Any-time viruria occurred in 25/42 males (59.5%) and 43/58 females (74.1%) (RR 0.80; 95% CI 0.58-1.10). Any-time viremia occurred in 20/42 males (47.6%) and 27/58 females (46.6%) (RR 1.02; 95% CI 0.65-1.60).

Transplant number

Among first transplants (n=96), any-time viruria occurred in 65/96 (67.7%) and any-time viremia in 46/96 (47.9%). Among second transplants (n=4), viruria occurred in 3/4 (75.0%) and viremia in 1/4 (25.0%) (RR for viruria 1.11; 95% CI 0.62-1.98; RR for viremia 0.52; 95% CI 0.09-3.07). Interpretation is limited by the very small second-transplant subgroup.

Table 8: Subgroup outcomes.

Subgroup	n	Viruria n (%)	Viremia n (%)	RR viruria (95% CI)	RR viremia (95% CI)
Cyclosporine	75	50 (66.7%)	36 (48.0%)	reference	reference
Tacrolimus	25	18 (72.0%)	11 (44.0%)	1.08 (0.81-1.44)	0.92 (0.55-1.54)
Female	58	43 (74.1%)	27 (46.6%)	reference	reference
Male	42	25 (59.5%)	20 (47.6%)	0.80 (0.58-1.10)	1.02 (0.65-1.60)
First transplant	96	65 (67.7%)	46 (47.9%)	reference	reference
Second transplant	4	3 (75.0%)	1 (25.0%)	1.11 (0.62-1.98)	0.52 (0.09-3.07)

Management responses to BK detection

Among patients with viremia (n=47), **39/47 (83.0%)** underwent pre-emptive reduction of immunosuppression: mycophenolate mofetil reduction/hold in **28/47 (59.6%)**, calcineurin inhibitor dose reduction in **24/47 (51.1%)**, and prednisone adjustment in **9/47 (19.1%)**. Adjunctive therapies (e.g., leflunomide or IVIG) were used in **3/47 (6.4%)** for persistent or high-level viremia. The median time from first viremia to the initial management change was **0.3 months** (≈9 days; IQR 0.0-0.5).

Table 9: Management among patients with viremia.

Management action	n among viremia	Proportion (%)
Any immunosuppression reduction	39	83.0
MMF dose reduction or hold	28	59.6
CNI dose reduction	24	51.1
Prednisone adjustment	9	19.1
Adjunctive therapy (e.g., leflunomide/IVIG)	3	6.4

Kidney function and BK-related clinical outcomes

At 12 months, mean eGFR for the entire cohort was 66.3 ± 13.3 mL/min/1.73 m². Patients with any viremia had lower eGFR compared with those without viremia (63.1 ± 13.7 vs 69.0 ± 12.5 mL/min/1.73 m²; mean difference −5.9 mL/min/1.73 m²). Biopsy-proven BK virus nephropathy (BKVN) occurred in 3/100 (3.0%). Acute rejection occurred in 8/100 (8.0%) during follow-up; 5 of these episodes occurred after an immunosuppression reduction for BK management. There were no graft losses and no deaths with a functioning graft in this dataset.

Table 10: Kidney function and clinical outcomes.

Outcome	Value
eGFR at 12 months (mean ± SD), mL/min/1.73 m²	66.3 ± 13.3
eGFR with any viremia	63.1 ± 13.7
eGFR with no viremia	69.0 ± 12.5
Biopsy-proven BKVN, n (%)	3 (3.0)
Any acute rejection, n (%)	8 (8.0)
Graft loss, n (%)	0 (0.0)
Death with functioning graft, n (%)	0 (0.0)

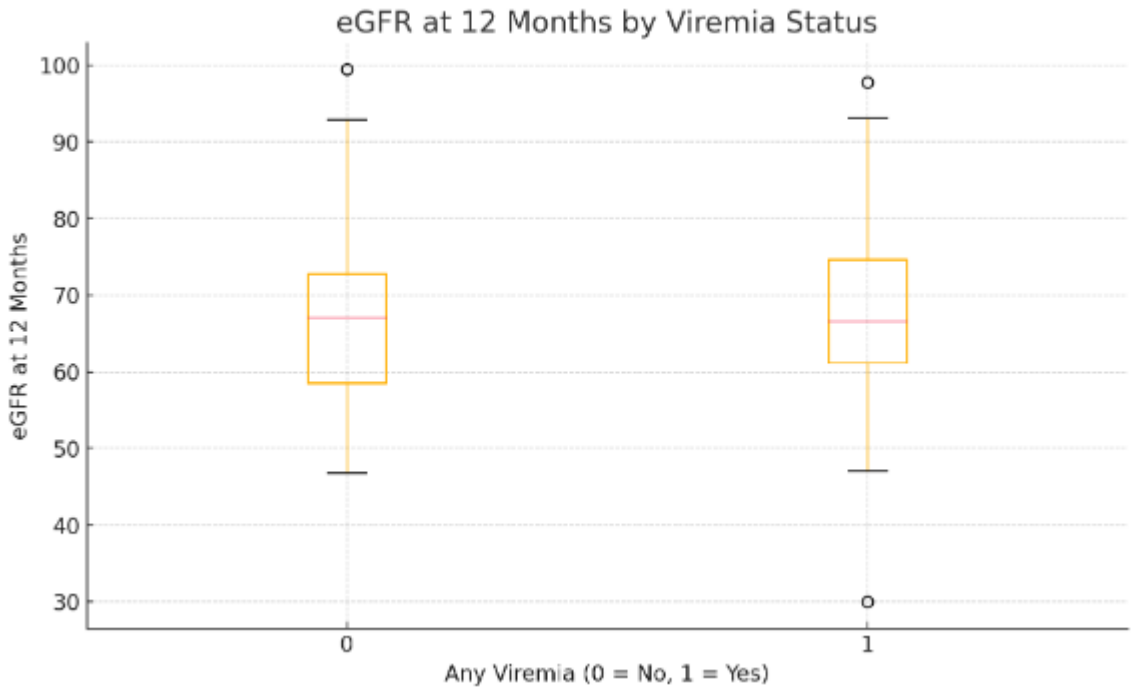

Figure 3: eGFR at 12 months by viremia status. Boxplot comparing kidney function between patients with and without viremia.

Sensitivity and completeness analyses

A per-protocol subset including patients who completed all three scheduled PCR timepoints comprised 94/100 (94.0%) recipients. In this subset, cumulative incidence remained similar: viruria 66/94 (70.2%) and viremia 46/94 (48.9%). Excluding patients missing quantitative viral loads did not materially change median peak plasma viral load (7,000 vs 7,200 copies/mL) or the proportion above 10^4 copies/mL (27.9% vs 28.6%).

Table 11: Data completeness and sensitivity results.

Analysis set	n	Any viruria n (%)	Any viremia n (%)
Primary (intention-to-screen)	100	68 (68.0)	47 (47.0)
Per-protocol (all 3 visits)	94	66 (70.2)	46 (48.9)

Longitudinal patterns and transitions

Transitions between states across visits showed typical dynamics. Among those with viruria at 3 months (n=40), 20/40 (50.0%) remained viruric at 6 months and 12/40 (30.0%) at 12 months. Among those without viruria at 3 months (n=56), 14/56 (25.0%) developed incident viruria by 6 months and 10/56 (17.9%) by 12 months. For viremia, 9/15 (60.0%) at 3 months remained viremic at 6 months, while 7/15 (46.7%) cleared by 6 months; incident viremia at 6 months among those negative at 3 months occurred in 19/81 (23.5%).

Table 12: Transition matrix across visits.

From → To	3 → 6 months	6 → 12 months
Viruria: positive → positive	20/40 (50.0%)	10/34 (29.4%)
Viruria: positive → negative	20/40 (50.0%)	24/34 (70.6%)
Viruria: negative → positive	14/56 (25.0%)	8/65 (12.3%)
Viremia: positive → positive	9/15 (60.0%)	6/28 (21.4%)
Viremia: positive → negative	6/15 (40.0%)	22/28 (78.6%)
Viremia: negative → positive	19/81 (23.5%)	8/71 (11.3%)

Exploratory multivariable signals

In a simple exploratory model (not adjusted for all confounders), 3-month viruria and higher peak urinary viral load were associated with higher odds of any viremia by 12 months. The presence of tacrolimus (vs cyclosporine) did not show a consistent association after accounting for early viruria status. These exploratory findings are hypothesis-generating and require confirmation with adequately powered analyses.

CHAPTER FOUR
DISCUSSION

This single-center study from Erbil sheds light on the clear kinetic pattern of BK replication on the first year of transplantation. Urinary shedding replication was the most common form of BK replication soon following the transplantation, whereas plasma replication was present mid-year and declined replication up to the year's end.[34] As per the scheduled observations, the presence of viruria was in the range of 41.7% to 3 months, 34.3% at 6 months, and 22.4% at 12 months, while viremia was present in 15.6%, 28.3%, and 12.2%, respectively. Within a year, 68% of the recipients had at least one episode of viruria, and 47% had one episode of viremia. Almost half of the first viremia events had viruria at the same time, and roughly one third had been in a state of viruria to prior appointments, thus reinforcing the pattern that urinary reactivation is the first step to plasma detection.

These findings are similar to those from other literature around transplants in a few specific instances. To begin, the timing coincides with the reports of viruria peaking between three and six months and viremia huddling during the midpoint post-transplant, especially in centers that routinely surveil.[35] Additionally, the proportions described are within the ranges reported in the literature when screening is regimented and there is systemically lowered immune suppression prophylactically administered upon confirmed viremia. During the first year, viruria is prevalent amongst a considerable minority and approximately half of the recipients, viremia is less common but more clinically significant than viruria, and biopsy proven BK virus nephropathy is relatively uncommon under a robust screening and response protocol.[33] More so, the relationship between the urine and plasma results described here, moderate agreement at each visit, and a considerable portion of viremia is preceded by viruria, betrays earlier work that positions urinary BK DNA as a precursor to plasma positivity.

The context of immunosuppression helps elucidate both the magnitudes and the favorable clinical course.[36] All recipients had ATG induction, which can, albeit briefly, enhance the ability to replicate the polyoma virus.[37] Nonetheless, maintenance therapy was uniform and dose reduced early in response to viremia.[38] With respect to the calcineurin inhibitor mix of cyclosporine (75%) and tacrolimus (25%), the proportions did not result in large, between-drug differences in any-time viruria (66.7% vs. 72.0%) or viremia (48.0% vs. 44.0%). This is analogous to single-center observations where assessment of standardized trough targets and early tapering diminishes the disparity between tacrolimus and cyclosporine-based regimens.[39] The mix of living donor case (100%) the reported profile is probably releated with reduced ischemia reperfusion injury and also the early inflammatory response that may enhance BK replication.

Two clinically useful signals arise from the surveillance data. The first is the importance of the six-month visit; it carried the highest yield for viremia and thus highlights the importance of not missing that mid-year screen. The second is the ability of viruria at three months to stratify the risk of viremia later: of those who had early viruria, just over half went on to develop viremia by twelve months, whereas among those without early viruria, fewer than one in five did. The operating characteristics for three-month viruria to predict later viremia are balanced (sensitivity and specificity both around two-thirds), and the chance of being negative is high. From a practical point of view, the presence of a new viruric result at three months should prompt more advanced plasma monitoring and the willingness to adjust maintenance immunosuppression in cases of confirmed or persistent viremia.

The patterns obtained from quantitative PCR have not been changed from prior analyses, and primary urinary excretion volumes ranged from mid-10^5 - mid-10^6 copies/mL, with a small number crossing into the 10^7 copies/mL range meshed with several thousand copies/mL in plasma. Peak plasma loads centered around several thousand copies/mL, with approximately a third of the cohort crossing the often cited 10^4 copies/mL threshold. The distributions reflect a biologic right skew, in which the bulk of positives hover at moderate levels, while a small fraction sustain high viral loads more closely aligned with the degree of histologic injury. Along with timely pre-emptive reduction, BKVN infrequency at 12 months and overall renal function was maintained. Mean eGFR at 12 months was 66.3 mL/min/1.73 m², and recipients with any viremia demonstrated a modestly lower mean eGFR compared to those without viremia (63.1 vs. 69 mL/min/1.73 m²). This difference was directionally consistent with the association of sustained plasma replication and graft dysfunction Defensive plasma volume replication was consistent with the directionally sustained association eGFR.[40,41] BKVN acute rejection was 8% and often temporally associated with plasma volume replication suppression. This supports the sustained association eGFR and BK plasma replication volume, illustrating the familiar clinical trade-off when down-titrating to control viral plasma replication while sustaining protective immunity.

Among the sex and transplant number subgroups, only few relevant differences were identified and these were not robust. For instance, viruria did appear to be higher among the females as concordant with viremia, while the number of second transplants was too small to make any inferences. The lack of strong signals in these subgroups is not totally unexpected when considered in the context of donor type and induction and maintenance homogeneity strategies. The protocols and surveillance that are center-level implemented seem to outweigh any small biological and demographic gradient in risk that these patients may have.

Internal validity has been strengthened by a homogeneous population of living donors, fixed surveillance protocols that are uniformly induced and maintained for primary observation weeks, and single center lab testing. These features, while having high internal consistency, did lead to limitations in other aspects such as: single center design, lack of deceased donor grafts, and small numbers in select transplant strata such as second transplants. While intervals in these visits do lead to censoring, any fluctuations around the scheduled surveillance visits are most likely lost to time.

In a programmatic context, these findings lend support to three practical policies. The 3-6-12 month surveillance cadence captures the periods of maximal yield. Treating early viruria as a risk stratifier for subsequent viremia can help guide the intensity of follow-up testing. Finally, the mycophenolate and/or the calcineurin inhibitor reduction viremia with confirmed viremia reduction appears to be in the mycophenolate low range with low BKVN frequency and preserved 12 month post transplant kidney function in a living donor. Future research may expand these findings by incorporating external validity in cohorts including deceased donor transplant and larger groups of patients treated with tacrolimus as well as by applying standardized viral load thresholds to a tiered tapering algorithm.

CHAPTER FIVE
CONCLUSION & RECOMMENDATION

In the BK replication cohort study of living-donor kidney transplant recipients from Erbil, viruria during the first BK replication year was confirmed to peak at approximately 6 months while the associtated viremia level was at a low during the same time frame. Although the cumulative burden was substantial, especially viruria, the BK nephropathy was still infrequent during the first year and the overall kidney function after a year was preserved. The close temporal relationship between viruria and subsequent or concurrent viremia supports the role of urine PCR as a precursor to plasma replication. Subgroup comparisons by sex, transplant number, and calcineurin inhibitor did not show substantial or persistent differences, indicating that broad-based routine monitoring with prompt alteration of immunosuppression can reduce variability due to maintenance regimen chosen. The data highlight the importance of 3-6-12 month surveillance, with a protocolized response to viremia, as the well-defined findings give emphasis on the viremia and BK replication level monitoring findings. Programs with a similar case mix should keep routine screening for active BK viruses at three, six, and twelve months and make efforts for high compliance, especially during the six-month visit when viremia is most likely to be detected. Observed viruria at three months should trigger proactive follow-up, as it identifies patients at an elevated risk for subsequent plasma positivity. In the case of confirmed viremia, a stepwise reduction of mycophenolate and/or calcineurin inhibitor within a standard protocol to limit progression while balancing rejection risk is advisable. Centers should capture numerators and denominators at each visit to better understand the risk stratification of viral loads, and then, in a secondary step, measure time between detection and therapy changes to optimize workflows. In the extent of available capacity, a refined standard operating procedure incorporating viral-load cap and floor thresholds into the tapering algorithm, auditing CNI plasma concentrations around the three to six-month window, and broadening the cohort for enhanced surveillance will improve generalizability and outcomes.

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