Risk factors and predictive model for mortality in patients undergoing allogeneic hematopoietic stem cell transplantation admitted to the intensive care unit

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Abstract. Hematological malignant tumors represent a group of major diseases carrying a substantial risk to the lives of affected patients. Risk factors for mortality in critically ill patients have garnered substantial attention in recent research endeavors. The present research aimed to identify factors predicting intensive care unit (ICU) mortality in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). Furthermore, the present study analyzed and compared the mortality rate between patients undergoing haploidentical hematopoietic stem cell transplantation (Haplo-SCT) and those undergoing identical sibling donor (ISD) transplantation. A total of 108 patients were included in the present research, 83 (76.9%) of whom underwent Haplo-SCT. ICU mortality was reported in 58 (53.7%) patients, with the values of 55.4 and 48.0% associated with Haplo-SCT and ISD, respectively (P=0.514). The mortality rate of patients undergoing Haplo-SCT was comparable to that of patients undergoing ISD transplantation. The present study found that reduced hemoglobin, elevated total bilirubin, elevated brain natriuretic peptide, elevated fibrinogen degradation products, need for vasoactive drugs at ICU admission, need for invasive mechanical ventilation and elevated APACHE II scores were independent risk factors for ICU mortality. Among patients presenting with 5-7 risk factors, the ICU mortality reached 100%, significantly exceeding that of other patients. The present research revealed that ICU mortality rates remain elevated among patients who underwent allo-HSCT, especially those presenting multiple risk factors. However, the outcome of patients undergoing Haplo-SCT were comparable to those of patients undergoing ISD transplants.

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Introduction

Hematological malignant tumors represent a group of major diseases carrying a substantial risk to the lives of affected patients (1). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) stands as the primary treatment approach for a wide range of hematologic conditions (such as acute myeloid leukemia and acute lymphoblastic leukemia) (2). The considerable advancement in the HSCT technique has resulted in a significant improvement in the survival rate of these patients (3).

However, post-hematopoietic stem cell transplantation has significant and potentially severe complications. These complications encompass organ damage resulting from pretreatment toxicity, prolonged impairment of immune reconstitution and concomitant opportunistic infections (4-6).These adverse events collectively exert a considerable impact on the prognosis of patients undergoing hematopoietic stem cell transplantation (5-8). In a comprehensive population-based cohort study involving 87,965 adults newly diagnosed with hematologic malignancies, patients admitted to the intensive care unit (ICU) were primarily those undergoing transplant procedures. The one-year incidence of ICU admissions stood at 13.9%, with differences observed across different hematologic conditions, ranging from 7.3% in cases of indolent lymphoma to as high as 22.5% in cases of acute myeloid leukemia (9). However, despite the utilization of diverse rescue interventions, the prognosis of patients with hematologic malignancies remains unsatisfactory (10). This persistent challenge underscores the critical and pressing imperative to identify the risk factors associated with unfavorable prognoses in these patients. Risk factors influencing mortality in critically ill patients have been a research focus in recent studies, with various variables being assessed. The acquired data have identified mechanical ventilation, the initial acute physiologic and chronic health assessment II (APACHE II) scores recorded on the day of ICU admission, compromised performance status, vasoactive therapy and the presence of malignant lymphoma as potential

risk factors for ICU mortality in patients with hematologic malignancies (11-17). However, it is important to note that the identified risk factors do not consistently align across different studies.

Some investigations have delved into specific categories of hematologic malignancies or certain complications of allo-HSCT to identify prognostic factors for ICU mortality (18,19). Several studies have also focused on allogeneic transplantation (20,21), including a multicenter study in Brazil that explored a cohort of patients that had undergone autologous hematopoietic stem cell transplantation with ICU admission (22). Additionally, a retrospective study in France evaluated whether haploidentical hematopoietic stem cell transplantation (Haplo-SCT) procedures affect the prognosis of critically ill recipients of allo-HSCT (23). However, few studies have explored the ICU mortality of patients undergoing Haplo-SCT and those undergoing identical sibling donor (ISD) transplantation.

Therefore, a retrospective analysis of the clinical features, treatment approaches and outcomes among patients undergoing allo-HSCT was conducted, aiming to identify risk factors for ICU mortality and develop predictive models. Furthermore, the present study analyzed and compared the mortality rate of patients who underwent Haplo-SCT and those who underwent ISD transplantation.

Materials and methods

Study design. The present single-center retrospective study collected data anonymously from adult patients diagnosed with hematological malignancies who underwent allo-HSCT at the ICU of the Haidian Branch of Peking University People's Hospital (Beijing, China). The data collection process spanned a defined timeframe, commencing on February 1, 2019, and concluding on March 30, 2021. The present study was approved by The Ethics Committee of Peking University People's Hospital (approval no. 2022PHB267-001; Beijing, China). Decisions regarding patient transfer to the ICU and informed consent procedures were jointly made by the ICU staff and hematologists, with consent obtained from the patients, their parents or their guardians.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Adult patients aged 18 years or older; ii) patients diagnosed with one or more hematologic malignancies; and iii) patients admitted to the ICU due to severe diseases during the specified period from February 1, 2019, to March 30, 2022. The exclusion criteria were as follows: i) Patients under the age of 18; and ii) those with nonmalignant hematologic disorders.

Data collection. The researchers collected a comprehensive dataset for each individual, including information regarding the age, sex, time of ICU admission, underlying disease, reason for ICU admission, laboratory test results, APACHE II score, treatment received on the day of admission, duration of ICU stay and hospitalization, therapeutic regimen prior to ICU admission and presence of organ failure of the patients. Additionally, for patients who survived, follow-up continued until August 1, 2022, to monitor their progress and outcomes.

Definition. Acute heart failure and infectious toxic shock were defined per the 2021 European Society of Cardiology Guidelines and the 2016 Infectious Toxic Shock Guidelines, respectively (24,25). Acute kidney injury was defined and treated per the 2012 Kidney Disease Outcomes Quality Initiative clinical guidelines (26). Liver failure was defined and treated in line with international recommendations (27,28). Patients received comprehensive treatment, including anti-infective therapy, continuous renal replacement therapy (CRRT), plasmapheresis, mechanical ventilation (MV) which encompassed both non-invasive ventilation (NIV) and invasive MV (IMV), hormone therapy and immunotherapy selected in accordance with the international recommendations (26,29-34).

Vasoactive drug administration upon admission was defined as any vasoactive drug or inotrope initiated within two hours of ICU admission. Neutropenia was defined as a neutrophil count $<0.5x10^9$/l.

Statistical analysis. The statistical methods employed in the present study were designed to analyze and evaluate the clinical outcomes. The primary clinical outcome was the ICU mortality, with a secondary emphasis on the 60-day mortality after ICU admission. Enumeration data were presented as percentages, and the inter-group comparisons were conducted utilizing the chi-square test. In cases where continuous variables did not conform to a normal distribution, the data were presented as median (interquartile range) [M (QL, QU)], and comparisons between independent samples were made via the Mann-Whitney U test. The ICU mortality hazard ratio was estimated utilizing both univariate and multivariate Cox regression analyses. These analyses provided insights into the risk factors associated with ICU mortality. The Kaplan-Meier curve, a valuable tool in survival analysis, was employed to estimate the probability of survival. $P<0.05$ was considered to indicate a statistically significant difference. The statistical analyses were carried out using SPSS 24.0 software (IBM Corp.) and R software (v 4.2.0; http://www.r-project.org).

Results

General features of the patients. The present research included a total of 108 patients, 58 of whom died in the ICU (53.7% ICU mortality); their general characteristics are described in Tables SI-III.

The primary causes leading to their admission to the ICU are outlined in Table SI. Among these, respiratory failure emerged as the most prevalent cause, accounting for a substantial portion of cases (52; 48.1% of the total study population). Following closely was liver failure, which constituted the cause of ICU admission in 23 patients (21.3% of the total study population). The median APACHE II score during admission was 20.0 (10.0-39.0). On the day of ICU admission, vasoactive drugs were administered to 29 patients (26.9%). Additionally, on the same day, 64 patients (59.3%) received NIV, 23 patients (21.3%) received IMV, 9 patients (8.3%) received CRRT and 28 patients (25.9%) received plasma exchange treatment (Table II).

As shown in Table I, ICU mortality was reported in 58 (53.7%) patients: of which 55.4 and 48.0% underwent

Table I. Clinical features of patients admitted to the intensive care unit.

Characteristics	All patients, n=108	Haplo-SCT, n=83	ISD, n=25	P-value
Median age (range), years	41 (18-69)	39 (18-69)	45 (20-63)	0.274
Sex, female, n (%)	35 (32.4)	29 (34.9)	6 (24.0)	0.743
Hematologic malignancies, n (%)				0.758
Acute leukemia	77 (71.3)	60 (72.3)	17 (68.0)	
Chronic leukemia	8 (7.4)	6 (7.2)	2 (8.0)	
Lymphoma	9 (8.3)	7 (8.4)	2 (8.0)	
Myelodysplastic syndromes	11 (10.2)	7 (8.4)	4 (16.0)	
Other	3 (2.8)	3 (3.6)	0 (0.0)	
Median WBC counts at diagnosis (range), $x10^9$/l	7.9 (0.8-399)	7.9 (0.8-310.0)	7.9 (1.2-399.0)	0.852
Median bone marrow blasts at diagnosis (range), %	44 (0-98.0)	42.7 (0-98.0)	45.0 (0-97.0)	0.748
Disease risk index before HSCT, n (%)				0.763
Low-risk	26 (24.1)	19 (22.9)	7 (28.0)	
Intermediate-risk	55 (50.9)	42 (50.6)	13 (52.0)	
High-risk	27 (25.0)	22 (26.5)	5 (20.0)	
Donor-recipient sex matching, n (%)				0.463
Male-female	19 (17.6)	15 (18.1)	4 (16.0)	
Male-male	38 (35.2)	30 (36.1)	8 (32.0)	
Female-female	16 (14.8)	14 (16.9)	2 (8.0)	
Female-male	35 (32.4)	24 (28.9)	11 (44.0)	
Relationship of donor, n (%)				<0.001
Parental	31 (28.7)	31 (37.3)	0 (0.0)	
Sibling	49 (45.4)	24 (28.9)	25 (100.0)	
Children	25 (23.1)	25 (30.1)	0 (0.0)	
Other	3 (2.8)	3 (3.6)	0 (0.0)	
Donor and recipient blood groups, n (%)				0.606
Same	61 (56.5)	48 (57.8)	13 (52.0)	
Different	47 (43.5)	35 (42.2)	12 (48.0)	
Homozygous loci, n (%)				<0.001
3/6	72 (66.7)	72 (86.7)	0 (0.0)	
4/6	11 (10.2)	11 (13.3)	0 (0.0)	
6/6	25 (23.1)	0 (0.0)	25 (100.0)	
GVHD after HSCT, n (%)				
aGVHD	32 (29.6)	24 (28.9)	8 (32.0)	0.767
cGVHD	10 (9.3)	6 (7.2)	4 (16.0)	0.351
Chimeric state after HSCT, n (%)				
Partial chimerism	2 (1.9)	2 (2.4)	0 (0.0)	1.000
Complete chimerism	106 (98.1)	81 (97.6)	25 (100.0)	
Leading cause for ICU admission, n (%)[a]				0.134
Respiratory failure	52 (48.1)	40 (48.2)	12 (48.0)	
Liver failure	23 (21.3)	17 (20.5)	6 (24.0)	
Acute kidney injury	5 (4.6)	5 (6.0)	0 (0.0)	
Disorders of consciousness	6 (5.6)	5 (6.0)	1 (4.0)	
Alveolar hemorrhage	5 (4.6)	5 (6.0)	0 (0.0)	
Septic shock	9 (8.3)	6 (7.2)	3 (12.0)	
Cerebrovascular disease	2 (1.9)	0 (0)	2 (8.0)	
Heart failure	1 (0.9)	1 (1.2)	0 (0.0)	
Other	5 (4.6)	4 (4.8)	1 (4.0)	
ICU death	58 (53.7)	46 (55.4)	12 (48.0)	0.514

Haplo-SCT, haploidentical hematopoietic stem cell transplantation; ISD, identical sibling donor; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; WBC, white blood cell; GVHD, graft vs. host disease. [a]For patients with several diseases at the time of ICU admission, only the most severe condition was considered as the cause for admission.

Table II. Characteristics of clinical tests on the day of ICU admission and treatments in ICU.

Characteristics	Haplo-SCT, n=83	ISD, n=25	P-value
Laboratory test on day of ICU admission			
Median lactate (range), mmol/l	1.30 (0.20-30.0)	1.10 (0.30-17.8)	0.754
Median white blood cell count (range), 10^9/l	4.12 (2.27-7.18)	5.47 (0.07-164.2)	0.076
Median neutrophil count (range), 10^9/l	1.89 (0-17.42)	3.03 (0-13.86)	0.133
Neutropenia, n (%)	16 (19.27)	4 (16.0)	0.937
Median lymphocyte count (range), 10^9/l	0.38 (0.0-4.85)	0.60 (0.0-2.48)	0.116
Median hemoglobin (range), g/l	74.00 (40.00-115.00)	88.00 (30.00-130.00)	0.013
Median platelet count (range), 10^9/l	28.00 (2.00-213.00)	43.00 (9.00-252)	0.037
Median creatinine (range), μmol/l	72.00 (21.00-685.50)	77.0 (37.0-346.0)	0.613
Median bilirubin (range), μmol/l	15.55 (7.85-45.83)	20.0 (4.2-595.0)	0.807
Median serum potassium (range), mmol/l	3.78 (2.18-6.06)	3.98 (2.83-5.82)	0.325
Median brain natriuretic peptide (range), pg/ml	240 (10-4580)	118 (8-4868)	0.098
Median fibrin degradation product (range), mg/l	6.60 (0.7-115.2)	6.80 (0.3-130.9)	0.796
Median D-dimer (range), μg/l	649 (57.2-13183.0)	714.0 (60.00-17594)	0.997
Median HCT-CI (range)	375 (2-592)	375 (78-600)	0.408
Median APACHE II score at admission (range)	20.0 (10.00-39.00)	22.0 (14.0-36.0)	0.542
Treatment at ICU admission, n (%)			
Use of vasoactive drugs	22 (26.5)	7 (28.0)	0.883
Invasive mechanical ventilation	18 (21.7)	5 (20.0)	0.857
Non-invasive mechanical ventilation	53 (63.9)	11 (44.0)	0.077
Continuous renal replacement therapy	9 (10.8)	0 (0.0)	0.191
Plasma exchange	21 (25.3)	7 (28.0)	0.787
Median length of ICU stay (range), days	9.0 (0-39.0)	9.0 (0-27.0)	0.615
Median follow-up of survivors (range), days	21 (0-1258)	19 (0-1167)	0.983

Haplo-SCT, haploidentical hematopoietic stem cell transplantation; ISD, identical sibling donor; HCT-CI, hematopoietic cell transplantation comorbidity Index; APACHE II, acute physiologic and chronic health assessment II; ICU, intensive care unit.

Haplo-SCT and ISD, respectively (P=0.514). The immediate causes of ICU mortality are shown in Table III. Furthermore, univariate Cox regression analyses are presented in Table SV and Fig. S1 and show the independent risk factors for the leading cause of ICU mortality.

The mortality of patients undergoing Haplo-SCT was comparable to that of patients undergoing ISD. It was observed that 40 (37.0%) patients survived for more than 60 days after ICU admission (Fig. 1A). Moreover, the ICU mortality did not differ statistically between the ISD and Haplo-SCT groups (Fig. 1B).

Univariate analysis of ICU mortality risk factors. In univariate analysis, ICU mortality was strongly related to ICU admission due to respiratory failure, high hematopoietic stem cell transplantation complication index score, need for vasoactive therapy during ICU admission, neutropenia during ICU admission, thrombocytopenia, reduced hemoglobin, elevated bilirubin, elevated fibrinogen degradation products (FDP), elevated brain natriuretic peptide (BNP), elevated lactate and high APACHE II scores (Table SIV).

Multivariate analysis of risk factors for ICU mortality. The patient condition-related indexes and treatment-related indexes were divided into two groups for Cox multivariate regression analysis. Decreased hemoglobin, elevated total bilirubin, elevated BNP, elevated FDP, and elevated APACHE II scores were recorded to be independent risk factors for ICU mortality in the patient condition-related group (Fig. 2A). On the other hand, the need for immediate initiation of vasoactive therapy and the need for IMV during ICU admission were recorded to function as independent risk factors for ICU mortality in the treatment-related group (Fig. 2B).

Risk model of ICU mortality. The patients were classified into the following three groups based on the number of risk factors they presented: i) Low-risk group, comprising patients with 0-2 risk factors (n=50); ii) intermediate-risk group, comprising patients with 3-4 risk factors (n=38); and iii) and high-risk group, comprising patients with 5-7 risk factors (n=20). The ICU mortality rates in these groups were as follows: 24.0% in the low-risk group, 68.4% in the intermediate-risk group and 100.0% in the high-risk group (χ^2=38.295; P<0.001). Moreover, significant differences were observed in the 60-day cumulative survival following ICU admission among the three groups. The models indicated a cumulative survival rate of 62.0% [95% confidence interval (CI), 49.9-77.0%] in the low-risk group and 23.7% (95% CI, 13.4-41.9%) in the intermediate-risk group (Fig. 3).

Table III. Immediate causes of ICU mortality.

Causes	All patients, n=108 (%)	Haplo-SCT, n=83 (%)	ISD, n=25 (%)	P-value
Respiratory failure	26 (24.1)	21 (25.3)	5 (20.0)	0.587
Liver failure	8 (7.4)	6 (7.2)	2 (8.0)	1.000
Gastrointestinal bleeding	5 (4.6)	5 (6.0)	0 (0)	0.588
Septic shock	9 (8.3)	6 (7.2)	3 (12.0)	0.429
Cerebrovascular disease	4 (3.7)	3 (3.6)	1 (4.0)	1.000
Cardiopulmonary arrest	6 (5.6)	5 (6.0)	1 (4.0)	1.000

ICU, intensive care unit; Haplo-SCT, haploidentical hematopoietic stem cell transplantation; ISD, identical sibling donor.

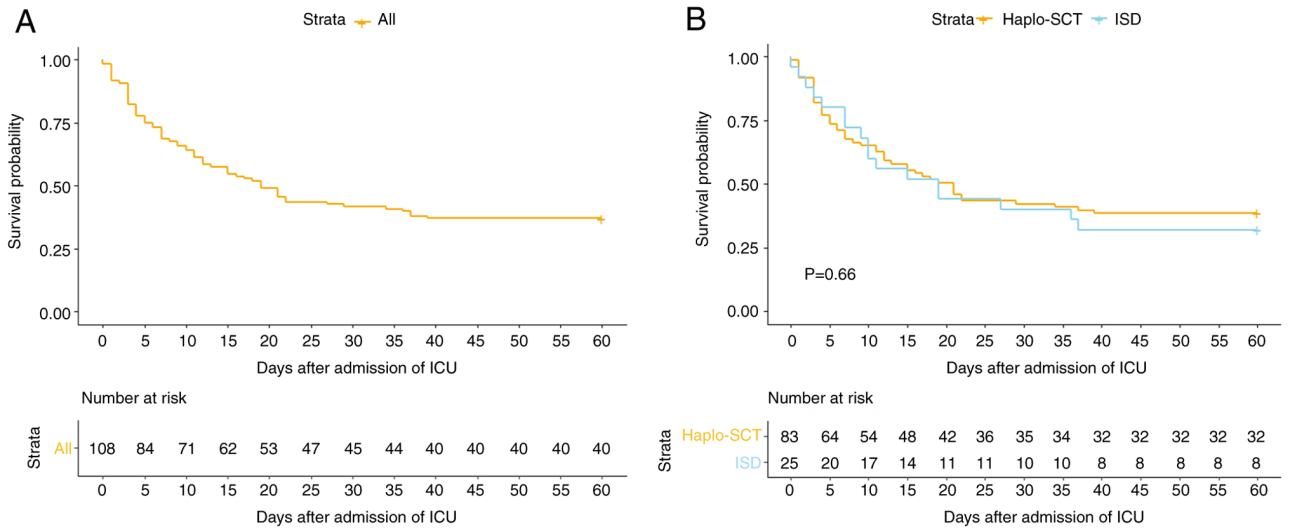

Figure 1. Kaplan-Meier curve showing the 60-day survival probability for (A) all patients; and (B) Haplo-SCT recipients and ISD HSCT recipients. The 60-day survival probabilities for the three aforementioned populations were 37.0% (95% CI, 29.0-47.4%), 38.5% (95% CI, 29.4-50.6%), 32.0% (95% CI, 18.1-56.7%), respectively, (P=0.66). Haplo-SCT, haploidentical hematopoietic stem cell transplantation; ISD, identical sibling donor; CI, confidence interval; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit.

Discussion

Critically ill patients suffering from hematologic disorders typically necessitate an extended period of treatment and care within medical facilities, which leads to a prolonged hospitalization duration (11). The intricate nature of their conditions often demands intensive and specialized interventions, leading to increased investment in healthcare resources and, consequently, elevated treatment costs (35). Despite the extensive medical attention and resources allocated, these patients commonly face a poor prognosis (36). The present study found that reduced hemoglobin, elevated total bilirubin, elevated BNP, elevated FDP, need for vasoactive drugs at ICU admission, need for IMV and elevated APACHE II scores were independent risk factors for ICU mortality. Furthermore, the ICU mortality rate considerably increased in patients with 5-7 risk factors. To the best of our knowledge, the present study represents the first analysis of risk factors for ICU mortality in patients admitted to the ICU after allo-HSCT in China. It also introduces the first prognostic model for predicting ICU mortality in such patients.

ICU admissions have an elevated mortality rate ranging from 27.6-84.1% (11,13-15,17). Notably, the ICU mortality rate associated with patients having undergone hematopoietic stem cell transplant is 53.7%, suggesting that these patients have a poor prognosis. In the present research, the median APACHE II score for admission was 20, a value consistent with those reported in other investigations involving patients with hematologic malignancies admitted to the ICU (initial APACHE II score, 19.4-25) (12-15,17). This similarity underscores the critical condition of patients upon admission to the ICU, highlighting the severity of their disease.

Short-term outcomes in critically ill patients with hematologic malignancies primarily depend on organ failure rather than the underlying malignancy features (37,38). In the present study, independent risk factors for ICU mortality in patients undergoing bone marrow transplantation included elevated total bilirubin, the need for IMV support and the need for vasoactive agents. These findings align with the results of numerous studies associated with severe hematologic disorders (38-40).

The present study observed a high risk of ICU mortality among patients with low hemoglobin levels. Hemoglobin is an important evaluation index for hematopoietic reconstruction

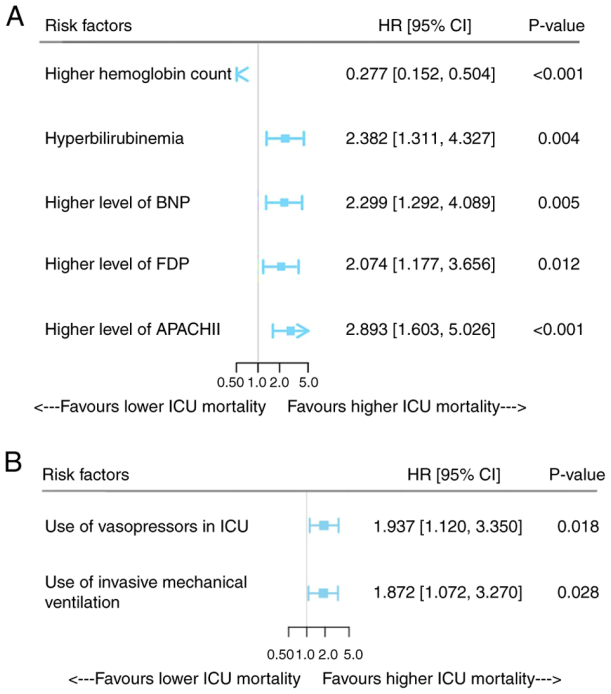

Figure 2. Multivariable analysis of risk factors for ICU mortality (A) for clinical characteristics; and (B) for ICU treatment. All of the variables were collected on the day of ICU admission. BNP, brain natriuretic peptide; FDP, fibrinogen degradation products; APACHII, acute physiologic and chronic health assessment II; ICU, intensive care unit.

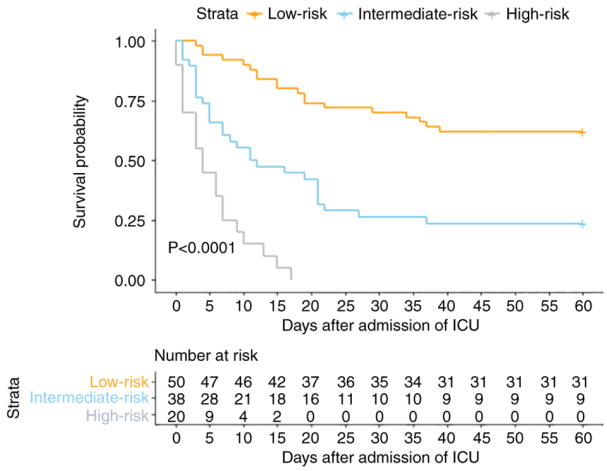

Figure 3. Kaplan-Meier curve showing the 60-day survival probability after ICU admission among low-, intermediate- and high-risk groups. The 60-day probability of survival of the low-risk group vs. intermediate-risk group: 62.0% (95% CI, 49.9-77.0%) vs. 23.7% (95% CI, 13.4-41.9%); P<0.001. ICU, intensive care unit.

after hematopoietic stem cell transplantation, and patients with poor hematopoietic reconstitution have an unfavorable prognosis (41,42). It was also found that reduced hemoglobin was an independent risk factor for mortality in respiratory failure. Due to the fact that arterial blood oxygen levels are contingent upon hemoglobin levels, anemia may hinder the delivery of oxygen. Hemauer *et al* (43) have shown that lower hemoglobin is associated with a higher probability of worsening respiratory dysfunction scores the following day. Anemia is usually associated with blood transfusion and positive fluid balance. Positive fluid balance was an independent risk factor associated with 90-day respiratory mortality in the ICU (44).

FDP is considered one of the markers of fibrin deposition cleavage (45). Toh *et al* (46) suggested that FDP serves as a risk factor for mortality in patients with toxic shock. In a prospective observational study conducted in Shanghai, both indicators of reactive hyperfibrinolysis, D dimer and FDP, were included. However, only FDP emerged as an independent risk factor for ICU mortality in the multivariate analysis (47). In the present study,further substantiates the significance of FDP as an independent risk factor for ICU mortality in patients admitted following allo-HSCT. Furthermore, Crone *et al* (48) suggested that elevated FDP concentrations have been associated with the development of adult respiratory distress syndrome. This study confirms that FDP is an independent risk factor for mortality in respiratory failure.

Patients who undergo allo-HSCT can acquire intense opportunistic infections pre- and post-treatment that can damage the myocardium (49). A previous study showed a 1.7% incidence of heart failure after hematopoietic stem cell transplantation, which was associated with a poor prognosis (4). The present study showed that elevated BNP during ICU admission acts as an independent risk factor for ICU mortality. Therefore, patients presenting elevated BNP levels upon ICU admission should receive close monitoring for myocardial protection and fine volume management to improve their overall outcomes.

Traditionally, ISDs had been considered the optimal donors (50,51). However, increasing evidence suggests that Haplo-SCT should be viewed as a safe and effective alternative, comparable to an ISD (52-54). This research reveals that the outcomes of patients with critical illness undergoing Haplo-SCT were comparable to those of patients undergoing ISD transplantation.

Based on multivariate analysis, a prognostic model was proposed, wherein patients with 5-7 risk factors exhibited an ICU mortality rate of >90%. In the era of widespread allo-HSCT usage, early identification of patients at a high risk of ICU mortality can assist ICU healthcare professionals in devising more effective diagnosis and treatment plans. Additionally, these findings can play a pivotal role in facilitating communication between healthcare providers and patients.

In summary, allo-HSCT stands as the primary treatment approach for a wide range of hematologic conditions. However, the post-hematopoietic stem cell transplantation landscape faces significant and potentially severe complications. Risk factors for mortality in critically ill patients have garnered substantial attention in recent research endeavors. However, only a limited number of studies have explored the ICU mortality in patients undergoing Haplo-SCT and those undergoing ISD transplantation.

The present research revealed that ICU mortality rates remain elevated among patients undergoing allo-HSCT. However, the outcomes of patients undergoing Haplo-SCT were comparable to those of patients undergoing ISD transplantation. The present study identified independent risk

factors for ICU mortality and proposed a prognostic model. These findings can provide valuable guidance for intensive care physicians and hematologists in optimizing clinical decisions.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PW and HZ conceptualized the study; PW, WH, SL and JL curated the data; PW performed the formal analysis. PW, WH, and YA performed the study methodology; PW and YA performed project administration; PW wrote the original draft of the manuscript. PW, WH and YA reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. HZ and JL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by The Institutional Review Board of Peking University People's Hospital (approval no. 2022PHB267-001; Beijing, China). Irrespective of this analysis, all patients provided informed consent before receiving treatment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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