Prevalence, Risk Factors, Treatment, and Overall Impact of BK Viremia on Kidney Transplantation

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ABSTRACT

BK viremia (BKV) is a recognized and potentially serious problem in renal transplantation. The risk factors and the impact of BKV on renal allograft and patient survival are controversial. This study reports an 8-year, single-center experience on the prevalence, risk factors, and outcomes of BKV in kidney transplant recipients. This is a retrospective analysis of all patients who received a kidney transplant at the University of Kentucky and had BK viral titers available from 2009 to 2017. BKV was defined by a polymerase chain reaction viral load of $\geq$ 10,000 copies per mL. Demographic, clinical, and laboratory data generated during routine outpatient follow up and inpatients records were collected. Independent risk factors for BKV were determined using uni- and multivariate analysis. Graft and patient survival was compared using Kaplan-Meier analysis, and the severity of polyomavirus nephropathy on biopsy was scored using the Banff 2017 classification. We identified 122 BK positive (19%) and 527 BK negative (81%) patients. BKV developed after a median of 115 days (range, 80–249 days) following kidney transplantation. The 1-, 5-, and 10-year graft survival was 97%, 75%, and 33% in the BKV group and 96%, 85%, and 71% in the BK negative group, respectively. Likewise, the 1-, 5-, and 10-year patient survival was 98%, 84%, and 52% in the BKV group and 98%, 92%, and 84% in the BK negative group. Male sex, age at transplantation, maintenance steroids, and alemtuzumab induction were associated with developing BKV in the multivariate analysis. We concluded that BKV is not uncommon after renal transplantation. The determinants for BKV are male sex, older transplant recipients, and maintenance steroids. BKV adversely affected graft and patient survival. A unified approach for BKV and polyomavirus nephropathy treatment is needed.

RENAL transplant recipients are at risk for developing infections with BK virus, a nonenveloped DNA virus from the Polyomaviridae family [1]. Prevalent in approximately 80% of the adult population, primary infection with BK virus occurs early in childhood, after which the virus becomes latent and persists indefinitely [2]. The presence of BK virus in the renal parenchyma, renal pelvis, and urinary bladder in immunocompetent individuals has been confirmed by autopsy studies [3]. Whether it remains latent or becomes active is under the control of the immune system.

In immunodeficiency states such as in renal transplantation, the BK virus can be reactivated from a state of latency, causing BK viremia (BKV) and tubulointerstitial nephritis. According to the literature, 30% to 60% of kidney transplant recipients develop BK viruria, 10% to 20% develop BKV, and 5% to 10% develop polyomavirus nephropathy (PVN), putting patients at risk for allograft loss [4–11].

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Table 1. Patients' Demographics, Clinical Parameters, and Laboratory Parameters

		BKV Group (n = 122)	Non-BKV Group (n = 527)	*P* Value
Sex, No. (%)	Male	88 (72.1)	308 (58.4)	.005
Race, No. (%)	White	100 (82.0)	436 (82.7)	.957
	African American	21 (17.2)	86 (16.3)	
	Other	1 (0.8)	5 (0.9)	
Transplant type, No. (%)	Living donor	27 (22.1)	155 (29.4)	.107
Age at transplantation, y		52.1 ± 12.5	48.2 ± 14.1	.005
Induction therapy, No. (%)	Thymoglobulin	88 (72.7)	429 (83.3)	.007
	Basiliximab	11 (9.1)	40 (7.8)	.629
	Alemtuzumab	17 (14.0)	42 (8.2)	.044
Maintenance therapy, No. (%)	**Steroid**	96 (80.0)	315 (60.3)	< .001
	Antimetabolite			
	Mycophenolate	108 (88.5)	484 (91.8)	.439
	Azathioprine	6 (4.9)	15 (2.8)	
	Calcineurin inhibitors			
	Tacrolimus	115 (94.3)	486 (92.2)	.739
	Cyclosporine	3 (2.5)	19 (3.6)	
Delayed graft function, No. (%)	Yes	7 (5.7)	47 (9.0)	.241
Acute rejections, No. (%)	Yes	7 (5.7)	21 (4.0)	.391

Currently, there is no effective prophylaxis for polyomavirus in immunosuppressed patients. Furthermore, treatment options are limited with the principle intervention being a reduction of the dose of immunosuppression [12]. However, reducing immunosuppression predisposes transplant patients to acute and/or chronic rejection and to the development of donor specific antibodies. Although no approved antiviral drug is available, leflunomide, mammalian target of rapamycin inhibitors, cidofovir, quinolones, and intravenous immunoglobulin (IVIG) have been used and demonstrated varying degrees of efficacy [13,14]. In 1 study, screening protocols have demonstrated improved outcomes for early detection and prevention of PVN [15]. The risk factors and the impact of BKV on renal allograft and patient survival are debatable. The aim of this study is to determine the prevalence, risk factors, therapeutic interventions, and impact of BKV on patient and graft survival. Furthermore, we studied the occurrence of rejection and the clinical utility of implementing the Banff 2017 PVN classification.

METHODS

This was a retrospective analysis of 649 patients who received a kidney transplant at the University of Kentucky from 2009 to 2017. Demographic, clinical, and laboratory data were collected during

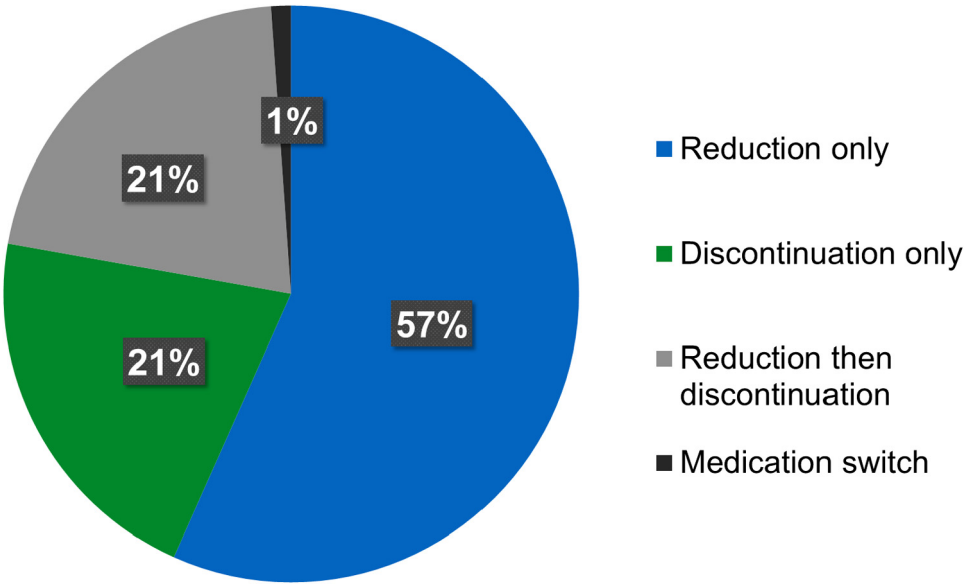

Fig 1. Immunosuppression adjustment in BKV patients. BKV, BK viremia.

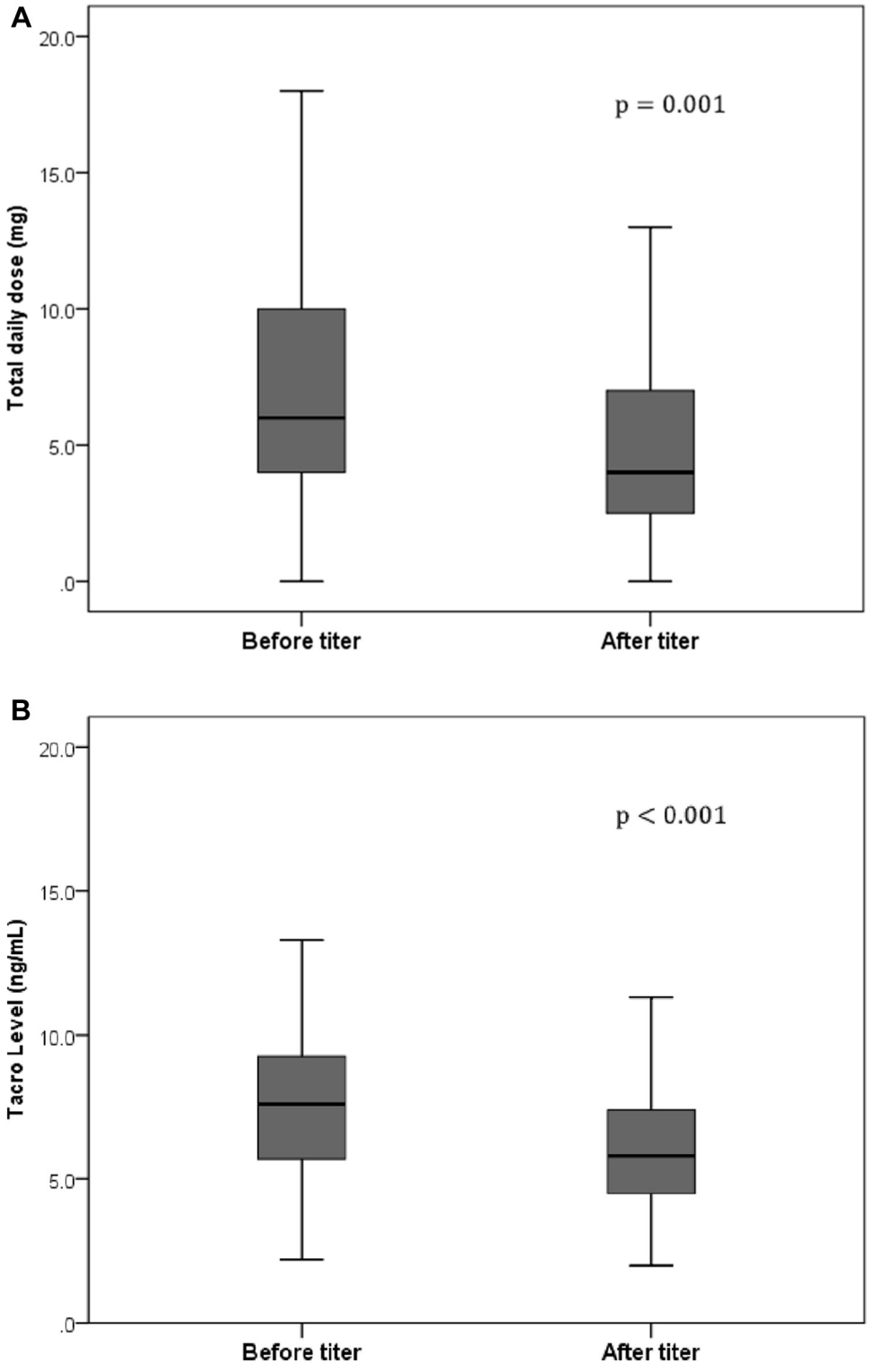

Fig 2. **(A)** Tacrolimus dose before the first positive BK titer and at the last positive BK titer. **(B)** Tacrolimus blood trough level before the first positive BK titer and at the last positive BK titer.

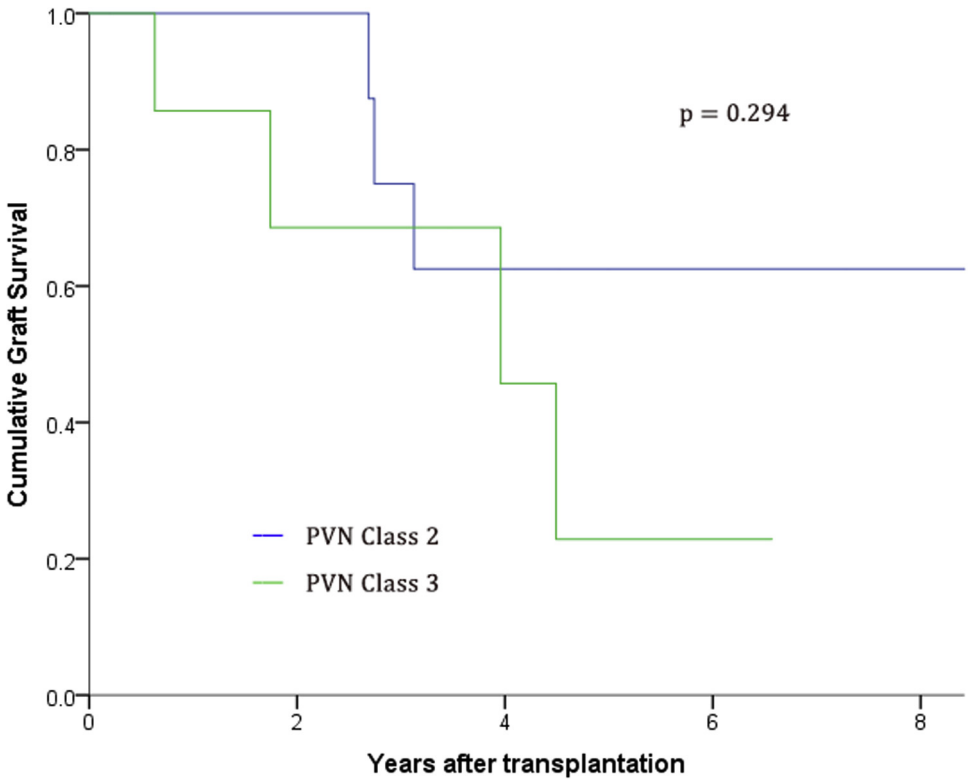

Fig 3. Kaplan-Meier analysis of graft survival in PVN class 2 and 3 patients. PVN, polyomavirus nephropathy.

the initial transplant admission, subsequent hospitalizations, and clinic visits. The study was conducted according to the Declaration of Helsinki, and the protocol was reviewed and approved by the Institutional Review Board of the University of Kentucky. Patients were screened for BK virus starting 8 weeks post transplantation and at every clinic visit for up to 3 years. We identified 122 BKV patients defined by blood polymerase chain reaction $\geq$ 10,000 copies per mL on at least 1 occasion, and of these, 21 had biopsy-proven PVN. Patient demographics included age, sex, and ethnicity. Additionally, the type of donor (living vs deceased), number and type of acute rejection episodes, and severity of PVN according to the 2017 Banff PVN classification were analyzed. Patients with PVN were categorized to PVN class 1, 2, and 3 based on the amount of intrarenal polyoma viral load and the degree of interstitial fibrosis (ci score) according to the 2017 Banff PVN classification. To examine the clinicopathologic significance of using the PVN classification, graft survival among the PVN classes was compared using Kaplan-Meier curves.

Our immunosuppressive regimen consisted of induction therapy using Thymoglobulin or alemtuzumab for high immunologic risk patients (African American, repeat transplant, calculated panel reactive antibody $>$ 20%, and $>$ 3 HLA mismatches) and basiliximab for low immunologic risk patients. The standard maintenance immunosuppressive protocol included tacrolimus, mycophenolate, and prednisone. In low immunologic risk patients with no clinical signs of rejection, prednisone was tapered off within 2 months. Infrequently, mycophenolate was replaced by mammalian target of rapamycin inhibitors when clinically indicated. The impact of different treatment regimens on BKV was identified.

Statistical Analysis

The means of continuous variables were compared using a t or Mann-Whitney test according to their distribution, and categorical variables were analyzed using the $\chi 2$ test. A P value $<$ .05 was considered significant. Wilcoxon sign test was used to compare the median daily dose of tacrolimus and the median tacrolimus level. The covariates, which were significant in univariate analysis, were used in a logistic regression analysis to determine independent risk factors for BKV and were adjusted for the following: age, sex, induction therapy, and steroid usage. A Kaplan-Meier analysis was performed to compare renal allograft and patient survival between the 2 groups using the log-rank test. Statistical analysis was performed using SPSS version 24 (IBM Inc, Armonk, NY, United States).

RESULTS

We identified 122 BKV (19%) and 527 non-BKV (81%) patients. Demographic, clinical, and laboratory data and immunosuppressive regimens are stated in Table 1. The mean age of patients at the time of transplantation was 52 $\pm$ 13 years in the BKV group and 48 $\pm$ 14 years in the non-BKV group (P = .005). The majority of the patients were men (72% of the BKV group and 58% of the non-BKV group [P = .005]) and Caucasian (82% of the BKV group and 83% of the non-BKV group [P = .957]). Seventy-eight percent of the BKV group and 71% of the non-BKV group

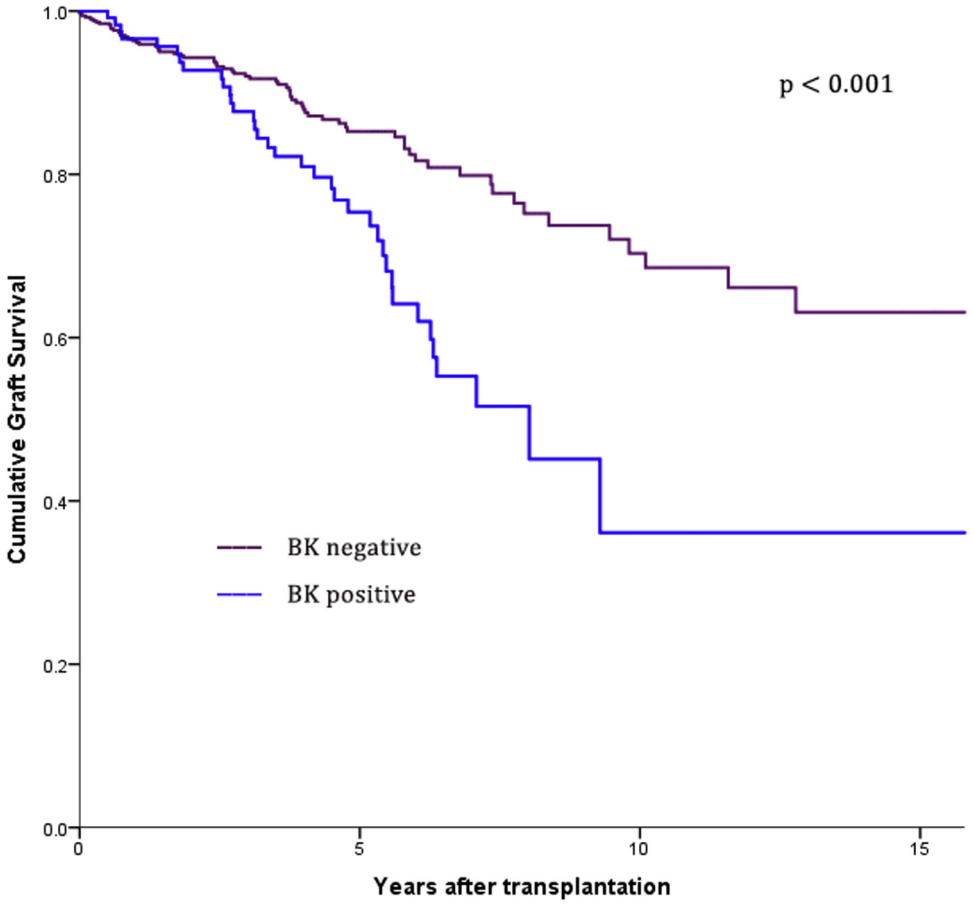

Fig 4. Kaplan-Meier analysis of cumulative graft survival of BKV vs non-BKV patients. BKV, BK viremia.

received deceased donor kidneys ($P = .107$). BKV developed after a median of 115 days (range, 80–249 days) after kidney transplantation.

Thymoglobulin was the most commonly used induction therapy (73%), followed by alemtuzumab (14%) and basiliximab (9%) in the BKV group. A total of 97% of patients received tacrolimus, 95% received steroids, and 93% received mycophenolate maintenance immunosuppression. Less frequently used immunosuppression included sirolimus (10%), azathioprine (6%), cyclosporine (3%), and everolimus (1%).

Acute cellular rejection occurred in 28 patients (23%) after the diagnosis of BKV. The most common therapy used for acute cellular rejection was intravenous methylprednisolone (93%), followed by Thymoglobulin (29%). The patients who had antibody-mediated rejection were treated with IVIG (32%), plasma exchange (14%), and rituximab (7%).

A total of 76% of BKV patients were treated with immunosuppression reduction and adjustment. Other interventions included the addition of ciprofloxacin (51%), leflunomide (29%), and IVIG (11%). Most patients received more than 1 therapeutic intervention (59%). The use of cidofovir was not required in any of the studied patients. No intervention was necessary in 24% of patients because of spontaneous decay of BKV.

Immunosuppression adjustment was further classified as either mycophenolate or tacrolimus dose reduction (57%), discontinuation of either (21%), and reduction followed by discontinuation (21%). Only 1% of patients were switched to another immunosuppressant (Fig 1). Tacrolimus dose and level trended down from before diagnosis to the last BKV titer (Fig 2). The median daily dose of tacrolimus was 6 mg (4–10 mg) before the first positive BK titer and 4 mg (2.5–7 mg) at the last BKV titer ($P = .001$). The median tacrolimus blood trough level before the first positive titer was 7.6 ng/mL (5.6–9.3 ng/mL) and 5.8 ng/mL (4.5–7.4 ng/mL) at the last titer ($P < .001$).

Renal allograft biopsy was performed in 61 patients (50%), of which 17 patients (28%) had PVN. A single patient had class 1, 9 patients had class 2, and 7 patients had class 3 PVN. There was no statistically significant difference in clinical, demographic, and laboratory parameters among the PVN groups. There was a trend toward better graft survival in PVN class 2 compared with class 3, but it failed to reach statistical significance (Fig 3).

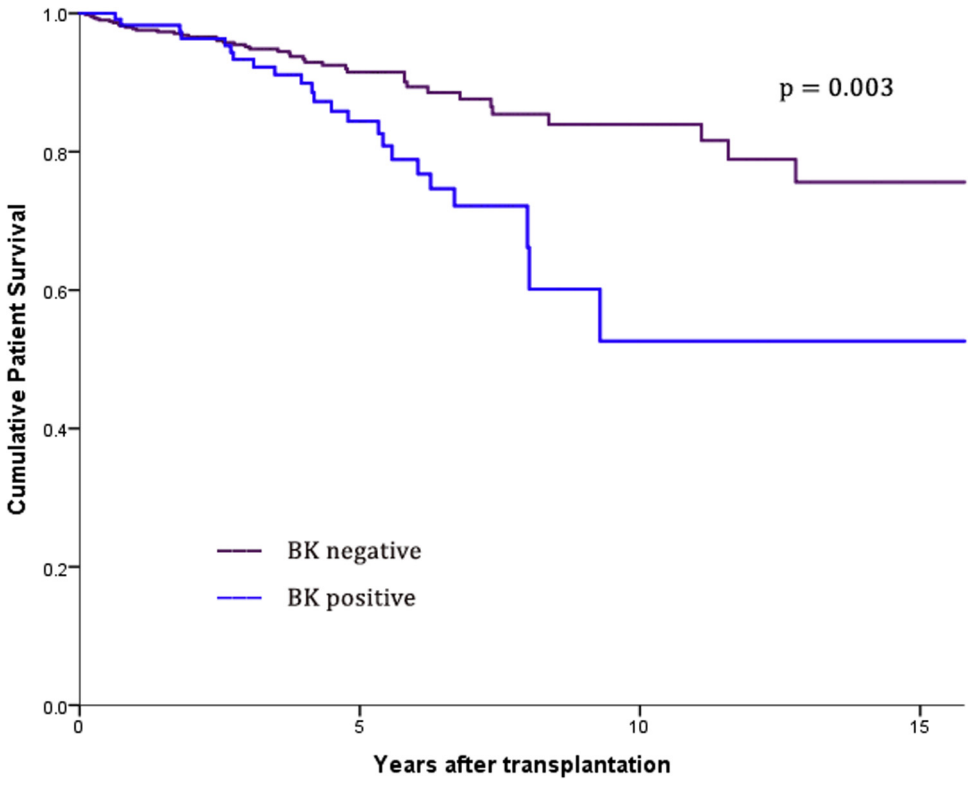

Fig 5. Kaplan-Meier analysis of cumulative patient survival in BKV vs non-BKV patients. BKV, BK viremia.

The 1-, 5-, and 10-year graft survival was 97%, 75%, and 33% in the BKV group and 96%, 85%, and 71% in the non-BKV group, respectively (Fig 4). The 1-, 5-, and 10-year patient survival was 98%, 84%, and 52% in the BKV group and 98%, 92%, and 84% in the non-BKV group (Fig 5). Likewise, the 1-, 5-, and 10-year death censored graft survival was 98%, 87%, and 66% in the BKV group and 99%, 93%, and 85% in the non-BKV group (Fig 6).

The odds ratio of BKV in the multivariate regression analysis was 1.2 for10 years of age ($P = .012$), 1.8 for men ($P = .009$), 2.9 for maintenance steroid usage ($P < .001$), and 2.3 for alemtuzumab compared with Thymoglobulin induction therapy ($P = .014$) (Table 2).

DISCUSSION

In this study, the prevalence of BKV was 19%, which was higher than reported by Jacobi et al (13.6%) [16], Dogan et al (15.8%) [17], Ziedina et al (16%) [18], and Brennan et al (11.5%) [19]. To the contrary, Yalci, et al [20] reported a prevalence of up to 20%. The differences in individual center prevalence could be explained by variation in immunosuppressive protocols, as the immune status of the renal transplant patient plays a decisive role in developing BKV.

Risk factors associated with the development of BKV were male sex, older age, maintenance steroids, and use of alemtuzumab induction. In concordance with this study, others showed that male sex was a risk factor for BKV [17,20–23]. Although, Hirsch et al [24] reported male sex was not a significant risk for developing BKV at 6 months, the risk significantly increased beyond 12 months post transplantation. In several studies, the recipient's age was a significant factor for developing BKV [16,21–24]. Conversely, Brennan et al [19] and Yeo et al [25] determined that both sex and age were not significant risk factors. The net effect of immunosuppression impacts viral latency, reactivation, and infection. Consistent with our results, the continued use of steroids was a risk factor for the development of BKV in other studies [26,27]. Finally, Schadde et al [28] found that patients who received alemtuzumab induction had a trend toward higher BKV, but their sample size was small and did not reach statistical significance.

One-quarter of the patients with BKV had spontaneous decay of the virus and were ultimately not treated. Of the patients who were treated, the standard treatment was reduction of immunosuppression. The approach to immunosuppression adjustment varied, with most patients requiring only a dose reduction. Other patients had their immunosuppression dose decreased and/or discontinued at the time of significant viremia. Reduction of the tacrolimus dose after minimizing or stopping mycophenolate was a common intervention leading to lower doses and blood trough levels over the course of BKV treatment. Switching

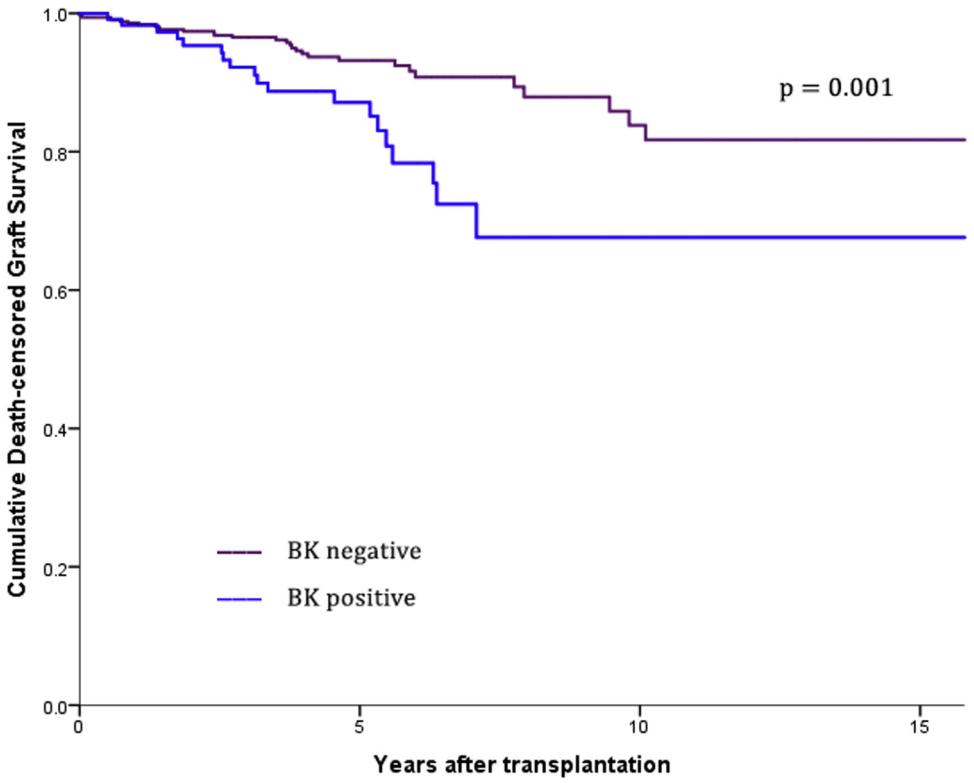

Fig 6. Kaplan-Meier analysis of cumulative death-censored graft survival in BKV vs non-BKV patients. BKV, BK viremia.

to a different immunosuppressive agent was not a frequent approach to treatment. Over half of the patients treated for BKV received more than 1 treatment modality. The most common intervention after immunosuppression adjustment was the addition of ciprofloxacin, which has been thought to reduce BKV DNA replication as well as lowering the cell release of viral progeny [29]. In addition, IVIG was used to mitigate rejection in patients who had their immunosuppressive agents reduced or stopped, particularly if they had elevated calculated panel reactive antibody or developed donor specific antibody. Also, IVIG has been shown to contain neutralizing antibodies against BK virus [21].

Table 2. Multivariate Logistic Regression Analysis for BKV Risk Factors

	Odds Ratio	95% Confidence Interval		*P* Value
		Lower	Upper	
Age at time of transplantation (per 10 y)	1.230	1.047	1.445	.012
Sex (male vs female)	1.832	1.165	2.883	.009
Maintenance steroid vs steroid free	2.871	1.744	4.727	< .001
Induction therapy				
Basiliximab vs Thymoglobulin	1.438	0.681	3.034	.340
Alemtuzumab vs Thymoglobulin	2.263	1.176	4.355	.014
Constant	0.017			.001

In this study, leflunomide was used in place of mycophenolate in a small number of patients because of its antiviral activity. Nesselhauf et al [30] and Hirsch et al [31] reported that appropriate leflunomide dosing and monitoring was crucial to avoid potential adverse events. Faguer et al [32] determined that leflunomide administration in transplant recipients with PVN was safe; however, they cautioned that antiviral activity should not be attributed to the drug until prospective trials demonstrate a clear benefit of therapy.

Biopsy-proven PVN has heretofore lacked consensus on histologic subclassification of viral nephropathy, albeit morphologic changes and clinical presentations differ [33]. There was a poor understanding of morphologic impact of BKV on clinical outcome. Tasked with developing a clinically relevant morphologic classification, the Banff 2017 working group defined 3 PVN classes. Class 1 was described as early PVN with favorable outcome on graft survival, whereas classes 2 and 3 had progressively worse histology and poor outcomes, respectively [34].

In this study, only 1 patient had class 1 PVN, so the allograft survival was compared between PVN classes 2 and 3, which was statistically insignificant, although a trend toward worse graft survival was observed in class 3. The lack of significant effect of the PVN classes might be explained

by the small sample size of our cohort. Currently, we are part of an ongoing multicenter clinical study examining the clinical significance of using the Banff 2017 PVN classification. Additionally, a prospective clinical study will be needed to examine the effect of PVN class on graft and patient survival.

Patients in this study who had a positive BKV titer had a considerably worse graft survival when compared with non-BKV patients. Similarly, patient survival and death-censored graft survival were inferior in the BKV group. Hirsch et al [31] and Jacobi et al [16] studied the effect of BKV on patient and graft survival, concluding that patients who developed a positive BKV titer had worse outcomes compared with their non-BKV counterparts.

Study Limitations

This was a retrospective, single-center analysis of BKV and PVN. Although this study included 649 patients, only a small number of biopsies were available for determination of PVN by Banff 2017 criteria. Therefore, no definitive clinicopathologic correlation could be established between PVN classes and overall graft survival. Furthermore, the logistic regression model was limited to the available data.

CONCLUSION

BKV is prevalent in kidney transplant recipients because of their net state of immunosuppression. Male sex, older age, alemtuzumab induction, and steroid maintenance were the determinants for BKV. The BKV group had inferior patient and graft survival. Prospective trials are needed to study the effect of various therapeutic interventions and the impact of PVN classes on patient and graft outcome.

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