

# Risk factors associated with hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation

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## Abstract

Hemorrhagic cystitis (HC) is a common complication of allogeneic hematopoietic stem cell transplantation (HSCT). The incidence is about 7% to 68%, and some patients have to suffer a long period of frequent, urgent, and painful urination, which brings great pain. This study aimed to analyze risk factors of HC and its effect on patient survival. We collected the medical records of 859 patients who underwent HSCT at our hospital between August 2016 and August 2020. Patients with and without HC were matched using propensity score matching at a 1:1 ratio based on sex, age, and diagnosis, and logistic regression analyses were used to identify factors associated with HC. We used Kaplan–Meier curves to analyze the survival rates of patients in the HC and non-HC groups. We also analyzed the relationship between BK viral load and the occurrence of HC using receiver operating characteristic curve (ROC) analysis. After propensity score matching, there were 131 patients each in the HC and non-HC groups. In the HC group, 89 patients (67.9%) had mild HC (stage II<sup>o</sup>) and 43 (32.1%) had severe HC (stage III–IV). The median interval between stem cell transplantation and HC development was 31 (3–244) days. Univariate analysis indicated that donor age, hematopoietic stem cell source, HLA, acute graft-versus-host disease, busulfan, anti-thymocyte globulin (ATG), total body irradiation, cytomegalovirus (CMV) (urine), and BK polyomavirus (BKV) (urine) were significantly associated with HC. ATG, CMV (urine), and BKV (urine) were independent risk factors for HC based on the multivariate analysis. The Kaplan–Meier survival analysis showed no significant difference between the HC and non-HC groups ( $P = .14$ ). The 1- and 2-year survival rates in the HC group were 78.4% and 69.6%, respectively, and the corresponding rates in the non-HC group were 84.4% and 80.7%, respectively. ROC analysis indicated that a urine BKV load of  $1 \times 10^7$  copies/mL was able to stratify the risk of HC. In conclusion, when the BKV load is  $>1 \times 10^7$ , we need to be aware of the potential for the development of HC.

**Keywords:** Allogeneic hematopoietic stem cell transplantation, Hemorrhagic cystitis, Prognosis, Risk factors

## 1. INTRODUCTION

Hemorrhagic cystitis (HC) is a common complication of allogeneic hematopoietic stem cell transplantation (HSCT). The incidence of HC is 7% to 68%.<sup>1</sup> The main clinical manifestations are frequent micturition, urgent micturition, and dysuria

accompanied by microscopic or gross hematuria.<sup>2</sup> HC can be divided into early-onset HC ( $\leq 72$  hours after hematopoietic stem cell infusion) and delayed-onset HC ( $>72$  hours after hematopoietic stem cell infusion). Early-onset HC is mainly associated with cytotoxicity during preconditioning. In contrast,

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late-onset HC is associated with various risk factors such as BK polyomavirus (BKV) reactivation and acute graft-versus-host disease (aGVHD). To define the risk factors of HC more comprehensively, we conducted a large-scale, comprehensive, retrospective study in patients who received HSCT between 2016 and 2020.

## 2. RESULTS

### 2.1. Patient characteristics

Between August 2016 and August 2020, a total of 859 allogeneic HSCTs were performed in our hospital, and 208 patients developed HC. After excluding patients with grade I HC, 131 patients with HC were included in this study. After propensity score matching based on sex, age, and diagnosis, 131 propensity score-matched non-HC patients were also included. In total, 262 patients were included in this study. Among them, 121 patients had AML (46.2%), 47 had ALL (17.9%), 36 had SAA (13.7%), 44 had MDS (16.8%), and 14 had other malignancies (5.3%). There were 80 HLA-identical sibling donors (30.5%), 45 HLA-mismatched sibling donors (17.2%), 12 HLA-mismatched unrelated donors (4.6%), 2 HLA-incomplete unrelated donors (0.8%), 120 haploidentical transplants (45.8%), and 3 other kinships (1.1%). The stem cell blood source was the peripheral blood in 239 patients (91.2%) and bone marrow combined with peripheral blood in 23 patients (8.8%). Among the 131 patients with HC, 89 (67.9%) had grade II HC, 19 (14.5%) had grade III HC, and 23 (17.6%) had grade IV HC. Therefore, 89 patients (67.9%) had mild HC (II), and 42 (32.1%) had severe HC (III-IV). The median interval between stem cell transplantation and development of HC was 31 (3–244) days. Table 1 shows the basic data and transplantation-related analyses of the two groups.

### 2.2. Risk factors for the development of HC

Univariate analysis showed that donor age, hematopoietic stem cell source, HLA matching, aGVHD, BU, ATG, TBI, CMV (urine), and BKV (urine) were associated with HC (all  $P < .05$ ). There were no significant differences between the two groups in sex, leukocyte count, hemoglobin level, platelet count, mononuclear cells, CD34+ cell dose, disease type, blood type compatibility of the donor and recipient, donor sex, or CY (all  $P > .05$ ). Variables with  $P \leq .10$  in the univariate analysis were included in the multivariate analysis. The multivariate analysis showed that ATG, CMV (urine), and BKV (urine) were independent risk factors for HC (Tables 1 and 2).

### 2.3. Comparison of survival between the HC and non-HC groups

We next analyzed the survival of the two groups. There were no significant differences in survival between the HC and non-HC groups (Fig. 1). The 1-year and 2-year survival rates in the HC group were 78.4% and 69.6%, respectively, and the corresponding rates in the non-HC group were 84.4% and 80.7%, respectively ( $P = .14$ ) (Table 3). We also assessed survival based on the severity of HC. There was no significant difference in survival between patients without HC and those with mild HC ( $P = .893$ ). However, patients with severe HC had worse survival than those without HC and those with mild HC ( $P = .007$ ) (Fig. 2).

### 2.4. The threshold BKV load for predicting HC

ROC curve analysis was used to analyze the ability of the BKV load to predict HC. The results showed that when the BKV load

was  $>1 \times 10^7$  copies/mL, the risk of HC was significantly increased. The area under the curve was 0.67 (Fig. 3).

## 3. DISCUSSION

HC is a common and severe complication of allogeneic HSCT. HC is defined as a diffuse inflammatory disease of the lower urinary tract. The occurrence of HC is mainly related to cytotoxic drugs during preconditioning, latent virus activation in vivo, and immune dysfunction after HSCT.<sup>6</sup>

BKV is detected in the urine of 80% of HC patients after HSCT; therefore, BKV is closely related to HC occurrence.<sup>7</sup> BKV is a common virus that infects up to 90% of children and is transmitted mainly through body fluids.<sup>8</sup> BKV resides in urinary epithelial cells with blood circulation after entering the human body. When the body's immune function decreases, BKV can be reactivated and cause shedding of the urinary epithelial cells, which leads to clinical manifestations of bleeding and bladder irritation symptoms.<sup>8</sup> We analyzed the BKV load during the disease course of the two groups through continuous assessment of the urine. The BKV load was significantly higher in patients with HC than in patients without HC ( $9.09 \pm 1.91$  copies/mL vs  $6.08 \pm 2.83$  copies/mL;  $P = .001$ ). However, some patients who undergo HSCT are infected with BKV but do not develop HC, which indicates that HC will not be induced until the BKV load reaches a critical value. Therefore, we used ROC curve analysis to analyze the cutoff value of the BKV load that predicts HC. The results showed that when the BK viral load was  $>1 \times 10^7$  copies/mL, the incidence of HC was significantly increased. The area under the ROC curve was 0.67. This cutoff value was similar to those previously reported in the literature.<sup>9–11</sup> Therefore, when the BKV load is  $>1 \times 10^7$  copies/mL, we need to be aware of the potential for the development of HC.

CMV reactivated was also an independent risk factor for HC in our study ( $P = .05$  in multivariate analysis). Many previous studies have also shown that CMV infection is a risk factor for HC.<sup>12–14</sup> Moreover, reactivation of CMV is often accompanied by the reactivation of other viruses, such as BKV.<sup>12</sup> This is consistent with our finding that BKV and CMV infections were both related to HC.

ATG was also an independent risk factor for HC ( $P = .04$ ). ATG is an effective immunosuppressant to prevent GVHD and is increasingly being administered to haploidentical transplant patients. Many studies have confirmed that the recovery of T cell function is significantly delayed in patients receiving ATG, which significantly impacts the reconstruction of immune function.<sup>15–17</sup> High-dose ATG has a more substantial inhibitory effect on immune reconstruction, which can increase the risk of infection and promote the reactivation of latent infections such as BKV and CMV, thereby inducing the incidence of HC.

We used Kaplan-Meier curves to analyze the survival rates of patients in the HC and non-HC groups. There was no significant difference in overall survival between the two groups ( $P = .14$ ). We also performed a survival analysis after separating patients with mild (stage II) and severe (stages III and IV) HC. Patients with severe HC had a significantly lower 2-year survival rate than the rest of the cohort ( $P = .007$ ). There was no significant difference in survival between patients without HC and those with mild HC ( $P = .893$ ), but there was a significant difference in survival between patients with mild HC and patients with severe HC ( $P = .008$ ), which is consistent with the results of previous studies.<sup>18</sup> It has been reported that patients with severe HC who need continuous bladder irrigation have worse survival, which is

**Table 1****Results of risk factor analysis for HC (univariate analysis).**

Factor	HC group	Non-HC group	P
Sex			.68
Male	92 (70.2%)	95 (72.5%)	
Female	39 (29.8%)	36 (27.5%)	
Age, y	31.69 ± 13.12	33.02 ± 13.14	.42
WBC ( $\times 10^9/L$ )*	35.86 ± 72.05	31.08 ± 59.44	.623
HB ( $\times g/L$ )*	88.99 ± 26.44	83.93 ± 27.10	.13
PLT ( $\times 10^9/L$ )*	74.12 ± 76.83	64.43 ± 63.60	.27
Number of infused MNCs ( $\times 10^8/kg$ )	11.39 ± 3.32	11.85 ± 4.73	.28
Number of infused CD34+ ( $\times 10^6/kg$ )	3.34 ± 1.28	3.16 ± 1.04	.20
Neutrophil engraftment time (d)	14.21 ± 3.45	13.93 ± 3.13	.50
Diagnosis			.69
AML	57 (43.5%)	64 (48.9%)	
ALL	27 (20.6%)	20 (15.3%)	
SAA	20 (15.3%)	16 (12.2%)	
MDS	20 (15.3%)	24 (18.3%)	
Others <sup>†</sup>	7 (5.3%)	7 (5.3%)	
Morphological remission before transplantation			.05
CR	123 (93.9%)	129 (98.5%)	
NR	8 (6.1%)	2 (1.5%)	
MRD			.05
Negative	107 (81.7%)	118 (90.1%)	
Positive	24 (18.3%)	13 (9.3%)	
Stem cell source			.04
PB	115 (87.8%)	124 (94.7%)	
PB + BM	16 (12.2%)	7 (5.3%)	
Blood type			.38
Match	68 (51.9%)	75 (57.3%)	
Mismatch	63 (48.1%)	56 (42.7%)	
HLA			.001
10/10 match	32 (24.4%)	64 (48.9%)	
Non-10/10 match	99 (75.6%)	67 (51.1%)	
Donor sex			.25
Male	89 (67.9%)	80 (61.1%)	
Female	42 (32.1%)	51 (38.9%)	
Donor age (y)	35.93 ± 12.92	32.00 ± 13.35	.01
aGVHD			.004
Yes	63 (48.1%)	40 (30.5%)	
No	68 (51.9%)	91 (69.5%)	
BU			.006
Yes	116 (88.5%)	99 (75.6%)	
No	15 (11.5%)	32 (24.4%)	
CY			.65
Yes	128 (97.7%)	129 (98.5%)	
No	3 (2.3%)	2 (1.5%)	
ATG			.001
Yes	116 (88.5%)	92 (70.2%)	
No	15 (11.5%)	39 (29.8%)	
TBI			.03
Yes	10 (7.6%)	21 (18.3%)	
No	121 (92.4%)	110 (81.7%)	
logCMV (PB)	3.22 ± 0.39	3.23 ± 0.39	.74
logEBV (PB)	3.01 ± 0.07	3.05 ± 0.26	.13
logBKV (urine)	9.09 ± 1.91	6.08 ± 2.83	.001
logCMV (urine)	3.16 ± 0.34	3.06 ± 0.23	.02

aGVHD = acute graft-versus-host disease, ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, ATG = anti-thymocyte globulin, BKV = BK polyomavirus, BM = bone marrow, BU = busulfan, CMV = cytomegalovirus, CR = complete remission, CY = cyclophosphamide, EBV = Epstein-Barr virus, HB = hemoglobin, HC = hemorrhagic cystitis, HLA = human leukocyte antigen, MDS = myelodysplastic syndrome, MNC = mononuclear cell, MRD = minimal residual disease, NR = non-remission, PB = peripheral blood, PLT = platelets, SAA = severe aplastic anemia, TBI = total body irradiation, WBC = white blood cells.

Data are presented as n (%) or median ± standard deviation.

Univariate analysis showed that stem cell source, HLA, donor age, aGVHD, BU, ATG, TBI, BKV (urine), and CMV (urine) were associated with HC ( $P < .05$ ).

\*Values at diagnosis.

<sup>†</sup>Chronic myeloid leukemia, chronic myelomonocytic leukemia, myelofibrosis, and Fanconi anemia.

**Table 2**  
Results of risk factor analysis for HC (multivariate analysis).

Results of multivariate analysis	P	HR (Exp)	95% CI
Morphological remission before transplantation (CR vs NR)	.27	3.98	0.34–46
MRD	.91	0.94	0.31–2.81
Stem cell source (PB vs PB+BM)	.36	2.08	0.43–10.09
HLA (10/10 match vs non-10/10 match)	.88	1.07	0.42–2.71
Donor age (y)	.49	1.02	0.97–1.07
aGVHD (Yes vs No)	.26	1.52	0.73–3.17
BU (Yes vs No)	.41	0.48	0.08–2.78
ATG (Yes vs No)	<b>.04</b>	2.77	0.07–0.96
TBI (Yes vs No)	.73	1.41	0.18–10.67
logEBV (PB)	.12	0.04	0.001–2.55
logBKV (urine)	<b>.001</b>	1.58	1.36–1.83
logCMV (urine)	<b>.05</b>	3.65	0.99–13.77

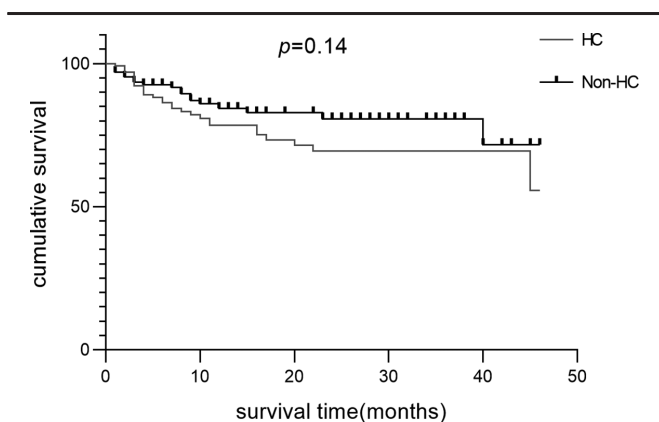
aGVHD=acute graft-versus-host disease, ATG=anti-thymocyte globulin, BKV=BK polyomavirus, BM=bone marrow, BU=busulfan, CI=confidence interval, CMV=cytomegalovirus, CR=complete remission, EBV=Epstein-Barr virus, HC=hemorrhagic cystitis, HLA=human leukocyte antigen, HR=hazard ratio, MRD=minimal residual disease, NR=non-remission, PB=peripheral blood, TBI=total body irradiation.

Multivariate analysis showed that ATG, urinary BKV, and CMV reactivation were independent risk factors for the development of HC (bold;  $P < .05$ ).

consistent with our results. A previous study found that the 90-day mortality rate of patients with severe HC was 73%. The authors believed that severe HC is a sign of severe urinary system injury and a manifestation of overall severe damage in patients undergoing HSCT. Hence, the mortality rate is significantly higher among patients with severe HC.<sup>19</sup>

HC is usually treated with hydration, alkalization, and continuous bladder lavage, and in severe cases, hyperbaric oxygen therapy, hyaluronic acid, and mesenchymal stem cell therapy.<sup>3,20</sup> In addition, because HC is often accompanied by BKV, CMV, and other viral infections, antiviral therapy is an indispensable part of HC treatment. Commonly used drugs include acyclovir, ganciclovir, foscarnet sodium, and cidofovir.

In conclusion, mild HC had no significant effect on survival in patients undergoing allogeneic HSCT. However, the survival rate of patients with severe HC was significantly decreased. Therefore, it is still necessary to be highly vigilant when HC occurs. Glucocorticoids, antiviral drugs, and auxiliary surgical treatment can be used to avoid disease progression and improve patient quality of life.



**Figure 1.** Overall survival in the HC and non-HC groups. HC=hemorrhagic cystitis.

## 4. MATERIALS AND METHODS

### 4.1. Case data

This was a retrospective analysis of patients who underwent allogeneic HSCT in our hospital between August 2016 and August 2020. This study was approved by the Ethics Committee of our hospital. HC patients were screened according to the European Conference on Information Literacy (ECIL) diagnosis and treatment guidelines.<sup>3</sup> Propensity score matching was performed according to the patient sex, age, and diagnosis. Patients were matched at a 1:1 ratio (HC:non-HC).

### 4.2. Preconditioning regimen

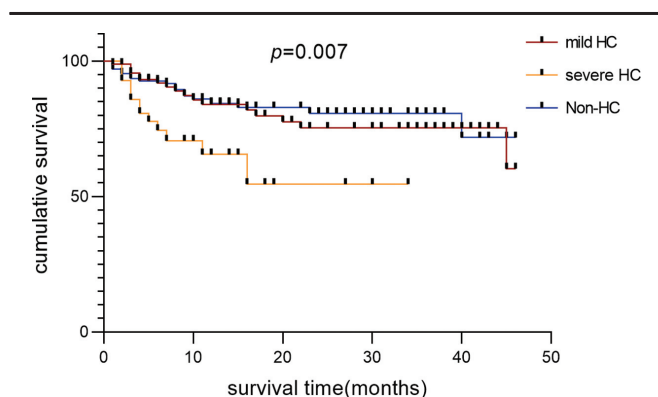
Most patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) were treated with busulfan [BU] (3.2 mg/kg × 3 days), cyclophosphamide (CY) (40 mg/kg × 2 days), Flu (30 mg/m<sup>2</sup> × 3 days), Ara-C (1 g/m<sup>2</sup> × 3 days), and anti-thymocyte globulin (ATG) (rabbit, 2.5 mg/kg × 4 days). Patients with acute lymphoblastic leukemia (ALL) and lymphoma were mainly treated with total body irradiation (TBI) (10 Gy), CY (40 mg/kg × 2 days), Flu (30 mg/m<sup>2</sup> × 3 days), and Ara-C (1 g/m<sup>2</sup> × 3 days); some patients were additionally treated with Idarubicin (10 mg/m<sup>2</sup> × 3 days) and Decitabine (20 mg/m<sup>2</sup> × 5 days). Patients with severe aplastic anemia (SAA) were treated with BU (3.2 mg/kg × 2 days), CY (40 mg/kg × 4 days), ATG (swine, 20 mg/kg × 5 days), and Flu (30 mg/m<sup>2</sup> × 5 days).

As prophylaxis for graft-versus-host disease (GVHD), patients with HLA-compatible sibling donors were administered cyclosporine A (1 mg/kg) or tacrolimus (0.03 mg/kg) combined

**Table 3**  
Survival analysis of the HC and non-HC groups.

	HC (95% CI)	Non-HC (95% CI)	P
1 year	78.4% (70.9–86.7)	84.4% (77.5–92.0)	.14
2 years	69.6% (60.1–80.5)	80.7% (72.5–89.8)	

CI=confidence interval, HC=hemorrhagic cystitis.

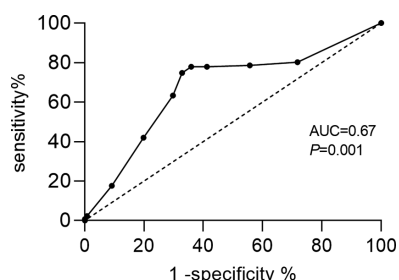


**Figure 2.** Survival in the non-HC, mild HC, and severe HC groups. There was no significant difference in survival between the mild HC group and the non-HC group ( $P=.893$ ), but the overall survival of the severe HC group was significantly worse than those of the non-HC and mild HC groups ( $P=.009$ ). HC=hemorrhagic cystitis.

with short-course methotrexate (15 mg/m<sup>2</sup> on day 1 and 10 mg/m<sup>2</sup> on days 3 and 6). Patients receiving stem cells from unrelated donors and those undergoing HLA-mismatched transplantation were supplemented with mycophenolate mofetil/mizoribine and ATG. GVHD diagnosis was based on the Seattle standard.<sup>4,5</sup>

#### 4.3. Diagnosis, grading, and treatment of HC

HC diagnosis and grading were based on the degree of hematuria according to the ECIL guidelines.<sup>3</sup> HC cases were divided into grade I (microscopic hematuria), grade II (gross hematuria), grade III (gross hematuria with a small blood clot), and grade IV (gross hematuria with a large blood clot complicated by urethral obstruction or requiring surgical treatment). Because grade I symptoms are mild, do not require treatment, and do not affect patient prognosis, only patients with grades II to IV HC were included in the study. Grade II was defined as mild, and grades III to IV were defined as severe. HC was treated by hydration, alkalization, continuous bladder irrigation of the indwelling catheter, hyaluronic acid intravesical infusion, and mesenchymal stem cell infusion. If necessary, glucocorticoids were administered. Patients positive for cytomegalovirus (CMV), BKV, Epstein-Barr virus (EBV), or other viruses were administered ganciclovir, sodium phosphonoformate, and cidofovir.



**Figure 3.** ROC curve analysis assessing the ability of urinary BKV to predict hemorrhagic cystitis. AUC=area under curve, BKV=BK polyomavirus, ROC=receiver operating characteristic curve.

#### 4.4. Follow-up

Outpatient and inpatient medical records were retrieved, and patients were followed up by telephone. The follow-up cutoff date was October 1, 2020. Total survival time was defined as the time from stem cell transplantation to the last follow-up or death.

#### 4.5. Statistical methods

R software was used to perform propensity score matching at a 1:1 ratio based on the patient's sex, age, and diagnosis. SPSS version 22.0 was used to perform *t*-test, chi-square test, Kaplan-Meier analysis, and logistic regression analysis to identify independent risk factors of HC. The multivariate analysis included variables with  $P \leq .10$  in the univariate analysis.  $P < .05$  was considered statistically significant. The effects of HC occurrence on patient survival were analyzed using GraphPad 8. In addition, the correlation between BKV load and HC occurrence was determined according to the area under the receiver operating characteristic curve (ROC) curve.

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