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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Early clearance of BK polyomavirus-DNAemia among kidney transplant recipients may lead to better graft survival

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Abstract

Introduction: BK polyomavirus (BKPyV)-DNAemia is a common complication in kidney transplant recipients (KTRs). The significance of achieving viral clearance at different time intervals is not well understood.

Methods: All adult KTRs transplanted between January 1, 2015 and December 31, 2017 who developed BKPyV-DNAemia were included. Outcomes were analyzed based on persistent clearance of BKPyV-DNAemia at 3-month intervals up to 2 years after initial detection, and for recipients with persistent BKPyV-DNAemia at last follow-up. Uncensored graft failure, death-censored graft failure (DCGF), and a composite outcome of DCGF or fall in estimated glomerular filtration rate (eGFR) by ≥50% from the time of initial BKPyV-DNAemia were outcomes of interest.

Results: Of 224 KTRs with BKPyV-DNAemia, 58 recipients (26%) achieved viral clearance by 3 months after initial detection, 105 (47%) by 6 months, 120 (54%) by 9 months, 141 (63%) by 12 months, 155 (69%) by 15 months, 167 (75%) by 18 months, 180 (80%) by 21 months, and 193 (86%) by 24 months. Nine recipients (4%) had persistent BKPyV-DNAemia at last follow-up. Compared to recipients who achieved viral clearance by 3 months, those who achieved clearance by 6 months (adjusted odds ratio [aOR]: 3.15; 95% confidence interval [CI]: 1.22–8.12; $p = .02$) and 9 months (aOR: 3.69; 95% CI: 1.02–13.43; $p = .04$) had significantly increased risk for uncensored graft failure. There was no significant association between time to viral clearance and DCGF or composite outcomes.

Conclusions: We found a trend of increased risk for uncensored graft failure among those who cleared BKPyV-DNAemia more slowly. Aiming to clear viremia early, without risking rejection, may be beneficial for allograft function and patient morbidity and mortality.

KEYWORDS
BK viremia, clearance, graft failure, outcomes

Abbreviations: aOR, adjusted odds ratio; BKPyV, BK polyomavirus; DCGF, death-censored graft failure; eGFR, estimated glomerular filtration rate; K–M, Kaplan–Meier; KTR, kidney transplant recipient; PCR, polymerase chain reaction; SD, standard deviation.

1 | INTRODUCTION

BK polyomavirus (BKPyV) is a ubiquitous human polyomavirus that infects the majority of the population without consequence. In kidney transplant recipients (KTRs), however, reactivation of this pathogen from either the donor organ or the recipient's latent infection can lead to deleterious graft outcomes including BK nephropathy and possible graft failure. Without intervention, reactivation follows a progression from viruria to viremia to BK nephropathy, with incidences in KTRs in the first year post-transplant of 30%–60%, 10%–30%, and 1%–10%, respectively.[1–4] Management of BKPyV-DNAemia is via immunosuppression reduction to allow for immune reconstitution and viral clearance. This is not benign either, as the balance between promoting immune reconstitution for viral clearance and preventing graft rejection is delicate and attempts at treating the viremia can increase the risk of episodes of antibody-mediated and T-cell-mediated rejection.[5]

KTRs who develop BKPyV-DNAemia usually do so within the first-year post-transplant, when the degree of immunosuppression is typically highest.[3] While most clear the virus after their immunosuppression is reduced, some go on to develop persistent viremia. Overall, the association between BKPyV-DNAemia and graft outcomes remains poorly understood. A previous study conducted at our center suggests that in the absence of BK nephropathy, there was no significant increase in the risk of rejection, infections, or graft failure among KTRs with BK viremia compared to those with undetectable viral levels.[6] This finding is supported by other studies including one that found no significant difference in adverse outcomes including estimated glomerular filtration rate (eGFR), graft failure, and death between KTRs who did not develop BKPyV-DNAemia and those who did but were appropriately managed.[7] Conversely, an association between BKPyV-DNAemia and acute rejection has also been demonstrated.[8]

Although BKPyV-DNAemia itself, in the absence of BK nephropathy, may not significantly increase the risk for poor outcomes, it can progress to BK nephropathy and therefore viral clearance is an important clinical goal. There is a paucity of the literature regarding the ideal timeline for achieving viral clearance. This study aims to address this gap in the literature by investigating the impact of time to BKPyV-DNAemia clearance on graft outcomes.

2 | METHODS

2.1 | Study population and design

The study population consisted of all adult patients (>18 years) who underwent a kidney transplant at the University of Wisconsin between January 1, 2015 and December 31, 2017, who developed plasma BKPyV-DNAemia within 2 years post-transplant. Recipients of multi-organ transplants were excluded. All data were prospectively collected. This study was approved by the University of Wisconsin Institutional Review Board (IRB protocol number: 2014-1072). This study was in adherence to the Declaration of Helsinki. The clinical and research activities being reported were consistent with the Principles of the Declaration of Istanbul as outlined in "The Declaration of Istanbul on Organ Trafficking and Transplant Tourism." Due to the nature of this study, we did not obtain informed consent pertinent to this study from patients.

To analyze graft outcomes based on time to BKPyV-DNAemia clearance, subgroups were created which consisted of all study participants who had achieved persistent viral clearance by each of the following time points: 3, 6, 9, 12, 15, 18, 21, and 24 months from initial detection. There was also a subgroup that had persistent BKPyV-DNAemia at the time of the last follow-up.

The primary objective of this study was to determine if there were significant differences in the outcomes of interest based on whether study participants cleared their BKPyV-DNAemia at one-time point versus another, from the initial BKPyV-DNAemia. Uncensored graft failure, death-censored graft failure (DCGF), and a composite outcome of DCGF or fall in eGFR by ≥50% from the time of initial viral detection were outcomes of interest.

2.2 | Variables and definitions

BKPyV-DNAemia was defined as a viral load of greater than 3 $\log_{10}$ copies/mL (>1000 copies/mL) detected via polymerase chain reaction (PCR) at any time post-transplant. This value was chosen because our center's protocol is to intervene, typically with a decrease in the immunosuppressant regimen, once BKPyV-DNAemia levels become greater than 1000 copies/mL. Persistent clearance of BKPyV-DNAemia was defined as three consecutive BKPyV-DNAemia levels less than 250 copies/mL, with tests obtained at least 2 weeks apart. Two hundred and fifty copies/mL was chosen because of our center's protocol to quantify only more than 250 copies/mL. Uncensored graft failure was defined as any cause of graft failure, including death, and DCGF was defined as requiring retransplantation or chronic dialysis.

2.3 | BKPyV-DNAemia screening protocols

As previously described, we routinely screen all KTRs at our center for BKPyV-DNAemia as follows: every 2 weeks for the first 3 months post-transplant, monthly for post-transplant months 3–6, and every 3 months for post-transplant months 6–18.[9] All screening was via BKPyV-DNAemia PCR and all patients with a detectable BKPyV-DNAemia level received close follow-up with repeat PCR testing at 2-week intervals until a <250 copies/mL test result was obtained three consecutive times (persistent viral clearance is achieved).

Throughout the study period, monitoring and treatment of BKPyV-DNAemia were fairly stable. Real-time PCR chemistry based on the principles of fluorescence resonance energy transfer was used during the entire study period. The threshold for detection of BKV was

250–10 000 000 copies/mL with a minimum detection limit of 50 copies/mL, which did not change during the study period.

2.4 | Immunosuppressive protocols

The majority of KTRs at our center were maintained on a triple immunosuppressive regimen of tacrolimus, mycophenolic acid, and prednisone. Induction immunosuppression was achieved with either a T-cell-depleting or nondepleting agent based on immunological risk factors. Patients with pretransplant donor-specific antibodies, and those with end-stage renal disease due to glomerulonephritis, usually received antithymocyte globulin at 4.5 mg/kg as induction and those planned for early steroid withdrawal were more likely to receive alemtuzumab 20 mg single dose as induction.

Treatment of kidney rejection was based on the type and severity of rejection and was graded by the Banff criteria as described before.[10] Briefly, acute T-cell-mediated rejection was treated with IV steroid pulse with or without antithymocyte globulin 6–10.5 mg/kg in 4–7 divided doses, while mixed rejection was treated with steroids, antithymocyte globulin, intravenous immunoglobulin, with or without plasmapheresis. Antibody-mediated rejection was treated with steroids and intravenous immunoglobulin, with or without rituximab and plasmapheresis.

When KTRs at our center develop BKPyV-DNAemia (plasma viral load >1000 copies/mL), the immunosuppressive regimen was typically reduced as follows: the antimetabolite (mycophenolic acid) dose was decreased by 25% for BKPyV-DNAemia PCR of 3 $\log_{10}$ copies/mL–4 $\log_{10}$ copies/mL (1000–10 000 copies/mL) or by 50% for >4 $\log_{10}$ copies/mL (>10 000 copies/mL).[11] If BKPyV-DNAemia levels remain >4 $\log_{10}$ copies/mL (>10 000 copies/mL) at ≥2 weeks after the antimetabolite dose was reduced, the calcineurin inhibitor (tacrolimus) trough level was then typically reduced as well. However, sometimes among recipients with calcineurin inhibitor levels persistently above the desired goal, the calcineurin inhibitor dose was usually adjusted first based on the physician's discretion.

2.5 | Statistical analysis

Continuous data were presented as mean ± standard deviation, while categorical data were presented as absolute numbers and percentages. Outcomes of interest were assessed using adjusted and unadjusted Cox regression analysis with reference to the clearance by 3 months post-transplant. Most of the pertinent baseline characteristics were included in the adjusted model. Although initially, we planned to assess outcomes for BKPyV-DNAemia clearance up to 24 months from initial detection, due to the limited sample size, clearance by 21 months or 24 months was not included. Uncensored and death-censored graft survival trends were compared using Kaplan–Meier (K–M) analyses. The *p*-value of ≤.05 was considered statistically significant.

TABLE 1 Baseline characteristics of all recipients with BK polyomavirus (BKPyV)-DNAemia.

Variables	
Total number	224
Male (%)	141 (63)
White (%)	172 (77)
Mean age at transplant (years ± standard deviation [SD])	55.5 ± 12.8
Cause of ESKD (%)	
Diabetes	66 (30)
Hypertension	37 (17)
Glomerulonephritis	58 (26)
Polycystic kidney disease	26 (12)
Other	37 (17)
Preemptive transplant (%)	34 (15)
Previous transplant (%)	66 (30)
Living donor (%)	87 (39)
Mean HLA mismatch of six	3.73 ± 1.53
Induction (%)	
Basiliximab	110 (49)
Antithymocyte globulin	78 (35)
Alemtuzumab	35 (16)
Steroid only	1
Maintenance immunosuppression (%)	
Mycophenolic acid	224 (100)
Tacrolimus	220 (98)
Cyclosporine	1
Belatacept	3 (1)
Prednisone continuation	188 (84)
Time from transplant to the detection of BKPyV-DNAemia (months)	5.1 ± 4.6
First intervention in response to BKPyV-DNAemia detection (%)	
Decrease mycophenolic acid	159 (71)
Decrease tacrolimus	39 (17)
Decrease prednisone dose	25 (11)
Decrease mycophenolic acid and prednisone dose	1
Rejection before BK virus (BKV) (%)	13 (6)
BKPyV-DNAemia persistent clearance (%)	
By 3 months after initial detection	58 (26)
By 6 months after initial detection	105 (47)
By 9 months after initial detection	120 (54)
By 12 months after initial detection	141 (63)
By 15 months after initial detection	155 (69)
By 18 months after initial detection	167 (75)
By 21 months after initial detection	180 (80)
By 24 months after initial detection	193 (86)
Persistent at last follow-up	9 (4)

(Continues)

TABLE 1 (Continued)

Variables	
Mean interval from first BKPyV-DNAemia to last follow-up (months)	68.5 ± 22.9

Abbreviations: ESKD, End-stage kidney disease; HLA, Human Leukocyte Antigen.

3 | RESULTS

A total of 848 adult kidney transplants were performed during the study period, and 224 (26%) KTRs fit our inclusion criteria. Of these 224 KTRs, 58 recipients (26%) achieved viral clearance by 3 months after initial detection, 105 (47%) by 6 months, 120 (54%) by 9 months, 141 (63%) by 12 months, 155 (69%) by 15 months, 167 (75%) by 18 months, 180 (80%) by 21 months, and 193 (86%) by 24 months. At the time of the last follow-up, nine recipients (4%) had persistent BKPyV-DNAemia. The majority of patients were male (63%) and white (77%). The mean interval from transplant to the first detection of BKPyV-DNAemia was 5.1 ± 4.6 months and, and the initial intervention in response to detection was a reduction in the mycophenolate dose in 159 (71%) recipients. The median follow-up from first BKPyV-DNAemia was 73.05 months. Additional baseline characteristics of patients included in the study are summarized in Table 1.

At the time of initial detection, patients had a mean BK PCR of 12 392 ± 17 675 IU/mL and eGFR of 53.2 ± 17.9 mL/min/1.73 m^2 (Table 2). The mean peak BK PCR was 186 400 ± 588 818 IU/mL. Among patients with ongoing BKPyV-DNAemia, mean BK PCR, serum creatinine, and eGFR at various time frames after initial viral detection can be found in Table 2. Mean serum creatinine levels and eGFR were similar regardless of the length of viremia and ranged from 1.41 to 1.5 mg/dL ±0.51–0.69 mg/dL and 52.6–56.8 mL/min/1.73 m^2 ± 18.1 to 22.7 mL/min/1.73 m^2, respectively.

Compared to the recipients who achieved viral clearance by 3 months, the overall group of patients who achieved clearance by 6 months had significantly increased odds of uncensored graft failure (adjusted odds ratio [aOR]: 3.15; 95% confidence interval [CI]: 1.22–8.12; $p = .02$), as did those who achieved clearance by 9 months (aOR: 3.69; 95% CI: 1.02–13.43; $p = .04$; Table 3). There was no significant difference in uncensored graft failure among the group of patients who achieved viral clearance at 18 months or those who had persistent plasma BKPyV-DNAemia at last follow-up compared to the group who achieved clearance by 3 months. Additionally, there was no significant difference in the odds of DCGF or the composite outcome of DCGF or fall in eGFR by ≥50% from the time of initial viral detection for any of the clearance groups relative to the clearance by 3-month group (Table 3). When looking at the outcomes for recipients who achieved viral clearance by 3 months versus those who did not, there was no significant difference in uncensored graft failure, DCGF, or composite outcomes between the two groups (Table 4).

When using K–M survival analysis to compare graft survival between KTRs who achieved viral clearance at different time frames, there was a statistically significant association between time to viral clearance and uncensored graft failure ($p = .05$; Figure 1A). There was, however, no statistically significant association between time to viral clearance and DCGF or the composite outcome of DCGF or fall in eGFR by ≥50% from the time of initial viral detection (Figure 1B,C). When evaluated using the methods of K–M, there was no significant difference in graft survival (uncensored or death-censored) or the composite outcome among KTRs who achieved viral clearance by 3 months and those who did not (Figure 2).

A total of 25 recipients had death with a functional graft at last follow-up. Among recipients with death, the most common cause of death listed was malignancy in six recipients, infection and sepsis in three recipients, cardiovascular disease in two, and in the remaining recipients, cause of death was not available. Among recipients with death due to malignancies, two were due to bladder cancer (one with clearance within 3 months and another with persistent BKPyV >18 months); and one each with lung cancer (persistent BKPyV >18 months group), metastatic skin cancer (persistent BKPyV >18 months group), leukemia (clearance of BKPyV within 6 months group), and post-transplant lymphoproliferative disease (persistent BKPyV >18 months group). Similarly, among three recipients with death due to infections, one each had *Pneumocystis jirovecii* pneumonia (clearance of BKPyV within 6 months group), bacterial pneumonia (clearance of BKPyV within 3 months group), and bacterial septicemia (persistent BKPyV >18 months group).

Among the entire cohort, 48 (21%) had acute rejection, of which 25 were T-cell-mediated rejection and the remaining 23 had antibody-mediated rejection or mixed rejection. Of these 48 recipients with acute rejection, nine (19%) were in clearance by 3 months, nine (19%) clearance by 6 months, three (6%) clearance by 9 months, four (8%) clearance by 12 months, eight (17%) clearance by 18 months, and 15 (31%) persistent beyond 18 months groups. Similarly, among the entire cohort, 30 (13%) had BK nephropathy. Of these 30 recipients with BK nephropathy, one (3%) were in clearance by 3 months, two (7%) clearance by 6 months, one (3%) clearance by 9 months, three (10%) clearance by 12 months, three (10%) clearance by 18 months, and 18 (60%) persistent beyond 18 months groups.

4 | DISCUSSION

In this single-center study of 224 KTRs who developed BKPyV-DNAemia during follow-up, we found recipients who achieved viral clearance more slowly, by 6 or 9 months postinitial detection, to have a significantly increased risk for uncensored graft failure compared to those who achieved viral clearance by 3 months. We did not observe a similar trend in DCGF, which suggests that the above finding was due to increased mortality among the recipients with slower viral clearance. Interestingly, the increased risk for uncensored graft failure seen in the clearance by 6 and 9 month groups was not observed in the clearance by 18 months or the persistent beyond 18 month groups, although both groups did have a nonstatistically significant trend toward increased risk.

TABLE 2 BK levels, serum creatinine, and estimated glomerular filtration rate (eGFR) at various time frames after initial BK detection among patients who had not yet achieved prolonged viral clearance.

Variables	BK polymerase chain reaction (PCR; IU/mL) ± standard deviation (SD)	log 10 ± SD	Scr ± SD	eGFR ± SD
At initial diagnosis ($n = 224$)	12 392 ± 17 675	3.8 ± 0.52	1.47 ± 0.51	53.2 ± 17.9
At peak BK polyomavirus (BKPyV)-DNAemia PCR	186 400 ± 588 818	4.5 ± 0.80		
3-month postinitial BKPyV-DNAemia	56 960 ± 191 543 ($n = 141$)	3.8 ± 0.84	1.50 ± 0.53	52.6 ± 18.7
6-month postinitial BKPyV-DNAemia	66 922 ± 270 679 ($n = 97$)	3.7 ± 0.89	1.46 ± 0.48	53.3 ± 18.1
9-month postinitial BKPyV-DNAemia	22 540 ± 72 436 ($n = 81$)	3.4 ± 0.80	1.45 ± 0.54	54.3 ± 18.8
12-month postinitial BKPyV-DNAemia	14 677 ± 33 281 ($n = 61$)	3.4 ± 0.78	1.41 ± 0.52	56.6 ± 19.2
15-month postinitial BKPyV-DNAemia	14 467 ± 46 965 ($n = 45$)	3.4 ± 0.73	1.43 ± 0.60	56.3 ± 20.2
18-month postinitial BKPyV-DNAemia	7044 ± 14 854 ($n = 47$)	3.3 ± 0.65	1.41 ± 0.56	56.3 ± 19.7
21-month postinitial BKPyV-DNAemia	19 701 ± 51 325 ($n = 32$)	3.4 ± 0.84	1.42 ± 0.56	56.3 ± 20.2
24-month postinitial BKPyV-DNAemia	29 916 ± 77 966 ($n = 30$)	3.6 ± 0.84	1.42 ± 0.55	55.9 ± 20.0
At last follow-up	2716 ± 5215 ($n = 9$)	3.0 ± 0.55	1.48 ± 0.69	56.8 ± 22.7

TABLE 3 Outcomes from initial BK polyomavirus (BKPyV)-DNAemia diagnosis to the last follow-up.

	BK levels	Odds ratio (OR; 95% confidence interval [CI]; p) (unadjusted)	OR (95% CI; p) (adjusted)
Uncensored graft failure (death + death-censored graft failure)	Clearance by 3 months of initial	Ref	Ref
	Clearance by 6 months	2.66 (1.07–6.60; $p = .03$)	3.15 (1.22–8.12; $p = .02$)
	Clearance by 9 months	2.29 (0.66–7.87; $p = .19$)	3.69 (1.02–13.43; $p = .04$)
	Clearance by 12 months	–	–
	Clearance by 18 months	1.91 (0.64–5.68; $p = .25$)	2.10 (0.66–6.63; $p = .20$)
	Persistent beyond 18 months	1.39 (0.53–3.67; $p = .50$)	1.05 (0.39–2.88; $p = .92$)
Death-censored graft failure (DCGF)	Clearance by 3 months of initial	Ref	Ref
	Clearance by 6 months	2.36 (0.56–0.12; $p = .24$)	1.88 (0.39–9.07; $p = .43$)
	Clearance by 9 months	1.17 (0.12–11.46; $p = .89$)	1.10 (0.09–13.03; $p = .94$)
	Clearance by 12 months	–	–
	Clearance by 18 months	2.82 (0.63–12.74; $p = .18$)	2.39 (0.48–12.01; $p = .29$)
	Persistent beyond 18 months	1.28 (0.29–5.72; $p = .75$)	0.74 (0.15–3.74; $p = .72$)
DCGF or fall in estimated glomerular filtration rate (eGFR) by ≥50% from initial BKPyV-DNAemia	Clearance by 3 months of initial	Ref	Ref
	Clearance by 6 months	1.54 (0.51–4.61; $p = .44$)	1.23 (0.39–3.94; $p = .72$)
	Clearance by 9 months	1.67 (0.41–6.79; $p = .48$)	1.87 (0.42–8.36; $p = .41$)
	Clearance by 12 months	1.31 (0.33–5.23; $p = .70$)	0.93 (0.22–4.02; $p = .92$)
	Clearance by 18 months	1.37 (0.39–4.90; $p = .62$)	1.26 (0.33–4.84; $p = .72$)
	Persistent beyond 18 months	1.21 (0.42–3.49; $p = .74$)	0.82 (0.26–2.58; $p = .73$)

Adjusted for patient age, sex, race, cause of ESKD (Diabetes Mellitus [DM] vs. other), types of transplant, HLA mismatch, induction (depleting vs. nondepleting), response to BKPyV-DNAemia (decrease myfortic vs. other), rejection before BKPyV-DNAemia.

Available literature suggests a median time to BKPyV-DNAemia clearance of anywhere from 3.5 to 9 months.[8,12–16] This wide range likely reflects different clinical practices among transplant centers regarding the aggressiveness of immunosuppression reduction and the use of adjuvant therapies. A previous study that included a small group of patients with BK nephropathy found 94.7% of KTRs with rapid viral load reduction (reduction by 1 $\log_{10}$ in ≤7 weeks) to have stable graft function compared to 44.4% with slow viral load reduction (reduction by 1 $\log_{10}$ in >7 weeks).[17] This study, like ours, suggests that more rapid viral clearance is preferable and leads to better patient and graft outcomes.

To the best of our knowledge, the finding of increased mortality among KTRs with slower BKPyV-DNAemia clearance has not been demonstrated in the past. Available literature includes a study by

TABLE 4 Outcomes based on the clearance of BK polyomavirus (BKPyV)-DNAemia at 3 months.

	BK levels	Odds ratio (OR; 95% confidence interval [CI]; *p*) (unadjusted)	OR (95% CI; *p*) (adjusted)
BK clearance at 3 months			
Uncensored graft failure (death + death-censored graft failure)	Yes	Ref	Ref
	No	0.59 (0.26–1.32; $p = .20$)	0.61(0.26–1.40; $p = .24$)
Death-censored graft failure	Yes	Ref	Ref
	No	0.62 (0.18–2.16; $p = .45$)	0.90 (0.23–3.45; $p = .88$)
DCGF or fall in estimated glomerular filtration rate (eGFR) by ≥50% from initial BKPyV-DNAemia	Yes	Ref	Ref
	No	0.72 (0.30–1.76; $p = .48$)	0.92 (0.36–2.36; $p = .86$)
BK clearance or decrease in log10 by ≥1 at 3 months			
Uncensored graft failure (death + death-censored graft failure)	Yes	Ref	Ref
	No	0.76 (0.39–1.49; $p = .43$)	0.77 (0.39–1.55; $p = .47$)
Death-censored graft failure	Yes	Ref	Ref
	No	0.75 (0.26–2.14; $p = .59$)	0.85 (0.27–2.65; $p = .78$)
DCGF or fall in eGFR by ≥50% from initial BKPyV-DNAemia	Yes	Ref	Ref
	No	0.75 (0.35–1.64; $p = .47$)	0.84 (0.37–1.91; $p = .67$)

Adjusted for patient age, sex, race, cause of ESKD (DM vs. other), types of transplant, HLA mismatch, induction (depleting vs. nondepleting), response to BKPyV-DNAemia (decrease myfortic vs. other), rejection before BKPyV-DNAemia.

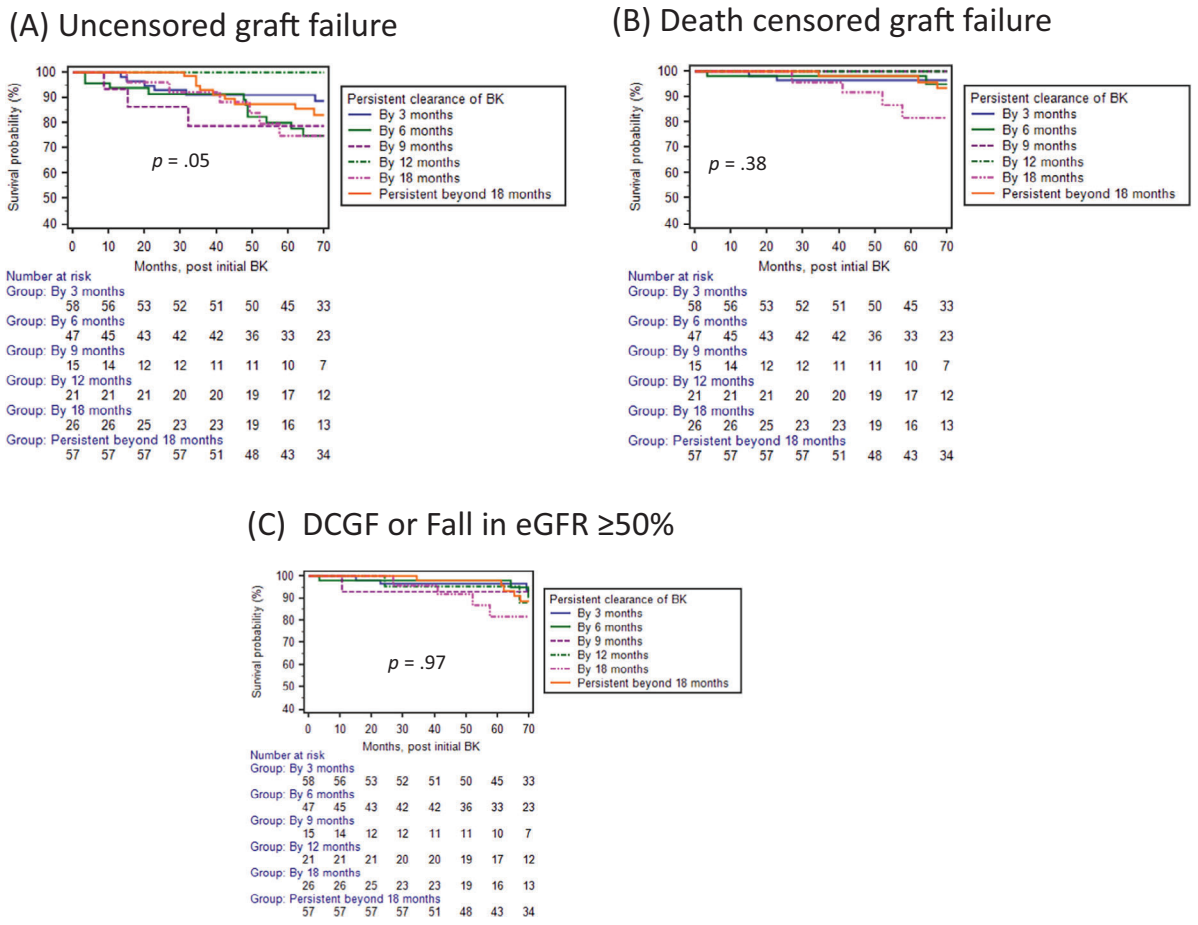

FIGURE 1 Outcomes of interest based on BK polyomavirus (BKPyV)-DNAemia clearance at various time frames.

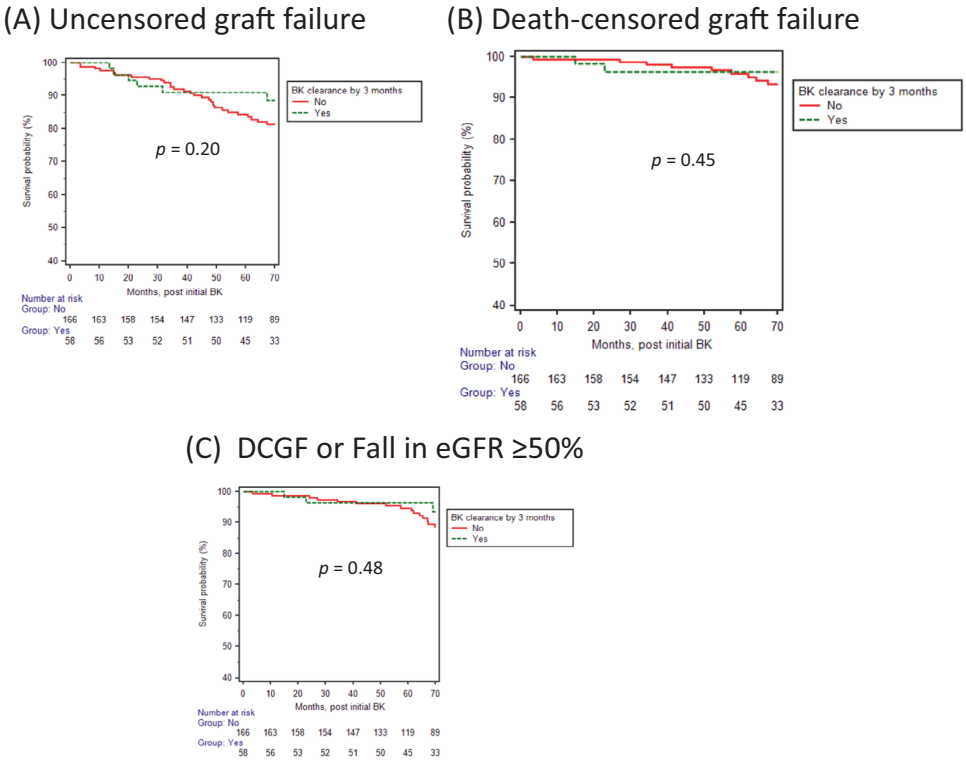

FIGURE 2 Outcomes of interest based on BK polyomavirus (BKPyV)-DNAemia clearance by 3 months versus beyond 3 months. eGFR, estimated glomerular filtration rate.

Elfadawy et al. which showed no significant difference in patient survival between KTRs with a duration of BKPyV-DNAemia less than 3 months compared to more than 3 months.[8] In the first year post-transplant, when the majority of BKPyV-DNAemia occurs, the most common causes of death in KTRs in order of decreasing prevalence are cardiovascular deaths, infection, and malignancy.[18,19] Causes of death in our study cohort were consistent with the literature, but with malignancy followed by infection then cardiovascular disease being the most common known causes of death.

One possible hypothesis for the increased risk for uncensored graft failure among KTRs who took longer to clear their BKPyV-DNAemia is that the persistence of viremia for a longer duration of time is an indication of a weaker immune system and therefore an increased risk for developing additional infections that could have contributed to their mortality. Coinfection is common in KTRs, with up to 42% being coinfected with ≥2 viruses, and an association has been found between BK infection and other pathogens including JC polyomavirus and cytomegalovirus (CMV).[7,20,21] In a study by Jorgenson et al., clinically significant BKPyV-DNAemia was associated with a 55% relative risk reduction in subsequent CMV infection.[22] This is because BKPyV-DNAemia management via immunosuppression reduction and the resulting immune reconstitution reduces the risk of CMV coinfection. From this we can hypothesize that the KTRs in our study who cleared their BKPyV-DNAemia faster did so because they achieved immune reconstitution faster, and this resulted in a lower risk of coinfection and possibly mortality.

Another hypothesis is that there is a relationship between BKPyV-DNAemia and malignancy which contributed to the finding of increased risk for uncensored graft failure among KTRs who took longer to clear their viremia. The oncogenic properties of BKPyV are well defined in both in vitro and in vivo experimental models, particularly for urinary bladder and uroepithelial cancers.23 In our study, 25 KTRs died with a functional graft. The cause of death was known in 11 of the 25, with six of the 11 known deaths (54.5%) being due to malignancy. Available literature suggests a pathogenic role for BKPyV-DNAemia in the development of malignancies such as urothelial carcinoma, especially rare and aggressive subtypes.[24] We can hypothesize that the longer BKPyV-DNAemia persists in a patient, the longer their immune system is in a weakened state and therefore susceptible to malignancies that may have a viral origin. Not only the pathogen itself, but the management of BKPyV-DNAemia can alter the risk of developing malignancy. It is well documented that immunosuppressed patients, including KTRs, are at an increased risk for developing malignancies caused by oncogenic viruses such as Epstein–Barr virus and human papillomavirus.[25] The aggressive reduction in immunosuppression that allows patients with BKPyV-DNAemia to clear their viremia quickly may also allow for enough immune reconstitution to reduce the risk of developing these oncogenic virus-associated malignancies. However, data available in this study are insufficient to support these hypotheses as the cause of death is lacking in most patients.

The results of this study are that of a single center, with a patient population and clinical practices that may not be

representative of other institutions. This possible limitation is reflected in the mostly male and white patient population in this study. Additionally, our persistent BKPyV-DNAemia group was small in size (4% of the total study population) and statistical analyses related to this group may therefore be underpowered. Additionally, not all recipients had the same immunosuppressive adjustments. Also, we were not able to identify the causes of death in a significant number of recipients, so it was not clear if death was associated with BKPyV or not. Strengths of this study include its moderate size with 224 participants in total as well as the consistency in BK viremia screening and management that come with being a single-center study.

The findings of this study are clinically relevant as BKPyV-DNAemia is a common problem in the postkidney transplant population with the potential for detrimental damage to the allograft if untreated. Importantly, our study suggests that early viral clearance, particularly clearance by 3 months postinitial detection, may have a mortality benefit compared to slower viral clearance achieved by 6 or 9 months postinitial detection. Therefore, it may be beneficial for the clinician to aim for early viral clearance, but only if this can be achieved safely with an acceptable level of risk of acute rejection caused by the reduction in immunosuppression required for viral clearance. In the absence of effective antiviral therapy, in clinical practice we are relying on early detection and screening for BKPyV reactivation, which follows a stepwise pattern from viruria to viremia to nephropathy.[26] For this purpose, targeted antiviral agents against BKPyV, which will permit rapid clearance of the virus, are of the most need.

AUTHOR CONTRIBUTIONS

Isabel Breyer: Concept; design; manuscript preparation. **Lucy Ptak**: Data collection; manuscript preparation; editing. **David Stoy**: Manuscript preparation, editing. **Didier Mandelbrot**: Manuscript preparation; editing. **Sandesh Parajuli**: concept; design; data analysis; manuscript preparation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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