Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Treatment for BK virus: incidence, risk factors and outcomes for kidney transplant recipients in the United States

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Keywords
BK virus nephropathy, graft survival, kidney transplantation, polyoma virus, post-transplant complications.

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Received: 1 September 2008
Revision requested: 30 September 2008
Accepted: 8 January 2009

doi:10.1111/j.1432-2277.2009.00842.x

Summary

There has been a notable rise of BK virus among kidney transplant recipients. Single-center reports have identified risk factors for development of BK virus. However, there has not been an assessment of risk factors and incidence of this complication at a national level. This study utilized newly collected follow-up information from the national SRTR database to investigate incidence, risk factors and outcomes for solitary kidney transplant recipients associated with treatment for BK virus (TBKV) from 2004 to 2006. Logistic and Cox models were utilized to assess risk factors and evaluate graft survival associated with TBKV. Incidence of TBKV was 1.6% at 6 months and 2.6% at 1 year following transplantation. Patients with and without TBKV at 6 months had 79% and 90% 3-year overall graft survival respectively. Risk factors included advanced donor age, pediatric, African American and male recipients, human leukocyte antigen-mismatching and tacrolimus and thymoglobulin induction as baseline immunosuppression. Acute rejection episodes were more frequent prior to and following TBKV. TBKV is a common and rising incidence, varies based on transplant characteristics and should be included as a safety endpoint in studies investigating immunosuppressive protocols. Careful monitoring and further understanding of disease etiology and treatment strategies are needed.

Introduction

BK virus nephropathy was described among kidney transplant recipients 30 years ago [1]. There has been a notable rise in the incidence of BK virus among kidney transplant recipients in recent years with many patients progressing to BK virus nephropathy [2,3]. Even though more intense screening protocols may in part contribute to the increased detection of this complication, there is also an indication that the more potent immunosuppression available in recent years with more efficacious rejection prophylaxis may be a primary driver for the increase in BK virus nephropathy [4,5]. Incidence of BK virus has been reported to be between 1% and 10% among kidney transplant recipients [4,6–10]. These wide variations in BK virus rates are likely partially reflective of differential diagnostic criteria utilized by centers. Most reports indicate that the development of BK virus occurs most frequently within a year after transplantation [6,10]. Incidence rates of BK virus nephropathy in pediatric kidney transplant recipients have been reported in a similar range as adult recipients [11,12]. BK virus nephropathy is associated with a significant risk for graft loss, with one report indicating that it is now the predominant cause for renal allograft graft loss after combined kidney–pancreas transplantation [13]. Thus far, besides reduction in overall immunosuppression, there is no a clear treatment for BK virus (TBKV) nephropathy [4,14–16].

Risk factors that have been implicated in the development of BK virus include human leukocyte antigen (HLA)-mismatching [17,18], stronger and specific immunosuppression agents [4,10,19–21], development of cytomegalovirus infection [22], acute rejection episodes [9,23], utilization of ureteral stents [24], recipient and donor gender and age [11,25,26]. However, identification of risk factors has been limited to characterization from single-center studies and in some cases these reports suggest conflicting predictors. As such, there is not a clear consensus on risk factors for development of BK virus and the impact of the development of BK virus and treatment strategies have similarly varied.

In recent years, a field has been introduced into follow-up forms collected by the Organ Procurement and Transplantation Network (OPTN) for kidney transplant recipients with documentation of TBKV. This newly collected information offers an opportunity to investigate association and outcomes associated with TBKV from a national perspective. The utilization of information about TBKV has both advantages and disadvantages that affect potential inferences that can be generated from a study. The clear limitation of this variable is that indications of treatment may be associated with significantly different levels of disease progression and severity (including treatment for viremia, viruria or in some cases BK nephropathy) and can rely on specific center protocols. Centers with less vigilant screening protocols may not detect lower levels of viremia and as such TBKV does not capture the incidence of all manifestations of disease progression. While these limitations reduce certain inferences from a study; there are also several advantages to these data. One of the advantages of these data is to provide an objective indication for the onset of this complication, in particular, whether the complication induced some form of treatment. As such, this information provides an indication of BK virus based on cases that led to clinical intervention and active management. Although the threshold and form of treatment remain variable and dependent on clinical practice, it is unlikely that it is reported differently among patient groups causing any systematic biases in the identification of particular risk factors. This definition is analogous to the definition of treatment for acute rejection, which is also utilized extensively in registry analyses. Moreover, the utility of this information from a broad national perspective allows for investigation of factors associated with TBKV with sufficient power, and to assess factors and outcomes that are reflective of average clinical practice and not solely attributable to individual centers' care patterns.

The primary study aims were to provide an evaluation of the incidence, risk factors and outcomes associated with TBKV for kidney transplant recipients in the United States. This information may be important for understanding the incidence of active management by transplant centers for this complication, confirm risk factors identified by prior single-center studies or suggest novel factors that may be unattainable with smaller study populations and to evaluate outcomes for patients that have been treated for BK virus over the most recent era. Cumulatively, this study may provide data about this complication applicable broadly to the US population that may be placed in context with important single-center studies.

Methods

The study examined solitary renal transplant candidates for the period ranging from 2004 to 2006 from the national SRTR database. Transplant recipient follow-up forms gathered by the OPTN include a field labeled 'Treatment for BK (polyoma) Virus' at 6 months, 1 year and subsequent years post-transplantation. Incidence rates were calculated with and without excluding missing indications. Six-month TBKV was indicated by a positive indication at 6-month follow up and 12-month TBKV was indicated by a positive indication at either 6- or 12-month follow up. As the relatively new variable was not initially consistently populated in forms by all centers, as a sensitivity analyses, estimates were repeated limited to centers without significant missing responses (>20%).

Immunosuppression information was based on treatment after discharge from the initial hospitalization associated with the transplant procedure. Induction agents were categorized as Thymoglobulin, IL-2 receptor blockers (RB), which included Zenapax and Simulect, Other or none. Other immunosuppressive medications were categorized as tacrolimus, sirolimus, or cyclosporine, which included Neoral and generic versions. Acute rejection was indicated by treatment for acute rejection during the time of initial hospitalization and within 6 and 12 months. Delayed graft function (DGF) was indicated by use of dialysis within the first week after transplantation or recipients' inability to produce 40 ml of urine within 24 h of transplantation.

A multivariate logistic model was utilized to investigate risk factors for TBKV at 12 months post-transplant. For this model, patients with a minimum of 12 months of follow up were included and covariates that were applicable for both living and deceased donor transplants were included. Models were then constructed, stratified by donor type, and pediatric versus adult recipients including covariates applicable to the specific forms of transplantation. Adjusted and unadjusted logistic models were also utilized to investigate TBKV rates with DGF and acute rejection during the initial hospitalization. These models

were adjusted for recipient and donor age, race and gender, recipient primary diagnosis, panel reactive antibody (PRA) level, donor source (living or deceased donor), HLA matching and recipient body mass index. Models were tested for adequacy of fit with the Hosmer–Lemeshow test.

Kaplan–Meier and multivariate Cox models were generated to investigate the association of overall and death-censored graft loss and patient death with TBKV. Models were generated initiated at 6 months post-transplant and 1 year post-transplant stratified by indication of treatment for TBKV in the prior periods. Kaplan–Meier plots were graphically displayed from the time of transplantation; however, log-rank tests were calculated based on data after 6 months and 1 year only. Similarly, Cox models were based after the time at which TBKV was indicated. Models were additionally stratified to evaluate whether the association of TBKV with graft survival was consistent within certain patient subgroups and associated with specific immunosuppressive medications. Chi-squared tests were utilized to assess the association of TBKV with demographic and transplant-related factors. All analyses were conducted with SAS (v.9.1.3; SAS, Cary, NC, USA).

Results

Study population and TBKV incidence

The study examined 42 838 kidney transplant recipients receiving a transplant during the period ranging from 2004 to 2006. Among the initial transplant population, 6737 recipients experienced either graft loss or death within 6 months and accordingly were not included in the analysis. Six- and 12-month incidence of TBKV was 1.6% and 2.6% respectively. Excluding missing indications of TBKV, rates slightly varied; 6-month incidence rates increased to 1.7% and 1-year incidence rates remained at 2.6%. In addition, after excluding patients at centers with >20% of missing indications of treatment for TBKV, the 1-year incidence was not significantly altered (2.7%). Table 1 displays demographic characteristics of patients with indications of TBKV in the first 12 months. Incidence of TBKV was highest among pediatric and elderly recipients, older donors, recipients without diabetes as a primary diagnosis, male recipients, female donors, African American recipients, and HLA-mismatched transplants. As displayed in Fig. 1, indications of TBKV increased over the study period, with almost 5% of deceased donor transplants in 2006 with TBKV within 1 year. Specific forms of TBKV are also included in follow-up forms, but approximately 36% of patients with 1-year incidence had missing or 'other' indications for the type of treatment. Among cases with documented treatment, 84% reported reduced immunosuppression, 11% indicated use of Cidofovir and 5% indicated use of IVIG.

Table 1. Recipient, donor and transplant characteristics by 12-month TBKV*.

Characteristic	Level	TBKV % (n = 34 937)	P-value†
Donor source	Deceased donor	2.8	0.07
	Living donor	2.5	
Recipient age (years)	0–11	4.8	<0.001
	12–17	3.8	
	18–35	2.5	
	36–54	2.3	
	55–64	2.7	
	65+	3.3	
Donor age (years)	0–11	3.2	<0.001
	12–17	2.4	
	18–35	2.3	
	36–54	2.7	
	55–64	2.9	
	65+	5.4	
Recipient PDGN	Diabetes	2.0	<0.001
	Other	2.8	
Recipient gender	Male	3.1	<0.001
	Female	2.0	
Donor gender	Male	2.5	0.04
	Female	2.8	
Recipient race	AA	3.2	<0.001
	Caucasian	2.8	
	Other	1.6	
Donor race	AA	2.7	<0.001
	Caucasian	2.8	
	Other	1.9	
Re-transplants	No	2.6	0.35
	Yes	2.9	
BMI‡	<30	2.8	0.11
	30+	2.5	
HLA (A,B,DR) mismatches	0	2.1	<0.001
	1–4	2.5	
	5–6	3.1	
PRA‡	0	2.7	0.02
	1–30	2.2	
	30+	2.8	
Pretransplant dialysis time (years)	0–1	2.6	0.88
	1–3	2.6	
	3+	2.7	
Overall		2.6	

AA, African American; PDGN, primary diagnosis; PRA, panel reactive antibody; HLA, human leukocyte antigen.
*Includes patients with 1-year graft survival and TBKV indicated by treatment at 6 months or 1 year post-transplantation.
†Testing the independence of characteristic with 1-year TBKV.
‡Missing values not included in calculation for proportions.

Risk factors for TBKV

Results of a multivariate logistic model for 12-month TBKV are displayed in Table 2. Significant independent risk factors included pediatric recipients, donors over the age of 65, recipients without diabetes as a primary

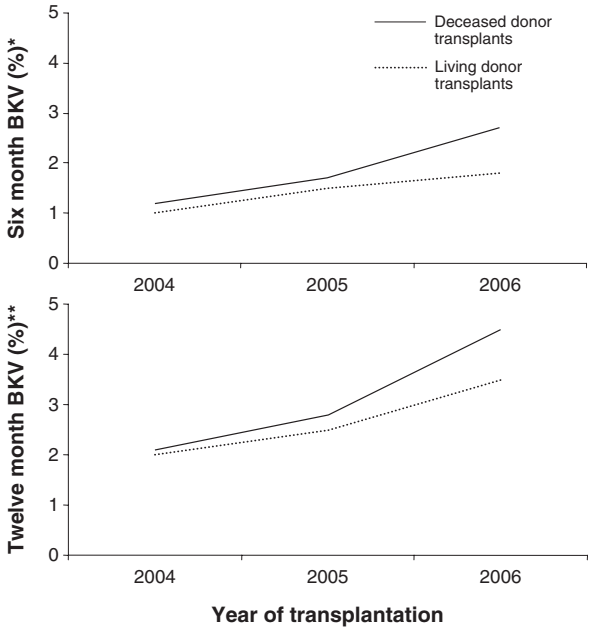

Figure 1 Six- and 12-month TBKV incidence by donor type. *Based on patients with a minimum 6-month graft survival. **Based on patients with a minimum of 12-month graft survival.

diagnosis, male recipients, female donors, five- and six-antigen mismatched transplants, recipients treated with thymoglobulin for induction and tacrolimus as baseline immunosuppression. The concordance index for the model is 0.66 and the Hosmer–Lemeshow test was insignificant ($P = 0.99$) suggesting adequate model fit. Limiting the model to deceased donor transplants only, risk factors from the primary model were generally consistent; however, in addition African American recipients [adjusted odds ratio (AOR) = 1.21, 95% CI 1.00–1.48], donors with a history of diabetes (AOR = 1.79, 95% CI 1.28–2.49) and nonheart beating donors (AOR = 1.46, 95% CI 1.08–1.96) were also significantly associated with 12-month TBKV. The model for living donor transplants also demonstrated similar risk factors with the exception that African American recipients were not associated with TBKV onset (AOR = 0.83, 95% CI 0.43–1.60). Models stratified by adult and pediatric recipients indicated similar factors associated with 12-month TBKV as in the primary model.

The associations of acute rejection episodes and DGF with TBKV are displayed in Fig. 2. There was no statistically significant association of 6-month TBKV with DGF (AOR = 1.08, 95% CI 0.88–1.33). There was a significant association of TBKV and acute rejection within the initial period of hospitalization in both the unadjusted and adjusted models. TBKV within 6 months also had a strong association with subsequent acute rejection between 6 and 12 months. For patients that had no prior acute rejections, patients with TBKV within 6 months had a twofold risk for acute rejection between 6 and 12 months in the adjusted model (AOR = 2.01, 95% CI 1.38–2.93). Among patients who had experienced prior acute rejection episodes, the association of 6-month TBKV and repeat rejections between 6 and 12 months was particularly strong (AOR = 4.81, 95% CI 3.32–6.96).

Table 3 displays the adjusted hazard ratios (AHR) associated with patients treated with tacrolimus relative to

Table 2. Logistic model for 12-month TBKV*.

Transplant characteristic (reference level)	Level	Adjusted odds ratio	95% CI
Recipient age (18–34), years	0–11	1.96	1.33–2.89
	12–17	1.48	1.03–2.13
	35–54	0.89	0.72–1.09
	55–64	1.08	0.86–1.35
	65+	1.17	0.91–1.52
Donor age (36–54), years	0–11	1.20	0.83–1.74
	12–17	0.83	0.59–1.17
	18–35	0.85	0.73–1.00
	55–64	1.04	0.84–1.29
	65+	1.88	1.35–2.61
Recipient PDGN (not diabetes)	Diabetes	0.73	0.61–0.87
Recipient gender (female)	Male	1.62	1.40–1.88
Donor gender (female)	Male	0.88	0.77–1.00
Recipient race (Caucasian)	African American	1.16	0.97–1.38
	Other	0.60	0.48–0.76
Donor race (Caucasian)	African American	0.92	0.75–1.15
	Other	0.88	0.70–1.09
Re-transplants (no)	Yes	1.06	0.85–1.32
BMI (<30 kg/m^2)†	>30 kg/m^2	0.91	0.77–1.07
HLA (A,B,DR) mismatches (0)	1–4	1.07	0.85–1.36
	5–6	1.36	1.07–1.73
PRA† (0)	1–30	0.86	0.73–1.01
	30+	1.16	0.95–1.42
Pretransplant dialysis time (none), years	0–1	1.13	0.78–1.64
	1–3	1.15	0.80–1.66
	3+	1.16	0.81–1.67
Baseline induction (IL-2 RB‡)	None	0.91	0.75–1.09
	Thymoglobulin	1.23	1.03–1.45
Baseline immunosuppression (cyclosporine)	Sirolimus	0.70	0.47–1.03
	Tacrolimus	1.35	1.04–1.74
Baseline antiproliferative medication (MMF)	None	0.82	0.66–1.02
	AZA	0.95	0.50–1.81

PDGN, primary diagnosis; BMI, body mass index; HLA, human leukocyte antigen; PRA, panel reactive antibody; MMF, mycophenalate mofetil.

*Patients with a minimum of 1-year graft survival.

†Missing levels not displayed.

‡Indication of Zenapax or Simulect as induction agents.

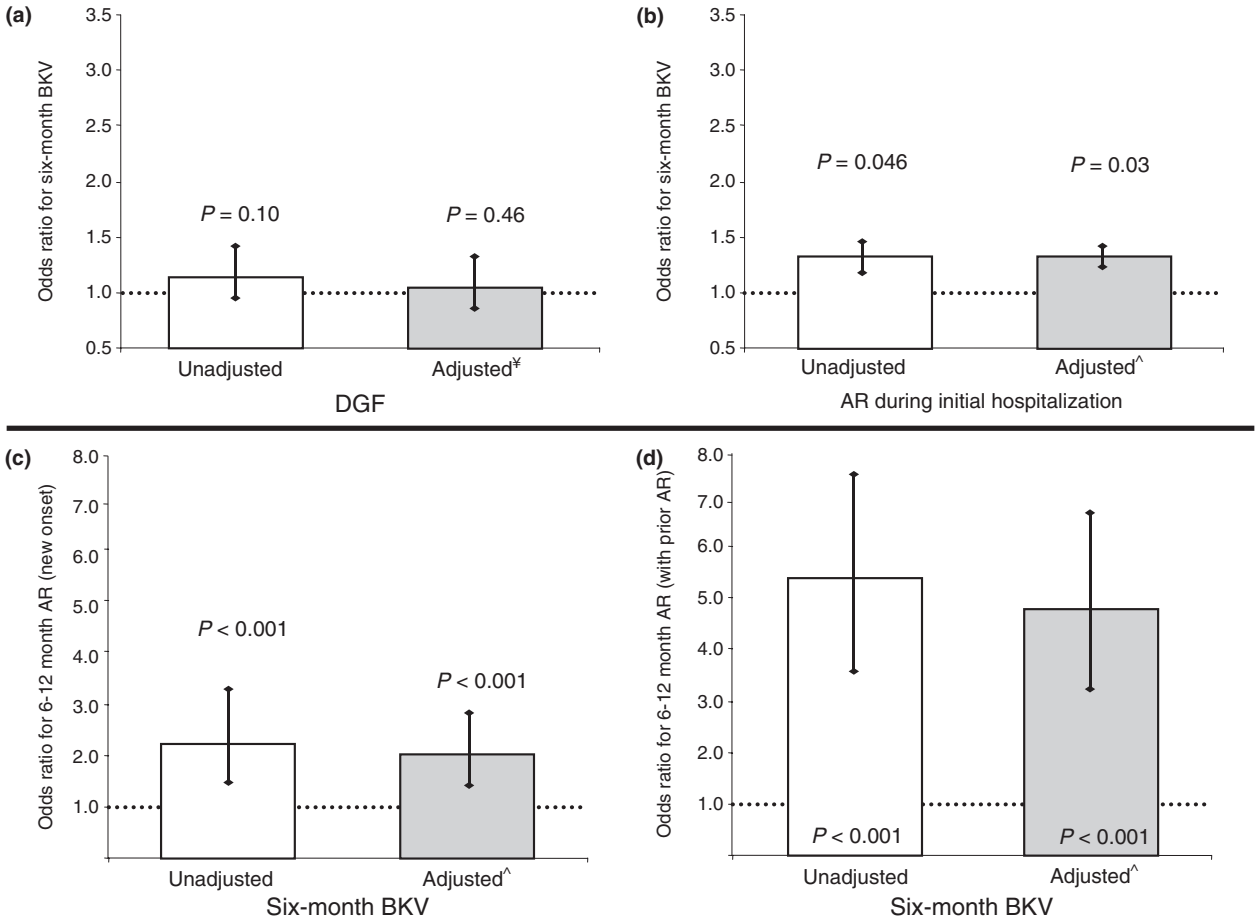

Figure 2 Association of clinical events with 6-month TBKV. (a) Association of DGF and 6-month TBKV; (b) association of AR during initial hospitalization with 6-month TBKV; (c) association of 6-month TBKV with new onset acute rejection (no previous events) between 6 and 12 months; (d) association of 6-month TBKV with a repeat acute rejection episode. ¥Model only included deceased donor transplants and adjusted for recipient and donor age, race and gender, recipient primary diagnosis, panel reactive antibody level, human leukocyte antigen matching and recipient body mass index. ^Models adjusted for recipient and donor age, race and gender, recipient primary diagnosis, panel reactive antibody level, donor source (living or deceased donor), human leukocyte antigen matching and recipient body mass index. Error bars represent 95% confidence intervals. DGF, delayed graft function; AR, acute rejection.

patients treated with cyclosporine during the initial hospital discharge within specific patient subgroups. For these models, odds ratios greater than one indicate a higher likelihood of TBKV for patients on tacrolimus at baseline as compared with patients on cyclosporine at baseline within the specific populations. Among the strata tested, there were no statistically significant interactions of TBKV with the patient groups. However, the estimated likelihood of TBKV was elevated in Caucasian recipients relative to African American recipients and patients treated with thymoglobulin as an induction agent relative to patients treated with an IL-2 RB. The association of patients treated with thymoglobulin as an induction agent relative to IL-2 RB with 1-year TBKV by patient groups is displayed in Table 4. There were no statistically significant interactions by patient groups tested, however, the estimated likelihood of TBKV among these patients was higher among living donor transplants relative to deceased donor transplants and patients treated with tacrolimus as concomitant immunosuppressive therapy relative to cyclosporine or sirolimus at baseline.

Outcomes following TBKV

Kaplan–Meier plots for overall graft survival, death-censored graft survival and patient survival for patients stratified by 6-month TBKV are displayed in Fig. 3a–c. Among patients with at least 6 months of follow up, overall graft survival at 3 years was 90% and 79% for patients without and with TBKV within the first 6 months ($P < 0.001$). Patient survival was not significantly different at 3 years between these groups, 95% and

Table 3. Likelihood of 1-year treatment for BK virus for patients treated with tacrolimus compared with cyclosporine at the time of transplantation.

Patient population* [no. patients with tacrolimus as baseline immunosuppression (*n*) = 24 646]	AOR for 1-year TBKV†	95% CI
Deceased donor transplants (*n* = 14 609)	1.36	0.97–1.90
Living donor transplants (*n* = 10 037)	1.34	0.91–1.99
African American recipients (*n* = 6125)	1.15	0.70–1.89
Caucasian recipients (*n* = 13 520)	1.56	1.11–2.21
Obese recipients‡ (*n* = 5806)	1.16	0.70–1.92
Nonobese recipients‡ (*n* = 15 934)	1.41	1.04–1.92
HLA-MM = 0–4 (*n* = 16 072)	1.43	1.02–2.01
HLA-MM = 5–6 (*n* = 8574)	1.18	0.80–1.75
Thymoglobulin as induction agent (*n* = 9927)	1.73	1.05–2.84
IL-2 RB as induction agent (*n* = 5704)	1.16	0.79–1.71

HLA, human leukocyte antigen; IL-2 RB, IL-2 receptor blockers; AOR, adjusted odds ratio.

*Patients included with a minimum of 1-year follow-up time.

†Reference group are patients with cyclosporine as baseline immunosuppressive medication; AOR > 1 indicate that tacrolimus had higher likelihood as compared with cyclosporine for TFBK within the specific patient population.

‡Patients with missing information not displayed.

Table 4. Likelihood of 1-year treatment for BK virus for patients treated with thymoglobulin as induction compared with IL-2 RB at the time of transplantation.

Patient population* [no. patients with thymoglobulin as baseline immunosuppression (*n*) = 13 160]	AOR for 1-year TBKV†	95% CI
Deceased donor transplants (*n* = 8237)	1.10	0.88–1.36
Living donor transplants (*n* = 4923)	1.42	1.08–1.87
African American recipients (*n* = 3520)	1.29	0.91–1.82
Caucasian recipients (*n* = 7316)	1.33	1.06–1.66
Obese recipients‡ (*n* = 3390)	1.16	0.80–1.67
Nonobese recipients‡ (*n* = 8496)	1.27	1.01–1.55
HLA-MM = 0–4 (*n* = 8297)	1.21	0.96–1.51
HLA-MM = 5–6 (*n* = 4863)	1.28	0.97–1.67
Tacrolimus as immunosuppressive agent (*n* = 9927)	1.29	1.07–1.57
CsA as immunosuppressive agent (*n* = 792)	0.97	0.52–1.79
Sirolimus as immunosuppressive agent (*n* = 1005)	0.92	0.47–1.83

HLA, human leukocyte antigen; IL-2 RB, IL-2 receptor blockers; AOR, adjusted odds ratio.

*Patients included with a minimum of 1-year follow-up time.

†Reference group are patients with IL-2 RB as baseline induction medication; AOR > 1 indicate that thymoglobulin had higher likelihood as compared with IL-2 RB for TFBK within the specific patient population.

‡Patients with missing information not displayed.

92% ($P = 0.08$). Death-censored graft survival was significantly different ($P < 0.001$), patients with TBKV within 6 months had 84% survival at 3 years post-transplantation while patients without TBKV had 94% death-censored graft survival at 3 years. After adjustment for potential confounding variables, 6-month TBKV was associated with almost a twofold risk for overall graft loss (AHR = 1.90, 95% CI = 1.44–2.51). The estimated hazards for overall graft loss within patient subgroups were relatively consistent with no statistically significant interaction for graft loss by race, age or donor type.

Discussion

There are several principal findings from our study examining TBKV in kidney transplant recipients using national registry data. First, the results indicate an overall incidence rate of TBKV of approximately 3% at 1 year post-transplantation. This rate increased over the study period, which may be an indication of more vigilant reporting and detection. Second, the study identified several significant risk factors associated with TBKV onset including recipient age, race, gender, donor characteristics, HLA-mismatching, acute rejection episodes and immunosuppressive therapy. Finally, results demonstrate a significant association of TBKV onset with graft loss among kidney transplant recipients and further that this risk appears to be applicable across patient subgroups. Cumulatively, these results confirm that TBKV has significant prevalence in the renal transplant population, confirms that certain patient groups and transplant characteristics are at elevated risk for TBKV onset and that TBKV is associated with a significant risk for graft loss.

The precise estimation of the incidence of TBKV across clinical settings is challenging based on differential criteria and protocols for diagnoses. However, the incidence rates which are reported in this study are relatively consistent with the existing literature stemming from single-center observations [11,12,19,25,27]. A sensitivity analysis, using data from centers with complete reporting did not alter the results suggesting that the estimates are less likely to be related to the method of data ascertainment. Beyond providing novel information from the national perspective, one significant advantage of this study is incorporat-

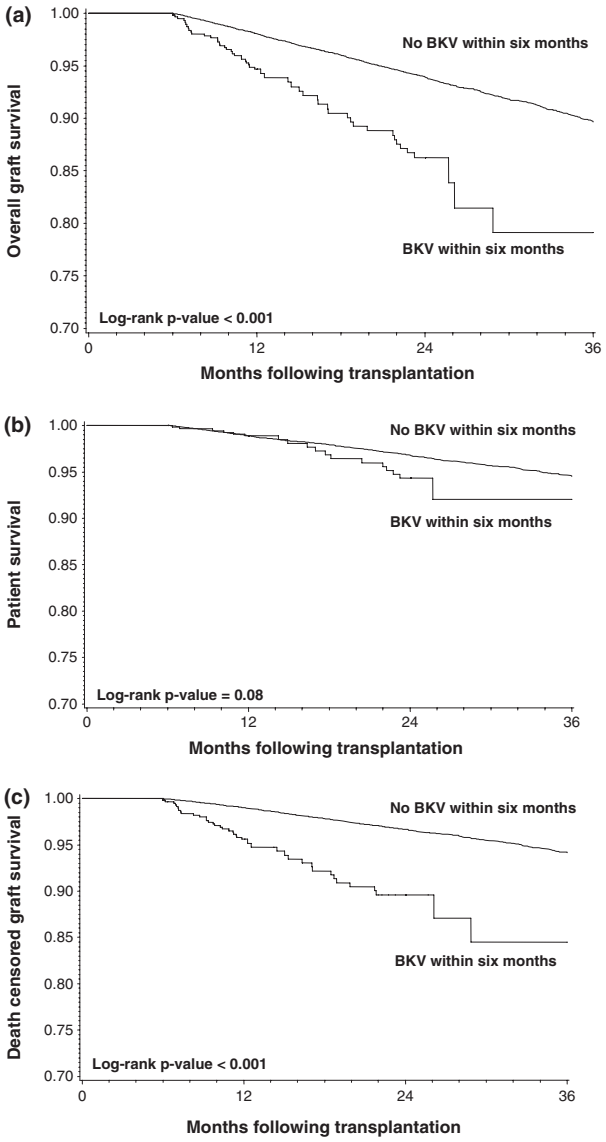

Figure 3 (a) Overall graft survival following 6-month TBKV. (b) Patient survival following 6-month TBKV. (c) Death-censored graft survival following 6-month TBKV.

ing a uniform indication of TBKV onset. Although this metric may still be an underestimate of the condition (as BK virus ultimately requires a renal transplant biopsy for diagnosis), it does provide an objective assessment that can be easily understood based on the need for a medical intervention. Incidence rates based on the requirement for treatment potentially eliminates events that are relatively mild (e.g. small fluctuations in viremia) and clinically unimportant. This is the same logic that is utilized when estimating acute rejection rates from registry information in a circumstance in which detection protocols may vary. However, it is also important to recognize that certain differences that were statistically significant may not be classified as clinically relevant and perspective of the magnitude of the risk factors is warranted. Ideally further information about the severity of TBKV and the specific rates of progression to BK virus nephropathy would also be useful but are limited by the available data.

These caveats must also be considered with respect to identification of risk factors and the association of TBKV with major clinical events. Specifically, underreporting may lead to decreased ability to identify certain risk factors for which more specific and detailed information would be advantageous. There is also potential that the likelihood for treatment is associated with patient prognosis and for those patients who experience side-effects or generally have a greater risk profile, treatment may be more common. Therefore, it is certainly possible that the likelihood of TBKV in healthier patient populations or patients not experiencing other complications within the time frame are higher than that estimated in this study. In a similar fashion, the association of TBKV with major clinical events is an important result of this study. Given that some underreporting may be evidenced, as described, TBKV onset reflects cases that required medical interventions. In particular, extrapolation of minor BK viremia changes to the risk for graft loss may not be warranted. Moreover, we cannot equate TBKV with indications of BK virus nephropathy as these are clearly not synonymous and the degree of overlap cannot be specifically ascertained with these data.

As a result of the epidemiology of the advent of BK virus, it has been assumed that onset is largely associated with more cumulative immunosuppression. In fact, our results appear to confirm the association of BK virus with stronger immunosuppression indicated by induction with thymoglobulin and use of tacrolimus. Certainly it is not possible to conclude that tacrolimus by itself directly causes TBKV in this retrospective analysis, it is possible that this is driven by increased exposure to MPA with tacrolimus. It is possible that increased immunosuppression mediates the increased risk for TBKV in African American and male recipients, high PRA recipients and pediatric recipients. Among elderly recipients possibly a certain degree of immunoincompetence might medicate a higher risk for TBKV. It is also possible that male recipients are at risk for BK virus associated with a higher incidence of obstructive uropathy. There is also some indication that intrinsic damage to the donor kidney might also mediate a risk for subsequent TBKV as donors after cardiac death, transplants from older donors and diabetic donor kidneys were at higher risk although interestingly there was not a significant association of TBKV with DGF. The association of TBKV with older age and

female donors is consistent with a recent study finding, but in this study they did not detect associations with acute rejection or immunosuppression [25]. In precisely these circumstances, it is useful to confirm these associations within the US population more broadly and potentially supplement findings that have been reported in other centers. It is not clear why patients with diabetes as a primary diagnosis had reduced likelihood for TBKV, whether this is related to competing risks or different management strategies, but to understand this clearly requires further investigation. HLA-mismatching has also previously been identified as a significant risk factor for TBKV, our results indicated that this was particularly evident in highly mismatched transplants, but there was no increased likelihood associated with one to four HLA (A,B,DR)-mismatched transplants relative to zero-mismatched transplants.

An important result of the study is confirming the significant risk for graft loss associated with TBKV. These results emphasize the need for the development of effective screening and treatment protocols. Particularly given the early onset of TBKV in our study and as indicated by other reports, early routine monitoring levels after transplantation appears warranted. Based on these results, this study suggests that TBKV onset has similar risk for graft loss among different patient subgroups. It may be reasonable to hypothesize that certain patients would be at heightened risk of other clinical events associated with TBKV and subsequent immunosuppression reduction (e.g. African Americans); however the findings of this study suggest that risk for graft loss was relatively equivalent. More generally, given the strong impact of TBKV on graft survival, which is greater that associated with acute rejection, TBKV should also be included as a safety endpoint in studies investigating new immunosuppressive protocols.

In summary, national data indicates that TBKV has a 1-year incidence of almost 3% and has been rising among renal transplant recipients. Demographic characteristics, HLA-matching, clinical events and specific immunosuppressive therapy appear to be significant risk factors for TBKV. A twofold risk for graft loss is associated with TBKV onset and careful early monitoring is warranted in this population. Further development of treatment strategies and understanding of disease progression is clearly needed.

Authorship

JDS: wrote the paper, designed study, and analyzed data. SR: performed research and drafted paper. LKK and JM: drafted paper and critical revisions. TRS and HM: performed research, designed study and critical revisions.

Acknowledgements

The data and analyses reported in this manuscript have been supplied by UNOS and Arbor Research under contract with HHS. The authors alone are responsible for reporting and interpreting these data.

We have had no involvements that might raise the question of bias in the work reported in the conclusions, implications or opinions stated.

The data reported here have been supplied by the Arbor Research Collaborative for Health (Arbor Research) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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