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The Outcomes and Risk Factors for Late-Onset Haemorrhagic Cystitis after Allogeneic Haematopoietic Transplantation for Acute Leukaemia: A Retrospective, Single-Centre Observational Study

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ABSTRACT: The study aims to identify risk factors for late-onset haemorrhagic cystitis (HC) and determine if the condition's prevalence and severity have an impact on the overall survival (OS) and disease-free survival (DFS) in patients with acute leukaemia (AL) receiving myeloablative conditioning (MAC) allogeneic transplantation. A total of 344 AL cases were included in this study, among which 55 cases (16.0%) had HC. Comprehensive clinical indicators were collected to analyse the risk factors related to HC. Propensity score matching (PSM) with the nearest neighbour method was used to match patients. The sensitivity and specificity of HC prediction were evaluated by ROC analysis. Survival analysis was employed to evaluate the impact of the occurrence and severity of HC on OS and DFS. In AL patients undergoing MAC allogeneic transplantation, factors such as donor versus recipient sex (D/R), time to platelet and WBC reconstitution, and copies CMV and BKV were associated with the occurrence of HC. Copies of BKV demonstrated the highest sensitivity (0.807) and specificity (0.943), followed by the sex of D/R. The state of minimal residue disease (MRD), HSCT mode, ABO blood type, and age of the donor had no significant effects on the occurrence of HC. The occurrence or severity of HC did not affect OS or DFS (P = 0.449 and 0.326). The prevalence of HC was associated with the sex of D/R, time of PLT and WBC reconstitution, copies of CMV, and BKV, with copies of BKV having the highest predictive accuracy for HC. This trial has been registered on chictr.org.cn as No. ChiCTR2200059020.

Keywords: Haemorrhagic cystitis; Allogeneic haematopoietic transplantation; Acute leukaemia

1. Introduction

Myeloablative conditioning (MAC) regimens are used in allogeneic hematopoietic stem cell transplantation (allo-HSCT), which is a universal treatment regimen for acute leukaemia (AL). Haemorrhagic cystitis (HC) is a common complication in MAC-based allo-HSCT, with incidences ranging from 7% to 68% [1–3]. HC is classified into two types based on when it appears after transplantation: early-onset HC and late-onset HC. Early-onset HC is typically linked to medications such as cyclophosphamide, while late-onset HC manifests more than two weeks after transplantation [4]. Early-onset HC can be detoxified with mesna infusion. In contrast, late-onset HC has few effective medications available, except for forced diuretic and alkalized urine, making grade III–IV HC a potentially life-threatening complication after allo-HSCT. Moreover, late-onset HC significantly prolonged hospital stays and caused higher health care reimbursements [5]. Precision prediction and timely treatment can help to improve the poor prognosis brought on by HC. As a result, it is critical to actively investigate indicators that can predict HC severity at an early stage.

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The pathogenesis of late-onset HC is currently unknown. Late-onset HC typically occurs within 100 days of transplantation, complicating the mechanism of HC and limiting treatment options. The majority of patients during this time are usually immunocompromised, receiving a variety of immunosuppressive agent treatments, and some of them have a disease that is combined with other infections or developed GVHD. Additionally, some patients with a tendency to relapse may begin preemptive anti-relapse treatments. Numerous researchers have sought to investigate the risk factors associated with HC, including advanced age [6], immune factors, thrombocytopenia, mismatch of human leukocyte antigen (HLA) [7,8], and viral infection (BK virus, CMV, adenovirus) [9,10], but with little success.

Among these, BK virus (BKV) is a well-recognized risk factor associated with HC complication in HSCT recipients [5,10]. BKV is part of the Polyomaviridae family of double-stranded DNA (dsDNA) viruses. In some immunocompromised individuals, such as those with HIV infection or those who have undergone transplantation, clinically significant reactivation of latent BKV can occur. BKV can persist in the host for their entire lifespan. It is still unknown whether BKV remains dormant in the host cell or maintains a low gene expression level during persistent infection. BKV encodes microRNAs (miRNAs) similar to herpesviruses, which act as viral replication regulators [1,7]. BKV replication is regulated by an elevated amount of miRNA expression complementary to the 3' end of the large T antigen mRNA. Dendritic cells and natural killer cells within the innate immune system and adaptive immune response will likely contribute to BKV infection management. In these cases, immune regulation relies on both $CD4^+$ and $CD8^+$ T cells, with the abundance of polyfunctional BKV-specific T cells being correlated with effective immune control [4]. Reconstitution of BKV-specific T cells is associated with better control of viruria and viremia. After HSCT, Najafabadi et al. [11] reported the *in vitro* generation of BK polyomavirus-specific T cells for adoptive cell therapy in refractory haemorrhagic cystitis patients. These cells could multiply and produce the cytokine IFN-gamma in reaction to BKV PepMixes. In addition, these T cells had cytotoxic ability against BKV antigen-expressing target cells.

To the best of our knowledge, however, several additional factors—some of which are questionable—affect the likelihood of HC. These factors include the recipient's blood type, gender mismatch, type of transplantation, and the time required for hematopoietic reconstruction. Although additional variables may not have been important, haematologists still place a high value on them. The risk factors for HC following MAC-based allo-HSCT have also not yet been demonstrated for the population of AL. Our research aimed to collect precise clinical data to address the risks associated with HC and to investigate the clinical applicability of diagnostic indicators used to predict the occurrence of HC.

2. Subjects and Methods

2.1 Study Design and Participants

This study was a retrospective, single-centre, observational trial conducted by the Department of Haematopoietic Stem Cell Transplantation, Medical Center of Haematology, Xinqiao Hospital, to identify risk factors for late-onset haemorrhagic cystitis (HC) and determine whether the condition's prevalence and severity have an impact on the OS and DFS in patients with AL receiving MAC-based HSCT. The trial was registered at www.clinicaltrials.gov (ChiCTR2200059020). The Ethics Committee of the Xinqiao Hospital of Army Medical University approved the protocol and all amendments. In accordance with the Declaration of Helsinki, all patients completed informed consent forms, or, if unable to grant consent, their legal guardians did so.

Eligible patients met the following criteria: patients were diagnosed with AL undergoing MAC allo-HSCT aged 0–60 years and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The exclusion criteria were as follows: HC was caused by drugs or platelet deficiency (early onset HC excluded); early death unrelated to HC during treatment and follow-up; serious organ dysfunction; leukaemia combined with other cancers; inability to schedule follow-up; brain dysfunction or severe mental illness preventing compliance with the study protocol. After enrolment, we collected data on patient characteristics such as primary disease, pretransplant remission status, minimal residue disease (MRD), HLA match mode (matched sibling donors, matched unrelated donors and haploidentical donors), sex of donor versus receipt (D/R), matching status of ABO blood group, donor age, counts of mononuclear cells and CD34-positive cells, white blood cell (WBC) count, platelet (PLT) reconstitution time, and copies of cytomegalovirus (CMV) and BKV detected in the serum and urine within 100 days. The primary objective of this one-year follow-up study was to identify risk factors associated with late-onset HC and to determine whether the prevalence and severity of the condition impact OS and DFS in AL patients undergoing MAC-based allogeneic hematopoietic stem cell transplantation (allo-HSCT).

The transplantation procedure was that all patients received a MAC regimen with a busulfan-cyclophosphamide (BUCY)-based regimen. The patients with haploidentical donors (HIDs) were transplanted with a combination of bone marrow (BM) and peripheral blood stem cell (PBSC) grafts, and the patients with HLA-matched sibling donors (MSDs) or HLA-matched unrelated donors (MUDs) received PBSC grafts. Cyclosporine A (CsA), methotrexate (MTX), and andmycophenolate (MMF) were administered to patients. The transplantation procedure conditioning therapy in MSDs and MUDs consisted of the following drugs: 3.2 mg/kg/d BU on days -7, -6, -5, -4; 60 mg/kg/d CY on days -3, -2; and 2.5 mg/kg/d antithymocyte globulin (ATG) on days -5, -4, -3, -2 for MUDs. Tacrolimus, MTX, and MMF were given to patients with HID to prevent GVHD.

The conditioning therapy in HIDs was as follows: semustine 200 mg/m^2 on day -9; cytosine arabinoside (Ara-c) 1.8 g/m^2 on days -8, -7, -3; BU 2 mg/kg/d on days -6, -5, -4; CY 1.8 g/m^2 on days -3, -2; ATG 2.5 mg/kg/d on days -5, -4, -3, -2. In all transplants, the patients received a combination of granulocyte colony-stimulating factor (G-CSF)-mobilized bone marrow (BM) and peripheral blood stem cells (PBSCs). The minimum number of CD34$^+$ cells was 2 × 10^6 cells/kg. All patients received G-CSF treatment from +6 days after transplantation until the neutrophil count was >1 × 10^9 cells/L. The prevention of uroepithelial damage by CY was mediated by mesna (20% of the CY dose, q4h × 4/d) and hydration (3.5–4 L/m^2) from commencement to 24 h after the end of CY infusion. Ganciclovir or acyclovir, amoxicillin, fluconazole, and compound sulfamethoxazole (SMZ) were used to prevent viral, bacterial, fungal, and protozoan infections, respectively. Treatment of HC was performed according to standard operating procedures.

HC is defined by microscopic or macroscopic haematuria and dysuria, followed by negative bacterial urine culture and the absence of other hemorrhagic diseases. HC symptoms are classified into grades as follows: Grade 1 indicates microscopic hematuria; Grade 2 involves macroscopic hematuria; Grade 3 includes macroscopic hematuria with clots; and Grade 4 encompasses macroscopic hematuria with clots, urinary obstruction, kidney damage, bladder damage, and the necessity for surgical intervention. OS is defined as the time from allo-HSCT to death. Reconstitution of WBCs is defined as achieving an absolute neutrophil count ≥ 0.5 × 10^9/L for 3 consecutive days. Reconstitution of PLT is defined as achieving a platelet count ≥ 20 × 10^9/L without transfusion support for consecutive testing.

2.2. Statistical Analysis

Categorical variables were compared using a nonparametric test, and continuous variables were transformed into categorical variables. Through nonparametric analysis of age (year), sex, FAB, WBC at diagnosis, HB at diagnosis, and PLT at diagnosis, risk stratification of leukaemia, statistically significant differences existed between the two groups, or mismatch between genders, white cell number (WBC), and risk stratification.

To minimize selection bias and confounding factors, we conducted a propensity score matching (PSM) analysis as described by Morgan (2018). We used the nearest-neighbor matching method with a caliper width set at 0.03. The ratio of the HC group to the non-HC group was 1:1. The C-statistic was calculated to assess the discriminatory power of the propensity score.

To evaluate factors influencing transplant outcomes in the matched group, we first conducted a univariate analysis before performing binary logistic regression. Factors considered included pre-transplant remission status, MRD, HLA match type (matched sibling donors, matched unrelated donors, and haploidentical donors), D/R sex, ABO blood group compatibility, donor age, MNC count, CD34$^+$ cell count, reconstitution time of WBCs and PLTs, and the number of CMV and BKV copies detected in serum and urine within 100 days, using nonparametric analysis. The patients in the matched cohort, namely, the matched HC group and matched non-HC groups, were calculated using logistic regression with the following factors: MRD, HLA match, sex of D/R, ABO blood group, donor age, time of PLT reconstitution, and copies of CMV and BKV. The *P* values of the above indicators were less than 0.05. Moreover, considering that the delayed reconstitution of WBCs may have connections with the development of HC, it was included in the binary logistic regression analysis, and the sensitivity and specificity of HC prediction were evaluated using ROC analysis.

OS and DFS were estimated using the Kaplan–Meier method and compared using Kaplan–Meier (K-M) survival analysis. All tests were two-sided, and *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 26 and R version 3.5.0 for data analysis.

3. Results

3.1. Primary Analysis Population

Table 1 lists the features of the patients and transplant recipients. A total of 344 AL cases were recruited from September 2019 to February 2022, including 133 (38.7%) cases of acute lymphoblastic leukaemia and 211 (61.3%)

cases of acute myeloid leukaemia and myelodysplastic syndromes (AML/MDS). Of these 344 patients, 55 had HC (HC group), and 289 did not have HC (noHC group). The overall incidence of HC was 16.0%, with grades I–II and III–IV of HC at 31 (56.3%) and 24 (43.6%), respectively, for the HC cohort. There were 25 cases of aGVHD in the 55 HC group and 107 cases in the 289 noHC group, with a total of 48 patients (given an incidence of 38.4%), with grade III–IV accounting for 14.0% of the total cases. Within the initial year of follow-up for 344 patients, 47 (13.7%) encountered relapse, and 2 (0.6%) passed away from infection.

Table 1. Patient characteristics [*n* (%)].

		HC		
Variables		**Yes**	**No**	***P* value**
		55	289	
Age (year)	1–14	3 (5.5)	39 (13.5)	0.841
	14–45	41 (74.5)	177 (61.2)	
	45–60	11 (20.0)	73 (25.3)	
Gender	F	10 (18.2)	154 (53.3)	0.000
	M	45 (81.8)	135 (46.7)	
FAB	AML/MDS	28 (50.9)	183 (63.3)	0.126
	ALL	27 (49.1)	106 (36.7)	
WBC at diagnosis	<4	24 (43.6)	93 (32.2)	0.007
	4–10	16 (29.1)	47 (16.3)	
	10–100	11 (20.0)	108 (37.4)	
	>100	4 (7.3)	41 (14.2)	
HB at diagnosis	<60	11 (20.0)	78 (27.0)	0.312
	60–90	20 (36.4)	100 (34.6)	
	>90	24 (43.6)	111 (38.4)	
PLT at diagnosis	<20	16 (29.1)	74 (25.6)	0.695
	20–50	15 (27.3)	96 (33.2)	
	50–90	12 (21.8)	39 (13.5)	
	>90	12 (21.8)	80 (27.7)	
Risk stratification	low/media risk	1 (1.8)	68 (23.5)	0.000
	high risk	54 (98.2)	221 (76.5)	

To identify risk factors associated with HC, detailed clinical indicators were collected. As shown in Table 1, all six elements—age at diagnosis, sex, FAB type of AL, WBC count at diagnosis, HB level at diagnosis, PLT count at diagnosis, and risk stratification, were taken as the baseline characteristics for AL. The results of a nonparametric study revealed that there were significant differences between the two groups (the noHC group and the HC group), including sex mismatches between donors and recipients (D/R), WBC counts at diagnosis, and risk stratification ($P < 0.05$).

The closest neighbour method and propensity score matching (PSM) were used to match patients. The main analysis population excluded patients who had missing data for any of the covariates evaluated because the estimation of PS necessitates full information for all covariates. After 1:1 optimal matching, the HC and non-HC groups were equally distributed. The final screening results identified 53 patients in the non-HC group and 55 patients in the HC group (Table 2). In terms of gender mismatch between donors and receivers, WBC count at diagnosis, risk classification, and PS matching resulted in balanced cohorts.

Table 2. Patient characteristics after PSM [*n* (%)].

		HC					
Variables		**Yes**	**No**	***P* value**	**Yes (Matched)**	**No (Matched)**	***P* value**
		55	289		55	53	
Age (year)	1–14	3 (5.5)	39 (13.5)	0.841	3 (5.5)	8 (15.1)	0.82
	14–45	41 (74.5)	177 (61.2)		41 (74.5)	27 (50.9)	
	45–60	11 (20.0)	73 (25.3)		11 (20.0)	18 (34.0)	
Gender	F	10 (18.2)	154 (53.3)	0.000	10 (18.2)	8 (15.1)	0.405
	M	45 (81.8)	135 (46.7)		45 (81.8)	45 (84.9)	
FAB	AML/MDS	28 (50.9)	183 (63.3)	0.126	28 (50.9)	34 (64.2)	0.156
	ALL	27 (49.1)	106 (36.7)		27 (49.1)	19 (35.8)	
WBC at diagnosis	<4	24 (43.6)	93 (32.2)	0.007	24 (43.6)	25 (47.2)	0.634
	4–10	16 (29.1)	47 (16.3)		16 (29.1)	14 (26.4)	
	10–100	11 (20.0)	108 (37.4)		11 (20.0)	10 (18.9)	
	>100	4 (7.3)	41 (14.2)		4 (7.3)	4 (7.5)	
HB at diagnosis	<60	11 (20.0)	78 (27.0)	0.312	11 (20.0)	17 (32.1)	0.159
	60–90	20 (36.4)	100 (34.6)		20 (36.4)	20 (37.7)	
	>90	24 (43.6)	111 (38.4)		24 (43.6)	16 (30.2)	
PLT at diagnosis	<20	16 (29.1)	74 (25.6)	0.695	16 (29.1)	13 (24.5)	0.328
	20–50	15 (27.3)	96 (33.2)		15 (27.3)	13 (24.5)	
	50–90	12 (21.8)	39 (13.5)		12 (21.8)	7 (13.2)	
	>90	12 (21.8)	80 (27.7)		12 (21.8)	20 (37.7)	
Risk stratification	low/media risk	1 (1.8)	68 (23.5)	0.000	1 (1.8)	49 (92.5)	0.358
	high risk	54 (98.2)	221 (76.5)		54 (98.2)	4 (7.5)	

3.2. Postmatch Comparison between the HC Group and the noHC Group

Following agreement with the clinical haematologist, the following clinical indicators were first nonparametrically analysed: donor age, MNC as well as CD34 counts, time of WBC as well as the time of platelet count, remission status of pretransplant, MRD, levels of ferritin pre-HSCT, HLA match (matched siblings donors, matched unrelated donors, and haploidentical donors), gender of D/R, matching status of ABO blood group, as well as the time of platelet (PLT) reconstitution, and copies of CMV and BKV detected from the serum and urine within 100 days. MRD, HLA match, D/R sex, ABO blood group, donor age, time after PLT reconstitution, and copies of CMV and BKV were among the initially screened parameters with variations between the two groups. The *P* value for the indicators mentioned above was less than 0.05. Furthermore, binary logistic regression analysis included delayed WBC reconstitution ($P = 0.052$) because it may be related to the emergence of HC. Binary logistic regression analysis revealed that in AL patients undergoing MAC-based allo-HSCT, D/R sex, WBC and PLT reconstitution time, CMV and BKV copies, and HC were related, with *P* values of 0.005, 0.004, 0.017, 0.017, and 0.000, respectively.

3.3. Sensitivity and Survival Analyses

Using ROC analysis, the sensitivity and specificity of HC prediction were assessed (Figure 1). Based on the area under the curve (AUC), copies of BKV (0.807), D/R sex (0.63), PLT reconstitution (0.403), WBC reconstitution (0.358), and copies of CMV were all in declining order (0.364). The incidence and severity of HC were evaluated using survival analysis to determine whether variables impacted OS and DFS. With a median follow-up of 422.51 days (post-transplantation range: 31–963 days), there was no significance in OS and DFS ($P = 0.449$ and 0.326, respectively). Additionally, with a *P* value of 0.409, no statistical significance was discovered between I–II grade HC and III–IV grade HC on OS (Figure 2).

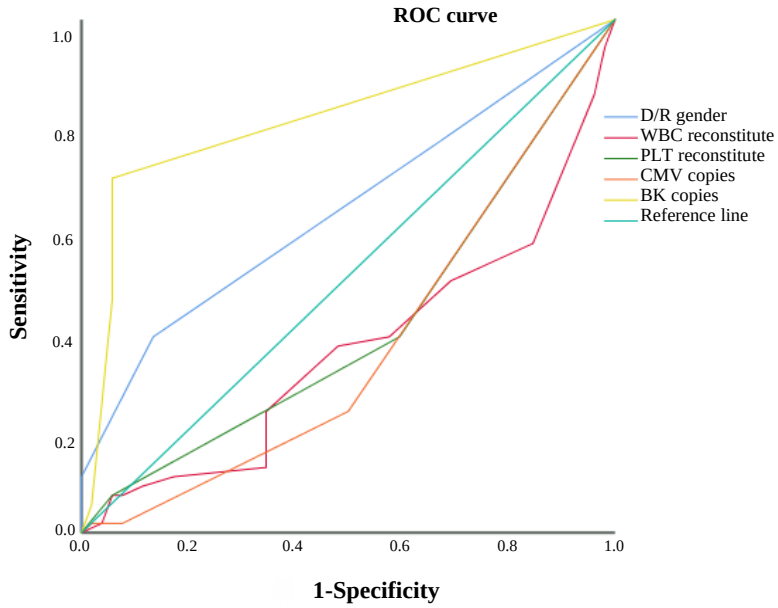

Figure 1. ROC curve of variables after logistic regression selection.

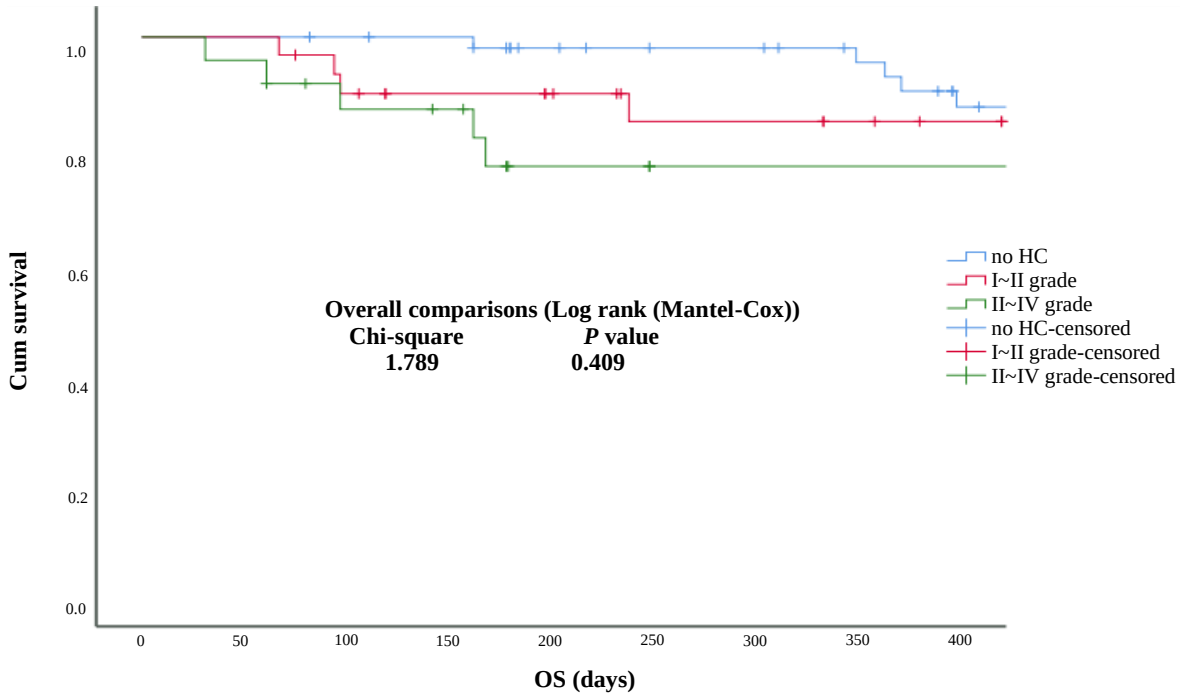

Figure 2. K-M survival plots of OS and DFS for noHC group, grade I–II HC group, and grade III–IV HC group.

4. Discussion

Haemorrhagic cystitis (HC) is a common complication in MAC-based HSCT, with incidence rates varying significantly across studies. We conducted a retrospective, single-center observational study to investigate late-onset outcomes and risk factors for HC after HSCT (AL). It was discovered that D/R sex, PLT, and WBC reconstitution time, CMV copy number, and BKV copy number were linked to the prevalence of HC. BKV copies, on the other hand, had the highest sensitivity (0.807) and specificity (0.943). The presence of HC had no appreciable impact on OS or DFS (*P* = 0.449 and 0.326, respectively).

The intestines, liver, lungs, kidneys, eyes, and central nervous system can all be affected by CMV, a human herpes virus [12]. Several centres reported on CMV's impact on late-onset HC, with varying results [3,8,13]. The prevalence of CMV reactivation in our experiment was 150 in 344 (43.6%) instances overall. Only 99 (28.8%) of the urine samples and 25 (7.3%) of the serum samples were positive, while the combined positive rate was 16 (4.7%). The preventative

treatment for CMV involves an infusion of ganciclovir or acyclovir combined with human immunoglobulin. In our population, CMV was associated with HC with an OR of 0.259, suggesting that the recreation of CMV has a preventative effect on the development of HC.

Many studies on BKV have been conducted. Even the cut-off value level > 0.75×10^3 of BKV DNA in the serum at day +21 was reported as a predictor of the occurrence of HC, with BKV reactivation being linked to HC. Regardless of the amount, we chose to create BKV in our study. There were 70 cases (20.3%) of BKV formation out of a total of 344 cases. While the percentages for serum and urine that are solely positive were 15 and 38, respectively, the percent is 26 (7.6%) when both are positive. Only forced diuretics and alkalized urine were used as unique BKV interventions. Our research indicated that BKV has a connection with the development of HC in the population of acute leukaemia patients who underwent MAC-based HSCT and that BKV recreation has a high sensitivity of 0.807 and a high specificity of 0.943 in predicting HC. It could be used in clinics early by paying special attention to increased risk when faced with BKV recreation.

There are significant differences between late-onset and early-onset HC, mostly because immunological and infectious variables play a role after transplantation. The relationship between HC and aGVHD was not well discussed in terms of immunological components. To examine the impact on the occurrence of HC, we included the sex of D/R, ABO blood type, age of donor, aGVHD, and HLA matching. The findings suggested that gender mismatch between donors and recipients might increase the likelihood of HC (OR = 4.029). However, no significant relationship was found between HC and factors such as aGVHD, HLA matching, or ABO blood type.

Because a large iron burden can cause harm to liver function, hepatic sinusoidal obstruction syndrome, infection, and elevated levels of pretransplantation ferritin were linked to worse OS and DFS in allo-HSCT [14,15,16]. Due to its direct immunosuppressive and proinflammatory activities, ferritin is a significant immune dysregulation mediator, especially in cases of extreme hyperferritinaemia. According to Vargas-Vargas et al., ferritin levels may play a significant role in determining the severity of COVID-19 [17]. Unfortunately, research involving ferritin and HC was not widely performed. In this instance, our analysis found no significant impact of the various levels of ferritin on HC when MAC-based HSCT was used in AL.

Pre-HSCT remission was discussed in relation to the prevalence of HC, including whether it has a protective effect. In our trial, 25 out of 344 patients (7.3%) did not achieve remission prior to HSCT. More specifically, 17 out of the 288 patients in the noHC group and 8 out of the 55 patients in the HC group did not achieve CR. 24 in 55 (43.6%) for the HC group was positive in MRD, and 72 in 217 (33.2%) for the noHC group. The findings indicated that while remission was not achieved, the MRD status significantly influenced the occurrence. Currently, the underlying mechanism cannot be explained.

For the analysis of the impact on HC, the quantity of stem cells and the duration required for WBC and PLT reconstitution, were also included. The only factor that could raise the risk of HC with an OR value of 1.683 was a prolonged reconstitution time of PLT after +21 days. The immune function of PLT and its vascular protection, which prevents vascular bleeding and is crucial to HC processes, may be the fundamental mechanism. Platelets exhibit toll-like receptors and actively bind to microorganisms, and in some cases, they can be directly cytopathic against bacteria. Platelets also store preformed and synthesized immunomodulatory molecules that can significantly influence immune responses [18]. They are the ultimate bacterial sentinels in the bloodstream because of this and their high circulation levels.

Investigating the BKV cut-off value is one potential solution to enhance the sensitivity and specificity of BKV. Our study is retrospective, but it is a single-centre study, which has implications for overcoming selection bias and can integrate more central data. Nevertheless, similar to the majority of the written research, it is necessary to conduct supporting fundamental research.

Since this study is retrospective, the conclusions may be limited by the natural effects of such studies. In addition, this study is a single-centre study. Due to the low incidence of the disease, the sample size is limited, necessitating multi-center studies for comprehensive statistical analysis. Furthermore, the results may be inflated because this observational clinical study does not investigate the underlying mechanisms.

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Author Contributions

H.Y, and X.Z. performed the conception and design; T.C., J.R., X.X., Y.L., L.Z. (Lu Zhao), J.L. (Jia Liu), L.Z. (Lidan Zhu), J.L. (Jiali Li), Y.F., and L.G. provided the study materials or patients; R.H. and X.W. performed the collection and assembly of data; X.D. and P.K. provided data analysis and interpretation; X.Z. supervised the research, edited the manuscript, and provided financial support.

Ethics Statement

The study protocol was approved by the Ethics Committee Review Board of the Second Hospital of Army Medical University. Since this was a retrospective analysis, a waiver/exemption regarding written informed was granted by the Ethics Committee.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Declaration of Competing Interest

The authors declared no conflict of interests.

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