Original Article

# BK Polyomavirus Hemorrhagic Cystitis in Hematopoietic Cell Transplant Recipients

**Sharon Anbumalar Lionel, Aby Abraham, Vikram Mathews, Kavitha Lakshmi, Asha Mary Abraham[1], Biju George**

Departments of Haematology and [1]Virology, Christian Medical College, Vellore, Tamil Nadu, India

## Abstract

**Introduction:** BK polyomavirus-associated hemorrhagic cystitis (BKPyV-HC) is a well-recognized infective complication of hematopoietic cell transplant (HCT) with increased organ dysfunction and mortality. This study was performed to describe the local incidence, risk factors, and outcomes of BKPyV infection. **Methods:** This retrospective case–control study was conducted between 2007 and 2016 from a tertiary hospital in South India. We identified HCT recipients diagnosed with BKPyV-HC and compared them with recipients over the same period who did not develop BK virus infection matched for age, sex, diagnosis, and donor type. We collected data from central electronic medical records and databases maintained in the departments of hematology and virology. **Results:** Over the study period, 1276 transplants were performed, of which 262 patients (20.5%) developed HC and 105 (8.2%) were BKPyV-positive. Grade 3 HC was most commonly (57.1%) seen, and the median time to develop BKPyV-HC was 35 (range 0–858) days. Survival was significantly lower in the cases (42.9% vs. 61%, $P < 0.05$). On univariate analysis, the protective effect of nonmyeloablative conditioning ($P = 0.04$), residual disease at the time of transplant in malignant conditions ($P = 0.001$), lower CD34 dose ($P = 0.006$), presence of acute graft versus host disease (GVHD, $P < 0.001$), reactivation of cytomegalovirus infection ($P < 0.001$), and presence of bacterial urinary tract infection (UTI) ($P < 0.001$) were significant factors. Multivariate logistic regression confirmed the presence of acute GVHD ($P = 0.041$), bacterial UTI ($P < 0.001$), and residual disease ($P = 0.009$) at HCT as significant risk factors for BKPyV-HC. **Conclusions:** Our study affirms the homogeneity of BKPyV-HC disease in low- and middle-income HCT settings with prior reports and the need for therapeutic strategies to reduce its resultant mortality.

**Keywords:** BK polyomavirus virus, hematopoietic cell transplant, hemorrhagic cystitis

## Introduction

BK polyomavirus (BKPyV)-associated hemorrhagic cystitis (HC) presents with a triad of cystitis, macro-hematuria, and BKPyV viruria. Current diagnostic criteria require exclusion of other relevant etiologies[1] and defines BKPyV viruria as >7 $\log_{10}$ copies/mL. BKPyV-related HC is common in hematopoietic cell transplant (HCT) recipients, with a reported incidence range of 7%–40% depending on HCT type, population (8%–25% of pediatric and 7%–54% of adult recipients),[1] and HC severity.[2,3] The presence of BKPyV-HC is associated with prolonged hospital stay[4] and increased morbidity and mortality.[3]

There are no previous descriptions of the prevalence and risk factors of BKPyV-induced HC in HCT recipients from low- and middle-income countries, although similar reports are well described in renal-allograft recipients.[5] These infections are likely to increase further with the increasing number of transplant centers and alternative donor transplants.[6] Therefore, the objective of this study was to characterize the prevalence and evaluation of risk factors in this setting.

## Methods

The retrospective case–control study was performed at a single tertiary care center in South India, where an average

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_139_21

**Address for correspondence:** Dr. Sharon Anbumalar Lionel, Department of Haematology, Christian Medical College, Vellore - 632 004, Tamil Nadu, India.
E-mail: sharonlionel@cmcvellore.ac.in



**How to cite this article:** Lionel SA, Abraham A, Mathews V, Lakshmi K, Abraham AM, George B. BK Polyomavirus hemorrhagic cystitis in hematopoietic cell transplant recipients. J Global Infect Dis 2022;14:17-23.

**Received:** 02 June 2021 **Revised:** 23 September 2021
**Accepted:** 30 September 2021 **Published:** 28 February 2022

of 150 allogeneic HCTs are performed every year. We included consecutive cases of post-HCT HC in all patients who underwent allogeneic HCT between January 2007 and December 2016. Data were cross-verified between the independently maintained databases of the departments of hematology and virology to prevent selection and ascertainment biases. The data were then quality checked by another investigator. Inclusion was cases required a positive BKPyV qualitative polymerase chain reaction (PCR) in urine with features of HC, as described in Figure 1. Controls were BKPyV negative on PCR and were selected from the same transplant cohort, matched for age, sex, diagnosis, and donor type in a 1:1 ratio by the investigators. The rationale for donor matching was the previously well-established evidence showing that cord blood units, haploidentical donors,[7] and unrelated donors are a well-established risk factor for BKPyV-HC.

Conditioning regimens, graft source, and graft versus host disease (GVHD) prophylaxis used depended upon the indication for HCT. Acute GVHD was graded as per Glucksberg *et al.*'s criteria,[8] while chronic GVHD was documented. Following a diagnosis of acute GVHD, patients were started on corticosteroids, and the doses of calcineurin inhibitors were optimized. Steroid-refractory GVHD was treated with mycophenolate mofetil, cyclophosphamide, basiliximab, or etanercept as per the treating physician's discretion. In addition, the pretransplant use of standard T cell depleting agents such as antithymocyte globulin (ATG) or cyclosporine in aplastic anemia or cyclophosphamide and fludarabine in chemotherapy protocols was ascertained.

## Hemorrhagic cystitis

The grading of severity of HC was reported as described by Droller *et al.*[9] in the context of cyclophosphamide-induced HC but is also presently used for all other etiologies. In summary, grade I includes microscopic bleeding (not visible), grade II has visible bleeding, grade III is bleeding with small clots, and grade IV is bleeding with clots large enough to cause obstruction. Grade 3 and 4 HC together is defined as severe HC. The maximum grade of HC and the time taken to manifest this were documented. We commonly employed supportive care with intravenous (IV) hydration, bladder relaxants, and platelet support to target a platelet count of at least 30–50 × $10^9$/L to prevent gross hematuria for all cases. Quinolones were prescribed in most cases. The treating physician decided on the use of cidofovir or foscarnet. IV immunoglobulin replacement was administered when the IgG level was less than 700 mg/dL as per the institutional standard international reference range.[10]

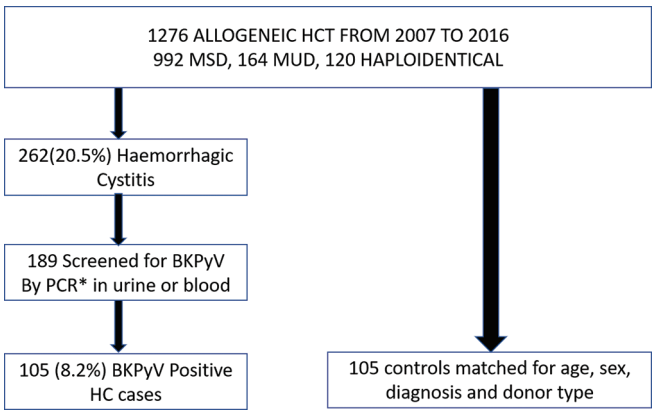


**Figure 1:** Study flowchart

## BK polyomavirus detection

Qualitative BKPyV PCR was performed on urine samples in post-HCT patients with cystitis symptoms and microscopic hematuria or gross hematuria. Two patients also tested positive for BKPyV PCR in the blood when tested as part of another assay. Qualitative real-time PCR was used to detect the VP1 region of the BK genome with a limit of 100 genome copies/ml since quantitative PCR was unavailable during the study period. A cycling time of less than 37 was considered positive.[11] Hence, any positive qualitative BKPyV PCR in urine with cystitis symptoms or evidence of HC was regarded as a BKPyV-HC case. Subsequently, we standardized a quantitative PCR using plasmids (based on the earlier qualitative PCR), for which a standard curve is generated for every run of the quantitative assay. This quantitative assay has a limit of detection of ≤1 plasmid/mL. Cytomegalovirus (CMV) was measured weekly after engraftment until day 100, and ganciclovir was initiated when copy levels were more than log 3 or >1000 copies/ml.[12] Bacterial urine cultures were also sent if there were symptoms of cystitis or pyelonephritis with pyuria by a midstream clean-catch method. More than $10^5$ colony forming units (CFUs) of a single organism or a lesser CFU with clinical and or radiological evidence of pyelonephritis was considered significant bacterial urinary tract infection (UTI).

## Statistical analysis

The descriptive data were reported as means with standard deviation (medians and interquartile range for nonparametric distributions) or frequencies with percentages as appropriate. Continuous data were compared with *t*-test or Mann–Whitney U-test as appropriate. Proportions were compared using the Pearson's Chi-square test or Fisher's exact test. Analysis of risk factors for survival and co-occurrence of BK-HC was calculated using Cox regression proportional hazards method. The Kaplan–Meier method was used to estimate overall survival, and comparisons were based on the log-rank test. All statistical tests were two-tailed, with a $P = 0.05$ or less considered statistically significant. Data were analyzed using the IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. (Armonk, NY: IBM Corp.). Our institutional review board and ethics committee approved the study and allowed for a waiver of consent under conditions of respecting the patient's anonymity (IRB Min. No. 13226).

# Results

## Baseline characteristics

We identified 105 cases of BKPyV-HC, and an equal number of matched controls were chosen. The cases and controls were matched for age, gender, diagnosis, and donor type.

Baseline characteristics of cases and controls are described in Table 1. Aplastic anemia was the most common indication for HCT (~32% in both groups). There was no difference in the use of ATG among cases and controls (6.7% vs. 8.6%, $P = 0.260$). The lack of adequate disease control at the time of HCT (partial remission) ($P < 0.001$) in patients with malignancies was significantly higher in the cases.

## BK polyomavirus-associated hemorrhagic cystitis [Table 2]

One hundred and five patients had BKPyV-HC, which was mild (grade 1 and 2) in 27 (25.7%), grade 3 in 60 (57.1%), and grade 4 in 18 (17.1%). Among the controls, seven patients had HC (grade 2 and 3) due to adenoviral infection in one and secondary to regimen-related toxicity in others. None of the controls had BKPyV-positive PCR. The median time to develop HC among cases was 35 days (range: 0–858). Treatment was supportive with hydration and analgesics in most of the cases and all the controls. Cidofovir (5, 4.8%) and foscarnet (1, 1%) were used in a small population. Surgical intervention with bladder irrigation, ureterostomy, and bladder cauterization was done in 3 patients. We observed a clinical resolution in 64 (61%) of the cases. The remaining 41 (39%) of the cases died before the resolution of HC. The median follow-up of these cases was 8 months (range: 0–135).

## Transplant outcomes

The median CD34-positive stem cell dose infused was higher in the controls ($10.46 \times 10^6$ CD34/Kg vs. $9.1 \times 10^6$ CD34/Kg, $P = 0.005$). The median time to neutrophil engraftment was 15.5 days (range 10–30) in cases and 15 days (range 9–24)

**Table 1: Baseline characteristics: Cases versus controls**

| Characteristics | BKPyV-HC (105; 100%), *n* (%) | Control (105; 100%), *n* (%) | *P* |
|---|---|---|---|
| Age (years), median (range) | 20 (1-59) | 19 (1-27) | 0.706 |
| Sex | | | |
| Male | 69 (65.7) | 71 (67.6) | 0.884 |
| Female | 36 (34.3) | 34 (32.4) | |
| Diagnosis | | | |
| Aplastic anemia | 33 (31.4) | 34 (32.4) | 1.000 |
| AML | 20 (19.0) | 19 (18.1) | |
| ALL | 16 (15.2) | 16 (15.2) | |
| Thalassemia major | 11 (10.5) | 12 (11.4) | |
| Lymphomas | 2 (1.9) | 2 (1.9) | |
| MDS | 9 (8.6) | 9 (8.6) | |
| CML | 4 (3.8) | 3 (2.9) | |
| Fanconi anemia | 5 (4.8) | 5 (4.8) | |
| Others | 5 (5) | 5 (5) | |
| Donor type | | | |
| MSD 6/6 | 56 (53.3) | 64 (61) | 0.331 |
| Mismatched sibling donor | 5 (4.8) | 1 (1) | |
| MUD 10/10 | 3 (2.9) | 7 (6.7) | |
| Mismatched unrelated donor | 17 (16.2) | 13 (12.4) | |
| Haploidentical | 16 (15.2) | 14 (13.3) | |
| MRD (nonsibling) | 8 (7.6) | 6 (5.7) | |
| Conditioning regimens | | | |
| Myeloablative | 60 (57.1) | 44 (41.9) | 0.086 |
| Nonmyeloablative | 36 (34.3) | 48 (45.7) | |
| RIC | 9 (8.6) | 13 (12.4) | |
| Disease status | | | |
| Partial remission | 37 (75.5) | 19 (38.8) | <0.001 |
| Complete remission | 6 (12.2) | 24 (49) | |
| Active disease | 6 (12.2) | 6 (12.2) | |
| CD 34 cell dose ($\times 10^6$) | 9.1 (2.13-29.80) | 10.46 (1.04-46) | 0.005 |
| Outcomes | | | |
| Dead | 60 (57.1) | 41 (39) | 0.013 |
| Alive | 45 (42.9) | 64 (61) | |
| Acute GVHD | | | |
| Yes | 56 (53.3) | 29 (27.6) | <0.001 |
| No | 49 (46.7) | 76 (72.4) | |

BKPyV-HC: BK polyomavirus hemorrhagic cystitis, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, MDS: Myelodydsplastic syndrome, CML: Chronic myeloid leukemia, MSD: Matched sibling donor, MUD: Matched unrelated donor, MRD: Matched related (nonsibling) donor, RIC: Reduced intensity conditioning, GVHD: Graft versus host disease

in controls. The median time to platelet engraftment was significantly higher (median 16.5 days [range 0–71 days] vs. 14.5 days [range 0–60 days], $P = 0.029$) in cases compared to controls. However, this was not a significant risk factor predicting BKPyV-HC in univariate or multivariate analysis. Acute GVHD occurred in 56 (53.3%) of the cases and 29 (27.6%) of the controls ($P < 0.001$). There was a significant difference between severe acute GVHD grades, i.e., grade 3 and 4, between the two groups (29.5% vs. 14.2%, $P \leq 0.001$). Chronic GVHD was seen in 26 (24.8%) cases and 14 (13.3%) controls ($P = 0.052$). Concomitant adenoviral infection was seen in nine out of the 88 cases and one out of the five evaluable controls (8% vs. 0.9%, $P < 0.009$). CMV reactivation was detected in 44 (41.9%) cases and 15 (14.3%) controls ($P < 0.000$). Concomitant bacterial UTI was also significantly ($P < 0.00$) higher in cases (69, 65.7%) than in controls (60, 57.1%).

Overall survival was significantly higher (61% vs. 41.9% hazard ratio, $P = 0.013$) in the control group than in cases [Figure 2]. The median time to death was 37 months (range 0–136) in the control group and 8 months (range 0–133) among cases. Infection (16.6%) and acute GVHD (12.3%) with or without infection (4.2%) were the primary cause of death ascertained using previously published algorithms for the same.[13] Disease relapse (5.9%) and graft failure (6.9%) were other causes of death and were not different between the cases and controls. HC was not the primary cause of death in any of the cases.

## Discussion

We performed this single-center retrospective study to determine the prevalence of BKPyV-HC in post-HCT recipients and the resultant impact on survival in a low- and middle-income transplant setting. Our study was performed before the availability of quantitative BKPyV PCR at our center. Despite these limitations, we identified similar risk factors and outcomes for post-HCT BKPyV-HC as described previously. BKPyV-HC infection was associated with reduced survival ($P = 0.048$). Our findings also suggest that the presence of acute GVHD, failure to achieve remission at HCT, and bacterial UTI were significant predictors of BKPyV-HC infection on multivariate analysis [Table 3]. Significant associations at the univariate level were myeloablative conditioning, a higher CD34 cell dose, and CMV reactivation [Table 3].

There are no previous descriptions of the prevalence and risk factors of BKPyV-induced HC in HCT recipients from low- and

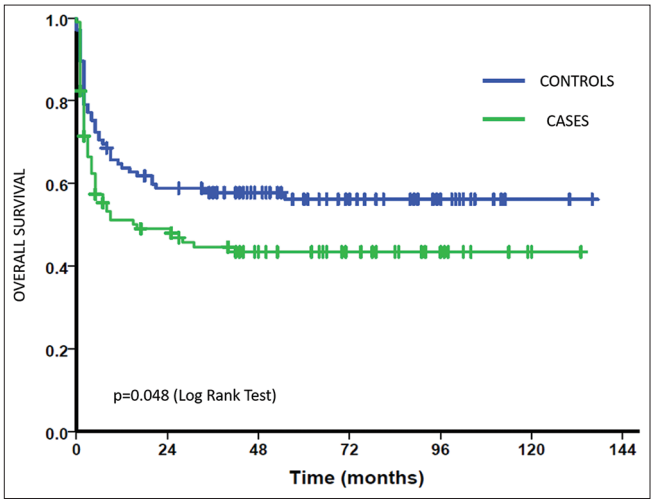


**Figure 2:** Kaplan–Meier survival curves between cases and controls

**Table 2: Hemorrhagic cystitis characteristics: Cases versus controls**

| Characteristics | BKPyV-HC cases, *n* (%) | Control, *n* (%) | *P* |
|---|---|---|---|
| Median time to development - Days posttransplant (range) | 35 (0-858) | | |
| Grade of HC | | | |
| Grade 1 | 6 (5.7) | 0 | 0.454 |
| Grade 2 | 21 (20) | 1 (14.3) | |
| Grade 3 | 60 (57.1) | 6 (85.7) | |
| Grade 4 | 18 (17.1) | 0 | |
| Treatment | | | |
| Supportive including quinolones | 76 (72.4) | 7 (100) | 0.760 |
| IVIG | 18 (17.1) | 0 | |
| Cidofovir | 5 (4.8) | 0 | |
| Surgical | 3 (2.9) | 0 | |
| Foscarnet | 1 (1.0) | 0 | |
| All the above except foscarnet | 2 (1.9) | 0 | |
| Clinical resolution | | | |
| No | 41 (39) | 3 (42.9) | 1.000 |
| Yes | 64 (61) | 4 (57.1) | |
| Adeno virus PCR in urine | | | |
| Yes | 9 (8.5) | 1 (0.9) | 0.441 |
| No | 79 (75.2) | 4 (3.8) | |
| Not determined | 17 (16.1) | 100 (95.3) | |

BKPyV-HC: BK polyomavirus hemorrhagic cystitis, HC: Hemorrhagic cystitis, IVIG: Intra venous immunoglobulin, PCR: Polymerase chain reaction

**Table 3: Univariate and multivariate analysis**

| Characteristics | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Risk (95% CI) | *P* | Risk (95% CI) | *P* |
| Nonmyeloablative conditioning | 0.5 (0.30-0.98) | 0.04 | NS | |
| Not in CR at time of transplant in malignancies | 7.8 (2.72-22.3) | <0.001 | 7.3 (1.65-32.52) | 0.009 |
| Lower CD34 dose | 0.9 (0.87-0.97) | 0.006 | NS | |
| Acute GVHD | 3.0 (1.68-5.32) | <0.001 | 3.5 (1.056-11.93) | 0.041 |
| CMV reactivation | 4.4 (2.21-8.45) | <0.001 | NS | |
| Concomitant bacterial UTI | 31.6 (12.6-79.14) | <0.001 | 37.1 (8.31-165.84) | <0.001 |

CR: Complete remission, GVHD: Graft versus host disease, CMV: Cytomegalovirus, UTI: Urinary tract infection, NS: Not significant, CI: Confidence interval

middle-income countries. In this context, we report a novel prevalence of BKPyV-HC at 8.2% (105). Since our diagnosis was based on qualitative PCR, an overestimation is possible. However, compared to previously published literature from high-income countries, this was a lower[2,4] prevalence. There are several reasons for this. First, a lower percentage of alternate donor transplants than higher-income centers considerably limit the incidence of BKPyV-HC. Second, similar clinical symptoms from regimen-related toxicity may have confounded clinical diagnosis, leading to inadequate testing. The presence of thrombocytopenia and the risk involved with the invasive nature of procedures in patients on immunosuppression precluded other diagnostic tests such as cystoscopy and biopsy.

We encountered a male preponderance (65% in cases) in our cohort, which is also previously observed with other viral causes of post-HCT HC.[14] Since BKPyV remains latent in the renal epithelium, the longer urothelial tract length and higher uroepithelial surface area in males may confer a greater risk of viral reactivation. The role of the prostate gland in harboring latent infection is less definite, but limited evidence suggests that chronic BKPyV infection may be associated with prostatic carcinoma.[15]

Persistent malignant disease and failure to reach complete remission emerged as a significant risk factor in univariate and multivariate analysis. This association has been published previously in the literature.[16] Persistent residual disease may be a surrogate marker of immune dysfunction, as posttransplant infection and disease relapse are often associated.[17] This may also explain the co-occurrence of CMV reactivation and bacterial UTI among cases.

Use of busulfan,[4] total body irradiation, and cyclophosphamide[18] containing regimens have been previously described as significant risk factors for BKPyV-HC. Our study demonstrated the protective effect of nonmyeloablative conditioning (0.5 [0.30–0.98], $P = 0.04$), as myeloablative conditioning results in more tissue trauma and increased effectors of acute inflammation. The resultant damage to the uroepithelium and subsequent uroepithelial regeneration provides an appropriate environment for BKPyV replication.[18]

The intensity of immunosuppression in HCT patients as a predictor of BKPyV-HC infection[19] has been postulated. Hence, we looked at T cell-depleting agents (ATG and cyclosporine for aplastic anemia and cyclophosphamide or fludarabine in malignancies) at any time for preconditioning but found that it was similar across both groups (22 vs. 19, $P = 0.648$).

A significantly delayed platelet engraftment was seen in our cases compared to the controls (14.5 vs. 16.5 days, $P = 0.029$) though it was not a significant risk factor for the development of BKPyV-HC. Moderate and severe thrombocytopenia complicates HC as there is inadequate hemostasis in areas of the denuded epithelium. There is increasing evidence that platelets contribute to innate and adaptive immunity.[20] Abudayyeh *et al*. studied the role of platelet engraftment on BKPyV infection and demonstrated an associated increased risk of BKPyV-HC in patients who did not attain platelet counts of ≥50,000 k/μL.[19] Cytopenia at the onset of symptoms also prolonged BKPyV-HC in a recent study.[21]

We found that acute GVHD was a risk factor for BKPyV infection. Acute GVHD and prednisolone use have been observed in BKPyV-HC[16,18,22] and other viral HCs.[14] The need to control acute GVHD with potent and sometimes prolonged immunosuppressive agents may hamper immune response and aid viral reactivation of latent infections.

Fluoroquinolones were used commonly in grades one and two BKPyV-HC before the onset of severe disease.[23] This was based on *in vitro* and retrospective studies showing inhibition of BKPyV replication by fluoroquinolones, including ciprofloxacin.[24] While there are no prospective randomized data to support its use in the allogeneic transplant setting, a randomized trial in renal-transplant recipients failed to benefit from fluoroquinolones.[25] The availability of generic cidofovir and the development of antiviral cytotoxic T lymphocytes have made ciprofloxacin usage redundant.

Our data suggest a possible association between bacterial urinary tract with BKPyV-HC. Previous reports describing this association are rare.[26,27] BKPyV-damaged urothelium may favor bacterial colonization or invasion, leading to bacterial infection. Similar sialic acid-containing ganglioside receptors are known to mediate epithelial attachment for both BKPyV[28] and certain bacteria such as *Escherichia coli*,[29] but direct viral–bacterial interactions facilitating coinfection are not

known. Other factors such as immunosuppression may also be contributory.

The current study shares the limitations inherent to all retrospective analyses that the advancements in diagnostic capabilities such as quantitative PCR were unavailable at that time and that we cannot exclude the possibility that some cases were undiagnosed. However, since this is a single-center study with uniform protocols, we were unlikely to miss any clinically relevant cases. To our knowledge, there are no published reports on the incidence, risk factors, and outcomes of BKPyV-HC post-HCT in the prequantitative-PCR setting, and this will prove helpful in similar low- and middle-income transplant centers.

## Conclusions

We identified prevalence, risk factors, and outcomes for post-HCT BKPyV-HC in HCT recipients from a low- and middle-income country setting. The risk factors in our patients were the presence of acute GVHD, residual malignant disease at the time of transplant, and the presence of a concomitant bacterial UTI. BKPyV-HC cases had decreased survival. Our study affirms the homogeneity of disease presentations between the varied HCT settings and the need for therapeutic strategies to reduce its resultant mortality.

### Research quality and ethics statement

This study was approved by the Institutional Review Board/ Ethics Committee (IRB Min. No. 13227). The authors followed applicable EQUATOR Network ("http://www.equator-network.org/) guidelines during the conduct of this research project.

### Financial support and sponsorship

Internal resources of the Christian Medical College, Vellore, supported the study.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Cesaro S, Dalianis T, Hanssen Rinaldo C, Koskenvuo M, Pegoraro A, Einsele H, *et al.* ECIL guidelines for the prevention, diagnosis and treatment of BK polyomavirus-associated haemorrhagic cystitis in haematopoietic stem cell transplant recipients. J Antimicrob Chemother 2018;73:12-21.
2. Cesaro S, Facchin C, Tridello G, Messina C, Calore E, Biasolo MA, *et al.* A prospective study of *BK-virus*-associated haemorrhagic cystitis in paediatric patients undergoing allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 2008;41:363-70.
3. Silva Lde P, Patah PA, Saliba RM, Szewczyk NA, Gilman L, Neumann J, *et al.* Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of *BK virus* infection, preparative regimen intensity and donor type. Haematologica 2010;95:1183-90.
4. Gilis L, Morisset S, Billaud G, Ducastelle-Leprêtre S, Labussière-Wallet H, Nicolini FE, *et al.* High burden of *BK virus*-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2014;49:664-70.
5. Gupta P, Gupta A, Bhalla AK, Malik M, Gupta A, Bhargava V, *et al.* *BK virus* nephropathy in living donor renal allograft recipients: An observational study from a large transplant center in India. Saudi J Kidney Dis Transpl 2018;29:1366-70.
6. Nair LG, Jotwani G, Kharkwal IG. National Guidelines for Hematopoietic Cell Transplantation; 2021. Available from: https://main.icmr.nic.in › files › Nat_Guide_HCTPDF. [Last accessed on 2021 Sep 20].
7. Irene GC, Albert E, Anna BV, Rahinatu A, Silvana N, Silvana S, *et al.* Patterns of infection and infectious-related mortality in patients receiving post-transplant high dose cyclophosphamide as graft-versus-host-disease prophylaxis: Impact of HLA donor matching. Bone Marrow Transplant 2021;56:818-27.
8. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, *et al.* Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18:295-304.
9. Droller MJ, Saral R, Santos G. Prevention of cyclophosphamide-induced hemorrhagic cystitis. Urology 1982;20:256-8.
10. Dati F, Schumann G, Thomas L, Aguzzi F, Baudner S, Bienvenu J, *et al.* Consensus of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in serum based on the standardization against the IFCC/BCR/CAP Reference Material (CRM 470). International Federation of Clinical Chemistry. Community Bureau of Reference of the Commission of the European Communities. College of American Pathologists. Eur J Clin Chem Clin Biochem 1996;34:517-20.
11. Jagannath S, Sachithanandham J, Ramalingam VV, Demosthenes JP, Abraham AM, Zachariah A, *et al. BK virus* characterisation among HIV-1-Infected individuals and its association with immunosuppression. Indian J Med Microbiol 2018;36:172-7.
12. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood 2009;113:5711-9.
13. Copelan E, Casper JT, Carter SL, van Burik JA, Hurd D, Mendizabal AM, *et al.* A scheme for defining cause of death and its application in the T cell depletion trial. Biol Blood Marrow Transplant 2007;13:1469-76.
14. Asano Y, Kanda Y, Ogawa N, Sakata-Yanagimoto M, Nakagawa M, Kawazu M, *et al.* Male predominance among Japanese adult patients with late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation. Bone Marrow Transplant 2003;32:1175-9.
15. Gorish BM, Ournasseir ME, Shammat IM. A correlation study of BK Polyoma virus infection and prostate cancer among Sudanese patients – Immunofluorescence and molecular based case-control study. Infect Agent Cancer 2019;14:25.
16. Arai Y, Maeda T, Sugiura H, Matsui H, Jo T, Ueda T, *et al.* Risk factors for and prognosis of hemorrhagic cystitis after allogeneic stem cell transplantation: Retrospective analysis in a single institution. Hematology 2012;17:207-14.
17. Auletta JJ, Lazarus HM. Immune restoration following hematopoietic stem cell transplantation: An evolving target. Bone Marrow Transplant 2005;35:835-57.
18. Leung AY, Yuen KY, Kwong YL. Polyoma *BK virus* and haemorrhagic cystitis in haematopoietic stem cell transplantation: A changing paradigm. Bone Marrow Transplant 2005;36:929-37.
19. Abudayyeh A, Hamdi A, Abdelrahim M, Lin H, Page VD, Rondon G, *et al.* Poor immune reconstitution is associated with symptomatic BK polyomavirus viruria in allogeneic stem cell transplant recipients. Transpl Infect Dis 2017;19. [doi: 10.1111/tid. 12632].
20. Semple JW, Freedman J. Platelets and innate immunity. Cell Mol Life Sci 2010;67:499-511.
21. Imlay H, Xie H, Leisenring WM, Duke ER, Kimball LE, Huang ML, *et al.* Presentation of BK polyomavirus-associated hemorrhagic cystitis after allogeneic hematopoietic cell transplantation. Blood Adv 2020;4:617-28.
22. Kaphan E, Germi R, Bailly S, Bulabois CE, Carré M, Cahn JY, *et al.* Risk factors of BK viral hemorrhagic cystitis in allogenic hematopoietic stem cell transplantation. Transpl Infect Dis 2021;23:e13601.
23. Miller AN, Glode A, Hogan KR, Schaub C, Kramer C, Stuart RK, *et al.* Efficacy and safety of ciprofloxacin for prophylaxis of polyomavirus

*BK virus*-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients. Biol Blood Marrow Transplant 2011;17:1176-81.
24. Portolani M, Pietrosemoli P, Cermelli C, Mannini-Palenzona A, Grossi MP, Paolini L, *et al.* Suppression of *BK virus* replication and cytopathic effect by inhibitors of prokaryotic DNA gyrase. Antiviral Res 1988;9:205-18.
25. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, Aljanabi A, *et al.* Efficacy of levofloxacin in the treatment of BK viremia: A multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol 2014;9:583-9.
26. Tzannou I, Papadopoulou A, Naik S, Leung K, Martinez CA, Ramos CA, *et al.* Off-the-shelf virus-specific T cells to treat BK virus, *Human herpesvirus* 6, *Cytomegalovirus*, Epstein-barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J Clin Oncol 2017;35:3547-57.
27. Gelbrich N, Stope MB, Bekeschus S, Weigel M, Burchardt M, Zimmermann U. *BK virus*-induced nephritis and cystitis after matched unrelated donor stem cell transplantation: A case report. Clin Case Rep 2020;8:2839-42.
28. Maginnis MS. Virus-receptor interactions: The key to cellular invasion. J Mol Biol 2018;430:2590-611.
29. Varki A. Sialic acids in human health and disease. Trends Mol Med 2008;14:351-60.