## **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°) 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  $P \le .10$  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. 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  $(9.09 \pm 1.91 \text{ copies/mL vs})$  $6.08 \pm 2.83$  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 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).

Sex         Sex           Male         92 (70.2%)         95 (72.5%)           Finale         39 (23.8%)         36 (27.5%)           Age, y         31.69 ± 13.12         33.02 ± 13.14           W6C (x1 (V1) <sup>4</sup> )         36.86 ± 72.05         31.09 ± 13.14           W6C (x1 (V1) <sup>4</sup> )         88.99 ± 26.44         83.93 ± 77.10           PIT (x1 (V1) <sup>4</sup> )         74.12 ± 76.83         64.43 ± 63.50           Number of intused MNCs (x1 0 <sup>5</sup> /kg)         13.3 ± 1.28         31.65 ± 1.44           Number of intused CM34 + (x1 0 <sup>5</sup> /kg)         3.3 ± 1.28         31.65 ± 1.44           Neutrophil engathment time (d)         14.21 ± 3.45         13.93 ± 3.13           Diagnosis         44.44         20.16 ± 3.35           AUL         27 (20.6%)         20.16 ± 3.36           AL         27 (20.6%)         20.16 ± 3.36           AUL         27 (20.5%)         24 (18.3%)           Mas         20.15 ± 3.36         7 (5.3%)           MS         8 (5.1%)         2 (1.5 5%)           NP         8 (5.1%)         2 (1.5 5%)           NP         8 (5.1%)         7 (5.3%)           Mas         2 (1.5 5%)         7 (5.3%)           Mas         2 (1.5 5%)         7 (5.3%)     <	Factor	HC group	Non-HC group	Р
Totale         92 (70.2%)         95 (72.5%)           Famile         30 (29.8%)         36 (27.5%)           Age, y         31 89 ± 13.1 2         33 80 ± 13.1 4           WBC (x10 <sup>1</sup> /1)         85 89 ± 20.6 4         83.33 ± 27.10           PL (x10 <sup>1</sup> /2)         74.12 ± 76.53         64.43 ± 61.60           Number of Indued MK2 (x10 <sup>1</sup> /kg)         11.39 ± 5.32         11.48 ± 4.73           Number of Indued MK2 (x10 <sup>1</sup> /kg)         3.34 ± 1.28         3.16 ± 1.04           Number of Indued MK2 (x10 <sup>1</sup> /kg)         3.34 ± 1.28         3.16 ± 1.04           Number of Indued MK3 (x10 <sup>1</sup> /kg)         3.34 ± 1.28         3.16 ± 1.04           Number of Indued MK3 (x10 <sup>1</sup> /kg)         3.24 ± 1.28         3.16 ± 1.04           Number of Indued MK3 (x10 <sup>1</sup> /kg)         3.24 ± 1.28         3.16 ± 1.04           Number of Indued MK3 (x10 <sup>1</sup> /kg)         3.24 ± 1.28         3.16 ± 1.04           Number of Indued MK3 (x10 <sup>1</sup> /kg)         3.24 ± 1.28         3.16 ± 1.04           Number of Indued MK3 (x10 <sup>1</sup> /kg)         3.24 ± 1.28         3.16 ± 1.04           ALL         27 (20.6%)         20 (15.3%)         24 (18.3%)           ALL         27 (20.5%)         20 (15.3%)         24 (18.3%)           NB         8 (6.1%)         2 (19.5%)         2 (19.5%)	Sex			68
Fermate         33 (29.8%)         36 (27.9%)           Ape, y         31 69 ± 13 12         33 0.22 ± 13 14           Ape, Y         31 69 ± 13 12         33 0.22 ± 13 14           Mole C(x10 <sup>4</sup> /L) <sup>1</sup> 88.89 ± 26.44         88.39 ± 27.10           PL (x10 <sup>2</sup> /L) <sup>1</sup> 74.12 ± 76.53         64.43 ± 63.60           Number of intesed MNCs (x10 <sup>4</sup> /kg)         11.39 ± 3.32         11.86 ± 4.73           Number of intesed CO34 + (x10 <sup>4</sup> /kg)         33.4 ± 1.28         31.6 ± 1.04           Neutrofil integratment time (0)         14.2 ± 7.63         64.43 ± 63.60           Diagnosis         20         15.3%)         64 (45.9%)           AL         57 (20.5%)         20 (15.3%)         64 (45.9%)           AL         57 (20.5%)         20 (15.3%)         24 (16.3%)           MDS         20 (15.3%)         24 (16.3%)         20 (15.3%)           MDF         20 (15.3%)         24 (16.3%)         20 (15.3%)           MDF         20 (15.3%)         21 (15.3%)         20 (15.3%)           MDS         20 (15.3%)         21 (15.3%)         20 (15.3%)           MDS         21 (15.3%)         21 (15.3%)         20 (15.3%)           MDS         21 (15.3%)         21 (15.3%)         20 (15.3%)	Male	92 (70,2%)	95 (72.5%)	.00
Ape         31 69 ± 13 12         33 02 ± 13 14           WBC (x + 10 <sup>1</sup> /L)         35 68 ± 72 05         33 08 ± 93 44           WBC (x + 10 <sup>1</sup> /L)         85 68 ± 72 05         33 08 ± 93 44           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         74 12 ± 76 83         64 44 ± 63 60           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.44           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.04           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.04           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.04           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.04           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.04           Number of Intused MNSs (x + 10 <sup>1</sup> /Mg)         33 4± 128         31 6± 1.04           Math         27 (0.0%)         20 (15 3%)         24 (16 3%)           ALL         27 (0.0%)         20 (15 3%)         24 (16 3%)           MDS         20 (15 3%)         24 (16 3%)         21 (15 %)           Morbiological remission before transplantation         7 (5 3%)         7 (5 3%)           Morbiological remission before transplantation         7 (5 3%)         7 (5 3%)           Morbiologi	Female	39 (29.8%)	36 (27.5%)	
\nd{BC} (x10^1/u)*         36.88 ± 2.05         31.03 ± 63.44           \HB (x10^1/u)*         88.99 ± 26.44         88.39 ± 27.10           \LT (x10^1/u)*         14.12 ± 76.83         64.43 ± 63.60           Number of intused MNGs (x10 <sup>1/k</sup> g)         13.34 ± 12.8         31.65 ± 1.04           Number of intused MNGs (x10 <sup>1/k</sup> g)         33.44 ± 12.8         31.65 ± 1.04           Neutrophil engratment time (d)         14.75 × 63.5%)         24.14 ± 3.45           Diagnosis         27.(20.6%)         20.16.3%)         20.16.3%)           AUL         57.(20.5%)         24.16.3%)         26.16.3%)           AAL         20.16.3%)         20.16.3%)         20.16.3%)           SAA         20.16.3%)         20.16.3%)         20.16.3%)           MST         7.15.3%         7.15.3%)         7.15.3%)           Moptiological remission before transplantation         21.09.3%)         18.60.1%)           CR         21.98.3.9%)         29.08.5%)         NR           NR         8.01.99.3         28.09.3%)         20.01.5%)           NR         8.01.99.4         10.76.7%)         14.64.7%)           PB         11.67.78%         7.6.5.3%)         MS           MED         11.67.78%         7.6.5.3%)         1	Age. v	$31.69 \pm 13.12$	$33.02 \pm 13.14$	.42
HE (xq0) <sup>1</sup> B8 99 ± 8: 44         B3 39 ± 27: 10           PLT (x10 <sup>2</sup> /1) <sup>2</sup> 74 12 ± 76 33         64 43 ± 63 60           Number of intised MNGs (x10 <sup>2</sup> /kg)         3.34 ± 123         3.15 ± 1.47           Number of intised C034 + (x10 <sup>2</sup> /kg)         3.34 ± 123         3.13 ± 1.21           Diagnosis	WBC $(\times 10^{9}/L)^{*}$	$35.86 \pm 72.05$	$31.08 \pm 59.44$	.623
PLT \sciPAL         74.12 ± 76.83         64.43 ± 63.60           Number of infused MXGs (x 10%)         11.39 ± 3.32         11.85 ± 4.73           Number of infused C024+ (x 10%)         3.34 ± 1.28         3.16 ± 1.04           Neutoph of infused C024+ (x 10%)         14.21 ± 3.45         3.13 ± 1.04           Neutoph of infused C024+ (x 10%)         14.21 ± 3.45         3.16 ± 1.04           Neutoph of infused C024+ (x 10%)         14.21 ± 3.45         3.16 ± 1.04           Neutoph of infused C024+ (x 10%)         14.21 ± 3.45         3.16 ± 1.04           Neutoph of infused C024+ (x 10%)         14.21 ± 3.45         3.16 ± 1.04           Neutoph of infused C024+ (x 10%)         2.01 (5.3%)         2.01 (5.3%)         2.01 (5.3%)           ALL         57 (6.5%)         2.01 (5.3%)         2.41 (8.3%)         0.16 (12.2%)           MDS         2.01 (5.3%)         2.41 (8.3%)         0.16 (12.2%)         7 (5.3%)           Maphological remission before transplantation         2.20 (9.6%)         13.16 (9.01%)         2.9 (9.6%)           NR         8.6 (6.1%)         7 (6.3%)         2.9 (9.6%)         NR           NB         11.6 (9.01%)         12.4 (4.7%)         7 (6.3%)           Pe et M         16 (12.2%)         7 (6.3%)           Boot togic	HB $(\times \alpha/L)^*$	88.99 + 26.44	83.93 + 27.10	.13
Number of Infused NMCs (>10 <sup>5</sup> Ng)         11.39±3.32         11.85±4.73           Number of Infused CO34+ (×10 <sup>6</sup> Ng)         3.34±1.23         13.39±3.13           Diagnotis	PLT (×10 <sup>9</sup> /L)*	74.12 + 76.83	64.43 + 63.60	.27
Number of Infused C034+ (x 10 <sup>6</sup> /kg)         3.34 ± 7.28         3.16 ± 7.04           Neutrophil engratment time (d)         1.42 ± 3.45         3.03 ± 3.13           Diagnoiss	Number of infused MNCs ( $\times 10^8$ /kg)	11.39 + 3.32	11.85 + 4.73	.28
Neutrophil equicationent time (d)         14.21 ± 3.45         13.93 ± 3.13           Diagnosis         -         -           AML         27 (20.5%)         64 (48.9%)           ALL         27 (20.5%)         16 (12.2%)           MOS         20 (15.3%)         24 (13.3%)           Others'         7 (5.3%)         7 (5.3%)           MOS         20 (15.3%)         7 (5.3%)           Others'         7 (5.3%)         21 (15.8%)           MOR         8 (6.1%)         21 (15.8%)           MR         8 (6.1%)         118 (90.1%)           Positive         2 (16.3%)         13 (9.3%)           Stem cell source         -         -           PB         15 (87.8%)         124 (94.7%)           Positive         2 (16.3%)         7 (5.3%)           Match         68 (51.9%)         67 (51.3%)           Dorl Or match         29 (75.5%)         67 (51.3%)           Dorl Or match         29 (75.5%)         67 (51.3%)           Dorl Or match         29 (27.9%)         63	Number of infused CD34+ ( $\times 10^{6}$ /kg)	$3.34 \pm 1.28$	$3.16 \pm 1.04$	.20
Diagnosis         57 (43.5%)         64 (48.9%)           AML         57 (43.5%)         20 (15.3%)           AAL         27 (20.6%)         20 (15.3%)           SAA         20 (15.3%)         64 (48.9%)           SAA         20 (15.3%)         64 (18.9%)           SAA         20 (15.3%)         64 (18.3%)           Others <sup>1</sup> 7 (5.3%)         7 (5.3%)           Others <sup>1</sup> 7 (5.3%)         7 (5.3%)           Morphological remission before transplantation         129 (98.5%)           NR         8 (6.1%)         2 (1.5%)           MRD         2 (1.5%)         7 (5.3%)           MRD         8 (6.1%)         118 (90.1%)           Stem cell source         7         7 (5.3%)           PB et BM         116 (87.5%)         7 (5.3%)           Blood type         7         7 (5.3%)           Match         63 (48.1%)         56 (42.7%)           HLA         10 (10 match         9 (27.6%)         80 (61.1%)           Non - 10 / 10 match         29 (24.4%)         64 (46.9%)           Non - 10 / 10 match         29 (24.3%)         51 (68.9%)           Dorn arge (y)         35 (38.1%)         90 (20.5%)           No	Neutrophil engraftment time (d)	$14.21 \pm 3.45$	$13.93 \pm 3.13$	.50
ĀLL         57 (43.5%)         64 (49.9%)           ALL         27 (20.6%)         20 (15.3%)           SAA         20 (15.3%)         21 (12.2%)           MDS         20 (15.3%)         7 (5.3%)           Others'         7 (5.3%)         7 (5.3%)           MOrphological remission before transplantation         7 (5.3%)         7 (5.3%)           MCN         129 (98.5%)         8 (15.5%)           NR         8 (6.15%)         121 (90.5%)           MED         116 (90.1%)         118 (90.1%)           Positive         24 (18.3%)         13 (9.3%)           Stem cell source         115 (67.8%)         124 (46.7%)           PB         115 (67.8%)         7 (5.3%)           Blood type         7 (5.3%)         13 (9.3%)           MRD         68 (51.9%)         75 (57.3%)           Match         68 (51.9%)         75 (57.3%)           Mastath         29 (27.6%)         64 (48.9%)           Non-10710 match         32 (24.4%)         64 (48.9%)           Non-10710 match         32 (24.1%)         61 (89.8%)           Donor say         9 (75.6%)         60 (61.1%)           Yes         32 (48.1%)         40 (30.5%)           No	Diagnosis			.69
AL         27 (20.6%)         20 (15.3%)         16 (12.2%)           MDS         20 (15.3%)         24 (18.3%)         0thers <sup>1</sup> MOrphological remission before transplantation         7 (5.3%)         7 (5.3%)           Morphological remission before transplantation         129 (96.5%)         34 (16.3%)           NR         8 (6.1%)         2 (15.3%)         20 (15.3%)           NR         8 (6.1%)         29 (96.5%)           NR         8 (6.1%)         2 (15.3%)           NR         8 (6.1%)         2 (15.3%)           Positive         24 (18.3%)         3 (9.3%)           Stem call source         7 (5.3%)         13 (9.3%)           PS + BM         10 (16.2%)         7 (5.3%)           Blood type         7 (5.3%)         6 (42.7%)           Match         63 (48.1%)         56 (42.7%)           Match         30 (24.8%)         50 (13.8)           Non - 10/10 match         32 (24.4%)         64 (48.9%)           Non - 10/10 match         32 (24.4%)         61 (38.9%)           Source = 10/10 match         20 (24.5%)         50 (38.9%)           Non - 10/10 match         20 (24.5%)         51 (38.9%)           Source = 10/10 match         20 (13.5%) <t< td=""><td>ÂML</td><td>57 (43.5%)</td><td>64 (48.9%)</td><td></td></t<>	ÂML	57 (43.5%)	64 (48.9%)	
SA         20 (15.3%)         16 (12.2%)           MDS         20 (15.3%)         24 (18.3%)           Others'         7 (5.3%)         7 (5.3%)           MOPhological remission before transplantation         129 (98.5%)           CR         8 (6.1%)         2 (1.5%)           NR         8 (6.1%)         2 (1.5%)           MBD         118 (90.1%)         Positive           Negative         24 (18.3%)         13 (9.3%)           Positive         24 (18.3%)         13 (9.3%)           Stem cell source         75 (57.3%)         124 (94.7%)           PB         115 (67.8%)         75 (57.3%)           Match         68 (51.9%)         75 (57.3%)           Match         68 (51.9%)         75 (57.3%)           Match         22 (24.4%)         64 (48.9%)           Non-10.10 match         32 (24.4%)         64 (84.9%)           Non-10.10 match         32 (24.4%)         65 (42.7%)           Donor sex         110 (10.1%)         32 (24.4%)           Ves         33 (48.1%)         40 (30.5%)           Donor sex         10 (61.9%)         32 (20.9%)           Ves         33 (48.1%)         40 (30.5%)           No         65 (15.9%)	ALL	27 (20.6%)	20 (15.3%)	
MDS         20 (15.3%)         24 (18.3%)           Others'         7 (5.3%)         7 (5.3%)           Orphological remission before transplantation         123 (93.9%)         129 (98.5%)           NR         8 (6.1%)         2 (1.5%)           MPD         107 (81.7%)         118 (90.1%)           Pagative         107 (81.7%)         118 (90.1%)           Positive         24 (18.3%)         13 (9.3%)           Stem cell source         115 (87.8%)         124 (94.7%)           PB         115 (87.8%)         124 (94.7%)           Bood type         7 (5.3%)         100 (91.3%)           Match         68 (61.9%)         7 (5.3%)           Moded type         110 (17.2%)         7 (5.3%)           HA         12 (24.4%)         56 (42.7%)           HA         12 (24.4%)         56 (42.7%)           HA         10/10 match         39 (75.6%)         67 (51.1%)           Donor sex         116 (86.5%)         90 (61.1%)           Female         42 (32.1%)         51 (38.9%)           Donor sex         110 (68.5%)         90 (75.6%)           No         12 (32.1%)         10 (30.5%)           No         12 (23.5%)         10 (75.6%)	SAA	20 (15.3%)	16 (12.2%)	
Others'         7 (5.3%)         7 (5.3%)           Morphological remission before transplantation         22 (93.9%)         129 (98.5%)           NR         8 (6.1%)         2 (1.5%)           NR         8 (6.1%)         2 (1.5%)           MRD         118 (90.1%)         20 (93.9%)           Pastive         107 (81.7%)         118 (90.1%)           Positive         2 (1.5%)         124 (94.7%)           Positive         15 (67.8%)         124 (94.7%)           PB + BM         16 (12.2%)         7 (5.3%)           Blood type         115 (67.8%)         124 (94.7%)           PB + BM         68 (51.9%)         75 (57.3%)           Mismatch         63 (48.1%)         5 (57.3%)           Mismatch         63 (48.1%)         64 (48.9%)           Non-10/10 match         92 (75.6%)         67 (51.1%)           Doror sex         10 (76.9%)         20 (1.35)           GKHD         20 (24.4%)         64 (48.9%)           No         93 (51.9%)         30 (61.1%)           Female         42 (32.1%)         63 (48.9%)         90 (75.6%)           Sol         63 (48.1%)         40 (30.5%)         90 (75.6%)           No         68 (51.9%)	MDS	20 (15.3%)	24 (18.3%)	
Morphological remission before transplantation         123 (93.9%)         129 (98.5%)           NR         8 (6.1%)         2 (1.5%)           MBD	Others <sup>†</sup>	7 (5.3%)	7 (5.3%)	
CR123 (93.9%)129 (98.5%)NR8 (6.1%)2 (1.5%)MRD	Morphological remission before transplantation		· · · · ·	.05
NR8 (6.1%)2 (1.5%)MRDNegative107 (81.7%)118 (90.1%)Positive24 (18.3%)13 (9.3%)Stem cell sourcePB115 (67.8%)124 (94.7%)P4-BM16 (12.2%)7 (5.3%)Blood typeMatch68 (51.9%)75 (57.3%)Mismatch63 (48.1%)56 (42.7%)HLA10/10 match32 (24.4%)64 (48.9%)Non-10/10 match99 (75.5%)67 (51.1%)Donor sexMale89 (67.9%)80 (61.1%)Female42 (32.1%)51 (38.9%)Donor sex (30.0000)35.93 ± 12.9232.001 ± 13.35aGVHDYes63 (48.1%)40 (30.5%)No68 (51.9%)91 (96.5%)EUYes116 (88.5%)92 (70.2%)No32 (2.3%)2 (1.5%)ATGYes128 (97.7%)32 (24.4%)CYYes128 (97.7%)32 (24.4%)No32 (23.3%)2 (1.5%)ATGYes16 (88.5%)92 (70.2%)No15 (11.5%)32 (24.4%)No15 (11.5%)32 (24.4%)No15 (11.5%)32 (24.4%)No15 (11.5%)32 (24.4%)No15 (11.5%)32 (24.4%)No15 (11.5%)32 (24.4%)No	CR	123 (93.9%)	129 (98.5%)	
MRD         Ng ative         107 (81.7%)         118 (90.1%)           Positive         24 (18.3%)         13 (9.3%)           Stem cell source	NR	8 (6.1%)	2 (1.5%)	
Negative         107 (81.7%)         118 (90.1%)           Positive         24 (18.3%)         10 (9.3%)           Stem cell source         7         5.3%)           PB         115 (67.8%)         124 (94.7%)           PB + BM         16 (12.2%)         7 (5.3%)           Blood type         7         5.57.3%)           Match         68 (51.9%)         56 (42.7%)           Match         63 (48.1%)         56 (42.7%)           HA         32 (24.4%)         64 (48.9%)           Non-10/10 match         99 (75.6%)         67 (51.1%)           Donor sex         89 (67.9%)         80 (61.1%)           Female         42 (32.1%)         51 (38.9%)           Donor sey (M)         33 (48.1%)         40 (30.5%)           VHO         99 (75.6%)         51 (38.9%)           Donor age (M)         33 (48.1%)         40 (30.5%)           Ves         63 (48.1%)         40 (30.5%)           No         68 (51.9%)         99 (75.6%)           No         32 (24.4%)         10 (89.5%)           Ves         116 (88.5%)         99 (75.6%)           No         3 (2.3%)         2 (1.5%)           No         3 (2.3%)         2 (1.5%) </td <td>MRD</td> <td></td> <td></td> <td>.05</td>	MRD			.05
Positive24 (18.3%)13 (9.3%)Stem cell source	Negative	107 (81.7%)	118 (90.1%)	
Stem cell source         PB         115 (87.8%)         124 (94.7%)           PB + BM         16 (12.2%)         7 (5.3%)           Blood type	Positive	24 (18.3%)	13 (9.3%)	
PB         115 (87.8%)         124 (94.7%)           PB + BM         16 (12.2%)         7 (5.3%)           Blood type	Stem cell source		- ( )	.04
PB+BM16 (12.2%)7 (5.3%)Blood type $-$ Match68 (51.9%)75 (57.3%)Mismatch63 (48.1%)56 (42.7%)HLA $-$ 10/10 match32 (24.4%)64 (48.9%)Non-10/10 match99 (75.6%)67 (51.1%)Donor sex $-$ Male89 (67.9%)80 (61.1%)Female42 (32.1%)51 (38.9%)Donor age (y)35.93 ± 12.9232.00 ± 13.35aGVHD $ -$ Yes63 (48.1%)40 (30.5%)No68 (51.9%)91 (69.5%)BU $ -$ Yes116 (88.5%)99 (75.6%)No3 (2.3%)2 (1.5%)No3 (2.3%)2 (1.5%)No15 (11.5%)39 (29.8%)No15 (11.5%)39 (29.8%)No15 (11.5%)39 (29.8%)TBI $ -$ Yes116 (88.5%)92 (70.2%)No15 (11.5%)39 (29.8%)No15 (11.5%)39 (29.8%)TBI $ -$ Yes10 (7.6%)21 (18.3%)No12 (92.4%)110 (81.7%)	PB	115 (87.8%)	124 (94.7%)	
Blood type       68 (51.9%)       75 (57.3%)         Match       68 (51.9%)       75 (67.3%)         Mismatch       63 (48.1%)       56 (42.7%)         HA       10/10 match       32 (24.4%)       64 (48.9%)         Non-10/10 match       32 (24.4%)       67 (51.1%)         Donor sex $W$ $W$ $W$ Male       39 (67.9%)       80 (61.1%)         Permale       42 (32.1%)       51 (38.9%)         Donor age (y)       35.93 ± 12.92       32.00 ± 13.35         aGVHD $W$ $W$ $W$ Yes       63 (48.1%)       40 (30.5%)         No       68 (51.9%)       91 (69.5%)         BU $W$ $W$ $W$ Yes       116 (88.5%)       99 (75.6%)         No       15 (11.5%)       32 (24.4%)         CY $W$ $W$ $W$ Yes       128 (97.7%)       129 (98.5%)         No       32 (23.9%) $W$ Yes       116 (88.5%)       92 (70.2%)         No       35 (13.5%) $M$ Yes       116 (88.5%)       92 (70.2%)         No       15 (11.5%)	PB + BM	16 (12.2%)	7 (5.3%)	
Match         68 (51.9%)         75 (57.3%)           Mismatch         63 (48.1%)         56 (42.7%)           HLA	Blood type		· · · · ·	.38
Mismatch $63 (48.1\%)$ $56 (42.7\%)$ HLA	Match	68 (51.9%)	75 (57.3%)	
HLA $32 (24.4\%)$ $64 (48.9\%)$ $10/10 match$ $99 (75.6\%)$ $67 (51.1\%)$ Donor sex $u$ Male $89 (67.9\%)$ $80 (61.1\%)$ Female $42 (32.1\%)$ $51 (38.9\%)$ Donor age (y) $35.93 \pm 12.92$ $32.00 \pm 13.35$ $aGVHD$ $u$ $u$ Yes $63 (48.1\%)$ $40 (30.5\%)$ No $68 (51.9\%)$ $91 (69.5\%)$ BU $u$ $u$ Yes $116 (88.5\%)$ $99 (75.6\%)$ No $15 (11.5\%)$ $32 (24.4\%)$ CY $u$ $u$ Yes $128 (97.7\%)$ $129 (98.5\%)$ No $3 (2.3\%)$ $2 (1.5\%)$ ATG $u$ $u$ Yes $116 (88.5\%)$ $92 (70.2\%)$ No $15 (11.5\%)$ $32 (29.8\%)$ TB $u$ $u$ Yes $10 (7.6\%)$ $21 (18.3\%)$ No $121 (92.4\%)$ $110 (81.7\%)$	Mismatch	63 (48.1%)	56 (42.7%)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	HLA	× 2	× ,	.001
Non-10/10 match99 (75.6%) $67$ (51.1%)Donor sex $Wale$ $89$ (67.9%) $80$ (61.1%)Female $42$ (32.1%) $51$ (38.9%)Donor age (y) $35.93 \pm 12.92$ $32.00 \pm 13.35$ aGVHD $W$ $W$ Yes $63$ (48.1%) $40$ (30.5%)No $68$ (51.9%) $91$ (69.5%)BU $W$ $W$ Yes $116$ (68.5%) $99$ (75.6%)No $15$ (11.5%) $32$ (24.4%)CY $W$ $129$ (98.5%)No $3$ (2.3%) $2$ (1.5%)ATG $W$ $Yes$ $116$ (68.5%)Yes $15$ (11.5%) $39$ (70.2%)No $15$ (11.5%) $39$ (270.2%)No $15$ (11.5%) $39$ (270.2%)No $15$ (11.5%) $39$ (28.8%)TEl $W$ $10$ (7.6%)Yes $10$ (7.6%) $21$ (18.3%)No $121$ (92.4%) $110$ (81.7%)	10/10 match	32 (24.4%)	64 (48.9%)	
Donor sexNumber89 (67.9%)80 (61.1%)Female42 (32.1%)51 (38.9%)Donor age (y) $35.93 \pm 12.92$ $32.00 \pm 13.35$ aGVHD $u$ Yes $63 (48.1\%)$ $40 (30.5\%)$ No $68 (51.9\%)$ $91 (69.5\%)$ BU $u$ Yes $116 (88.5\%)$ $99 (75.6\%)$ No $15 (11.5\%)$ $32 (24.4\%)$ CY $u$ Yes $128 (97.7\%)$ $129 (98.5\%)$ No $3 (2.3\%)$ $2 (1.5\%)$ ATG $u$ Yes $116 (88.5\%)$ $92 (70.2\%)$ No $15 (11.5\%)$ $39 (29.8\%)$ TBI $u$ $u$ Yes $10 (7.6\%)$ $21 (18.3\%)$ No $121 (92.4\%)$ $110 (81.7\%)$	Non-10/10 match	99 (75.6%)	67 (51.1%)	
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           aGVHD             Yes         63 (48.1%)         40 (30.5%)           No         68 (51.9%)         91 (69.5%)           BU             Yes         116 (88.5%)         99 (75.6%)           No         15 (11.5%)         32 (24.4%)           CY             Yes         128 (97.7%)         129 (98.5%)           No         3 (2.3%)         2 (1.5%)           ATG             Yes         116 (88.5%)         92 (70.2%)           No         3 (2.3%)         2 (1.5%)           ATG             Yes         116 (88.5%)         92 (70.2%)           No         15 (11.5%)         39 (29.8%)           TBI             Yes         10 (7.6%)         21 (18.3%)           No         121 (92.4%)         110 (81.7%)	Donor sex			.25
Female $42 (32.1\%)$ $51 (38.9\%)$ Donor age (y) $35.93 \pm 12.92$ $32.00 \pm 13.35$ aGVHD $u$ $u$ Yes $63 (48.1\%)$ $40 (30.5\%)$ No $68 (51.9\%)$ $91 (69.5\%)$ BU $u$ $u$ Yes $116 (88.5\%)$ $99 (75.6\%)$ No $15 (11.5\%)$ $32 (24.4\%)$ CY $u$ $u$ Yes $128 (97.7\%)$ $129 (98.5\%)$ No $3 (2.3\%)$ $2 (1.5\%)$ ATG $u$ $u$ Yes $116 (88.5\%)$ $92 (70.2\%)$ No $15 (11.5\%)$ $39 (29.8\%)$ TB $u$ $u$ Yes $10 (7.6\%)$ $21 (18.3\%)$ No $121 (92.4\%)$ $110 (81.7\%)$	Male	89 (67.9%)	80 (61.1%)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Female	42 (32.1%)	51 (38.9%)	
aGVHD         Yes       63 (48.1%)       40 (30.5%)         No       68 (51.9%)       91 (69.5%)         BU	Donor age (y)	$35.93 \pm 12.92$	$32.00 \pm 13.35$	.01
Yes       63 (48.1%)       40 (30.5%)         No       68 (51.9%)       91 (69.5%)         BU	aGVHD			.004
No         68 (51.9%)         91 (69.5%)           BU	Yes	63 (48.1%)	40 (30.5%)	
BU       Yes       116 (88.5%)       99 (75.6%)         No       15 (11.5%)       32 (24.4%)         CY        7         Yes       128 (97.7%)       129 (98.5%)         No       3 (2.3%)       2 (1.5%)         ATG        7         Yes       116 (88.5%)       92 (70.2%)         No       15 (11.5%)       39 (29.8%)         TBI        7         Yes       10 (7.6%)       21 (18.3%)         No       121 (92.4%)       110 (81.7%)	No	68 (51.9%)	91 (69.5%)	
Yes       116 (88.5%)       99 (75.6%)         No       15 (11.5%)       32 (24.4%)         CY           Yes       128 (97.7%)       129 (98.5%)         No       3 (2.3%)       2 (1.5%)         ATG           Yes       116 (88.5%)       92 (70.2%)         No       15 (11.5%)       39 (29.8%)         TBI           Yes       10 (7.6%)       21 (18.3%)         No       121 (92.4%)       110 (81.7%)	BU			.006
No       15 (11.5%)       32 (24.4%)         CY	Yes	116 (88.5%)	99 (75.6%)	
CY       Yes       128 (97.7%)       129 (98.5%)         No       3 (2.3%)       2 (1.5%)         ATG	No	15 (11.5%)	32 (24.4%)	
Yes       128 (97.7%)       129 (98.5%)         No       3 (2.3%)       2 (1.5%)         ATG	CY			.65
No     3 (2.3%)     2 (1.5%)       ATG	Yes	128 (97.7%)	129 (98.5%)	
ATG       92 (70.2%)         No       116 (88.5%)       92 (70.2%)         No       15 (11.5%)       39 (29.8%)         TBI       748       10 (7.6%)       21 (18.3%)         No       121 (92.4%)       110 (81.7%)	No	3 (2.3%)	2 (1.5%)	
Yes         116 (88.5%)         92 (70.2%)           No         15 (11.5%)         39 (29.8%)           TBI         7es         10 (7.6%)         21 (18.3%)           No         121 (92.4%)         110 (81.7%)	ATG			.001
No         15 (11.5%)         39 (29.8%)           TBI         749         10 (7.6%)         21 (18.3%)           No         121 (92.4%)         110 (81.7%)	Yes	116 (88.5%)	92 (70.2%)	
TBI         21 (18.3%)           Yes         10 (7.6%)         21 (18.3%)           No         121 (92.4%)         110 (81.7%)	No	15 (11.5%)	39 (29.8%)	
Yes10 (7.6%)21 (18.3%)No121 (92.4%)110 (81.7%)	TBI			.03
No 121 (92.4%) 110 (81.7%)	Yes	10 (7.6%)	21 (18.3%)	
	No	121 (92.4%)	110 (81.7%)	
logCMV (PB) 3.22±0.39 3.23±0.39	logCMV (PB)	$3.22 \pm 0.39$	$3.23 \pm 0.39$	.74
logEBV (PB) 3.01±0.07 3.05±0.26	logEBV (PB)	$3.01 \pm 0.07$	$3.05 \pm 0.26$	.13
logBKV (urine) 9.09±1.91 6.08±2.83	logBKV (urine)	$9.09 \pm 1.91$	$6.08 \pm 2.83$	.001
logCMV (urine) $3.16 \pm 0.34$ $3.06 \pm 0.23$	logCMV (urine)	3.16±0.34	$3.06 \pm 0.23$	.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  $\pm$  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**

	Р	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)	.04	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)	.001	1.58	1.36-1.83
logCMV (urine)	.05	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 90day 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  $\times$  3 days), cyclophosphamide (CY) (40 mg/kg  $\times$  2 days), Flu (30 mg/m<sup>2</sup>  $\times$  3 days), Ara-C (1g/m<sup>2</sup>  $\times$  3 days), and anti-thymocyte globulin (ATG) (rabbit, 2.5 mg/kg  $\times$  4 days). Patients with acute lymphoblastic leukemia (ALL) and lymphoma were mainly treated with total body irradiation (TBI) (10 Gy), CY (40 mg/kg  $\times$  2 days), Flu (30 mg/m<sup>2</sup>  $\times$  3 days), and Ara-C (1g/m<sup>2</sup>  $\times$  3 days); some patients were additionally treated with Idarubicin (10 mg/m<sup>2</sup>  $\times$  3 days) and Decitabine (20 mg/m<sup>2</sup>  $\times$  5 days). Patients with severe aplastic anemia (SAA) were treated with BU (3.2 mg/kg  $\times$  2 days), and Flu (30 mg/m<sup>2</sup>  $\times$  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)	Р		
1 year	78.4% (70.9–86.7)	84.4% (77.5–92.0)	.14		

CI = confidence interval, HC = hemorrhagic cystitis.

2 years

69.6% (60.1-80.5)

80.7% (72.5-89.8)



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.

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#### 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  $P \le .10$  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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**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  $(15 \text{ mg/m}^2 \text{ on day } 1 \text{ and } 10 \text{ mg/m}^2 \text{ on days } 3 \text{ and } 6)$ . 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.

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