

# Risk Factors and Outcome of Hemorrhagic Cystitis in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplant

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## Abstract

**Background:** Hemorrhagic cystitis (HC), a significant complication of hematopoietic stem cell transplantation (HSCT) linked to chemotherapy-induced injury and viral reactivation. Given its impact on morbidity, mortality, and quality of life, we conducted a retrospective analysis to identify key risk factors associated with HC. The objective is to evaluate the relationship between transplant-related variables and outcomes, aiming to improve risk stratification and guide early, targeted interventions in post-HSCT care. **Methodology:** This study was carried out retrospectively at tertiary care hospital in Rawalpindi between 2013 and 2024 including 138 patients who underwent allogeneic HSCT. Data collected included demographic characteristics, transplant variables, post-transplant complications such as graft-versus-host disease (GVHD), cytomegalovirus (CMV) reactivation, BK viruria, and hemorrhagic cystitis (HC). HC was graded from microscopic hematuria to severe cases requiring surgical intervention. Engraftment times, infection rates, and overall survival (OS) were analyzed. OS was defined from the start of conditioning to death or last follow-up and was assessed using Kaplan-Meier curves.

**Results:** 138 patients (mean age 21.3 years) who underwent allogeneic HSCT from 2013 to 2024 were included. The majority were male (73.9%), and the most common underlying disorder was Beta Thalassemia Major (43.5%), followed by Aplastic Anemia and Acute Lymphoblastic Leukemia. Fully HLA-matched sibling donors were donors in majority cases, with bone marrow harvest as the predominant stem cell source. Myeloablative conditioning was administered to 66.7% of patients. HC occurred in 55.8% of patients, mostly as grade 1–2. Significant associations were observed between HC and GVHD prophylaxis involving cyclosporine (particularly CSA+MTX), BK virus reactivation (59.7% of HC cases), chronic GVHD, and secondary graft failure ( $p < 0.05$ ). No significant correlation was found with donor gender, conditioning regimen, or CMV reactivation. Most HC cases (85%) responded to supportive management including hydration, bladder irrigation, and antivirals. Responders showed a higher overall survival (OS) rate of 97%, while non-responders had poor outcomes. OS in HC patients was 87% at 100 days post-transplant, dropping to 66.7% at a cumulative follow up of 10 years.

**Conclusion:** Our study identifies BK virus reactivation, cyclosporine-based GVHD prophylaxis, and chronic GVHD as significant contributors to HC following allogeneic HSCT. Despite limited therapeutic options, supportive care proved effective in most cases. The high incidence and associated morbidity of HC highlights the need for early risk stratification, viral monitoring, and improved access to targeted therapies. **Key words:** Hemorrhagic Cystitis, Allogeneic Hematopoietic Stem Cell Transplant, Developing Country

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## Introduction

Hematopoietic stem cell transplantation (HSCT) is a well-established treatment for various malignant and nonmalignant hematological disorders.<sup>1</sup> Despite its therapeutic benefits, HSCT is often complicated by a range of adverse effects, among which hemorrhagic cystitis (HC) is particularly significant. HC is a well-recognized complication contributing to significant morbidity and mortality in HSCT recipients with widely

varying incidence rates.<sup>2</sup> The reported incidence of HC in allogeneic HSCT patients is 8%–25% in pediatric and 7%–54% in adult patients.<sup>3,4</sup> HC can result from direct bladder mucosal injury caused by high-dose chemotherapy agents such as Cyclophosphamide and Busulfan. Additionally, viral reactivation, notably BK virus (BKV), adenovirus, and Cytomegalovirus, has been strongly implicated in pathogenesis.<sup>5</sup>

Clinical manifestations of HC vary from asymptomatic microscopic hematuria, dysuria, irritative urinary symptoms to hydronephrosis, renal failure severe, life-threatening bleeding and urinary tract obstruction.<sup>6</sup> This complication significantly deteriorates patients' quality of life and prolongs hospitalization. Virus-associated HC has

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been linked to increased post-transplant mortality. Currently, no FDA approved therapies exist for virus-associated HC and management remains supportive and includes bladder irrigation to prevent clot retention, transfusions to manage bleeding, narcotics for pain, and, in severe cases, cystectomy or dialysis.<sup>7</sup>

HC is classified based on the timing of onset: early-onset (within 72 hours of conditioning) is attributed to urothelial damage caused by chemotherapy and radiotherapy<sup>8</sup>, while late-onset (after 72 hours) is frequently associated with viral reactivation, older age, acute graft-versus-host disease (aGVHD), HLA mismatch, T-cell depletion, and severe immunosuppression.<sup>9</sup>

To elucidate the risk factors contributing to HC, we performed a retrospective analysis of HSCT patients, focusing on identifying risk factors for developing HC and subsequent outcomes including chronic GVHD and overall survival. This study aims to evaluating the relationship between HSCT-related variables and transplant outcomes to identify key predictors of HC development, to guide early intervention and improve the quality of life in this patient population.

## Methodology

This study was carried out retrospectively at tertiary care hospital in Rawalpindi between 2013 and 2024 following ethical approval. A total of 138 patients were included.

All patients, irrespective of gender, diagnosed with hematological disorder who underwent Allogeneic HSCT during the defined the course of the study at our institute, having complete clinical records, including diagnostic work-up, treatment response and follow-up data were included.

Patients with missing or insufficient data regarding diagnosis, treatment course, or follow-up outcomes or with a history of other hematological or solid organ malignancies or whose treatment and outcome status could not be ascertained were excluded from the study.

Data was collected from patient's clinical records. Demographic variables included age, sex, blood group, diagnosis, Human Leukocyte Antigen (HLA) match, GVHD prophylaxis, conditioning chemotherapy, source of stem cells and various transplant related complications i-e Cytomegalovirus (CMV) reactivation, BK viremia, presence or absence of graft-vs.-host disease (GVHD)

while quantitative variables included CD34 cells and TNC dose, neutrophil and platelets engraftment time, day of developing HC. Post-transplant follow-up included monitoring for engraftment delays, development of acute and chronic GVHD and graft function assessment. CMV reactivation was tested weekly using quantitative PCR, and patients with reactivation were treated with antiviral therapy. Acute and chronic GVHD was categorized based on MAGIC criteria. BK viremia was tested once hematuria was documented. The main variables analyzed defined as:

1. Overall Survival (OS): Time from HSCT to death from any cause or last follow-up
2. Graft-versus-Host Disease (GVHD): Graded using the Magic criteria for acute and chronic GVHD.
3. Cytomegalovirus (CMV) Reactivation: Monitored using weekly CMV PCR testing post-transplantation.
4. BK Viruria: Monitored using BKV PCR testing post-transplant from the initiation of symptom.
5. Neutrophil Engraftment: Defined as three consecutive days with an absolute neutrophil count (ANC)  $\geq 0.5 \times 10^9/L$ .
6. Platelet Engraftment: Defined as the first day with a platelet count  $\geq 20 \times 10^9/L$  without transfusion support for at least seven days.
7. Hemorrhagic Cystitis (HC): After the transplantation, microscopic or macroscopic hematuria, with or without urinary frequency, urgency, urinary pain and other bladder irritation symptoms. According to the degree of hematuria, the clinical classification of HC is as follows<sup>10</sup>
  - a. 1<sup>st</sup> Degree: Hematuria under microscope
  - b. 2<sup>nd</sup> Degree: Gross hematuria
  - c. 3<sup>rd</sup> Degrees: Naked eye hematuria with clot
  - d. 4<sup>th</sup> Degrees: Clot obstruction urethra, this should take measures to remove blood clots or require surgical intervention.

SPSS software (IBM SPSS Statistics, New York, USA, version 27.0) was used to calculate the frequency and percentages of qualitative variable and mean, median and standard deviation of quantitative variables. OS was plotted using Kaplan-Meier curves. P values < 0.05 was considered statistically significant.

## Results

A total of 138 patients were enrolled in the study, with a mean age of 21.3(range 4.9-37.7 years). The cohort comprised 102 males (73.9%) and 36 females (26.1%). All patients included had a diagnosed hematological disorder requiring HSCT during the study period. The most common underlying diagnosis was Beta Thalassemia Major (BTM), accounting for 43.5% (n=60) cases, followed by Aplastic Anemia (AA) in 19.6% (n=27), and Acute Lymphoblastic Leukaemia (ALL) in 14.5% (n=20). All patients underwent Allo-HSCT with fully HLA-matched sibling donors. Major ABO incompatibility was 16.7% cases 12.3% had minor ABO mismatched, and 7.2% of patients had bidirectional ABO mismatches. The predominant source of stem cells was bone marrow harvest (BMH) (n=113) (81.9%) and 8.7% (n=12) received stem cells via peripheral blood stem cell collection (PBSC). Myeloablative conditioning regimens (MAC) was given in (66.7%, n=92), while reduced intensity regimen was administered to 33.3% (n=46). Busulfan was used as myeloablative agent, with the majority receiving a cumulative dose of 16 mg/kg oral equivalent/ (12.8 mg/kg) IV. Cyclophosphamide was used in 79.7% (n=110) of patients, at a dose of 160 mg/m<sup>2</sup>. Immunosuppressive therapy consisted of fludarabine (120 mg/m<sup>2</sup>) and anti-thymocyte globulin (ATG; 10 mg/m<sup>2</sup>). Graft-versus-host disease (GVHD) prophylaxis included combination of cyclosporine (CSA) and methotrexate (MTX), MMF, PTcy, in combinations as detailed below in table given. A detailed summary of patient demographics and treatment-related variables is presented in Table I.

The mean day of Neutrophil engraftment was  $14.39 \pm 3.4$  days and mean day for platelet engraftment was  $30.70 \pm 85.35$  days. Mean CD34 dose was  $6.26 \pm 3.64 \times 10^6/\text{Kg}$  and TNC was  $4.95 \pm 2.00 \times 10^8/\text{Kg}$ . Eight percent (n=11) developed primary graft failure and 16.7% (n=23) developed secondary graft failure. Thirty-three percent (n=46) of the patient had BK virus reactivation and 64.5% (n=89) had CMV reactivation. Acute GVHD (all grades) was recorded in 31.9% (n=44) of patients. Two patient needed hospitalization for grade IV acute GVHD. Chronic GVHD was seen in 21.7% (n=30) cases. Transplant parameters post HSCT are shown below in Table II.

Hemorrhagic Cystitis (HC) was developed by 55.8% (n=77) patients post HSCT with majority having grade 1 or 2 HC i.e. 15.9 (n=22) and 26.1 (n=26.1) respectively. HC

association with variables to find out statistical significance was determined by using chi square test for categorical variables and log regression analysis. In our studies occurrence of HC significantly associated with type of GVHD prophylaxis, with highest number in patients who received CSA and MTX combination followed by CSA only, CSA +MMF cohorts with a p value of (<0.05). Post-transplant cyclophosphamide did not have statistical significance association. No statistically significance was found between GvHD prophylaxis in patients with secondary graft failure, similarly no significance was established between occurrence of HC and type of conditioning chemotherapy in our study. BK virus reactivation was found in 46 out of 77 cases (59.7%) was with a P value<0.05. No statistically significant association was found with CMV and Adenovirus. Finding are summarized in the table given below Table III.

Patients with HC were managed with supportive care i.e. replacing the lost volume with blood products or intravenous crystalloids, bladder irrigation and antiviral therapy. Sixty-six patients i.e. 85% responded to supportive care while 15% (N=11) had no response to supportive care. The OS among treatment responsive patients was 97% almost same as to patients without HC 88.5% (p value < 0.05). Patient with persistent HC was only 18.2%. The overall survival (OS) of patients with HC was 87% in first 100 days' post HSCT, which dropped to 66.7% on longer follow up (median follow-up duration of 10 years). The survivals graphs are depicted in Figure 1 and Figure 2.

## Discussion

We conducted a retrospective study to document the incidence of HC among patient undergoing Allogeneic HSCT for hematological disorders. The study documents that HC remains a significant complication with the incidence of HC was notably high at 55.8%, highlighting the clinical burden of this complication, particularly in developing world where the treatment options are very limited. A study conducted for the incidence of HC in pediatric SAA flowing HSCT, report a frequency of 26.8%.<sup>11</sup>

The pathogenesis of developing HC post high-dose Busulfan and Cyclophosphamide is well known. Patients receiving these agents, especially those receiving in combination, exhibited higher risk of developing HC.

Table I: Demographics of the patients undergoing Allogeneic HSCT and Pre-HSCT parameters.

|                                                             | N          | %         |
|-------------------------------------------------------------|------------|-----------|
| Mean age of the patients $\pm$ S.D: 21.34 $\pm$ 16.49 years |            |           |
| Gender of the Patients                                      |            |           |
| Male                                                        | 102        | 73.9      |
| Female                                                      | 36         | 26.1      |
| Underlying Haematological disorder                          |            |           |
| Beta Thalassemia Major                                      | 60         | 43.5      |
| Aplastic Anaemia                                            | 27         | 19.6      |
| Acute Lymphoblastic Leukaemia                               | 20         | 14.5      |
| Myelodysplastic Syndrome                                    | 5          | 3.6       |
| Acute Myeloid Leukaemia                                     | 4          | 2.9       |
| Chronic Myeloid Leukaemia                                   | 3          | 2.2       |
| Glanzmann Thrombasthenia                                    | 2          | 1.4       |
| Others                                                      | 17         | 12.3      |
| Type of HSCT                                                |            |           |
| Fully Matched Allogeneic HSCT                               | 127        | 92        |
| Haplo Matched Allogeneic HSCT                               | 11         | 8         |
| Gender of Donor                                             |            |           |
| Male                                                        | 69         | 50        |
| Female                                                      | 69         | 50        |
| Relation of Donor with the patient                          |            |           |
| Brother                                                     | 64         | 46.4      |
| Sister                                                      | 64         | 46.4      |
| Father                                                      | 5          | 3.6       |
| Mother                                                      | 5          | 3.6       |
| Conditioning Chemotherapy                                   |            |           |
| Myeloablative Conditioning (MAC)                            | 92         | 66.7      |
| Reduced Intensity Conditioning (RIC)                        | 46         | 33.3      |
| Conditioning Chemotherapy                                   | Yes, % (n) | No, % (n) |
| Fludarabine                                                 | 73.2 (101) | 26.8 (23) |
| Busulfan                                                    | 76.1 (105) | 23.9 (33) |
| Cyclophosphamide                                            | 79.7 (110) | 20.3 (28) |
| Anti-Thymocyte Globulin                                     | 88.4 (122) | 11.6 (16) |
| GVHD* Prophylaxis                                           |            |           |
| Cyclosporine + MTX**                                        | 75         | 54.3      |
| Cyclosporine only                                           | 23         | 16.7      |
| Cyclosporine + MMF                                          | 16         | 11.6      |
| Cyclosporine + MTX + MMF                                    | 11         | 8.0       |
| Cyclosporine + MMF + PT Cy***                               | 6          | 4.3       |
| Cyclosporine + Steroids                                     | 3          | 2.2       |
| Cyclosporine + MTX + MMF + Methyl Prednisolone              | 1          | 0.7       |
| Cyclosporine + PT Cy                                        | 1          | 0.7       |
| Cyclosporine + MTX +MMF + Tacrolimus                        | 1          | 0.7       |
| Cyclosporine + MMF + Tacrolimus                             | 1          | 0.7       |
| ABO- Mismatch                                               |            |           |
| No Mismatch                                                 | 88         | 63.8      |
| Major Mismatch                                              | 23         | 16.7      |
| Minor Mismatch                                              | 17         | 12.3      |
| Bi-directional Mismatch                                     | 10         | 7.2       |
| Stem cell Collection Source                                 |            |           |
| Bone Marrow Harvest                                         | 113        | 81.9      |
| Peripheral Blood Stem cells Collection                      | 12         | 8.7       |
| Bone Marrow Harvest + Peripheral Blood Stem Cell Collection | 13         | 9.4       |
| *GVHD: Graft Vs Host Disease                                |            |           |
| **MTX: Methotrexate                                         |            |           |
| ***PT Cy: Post Transplant Cyclophosphamide                  |            |           |

Table II; Parameter of Post Hematopoietic Stem Cell Transplant

|                                                                    |     |      |
|--------------------------------------------------------------------|-----|------|
| Mean CD34 Dose $\pm$ S.D: $6.26 \pm 3.64 \times 10^6/\text{Kg}$    |     |      |
| Mean MNC/TNC Dose $\pm$ S.D: $4.95 \pm 2.00 \times 10^8/\text{Kg}$ |     |      |
| Primary Graft Failure                                              |     |      |
| Yes                                                                | 11  | 8.0  |
| No                                                                 | 127 | 92.0 |
| Secondary Graft Failure                                            |     |      |
| Yes                                                                | 23  | 16.7 |
| No                                                                 | 115 | 83.3 |
| Viral Re-activation                                                |     |      |
| BK Virus                                                           | 46  | 33.3 |
| CMV                                                                | 89  | 64.5 |
| None                                                               | 3   | 2.1  |
| Acute GVHD (n= 44)                                                 |     |      |
| Grade I                                                            | 20  | 14.5 |
| Grade II                                                           | 15  | 10.9 |
| Grade III                                                          | 7   | 5.1  |
| Grade IV                                                           | 2   | 1.4  |
| Chronic GVHD (n= 30)                                               |     |      |
| Grade I                                                            | 10  | 7.2  |
| Grade II                                                           | 12  | 8.7  |
| Grade III                                                          | 8   | 5.8  |

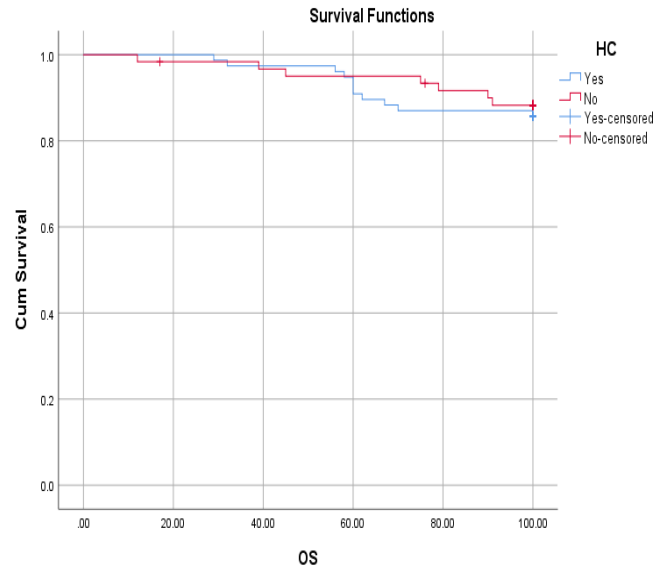


Figure 1. 100 days survival of patient with HC undergoing HSCT .

Existing studies report a 23–28% incidence of HC following MAC protocols incorporating these drugs.<sup>12</sup> Although some other studies also report MAC regimens

Table III: Statistically significant association between HSCT related variables and HC.

|                            |      | OR    | 95% C.I |       | P-value |
|----------------------------|------|-------|---------|-------|---------|
|                            |      |       | Lower   | Upper |         |
| Gender                     | Male | 0.63  | 0.29    | 1.35  | 0.23    |
| Donor gender               | Male | 0.75  | 0.38    | 1.46  | 0.39    |
| Donor relation             |      |       |         |       |         |
| Brother                    |      | 0.17  | 0.02    | 1.62  | 0.12    |
| Sister                     |      | 0.21  | 0.02    | 1.96  | 0.17    |
| Father                     |      | 0.17  | 0.01    | 2.82  | 0.21    |
| ABO incompatibility        |      |       |         |       |         |
| Major mismatch             |      | 1.71  | 0.68    | 4.32  | 0.26    |
| Minor mismatch             |      | 0.72  | 0.24    | 2.11  | 0.55    |
| Bidirectional mismatch     |      | 0.88  | 0.23    | 3.33  | 0.85    |
| Type of HSCT               | Allo | 0.42  | 0.11    | 1.51  | 0.18    |
| CD34 source                |      |       |         |       |         |
| BMH                        |      | 1.99  | 0.58    | 6.83  | 0.28    |
| PBSC                       |      | 1.13  | 0.21    | 6.05  | 0.89    |
| Primary graft failure      | Yes  | 2.37  | 0.66    | 8.49  | 0.19    |
| Secondary graft failure    | Yes  | 0.15  | 0.04    | 0.52  | 0.00    |
| CMV reactivation           | Yes  | 0.92  | 0.46    | 1.86  | 0.81    |
| Immunosuppression post BMT | CSA  | 10.16 | 2.19    | 47.00 | 0.00    |
| aGVHD                      | Yes  | 1.22  | 0.59    | 2.52  | 0.59    |
| cGVHD                      | Yes  | 4.15  | 1.57    | 10.96 | 0.00    |

Note: logistic regression test was applied.

Reference category: Female in gender, female in donor gender, mother in donor relationship, no mismatch in ABO incompatibility, Haplo in type of HSCT, BMH+PBSC in CD34 source, CSA+MMF in immunosuppression post BMT and No: in primary, secondary GF , CMV reactivation, aGVHD and cGVHD.

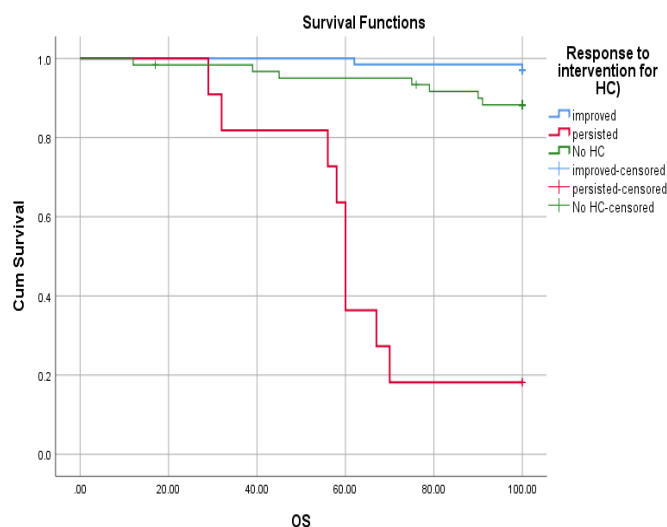


Figure 1. Overall survival (OS) vs response to the Treatment (P = 0.001)

were more strongly associated with HC than RIC<sup>13</sup>, likely due to their higher toxicity, but our study did not show significant association. The cytotoxic effect of cyclophosphamide and Busulfan on the urothelium, coupled with their metabolites, contributes to mucosal injury, hemorrhage, and increased susceptibility to infections including BK virus (BKV).<sup>14</sup>

BKV reactivation was a prominent contributor in our study, it is consistent with the literature which reported BKV in approximately 58% of HC cases.<sup>15</sup> About one-third of our patients had documented BKV viruria, highlighting its frequent association with HC. A higher incidence i.e. upto 75% BKV induced HC has been reported previously among patients receiving post-transplant cyclophosphamide (PTCy).<sup>16</sup> Some studies report that receiving PTCy based GVHD prophylaxis had a higher incidence of HC as compared to those receiving methotrexate based regimens, our analysis did not show a statistically significant correlation between PTCy, in contrast we report a strong association of CSA only or in combination with MTX or MMF with HC.

The link between impaired immune reconstitution and viral reactivation is reported in a number of studies, particularly in the presence of graft-versus-host disease (GVHD) and its immunosuppressive treatment regimens.<sup>17</sup> The association between GVHD and HC remains controversial in literature. While many studies report no statistically significant correlation, our results demonstrate a significant association between chronic GVHD and the

development of HC, possibly due to cumulative immunosuppression and immune dysregulation that enhance viral reactivation. Acute GVHD was more prevalent in the HC group, but not statistically significant in a multivariate analysis. Another meta-analysis conducted to explore risk factors for HC in pediatric patients undergoing HSCT, analyzing 12 studies with 2,764 patients, did not find significant associations between GVHD and HC.<sup>18</sup> Our results also demonstrate that there was no significant difference regarding stem cell source (bone marrow, peripheral blood) and developing HC which is in line with the findings of another meta-analysis.<sup>19</sup>

Additionally, a meta-analysis reports that receiving grafts from unrelated or HLA-mismatched donors was associated with increased HC risk.<sup>20</sup> Our results, when analyzed did not show any significant association of HLA mismatch with the HC. Literature also shows that delayed platelet engraftment and thrombocytopenia were more common in patients with BKV-HC. The presence of thrombocytopenia and delayed platelet engraftment at HC onset can exacerbate hematuria.<sup>21</sup>

Notably, our data showed no significant associations between HC and HLA mismatch, stem cell source (bone marrow vs. peripheral blood), CD34+ cell dose, or total nucleated cell dose (TNC), diverging from the findings of earlier studies and meta-analyses. However, a higher mononuclear cell (MNC) dose did emerge as a significant risk factor in other multivariate pediatric studies. Notably, high MNC doses (cutoff:  $8.53 \times 10^8/\text{kg}$ ) may contribute to bladder epithelial damage, highlighting the importance of dose optimization,<sup>22</sup> suggesting the potential for a dose-dependent bladder toxicity mechanism, although this was not observed in our analysis.

The management of HC in our resource-limited setting relied heavily on supportive care, including hydration, transfusions, and bladder irrigation. Only one patient received Cidofovir, but it did not result in clinical improvement. Advanced therapies such as virus-specific T-cell infusions (VSTs), hyperbaric oxygen, or mesenchyme stromal cells were not available. Literature indicates that VSTs are particularly effective, achieving resolution in up to 82% of cases.<sup>23</sup> Nevertheless, our supportive approach resolved HC in 85% of patients, though 15% progressed to fatal outcomes, often due to overlapping complications such as GVHD or infection.

Finally, overall survival was 87% at day 100 but declined to 66.7% over time, reflecting the persistent morbidity associated with HC and its interaction with other transplant-related complications. Secondary graft failure, which was also more frequent among HC patients, likely compounded these outcomes due to prolonged immunosuppressive exposure and recurrent infections.

### Limitations of the Study

Limitations include the retrospective design, small sample size, and confounding factors such as the overlap between age and conditioning intensity. The study has retrospective single-center design. Prospective studies are needed to better define predictive markers and optimize preventive strategies for BKV-HC. Additionally, our cohort mostly comprised young patients with non-malignant disorders (e.g., thalassemia), limiting generalizability to adult or myeloablative-transplanted malignant disease cohorts.

### Conclusion

Our study highlights that BKV reactivation, CSA and MTX/MMF based GVHD prophylaxis and chronic GVHD are major contributors to HC development post-HSCT. These findings, while consistent with some published literature, also differ in key areas such as the impact of PTCy and donor matching. Larger, prospective studies are needed to clarify these relationships, explore preventive strategies such as early viral monitoring, and improve access to effective antiviral and cellular therapies, especially in resource-limited settings. Our overall survival rate of 87% at day 100 decreased to 66.7% overtime, reflecting the ongoing burden of complications like HC, GVHD, and viral reactivations.

### Limitations of the Study

Retrospective study design, small sample size, and confounding factors such as the overlap between age and conditioning intensity are some of the limitations. Additionally, our cohort mostly comprised young patients with non-malignant disorders (e.g., thalassemia), limiting generalizability to adult or myeloablative-transplanted malignant disease cohorts. Prospective studies are needed to better define predictive markers and optimize preventive strategies for BKV-HC

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