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ORIGINAL ARTICLE

BK Virus Epidemiology, Risk Factors, and Clinical Outcomes: An Analysis of Hematopoietic Stem Cell Transplant Patients at Texas Children's Hospital

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Background. BK virus-associated hemorrhagic cystitis (BKV-HC) is a serious complication after hematopoietic stem cell transplantation (HSCT).

Methods. A retrospective review was performed to determine the frequency of BKV-HC and identify risk factors and renal morbidity associated with BKV-HC in pediatric HSCT recipients at our institution.

Results. A total of 314 pediatric recipients underwent allogeneic HSCT for either malignant (173, 55.1%) or nonmalignant disorders (141, 44.9%) from January 1, 2011, to December 31, 2015, with a minimum follow-up of 5 years post-HSCT. Severe BKV-HC (grades 3 and 4) was prevalent in 46 out of 67 (68.7%) recipients. Timing to presentation of severe BKV-HC (grades 3 and 4) occurred at a median of 37 days (26, 74; IQ1, IQ3) post-HSCT, with the duration of macroscopic hematuria lasting a median of 37.5 days (18, 71; IQ1, IQ3). In the first 60 days post-HSCT, peak acute kidney injury (AKI) stages 2 and 3 were seen more frequently in HSCT recipients who developed BKV-HC than those without ($P = .004$). Similarly, during post-HSCT days 61 to 100, peak AKI stage 3 was also more frequently seen in HSCT recipients who already developed BKV-HC prior to or during this time period than those without BKV-HC ($P = .0002$). Recipients who developed BKV-HC within 1 year of HSCT had more frequent mild to moderate chronic kidney disease (CKD stages 2-3) than those without BKV-HC ($P = .002$ and .007, respectively). On multivariate analysis, BKV-HC was associated with all-cause mortality (hazard ratio [HR]: 2.22; 95% confidence interval [CI]: 1.35-3.65). The following clinical variables were associated with time to development of HC on multivariate analysis: age (subdistribution HR [sHR] 1.11; 95% CI: 1.06-1.16) and myeloabalative conditioning regimen (sHR 4.2; 95% CI: 2.12-8.34).

Conclusions. Pediatric HSCT patients with BKV-HC experience significant morbidity and mortality. Renal morbidity, including AKI and CKD, is associated with BKV-HC.

Key words. BK virus; hematopoietic stem cell transplant; hemorrhagic cystitis.

BK virus (BKV) is a ubiquitous human polyomavirus that causes severe morbidity in immunosuppressed hosts. BKV has known tropism for uroepithelium, and genitourinary tract disease is the most common manifestation of BKV infection in hematopoietic stem cell transplantation (HSCT) recipients [1]. HSCT recipients are particularly susceptible to developing BKV-associated hemorrhagic cystitis (BKV-HC), which can manifest asymptomatically with microscopic hematuria or with urinary symptoms of dysuria, urgency, frequency, and/or suprapubic pain. In cases of severe BKV-HC, blood clots can deposit in the urinary tract leading to urinary obstruction, acute renal failure, prolonged hospitalization, increased transfusions, and increased mortality [2–4].

Often acquired in early childhood, primary BKV infection is usually asymptomatic or associated with mild upper respiratory symptoms in immunocompetent hosts [5]. Seroprevalence rates in children have been reported to be approximately 50% by 3–4 years of age [2] and as high as 91% by 5–9 years of age [6]. Transmission may occur by means of exposure to bodily fluids, such as oral secretions, transplacental passage [5], or via solid organ transplantation. While renal transplant recipients can acquire BKV from their donors [7], there is no known transmission from HSCT donors to recipients. BKV infection in pediatric HSCT recipients may represent primary infection or reactivation of latent infection. Risk factors for reactivation include BKV seropositivity and older age [2].

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The epidemiology of BKV-HC has been described in pediatric HSCT recipients in previous studies [8–15]. Our work adds to existing data by describing the prevalence of BKV-HC in the largest retrospective pediatric allogeneic HSCT (allo-HSCT) cohort to date, over a prolonged follow-up period. Our cohort includes multiple recipients who required HSCT for nonmalignant underlying diseases, a contemporary population that is not well studied in past studies. The final unique aim of our study was to evaluate associations between acute and chronic genitourinary outcomes and BKV-HC, outcomes that have not been previously described in a pediatric cohort.

METHODS

Patient and Donor Characteristics

All consecutive patients who underwent their initial allo-HSCT from January 1, 2011, to December 31, 2015, at Texas Children's Hospital (TCH) in Houston, Texas, were included in this retrospective cohort study. The Baylor College of Medicine Institutional Review Board approved this research protocol.

Electronic medical records were reviewed from the time of transplant until a minimum of 5 years post-HSCT. The following independent variables were identified: recipient demographics, days to engraftment, chemotherapy conditioning regimen, immunosuppressive medications, underlying diagnosis, donor sex, donor human leukocyte antigen (HLA) match, graft source, previous transplantation status, graft vs host disease (GVHD), BKV load in the urine and blood, complete blood counts at HSCT day +30/60/100, and presence of concomitant viral infection(s) (adenovirus, cytomegalovirus [CMV], and JC virus [JCV]).

Outcome variables included BKV-HC classification by severity, peak acute kidney injury (AKI) during post-HSCT days 1–60 and 61–100, chronic kidney disease (CKD) grade at 1-year post-HSCT, and all-cause mortality.

BKV Testing

At our institution, pediatric HSCT recipients do not undergo standardized posttransplant screening for BKV. Point-of-care urinalysis is performed on every void (including diapered patients) during initial inpatient hospitalization, along with complete microscopic urinalysis every 1–2 weeks for the first 100 days posttransplant. BKV testing is exclusively reserved for the clinical indication of microscopic/macroscopic hematuria or symptoms of cystitis.

Initial BKV testing was performed by real-time quantitative urine polymerase chain reaction (PCR) (assay range 500-1 × 10^{10} copies/mL) with nucleic acid primer/probe pairs specific for conserved regions of the BK virus genome (Viracor laboratories). Plasma BKV testing (assay range 39-1 × 10^{10} copies/mL, Viracor laboratories) may have been subsequently ordered at the discretion of the attending physician.

Variable Definitions

Acute GVHD grading of the skin, liver, and gastrointestinal tract was determined via the modified Glucksberg criteria [16, 17]. Severe GVHD was defined if there was single organ involvement greater than stage 2, or if there was multiorgan involvement. For GVHD symptoms persisting beyond post-HSCT day 100, chronic GVHD was diagnosed [18].

Donor to recipient matching was defined by HLA matching association and relationship status. Donor grafts were categorized as follows: matched related donor (MRD: HLA match 10/10); mismatch related donor/haploidentical donors (MMRD: HLA mismatch at 1 or more loci in a family relative); matched unrelated donor (MUD: HLA match 10/10); and mismatch unrelated donor (MMUD: HLA mismatch at 1 or more loci). Conditioning regimens were categorized into myeloablative (MA) and reduced-intensity conditioning based on the American Society of Blood and Marrow Transplantation definitions [19].

Hematuria severity is commonly described as microscopic (grade 1), macroscopic (grade 2), macroscopic with clots (grade 3), or macroscopic with clots and post-renal failure secondary to urinary tract obstruction (grade 4) [20]. Subsequently, BKV-HC grading was defined via the European Conference on Infections in Leukemia (ECIL) consensus document, which required the triad of (1) clinical symptoms/signs of cystitis, (2) a hematuria grade ≥ 2, and (3) the demonstration of BKV viruria of >7 $\log_{10}$ copies/mL [20]. Additionally, all HSCT recipients meeting the BKV-HC criteria were then determined not to have an alternative HC etiology (ie, concurrent adenovirus viruria).

AKI stage was defined via kidney disease improving global outcomes (KDIGO) guidelines [21] and calculated by comparing peak creatinine level at 2 timeframes (days 1-60 and 61-100 post-HSCT) to baseline creatinine at the time of HSCT. Estimated glomerular filtration rate (eGFR), calculated via the Schwartz "bedside" formula [22], at 1-year post-HSCT was compared with baseline eGFR at time of HSCT, to determine CKD stage (as per KDIGO guidelines) [23]. To evaluate the hypothesis of whether BKV-HC was associated with either AKI or CKD, BKV-HC that occurred prior to these outcome measurements was documented.

Patients were classified as having a concomitant viral infection if CMV or adenovirus blood PCR testing was (>200 copies/mL) on at least 2 consecutive samples after HSCT. JCV coinfection was identified if any positive urine or plasma levels were identified. At our institution, blood CMV and adenovirus PCR testing are sent for both clinical indication and routine surveillance.

Statistical Analysis

Patient and transplant characteristics were summarized using descriptive statistics. Differences between groups were tested using Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables and Fisher's exact test or Chi-square test for categorical variables.

Overall survival (OS) was calculated from the time of initial HSCT to death from any cause; observations were censored at the time of last follow-up or at the time of the repeat HSCT. Kaplan-Meier curves were generated to estimate OS. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). The effects of covariates were assessed on univariate and multivariate analyses. The occurrence of HC was modeled as a time-dependent covariate in the analyses as it changed over time during the follow-up period. Multivariate Cox regression analysis was adjusted with all variables to evaluate the association between HC and survival outcome.

We also conducted competing risk analyses to evaluate the effects of covariates on the occurrence of HC in the presence of competing risks. Cumulative incidence of HC post-HSCT was calculated and plotted by the competing risk method as described in the study of Gray [24]. Univariate and multivariate Fine and Gray [25] subdistribution hazard models were carried out to estimate subdistribution hazard ratios (sHRs) and the corresponding 95% CIs of covariates with death as a competing event. Covariates were included in the multivariate model if they were associated with HC in the univariate analysis or potential confounders associated with HC. All analyses were performed using SAS 9.4 or R3.4.3. All tests were 2-sided with $P < .05$ being considered significant.

RESULTS

Demographics, Clinical Characteristics, and Laboratory Findings

Three hundred fourteen recipients underwent their first allo-HSCT at TCH during the study period. Overall, 67 of the 314 (21.3%) total recipients developed BKV-HC. The severity of BKV-HC was further classified as follows (Figure 1A): 21 (31.3%) recipients with BKV-HC grade 2 and 23 (34.3%) recipients each with grades 3 and 4. Of the 247 recipients who did not develop BKV-HC, 108 (43.7%) tested negative for BKV (either urine or plasma testing on at least 1 occasion), 85 (34.4%) were never tested for BKV, and 54 tested positive for BKV infection but did not meet the ECIL criteria for BKV-HC. Five HSCT recipients developed HC that was noninfectious in etiology and 1 HSCT recipient developed adenovirus-associated HC.

During the study period, 26 recipients required a second HSCT due to either graft failure or recurrence of underlying disease. Seven of these recipients developed BKV-HC after their first HSCT (Figure 1B). Three HSCT recipients required a total of 3 different HSCTs during the study period, with only 1 recipient developing BKV-HC grade 3 during his second HSCT (Figure 1C).

HSCT recipient demographics and clinical characteristics are shown in Table 1. Demographic and clinical characteristics that differed between those with BKV-HC compared with those without BKV-HC included: patient age ($P < .0001$), malignant vs nonmalignant underlying disease ($P < .0001$), recipient CMV-positive serology ($P = .016$), peripheral blood stem cell (PBSC) source ($P = .016$), MA conditioning regimen ($P = .002$), use of cyclophosphamide conditioning agent ($P = .027$), severe GVHD ($P = .028$), concomitant viremia with CMV and or adenovirus ($P < .0001$), and concomitant viremia with CMV alone ($P < .0001$). Laboratory findings that differed between groups included absolute lymphocyte count at day 30 ($P = .002$) and day 60 ($P < .0001$) post-HSCT.

Clinical, Laboratory, and Urologic Imaging Findings During BKV-HC Episode

Recipients with BKV-HC required a total of 54 admissions for HC (0-5 admissions/patient). The median duration of macroscopic hematuria was increased with severity of BKV-HC (5, 23, and 64 days for grades 2, 3, and 4, respectively) ($P < .0001$) (Table 2). Time to development of hematuria was a median of 37 days post-HSCT, with no difference between BKV-HC groups. There was a significant difference in peak viremia ≥10 000 copies/mL among HSCT recipients with different BKV-HC grades ($P = .038$): 33.3% for grade 2, 39.1% for grade 3, and 69.6% for grade 4.

Renal ultrasound (RUS) evaluation in HSCT recipients is not protocolized at our institution and is at the clinician's discretion. For patients who received RUS, there was a significant difference in hydronephrosis (unilateral or bilateral) as well as in bladder wall thickening among HSCT recipients with different BKV-HC grades ($P = .001$ and $P < .001$, respectively).

To relieve urinary obstruction in recipients with BKV-HC grade 4, 26.1% required single or intermittent Foley catheter placement, and 73.9% underwent continuous bladder irrigation. Nephrostomy tube(s) placement was required in 34.8% of recipients with BKV-HC grade 4.

Renal Morbidity

In the first 60 days post-HSCT, peak AKI stages 2 and 3 were seen more frequently in HSCT recipients who developed BKV-HC ($P = .004$, Table 3). Similarly, during post-HSCT days 61 to 100, there was a higher incidence of peak AKI stage 3 in HSCT recipients who already developed BKV-HC prior to or during this time period ($P = .0002$). During a specific episode of BKV-HC, peak AKI stage 3 was more common in recipients with BKV-HC grade 4 (73.9%) than those with BKV-HC grade 2 or 3 (4.8% and 8.7%, respectively, $P < .0001$, Table 2). Additionally, recipients with BKV-HC within the first year

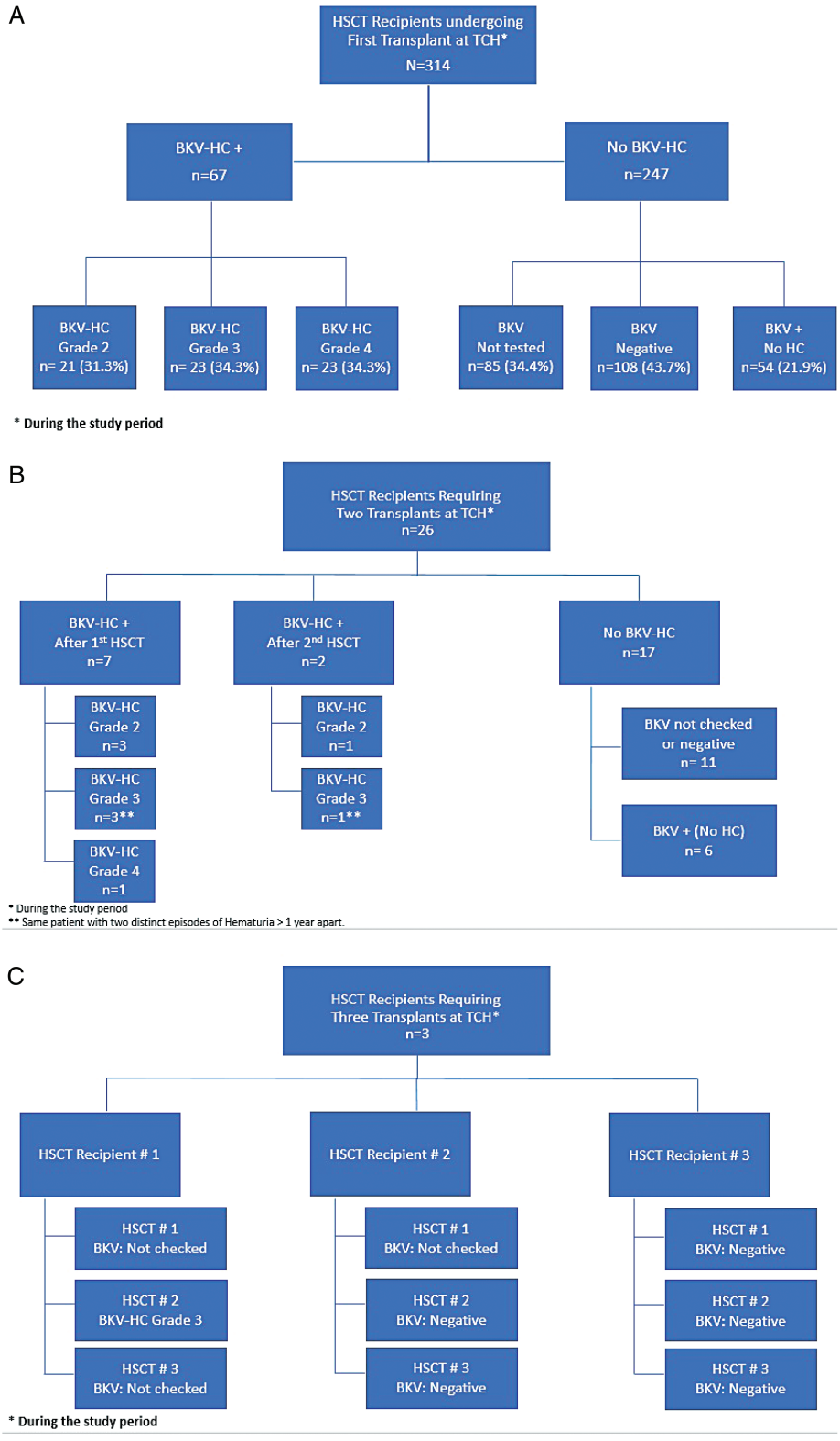

Figure 1. (A) Flow diagram of all first-time allogeneic hematopoietic stem cell transplantation (HSCT) recipients at Texas Children's Hospital (TCH) from 2011 to 2015 by BKV-associated hemorrhagic cystitis (BKV-HC) status and subsequently by BKV testing for those without BKV-HC. (B) Flow diagram of HSCT recipients requiring 2 transplantations at TCH during the study period. (C) Flow diagram of HSCT recipients requiring 3 transplantations at TCH during the study period.

Table 1. Patient Demographics and Clinical Characteristics of HSCT Recipients at TCH[a]

Total Allogeneic HSCT Recipients (N = 314)	BKV (+) Hemorrhagic Cystitis (n = 67)	No BKV Hemorrhagic Cystitis (n =247)	*P*-value*
Age (years)			
Median (IQR1, IQR3)	12.7 (7.4, 15.2)	6.6 (2.2, 12.1)	**<.0001**
Gender			
Male (n = 202)	43 (64.2%)	159 (64.4%)	.977
Underlying disease			
Malignant (n = 173)	51 (76.1%)	122 (49.4%)	**<.0001****
Leukemia (n = 128)	36 (53.7%)	92 (37.2%)	
Lymphoma (n = 28)	5 (7.5%)	23 (9.3%)	
MDS (n = 16)	9 (13.4%)	7 (2.8%)	
JXD (n = 1)	1 (1.5%)	0	
Nonmalignant (n = 141)	16 (23.9%)	125 (50.6%)	
Immunodeficiency (n = 48)	6 (9.0%)	42 (17.0%)	
SAA (n = 34)	3 (4.5%)	31 (12.6%)	
Hemoglobinopathy (n = 25)	3 (4.5%)	22 (8.9%)	
HLH (n =22)	0	22 (8.9%)	
Congenital cytopenia (n = 8)	3 (4.5%)	5 (2.0%)	
Metabolic/endocrine (n = 4)	1 (1.5%)	3 (1.2%)	
Donor type			
MRD (n = 90)	11 (16.4%)	79 (32.0%)	.072
MMRD/Haplo (n = 40)	12 (17.9%)	28 (11.3%)	
MUD (n = 86)	20 (29.9%)	66 (26.7%)	
MMUD (n = 98)	24 (35.8%)	74 (30.0%)	
Donor sex			
Male (159)	35 (52.2%)	124 (50.2%)	.768
Donor CMV positive (n = 154)	35 (52.2%)	119 (48.2%)	.595
Recipient CMV positive (n = 218)	54 (80.6%)	164 (66.4%)	**.016**
Stem cell source			
Bone marrow (n = 208)	45 (67.2%)	163 (66.0%)	**.016**
PBSC (n = 63)	19 (28.4%)	44 (17.8%)	
Cord blood (n = 43)	3 (4.5%)	40 (16.2%)	
Conditioning regimen			**.002**
Full myeloablative (n = 209)	55 (82.1%)	154 (62.3%)	
Reduced intensity (n = 105)	12 (17.9%)	93 (37.7%)	
Conditioning agents			
Busulfan (n = 135)	33 (49.3%)	102 (41.3%)	.243
Cyclophosphamide (n = 229)	56 (83.6%)	173 (70.0%)	**.027**
GVHD (at any point)			
Acute (n = 144)	35 (52.2%)	109 (44.1%)	.237
Severe (n = 48)	16 (23.9%)	32 (13.0%)	**.028**
Chronic (n = 49)	14 (20.9%)	35 (14.2%)	.179
Prior transplant (n = 10)	2 (3.0%)	8 (3.2%)	1.000
Concomitant viremia			
CMV and or Adenovirus (n = 135)	46 (68.7%)	89 (36.0%)	**<.0001**
CMV (n = 106)	38 (56.7%)	68 (27.5%)	**<.0001**
Adenovirus (n = 42)	13 (19.4%)	29 (11.7%)	.120
JC virus (including viruria) (n = 6)	3 (4.5%)	3 (1.2%)	.668
Immunosuppression drugs			
ATG (n = 19)	4 (6.0%)	15 (6.1%)	1.000
Tacrolimus (n = 168)	37 (55.2%)	131 (53.0%)	.750
Cyclosporine (n = 118)	20 (29.9%)	98 (39.7%)	.141
Mycophenolate mofetil (n = 78)	18 (26.9%)	60 (24.3%)	.665
Mini-methotrexate (n = 150)	38 (56.7%)	112 (45.3%)	.098
Steroids (n = 165)	39 (58.2%)	126 (51.0%)	.295
Days until engraftment: Median (IQR1, IRQ3) (n = 303)	18 (15, 21)	18 (15, 20)	.937
Complete blood counts: median (IQR1, IRQ3)			
ANC day +30 (n = 312)	2.25 (1.34, 4.03)	1.90 (1.27, 3.12)	.120
ANC day +60 (n = 294)	2.86 (1.69, 3.79)	2.49 (1.48, 3.51)	.380
ANC day +100 (n = 270)	2.24 (1.4, 3.7)	2.66 (1.78, 3.91)	.178
ALC day +30 (n = 312)	0.13 (0.04, 0.29)	0.25 (0.08, 0.44)	**.002**
ALC day +60 (n = 294)	0.31 (0.16, 0.57)	0.62 (0.34, 0.99)	**<.0001**
ALC day +100 (n = 270)	0.73 (0.36, 1.12)	0.78 (0.5, 1.39)	.057

Abbreviations: MDS, myelodysplastic syndrome; JXD, juvenile xanthogranuloma; SAA, severe aplastic anemia; HLH, hemophagocytic lymphohistiocytosis; ATG, anti-thymocyte globulin; MRD, matched related donor; MMRD, mismatch related donor; MUD, matched unrelated donor; MMUD, mismatch unrelated donor; PBSC, peripheral blood stem cell; CMV, cytomegalovirus; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; IQR, interquartile range; TCH, Texas Children's Hospital.

[a]First transplant at TCH during the study period.

*All *P*-values are based on Chi-square or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables; **comparison between malignant vs. nonmalignant. Significant *P*-values are bolded and represent a *P*-value <.05.

post-HSCT were more likely to develop acute renal failure requiring dialysis ($P = .007$).

Recipients who developed BKV-HC within 1 year of HSCT had more frequent mild to moderate CKD (stages 2and 3, $P = .002$). End stage renal disease developed in 1 recipient who required continued dialysis after 1-year post-HSCT.

Risk Factors for BKV-HC and OS

The 2-year cumulative incidence of BKV-HC was 21.4% (95% CI: 17.0%-26.1%) (Figure 2A), with the majority of cases occurring in the first 4 months post-HSCT (Figure 2B). There was a significant difference in the 1-year cumulative incidence of BKV-HC between malignant and nonmalignant underlying HSCT diagnoses (Figure 2C). The 1-year cumulative incidence of BKV-HC was 28.4% (95% CI: 21.8%-35.2%) for malignant and 11.4% (95% CI: 6.8%-17.2%) for nonmalignant recipients. The cumulative incidence of BKV-HC was similar among patients who underwent transplantations by year over the study period (Figure 2D).

On univariate analysis, patients with BKV-HC had significantly worse OS (HR: 2.54, 95% CI: 1.64-3.93, $P = .012$). Factors such as age at transplant ($P = .012$), underlying diagnosis ($P = .002$), donor type ($P < .0001$), and stem cell source ($P < .0001$) were significantly associated with OS and summarized in Table 4. On multivariate analysis, HC remained a significant factor associated with an increased risk of poor OS (HR: 2.22, 95% CI: 1.35-3.65, $P = .002$) after adjustment for other factors.

A competing risk analysis for the development of BKV-HC was performed using patient characteristics at the time of transplant (Table 5). On multivariate analysis, age at transplant and full MA conditioning regimen (compared with reduced intensity) were both associated with a higher risk of developing

Table 2. Clinical, Laboratory, and Imaging Findings During First BKV-HC Episode

Total patients (N = 67)	BKV-HC Grade 2 N = 21	BKV-HC Grade 3 N = 23	BKV-HC Grade 4 N = 23	*P*-value*
Timing of BKV-HC episode (days post-HSCT) Median (IQR1, IQR3)	35 (22, 52)	37 (26, 95)	37 (24, 69)	.756
Duration of BKV-HC episode (days) Median (IQR1, IQR3)	5 (3,11)	23 (10, 48)	64 (35, 75)	**<.0001**
Hydronephrosis during HC on RUS				
None	11 (91.7%)	17 (85%)	8 (34.8%)	**.001**
Unilateral or Bilateral	1 (8.3%)	3 (15%)	15 (65.2%)	
RUS not performed	9	3	0	
Bladder wall thickening during HC on RUS				
No	8 (72.7%)	2 (10%)	1 (4.3%)	**<.0001**
Yes	3 (27.3%)	18 (90%)	22 (95.7%)	
RUS not performed	10	3	0	
Clot present during HC on RUS				
No	NA	5 (25.0%)	0(0%)	
Yes		15 (75.0%)	23 (100%)	
RUS not performed		3	0	
Foley catheter during HC				
Yes (once or intermittent)	NA	NA	6 (26.1%)	
Yes (continuous bladder irrigation)			17 (73.9%)	
Nephrostomy tubes during HC				
No	NA	NA	15 (65.2%)	
Yes			8 (34.8%)	
Viremia				
Peak ≥ 10 000 copies/mL	7 (33.3%)	9 (39.1%)	16 (69.6%)	**.038**
Peak < 10 000 copies/ mL	14 (66.7%)	14 (60.9%)	7 (30.4%)	
Peak AKI during BKV-HC episode				
None	11 (52.4%)	7 (30.4%)	2 (8.7%)	**<.0001**
Stage 1	5 (23.8%)	5 (21.7%)	0 (0%)	
Stage 2	4 (19.0%)	8 (34.8%)	3 (13%)	
Stage 3	1 (4.8%)	2 (8.7%)	17 (73.9%)	
Censored due to death/repeat HSCT	0	1	1	

Abbreviations: AKI, acute kidney injury; BKV-HC, BK virus-hemorrhagic cystitis; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; RUS, renal ultrasound; NA, not applicable.
*Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Significant *P*-values are bolded and represent a *P*-value <.05.

BKV-HC (sHR: 1.11, 95% CI: 1.06-1.16, $P < .0001$) and (sHR: 4.2, 95% CI: 2.12-8.34, $P < .0001$, respectively).

DISCUSSION

In this study, we report the clinical characteristics of BKV-HC in a large pediatric HSCT patient cohort. Unique features of our study include our diverse patient population of both malignant and nonmalignant disorders, long-term patient follow-up (5-9 years), and assessment of acute and chronic renal and genitourinary morbidity.

Twenty-one percent of recipients developed BKV-HC, which is slightly higher than previously studied allo-HSCT pediatric cohorts. In the 2 largest published pediatric retrospective studies to date, Haines et al [9] reported that 9.9% of 313 allo-HSCT recipients developed BKV-HC, while Oshrine et al [10] reported 19.9% of 221. Similar rates of BKV-HC were found in pediatric prospective studies. Cesaro et al [8] reported a 100-day cumulative BKV-HC incidence of 18.8% in 107 allo-HSCT recipients, while Gorczynska et al identified BKV-HC in 20.6% of 102 patients [12]. In a large retrospective adult study looking at 323 consecutive allo-HSCT recipients, only 30 patients (9.3%) developed BKV-HC grades 2 and above [26]. Of note, these aforementioned studies were performed prior to the recently published stricter ECIL BKV-HC guidelines and, therefore, may be an overrepresentation of BKV-HC incidence [20].

In our study, multivariate associations with BKV-HC included older age at transplantation and full MA conditioning regimen. Previous pediatric studies have identified similar risk factors for developing BKV-HC, specifically older recipient age (>6 and 7 years, respectively) [13, 14] and conditioning with high-dose chemotherapy [12]. While the PBSC source was only associated with BKV-HC in our univariate analysis, a large adult cohort found this variable to be associated with developing BKV-HC in multivariate analysis [26].

Forty-five percent of our cohort underwent allo-HSCT for nonmalignant conditions, which is higher than what has been

Table 3. Renal Morbidity in Patients With and Without BKV-HC (All First-Time HSCT)

	BKV-HC Prior to Outcome Measurement	No BKV-HC Prior to Outcome Measurement	*P*-value*
Peak AKI D+ (1-60)	N = 45	N = 269	
None	6 (13.3%)	61 (22.7%)	**.004**
Stage 1	7 (15.6%)	94 (34.9%)	
Stage 2	18 (40%)	68 (25.3%)	
Stage 3	14 (31.1%)	46 (17.1%)	
Peak AKI D+ (61-100)	N = 52	N = 239	
None	14 (26.9%)	107 (44.8%)	**.0002**
Stage 1	10 (19.2%)	70 (29.3%)	
Stage 2	10 (19.2%)	38 (15.9)	
Stage 3	18 (34.6%)	24 (10.0%)	
Censored due to death/repeat HSCT	7	16	
CKD D+365	N = 40	N = 149	
No CKD	21 (52.5%)	117 (78.5%)	**.002**
Mild-moderate CKD (stages 2 and 3)	18 (45.0%)	27 (18.1%)	
Severe CKD (stages 4 and 5)	1 (2.5%)	5 (3.4%)	
Censored due to death/repeat HSCT	25	100	
Dialysis (up to D+365)	N = 65	N = 249	
No	58 (89.2%)	243 (97.6%)	**.007**
Yes	7 (10.8%)	6 (2.4%)	

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; BKV-HC, BK virus-hemorrhagic cystitis; HSCT, hematopoietic stem cell transplantation.
*Fisher's exact test. Significant *P*-values are bolded and represent a *P*-value <.05.

described in other retrospective studies [10, 26]. We found that the 1-year cumulative incidence of BKV-HC was higher in patients with malignant vs nonmalignant conditions [10, 26]. We speculate that this is due to patients with malignant disorders being more immunosuppressed coming to HSCT and that the majority of patients with nonmalignant disorders were younger at the time of transplant.

Our study showed that concomitant CMV and/or adenovirus viremia was associated with BKV-HC, a finding that has not been commonly reported. A prospective pediatric study found that recipients with HC were more likely to develop adenoviremia at any time during the first 100 days [14]. In a large retrospective adult cohort of 339 patients, CMV viremia was associated with BKV-HC [27]. Viral coinfections, especially CMV, can have an immunomodulatory effect on the graft and may explain the higher frequency of BKV-HC. This association may also simply reflect an overall poor immune reconstitution and decreased ability to handle viral infections.

While there are strong data showing severe BKV-HC and high BKV plasma loads are associated with nephropathy and graft loss in renal transplant recipients [7], the relationship of BKV to acute genitourinary morbidity in allo-HSCT recipients is less well documented. Haines et al [9] reported that pediatric patients with high BK viremia had a higher serum creatinine after BKV detection than their pre-HSCT baseline, along with a greater need for dialysis. A prospective study of 124 adult HSCT recipients identified that BK viremia was the greatest

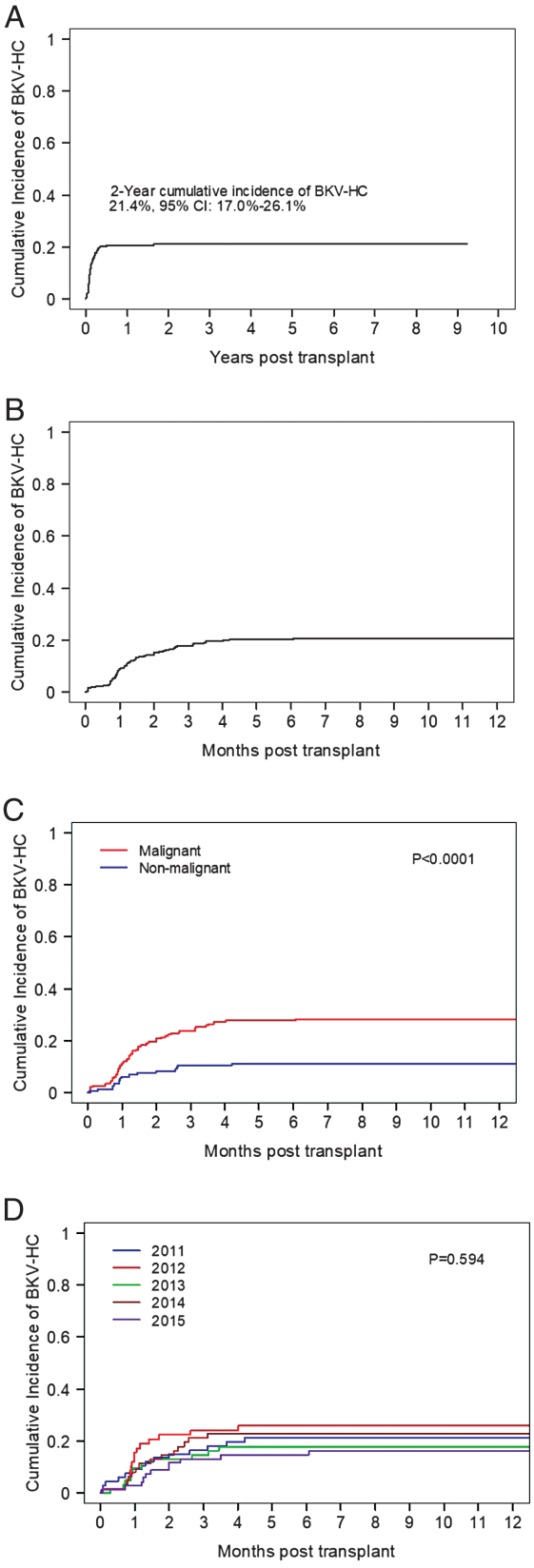

Figure 2. Kaplan-Meier curve analysis indicating (A) 2-year cumulative incidence of BKV-HC, (B) 1-year cumulative incidence of BKV-HC, (C) 1-year cumulative incidence of BKV-HC by underlying malignant vs. nonmalignant disease, and (D) 1-year cumulative incidence of BKV-HC by transplant year (2011-2015).

Table 4. Risk Factors for All-Cause Mortality

	Univariate Analysis HR (95% CI)	*P*-value	Multivariate Analysis HR (95% CI)	*P*-value
Age at transplant	1.04 (1.01-1.08)	**.012**	1.01 (0.96-1.05)	.742
Hemorrhagic cystitis	2.54 (1.64-3.93)	**<.0001**	2.22 (1.35-3.65)	**.002**
Gender				
Male	1.06 (0.69-1.62)	.793	1.14 (0.74-1.78)	.550
Female	1.00		1.00	
Underlying diagnosis				
Nonmalignant	1.00	**.002**	1.00	.082
Malignant	2.05 (1.32-3.2)		1.62 (0.94-2.78)	
Donor type				
MRD	1.00	**<.0001**	1.00	**.027**
MMRD/Haplo	5.1 (2.73-9.52)		4.04 (1.62-10.07)	
MMUD	1.72 (0.93-3.18)		1.55 (0.8-2.99)	
MUD	1.54 (0.81-2.92)		1.4 (0.73-2.69)	
Donor sex				
Male	1.00	.710	1.00	.693
Female	0.93 (0.62-1.39)		1.09 (0.71-1.67)	
Stem cell source				
Bone marrow	1.00		1.00	.940
PBSC	2.61 (1.68-4.04)	**<.0001**	0.95 (0.46-1.96)	
UCB	0.85 (0.42-1.73)		1.15 (0.49-2.68)	
BMT regimen				
Reduced intensity	1.00	.363	1.00	.086
Full myeloablative	0.82 (0.54-1.25)		0.64 (0.39-1.07)	

Abbreviations: BMT, bone marrow transplant; CI, confidence interval; HR, hazard ratio, MRD, matched related donor; MMRD, mismatch related donor; MUD, matched unrelated donor; MMUD, mismatch unrelated donor; PBSC, peripheral blood stem cell; UCB, umbilical cord blood. Significant *P*-values are bolded and represent a *P*-value <.05.

Table 5. Competing Risk Analysis for Development of BKV-HC

	Univariate Analysis sHR (95% CI)	*P*-value	Multivariate Analysis sHR (95% CI)	*P*-value
Age at transplant	1.10 (1.07-1.14)	**<.0001**	1.11 (1.06-1.16)	<**.0001**
Gender				
Male	1.01 (0.61-1.65)	.976	0.87 (0.53-1.44)	.598
Female	1.00		1.00	
Underlying diagnosis				
Nonmalignant	1.00	**.0003**	1.00	.872
Malignant	2.86 (1.63-5.02)		1.06 (0.52-2.17)	
Donor type				
MRD	1.00	.100	1.00	.064
MMRD/Haplo	2.68 (1.18-6.08)		2.97 (0.95-9.3)	
MMUD	2.16 (1.05-4.43)		2.85 (1.28-6.38)	
MUD	1.95 (0.94-4.06)		2.49 (1.16-5.35)	
Donor sex				
Male	1.00	.820	1.00	.963
Female	0.95 (0.59-1.53)		1.01 (0.61-1.69)	
Stem cell source				
Bone marrow	1.00	**.034**	1.00	.363
PBSC	1.45 (0.85-2.46)		1.03 (0.47-2.27)	
UCB	0.30 (0.09-0.97)		0.37 (0.09-1.46)	
BMT regimen				
Reduced intensity	1.00	**.003**	1.00	**<.0001**
Full myeloablative	2.54 (1.37-4.72)		4.2 (2.12-8.34)	

Abbreviations: CI, confidence interval; sHR, subdistribution hazard ratio; MRD, matched related donor; MMRD, mismatch related donor; MUD, matched unrelated donor; MMUD, mismatch unrelated donor; PBSC, peripheral blood stem cell; UCB, umbilical cord blood. Significant *P*-values are bolded and represent a *P*-value <.05.

independent risk factor for deterioration of renal function [28]. Similarly, we found that BKV-HC was associated with higher peak AKI within the first 60 and 100 days post-HSCT and that patients with BKV-HC were more likely to require dialysis during the first year post-HSCT.

The association between BKV-HC with long-term kidney injury is less well established, and while kidney injury is common after HSCT, the etiology of CKD is considered to be multifactorial and difficult to study [29]. Abudayyeh et al reported in a large retrospective study of adult stem cell transplant recipients that for every 10-fold increase in the BK urine viral load, there was a higher risk of kidney function decline, defined as a confirmed persistent reduction in eGFR of at least 25% from baseline [29]. Our study uniquely explored long-term kidney function in pediatric HSCT patients with and without BKV-HC. Patients with BKV-HC had higher rates of CKD at 1-year posttransplant. Our findings cannot assume causality given the retrospective study design, and other confounding variables such as the use of concomitant nephrotoxic medications were not systematically assessed. We identified, however, an association between genitourinary morbidity and BKV-HC in this population, and additional studies are warranted to further understand these findings.

Finally, our data show an association between all-cause mortality and BKV-HC. Haines et al [9] similarly reported a lower 1-year OS in pediatric HSCT recipients with high viremia. In a prospective study with a median follow-up of 1.8 years, Cesaro et al [11] showed that patients with HC had a lower OS than those without HC. This is in contrast to a retrospective pediatric cohort of 67 children from the Netherlands, where Kloos et al [13] found no significant difference in survival between patients with HC (71%) compared with patients without HC (78%). We do not believe that BKV-HC directly leads to mortality, but that the presence of BKV-HC is an indicator of a more ill patient, with likely worse immune reconstitution.

Our study was limited by being a single-center cohort, retrospective study design, and nonuniform serial testing for BKV across subjects.

Additional large-scale, well-controlled prospective studies are warranted to identify the true incidence of BKV-HC in pediatric HSCT patients and also to identify both host factors and possible BK viral genetic factors that contribute to the development of HC. BKV-HC is clearly a frequent complication after allo-HSCT that causes pain and suffering as well as genitourinary morbidity in this extremely vulnerable population. Further studies are needed to identify effective antiviral therapeutic options for BKV-HC; BKV-specific cytotoxic T lymphocytes appear to be a promising therapeutic option [3].

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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