**Multivariate analysis of factors predicting surgical intervention for hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation**

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Hemorrhagic cystitis (HC), which is characterized by a congested vasculature and extensive hemorrhage in the bladder lamina propria, is often secondary to chemotherapy, external radiation therapy, allogeneic hematopoietic stem cell transplantation (Allo-HSCT), and/or opportunistic infection.\(^1\) The incidence of HC after Allo-HSCT has been reported to range between 1.3% and 20%.\(^2\) The severity of HC may vary from bladder irritation symptoms with mild hematuria, which is observed in most cases and is resolved with conservative management, such as adequate hydration and bladder irrigation, to transfusion-dependent hemorrhage and/or a lower urinary tract obstruction post renal failure. Other strategies, including bladder irrigation with intravesical alum, formalin, aminocaproic acid, or prostaglandin and hyperbaric oxygen therapy, have been reported, with the resolution of bleeding in the majority of cases.\(^3\) However, for patients in whom these measures fail and the lower urinary tract becomes obstructed by numerous blood clots, further surgery, including internal iliac angioembolization, cystoscopy with control of bladder hemorrhage and cystectomy, should be considered.\(^4\)

However, patients who have severe HC after Allo-HSCT are infirm and often have contraindications for surgery, such as seriously decreased platelet counts and low hemoglobin. This is a challenging dilemma for urologists and hematologists as surgery may even endanger patients’ lives, thus emphasizing the need for early targeted therapies for those at high risk for emergency surgery requirements. We report an analysis of hematological variables and treatment outcomes of patients with HC after Allo-HSCT at our center. We hypothesized that patients with HC at the initial stage of the disease have a few clinical and hematological characteristics that can predict the risk of medical treatment failure of HC and the need for subsequent surgery. Thus, we aimed to identify these predictors to guide clinical management.

The medical records of inpatients who had HC after Allo-HSCT at our center from January 2017 to December 2019 were analyzed retrospectively. The exclusion criteria were as follows: (1) patients who were diagnosed with urolithiasis at the same time or (2) patients who complained about signs of bladder irritation without signs of HC. Finally, a total of 304 patients were included in this study. We identified patients with HC and follow-up data collected in the electronic medical record system. Demographic and clinical parameters were collected at the time when microscopic hematuria was detected, and the patients were followed for >6 months after diagnosis. The parameters included sex, age, primary diseases, sex-mismatch in recipients, delayed onset time of HC, exposure to cyclosporine A, haploidentical HSCT, cytomegalovirus (CMV) viremia, Epstein-Barr (EB) viremia, hemoglobin level, platelet count, serum creatinine, C-reactive protein (CRP), serum albumin, and D-dimer within 1 week of the initial diagnosis of HC. A complete-case analysis was performed and patients with missing data were excluded from the analysis. The primary outcome was the HC grade and emergency surgical intervention requirement independently assessed by two trained doctors.

An HC grade was assigned according to the scale proposed by Droller et al.\(^2\) With conservative treatment for HC, transfusion-dependent continuous hemorrhage for 5 days and/or lower urinary tract obstruction by blood clots, resulting in urinary retention, was judged to be an emergency surgical intervention requirement. Quartiles were formed based on the time from transplantation to the onset of HC in days, with a delayed onset time of HC as the fourth quartile. Therefore, the delayed onset time of HC was defined as >60 days in this study.

**Clinical Observation**

**Chinese Medical Journal**

**Access this article online**

Quick Response Code: Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001295

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Chinese Medical Journal 2020;Vol(No) Received: 04-09-2020 Edited by: Peng Lyu
Subsequently, factors that were found to be significant at the 0.05 level by univariate analysis were analyzed by multivariate analysis, which was performed using binary logistic regression. A stepwise model selection procedure was used to produce models for multivariate analyses. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

At our center, a total of 304 patients with HC after Allo-HSCT were identified from 2017 to 2019, of which 14 (4.6%) were lost to follow-up. Among the 290 patients, HC was of grades I, II, III, and IV in 63 (22%), 110 (38%), 75 (26%), and 42 (14%) patients, respectively. The patient’s age at diagnosis was 25.6 ± 14.2 years, and approximately half of the patients (54%, 156 out of 290) were males. The HC onset occurred at a median of 31 (interquartile range, 23–60) days after initial Allo-HSCT, with a right-skewed distribution. Only observation and conservative treatment (including hydration, alkalinization, diuresis, antivirals, reduction of related drugs, etc.) were needed in 247 (83%) patients, while 43 (15%) patients required emergency surgery for HC.

Univariate analysis demonstrated a delayed onset time of HC had the greatest association with the HC emergency surgery requirement (odds ratio [OR] = 19.550; P < 0.001). Additionally, univariate analysis showed that EB viremia (OR = 3.364), albumin < 30 mg/L (OR = 4.365), serum creatinine ≥ 84 mg/L (OR = 3.353), declined hemoglobin and blood platelets, and CRP > 10 mg/L were significantly associated with the HC emergency surgery requirement (P < 0.05). Multivariate analysis [Table 1] indicated the independent effects of the delayed onset time of HC (OR = 12.273, P < 0.001), CRP > 10 mg/L (OR = 8.192, P < 0.001), EB viremia (OR = 4.074, P = 0.007), and hemoglobin level (OR = 0.946, P < 0.001).

HC grade IV was statistically associated with a delayed onset time of HC (OR = 2.571, P = 0.005) and CRP > 10 mg/L (OR = 2.026, P = 0.037) in univariate analysis. Multivariate analysis indicated the independent effects of the delayed onset time of HC (OR = 2.184, P = 0.04) on HC grade IV. We also compared the odds of high-grade (III and IV) and low-grade (I and II) HC and demonstrated a persistent independent effect of CRP > 10 mg/L (P = 0.044, OR = 1.693) in multivariate analysis. Other factors did not maintain significance in the multivariate model.

### Table 1: Multivariate analysis of factors predicting surgical intervention for HC after Allo-HSCT.

| Parameters | Estimated OR (95% CI) | P value |
|------------|-----------------------|---------|
| EB (vs. none) | 4.074 (1.481–11.209) | 0.007   |
| CRP > 10 (vs. < 10 mg/L) | 8.192 (3.350–20.031) | <0.001 |
| Hemoglobin | 0.946 (0.918–0.975) | <0.001 |
| Delayed onset time of HC | 12.273 (5.024–29.985) | <0.001 |

Delayed onset time of HC, Quartiles were formed based on the time from transplantation to the onset of HC, in days, with a delayed onset time of HC as the fourth quartile. Therefore, the delayed onset time of HC was defined as more than 60 days in this study. Allo-HSCT: Allogeneic hematopoietic stem cell transplantation; CI: Confidence interval; CRP: C-reactive protein; EB: Epstein-Barr virus; HC: Hemorrhagic cystitis; OR: Odds ratio.

Despite the exponential increase in the recognition of HC damage after Allo-HSCT in the last decade, the available clinical guidelines are elusive and treatment options are not standardized in this regard. To our knowledge, this study reports the largest single-center series of cases with HC after Allo-HSCT to date. We found that the delayed onset time of HC (OR = 12.273, 95% confidence interval [CI]: 5.024–29.985), abnormal CRP (OR = 8.192, 95% CI: 3.350–20.031), hemoglobin level (OR = 0.946, 95% CI: 0.918–0.975), and EB viremia (OR = 4.074, 95% CI: 1.481–11.209) were independent prognostic factors for the need of emergency surgical intervention (P < 0.05). In previous studies, CRP and hemoglobin levels have not been reported as independent prognostic factors for the HC grade or treatment outcome. In this study, we found that patients with a delayed onset of HC after transplantation were more likely to require invasive surgery. In 2016, Johnston et al. reported that the delayed onset of HC was an independent prognostic factor for the requirement of invasive management of HC in children. The study further confirmed that the delayed onset time of HC was still an independent prognostic factor for the requirement of emergency surgical intervention for HC in a broader age range.

However, this study brought other serological indicators such as CRP at the initial diagnosis of HC into studies reported to date rarely. Although CMV viremia was not statistically associated with the requirement of emergency surgical intervention for HC by multivariate analysis in this study, CRP > 10 mg/L (OR = 8.192, 95% CI: 3.350–20.031, P < 0.001) was independently associated with HC requiring emergency surgical intervention.

The limitations of this study include the retrospective nature, as well as the small number of patients with grade IV HC, which limited further multivariate analysis of prognostic factors for surgery treatment outcomes for refractory HC after Allo-HSCT.

The outcome indicator or the endpoint was the emergency surgery requirement rather than the actual surgical intervention. However, because in patients with severe HC, operative indications are often combined with multiple surgical contraindications and these patients cannot undergo surgical intervention, early identification of such patients is clinically significant, and therefore, patients with grade IV HC should have been included in this study. Additionally, the study only included data from a single center. However, our center has a large number of relevant bone marrow transplant patients from all over the country, with sufficient disease sources, and thus, clinically relevant factors could still be derived from this single-institution study. Despite these limitations, this study effectively revealed the impacts of serum albumin, CRP, and hemoglobin levels, as well as viral infection, on the failure of medical treatment of HC and surgery requirements.

In addition to conventional treatment, monitoring hemoglobin and CRP levels is a potential measure to prevent HC from further deterioration and avoid surgical intervention. Patients with a delayed onset of HC after transplantation have a higher risk of medical treatment failure and should receive targeted and more active interventions at an early stage.
Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Funding

The study was supported by the General Project of the National Natural Science Foundation of China (No. 81872086).

Conflicts of interest

None.

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How to cite this article: Yang WB, Du YQ, Bai WJ, Yu LP, Zhang XP, Wang Q, Zhang XW, Li Q, Xu T. Multivariate analysis of factors predicting surgical intervention for hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. Chin Med J 2020;00:00–00. doi: 10.1097/CM9.0000000000001295