Prognostic factors and outcome of patients undergoing hematopoietic stem cell transplantation who are admitted to pediatric intensive care unit

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Abstract

Background: There are many studies about the prognosis and possible predictive factors of mortality for pediatric allogeneic hematopoietic stem cell transplantation (HSCT) recipients requiring pediatric intensive care unit (PICU) treatment, but the related study in China is lacking. This study investigates the data of these special patients in our center.

Methods: This retrospective analysis is based on data from bone marrow center and PICU of our hospital. A total of 302 patients received allogeneic HSCT from January 2000 to December 2012, 29 of them were admitted to PICU because of various complications developed after transplantation. We collected the clinical data, identified the reasons why the patients to PICU, analyzed the mortality of these patients in PICU, and the prognostic factors of these patients.

Results: The main reasons for admission were: respiratory failure (62.07 %), neurological abnormalities (13.79 %), renal failure (13.79 %) and others (10.35 %). Twenty-one cases (72.41 %) died. Compared with survivors, the deaths cases had lower pediatric critical illness score (77 vs. 88, \( p = 0.004 \)); higher levels of lactic acid and serum urea nitrogen (4.02 vs. 1.19 mmol/L, \( P = 0.008 \); 11.56 vs. 7.13 m mol/L, \( P = 0.045 \)); more organs damaged (2.05 vs. 1.38, \( P = 0.01 \)), and required more supportive treatments (1.52 vs. 0.63, \( P = 0.02 \)). Univariate analysis identified pediatric critical illness score, use of mechanical ventilation, and the number of supportive treatment as the significant predictors to prognosis. Multivariate analysis by regression showed that pediatric critical illness score was the only independent prognostic factor \( (P = 0.035) \).

Conclusions: In our study, pediatric allogeneic HSCT recipients who had PICU care had a high rate of mortality. Pediatric critical illness score was the independent prognostic factor for these patients.

Keywords: Hematopoietic stem cell transplantation, Prognosis, Child, Pediatric intensive care unit

Background

Since the first patient received bone marrow transplantation in 1950, HSCT has progressed to be widely used in a range of malignant or nonmalignant diseases [1]. In 2008, approximately 2,400 children received HSCT in North America. Of those, approximately 90 % of the indication for transplant was malignancy [2, 3]. With the increase of patients who have received HSCT, there has been an increasing necessity for adequate ICU service to manage various transplant related complications. It is reported that about 3.3–35 % of patients receiving HSCT will require ICU admission, and of those requiring ICU admission the mortality ranged from 37–74 % [4–12]. Although there have been many studies abroad, there is limited data from China. Our study aims to investigate the prognosis of HSCT patients in our center, and to elucidate any possible predictors of mortality.
Methods

Population
This is a retrospective case–control study. Tertiary PICU. The study cohort consisted of patients less than 18 years old who were admitted to PICU from January 2000 to December 2012 because of various complications developed after allogeneic HSCT. The doctors of BMT and PICU co-managed the patients. All patients’ legal guardians signed an informed consent form. The Institutional Review Board at the Shanghai Children’ Medical Center approved the study protocol.

From a chart review, general demographic data, underlying diseases, duration of pre-transplant, transplant type, donor source, and preprocessing scheme (myeloablative, non-myeloablative) were collected. Additionally, all prior post-transplant history was reviewed. Within the first day of admission to PICU, the time from transplant was determined, the pediatric critical illness score (PCIS) was calculated, laboratory tests were completed (complete blood count, hepatic, renal, coagulation studies, and arterial blood gas), and the type of supportive treatment required was documented (mechanical ventilation, vasoactive agents therapy, renal replacement therapy). The duration of mechanical ventilation, length of PICU stay, and outcome of PICU was collected. Additionally, 30-day and 6-month follow up occurred to determine survival at these time intervals.

Statistical analysis
Continuous variables were compared using the Mann—Whitney U-test. Categorical characteristics were assessed by the Fishers-exact test. Correlations between patient characteristics and prognosis were assessed using univariate and multivariate logistic regression models. All tests were two-sided and a P-value below 0.05 was regarded as significant. SPSS 17.0 was used for all analyses.

Results
A total of 302 patients received allogeneic HSCT during the study period. The underline diseases are shown in Table 1. The duration of underline diseases before transplant ranged from 1 month to 37 months (median, 9 months). The demographics and transplant-related data are shown in Table 2.

Of these patients, 29 cases made 31 total admissions to PICU during the study period. Twenty-one (72.41 %) died, 8 patients (27.59 %) were discharged from PICU. The 30-day survival rate was 27.59 % (8/29). 6-month survival rate was 24.14 % (7/29).

The most common indication for PICU admission was respiratory failure (18 cases, 62.07 %). Of these patients, 4 cases had cardiovascular failure and 2 had renal failure simultaneously. Four (13.79 %) patients presented with neurological symptoms. Four (13.79 %) patients occurred isolated renal failure. One presented with cardiac arrest. The most common cause of respiratory failure was severe pneumonia (72 %). The most common cause of neurological pathology was central nervous system infection. Twenty patients (68.97 %) required mechanical ventilation. Of those requiring mechanical ventilation, 17 died and 3 were extubated successfully. Thirteen patients received vasoactive agents. Four patients required renal replacement therapy, and 3 of them died.

The comparisons of continuous and categorical clinical variables between survivors and non-survivors are shown in Tables 3 and 4. In their initial lab work, the patients who died had a higher level of lactic acid (4.02 vs. 1.19 mmol/L, P = 0.008) and blood uria nitrogen (11.56 vs. 7.13 mmol/L, P = 0.045); lower pediatric critical illness score (77 vs. 88, p = 0.004), more organs damaged (2.05 vs. 1.38, P = 0.01); more supportive therapies (1.52 vs. 0.63, P = 0.02), higher incidence of ventilator use (P = 0.04) and vasoactive agents use (P = 0.04). Univariate analysis (Table 5) identified pediatric critical illness score (PCIS), use of mechanical ventilation, number of supportive therapy as the significant predictors of prognosis.

Table 1

| Underlying disease | Number |
|--------------------|--------|
| Malignant diseases: | 169    |
| ALL                | 56     |
| AML               | 44     |
| MDS               | 30     |
| CML               | 27     |
| JMML             | 9      |
| HPS             | 2      |
| NHL             | 1      |
| Nonmalignant diseases: | 133 |
| AA            | 84     |
| PID             | 4      |
| SCID           | 7      |
| Non-SCID        | 13     |
| MPS            | 12     |
| Mediterranean anemia | 10   |
| NPD            | 3      |
| Pure red cell aplasia | 2    |
| Fanconi anemia    | 1      |
| Pyruvate kinase deficiency | 1 |

**ALL**: acute lymphoblastic leukemia; AML: Acute myeloid leukemia; MDS: myelodysplastic syndromes; CML: chronic myelogenous leukemia; JMML: juvenile myelomonocytic leukemia; HPS: hemophagocytic syndrome; NHL: Non-Hodgkin's Lymphoma; AA: aplastic anemia; PID: primary immunodeficiency diseases; SCID: severe combined immunodeficiency disease; MPS: mucopolysaccharidosis; NPD: Niemaoh-Pickdisease
Multivariate analysis by regression (Table 6) showed that PCIS was an independent prognostic factor ($P = 0.035$).

**Discussion**

It is necessary to introduce the current situation of Chinese pediatric HSCT. The pediatric transplantation centers mainly concentrate in Beijing, Shanghai, and Guangzhou in China. Most of the patients were treated by specialized pediatric transplant physicians. A small percentage of patients received HSCT in adult department of Hematology/Oncology. The precise number of pediatric HSCT per year is not clear; however, in the first six months of 2015, the transplantations included by the Chinese Transplant group increase to 5000 cases, there are 800 under 20 years old, so we speculate that pediatric transplantations possibly reach 500 cases. As for our center, from 2001–2005, a total of 31 cases underwent HSCT, from 2006–2010, 140 patients underwent HSCT, from 2011–2014, 321 cases underwent HSCT. With the increase of patients who have received HSCT, there has been an increasing necessity for adequate PICU service to manage various transplant related complications. The supportive treatments provided include: laminar flow, continuous renal replacement therapy, peritoneal dialysis, noninvasive mechanical ventilation, invasive mechanical ventilation, and central venous pressure monitoring.

In this study we analyzed the outcome and prognostic factors of these special patients in our center. The most common indication for PICU admission was respiratory failure; the most common cause of respiratory failure was pneumonia, followed by diffuse alveolar hemorrhage. Previous studies also demonstrated that respiratory failure was the main indication for admission [13, 14]. Similar studies showed the most common cause of respiratory failure was pneumonia (41%, 43%), followed by diffuse alveolar hemorrhage (37%, 29%) [15, 16]. Fungal and viral infections were common in these patients [16, 17]. Recent studies have suggested that the effective use of non-invasive ventilation as early as possible can reduce mortality [18, 19].

The other main reasons for admission to PICU were neurological abnormalities and renal failure. The most

| Table 2 | Demographics and transplant-related data of patients who were admitted to PICU ($n = 29$) |
|---------|--------------------------------------------------------------------------------------------|
| Variable | Number |
| Median age (year) | 6 |
| Range | 0.5-16 |
| Gender | Male 20, Female 9 |
| Underlying disease | Malignant: AML 5, ALL 4, MDS 3, JMML 1, Burkitt lymphoma 1, CML 1, Non-malignant: AA 8, PID-SCID 5, PID-non-SCID 1, Transplant type: Related 11, Unrelated 18 |
| aGVHD(I-IV) | 0-I 20, II-IV 9, cGVHD 0 |
| Preprocessing scheme | Myeloablative 18, Non-myeloablative 9, No 2 |
| Median time of duration pre-transplant (month) | 9 |
| Median time of duration after completed transplantation (day) | 74 |

| Table 3 | Comparison of continuous clinical variables between survivors and non-survivors |
|---------|---------------------------------------------------------------------------|
| Variable | Survivor | Non-survivor | $Z$ | $P$ |
| Types of supportive therapies | 0.63 | 1.52 | −2.268 | 0.02 |
| Duration after completed transplantation (day) | 84 | 125.33 | −0.098 | 0.994 |
| PCIS | 88 | 77 | −2.792 | 0.004 |
| Duration of MV (day) | 4.88 | 4.67 | −1.227 | 0.23 |
| Length of PICU (day) | 9.5 | 6.33 | −1.720 | 0.09 |
| Hospitalization time (day) | 44.5 | 28.95 | −1.294 | 0.20 |
| Time course of disease before transplant (months) | 16.25 | 9.76 | −1.47 | 0.15 |
| Number of organs involved | 1.38 | 2.05 | −2.450 | 0.01 |
common cause of neurological abnormalities was central nervous system infection. For children who had renal failure, the mortality rate was as high as 75%. Previously described common causes of renal failure in this patient population were fluid overload due to hyper hydration, intravenous antibiotics, and renal toxicity induced by conditioning regimen [20]. Aggressive use of diuretics and early initiation of renal replacement therapy can prevent further deterioration of fluid overload, and improve the prognosis of these children [21].

The proportion of patients requiring mechanical ventilation and/or vasoactive agents was significantly higher in non-survivor group. Our analysis showed that gender, underlying disease, conditioning regimen, donor type, and presence of graft-versus-host disease had no significant difference between the two groups.

Previous studies have reported prognostic risk factors including: pulmonary infection, respiratory failure, multiple organ failure (especially pulmonary failure and neurological deterioration), mechanical ventilation, and vasoactive agent support [6, 12, 15, 22]. Our study showed that mechanical ventilation ($P = 0.03$), pediatric critical illness score ($P = 0.02$), the number of supportive therapies ($P = 0.04$) were risk factors for death. Although not significant at the $P = 0.05$ level, it is also notable that the use of vasoactive agents may also be predictive ($P = 0.053$). Multivariate analysis by regression showed that PCIS was the only independent prognostic factor ($P = 0.035$).

PCIS is a widely used scoring system in China. The emergency group of Chinese pediatric society, Chinese medical association drew up it in 1995. The evaluated objects, in addition to neonate, can be divided into two groups according to age ($\geq 1$ year old or $< 1$ year old). Ten physiological indexes are enrolled: heart rate, systolic blood pressure, spontaneous breath rate, oxygen partial pressure under breathing room air, PH value of arterial blood gas, serum sodium, potassium, creatinine or urea nitrogen, hemoglobin, gastrointestinal system condition (stress ulcer hemorrhage and intestinal paralysis, only stress ulcer hemorrhage or other). The scoring criteria is in accordance with the prescribed scope or situation for each item, and then calculate the sum, if there are more than one result of some indexes in the same day, choose the most abnormal one. Total score is 100, if the patients’ score $> 80$, were divided into non-critical group, between 71 ~ 80, were critical group, 70 or less were extremely critical group. The pediatric emergency group had organized two large-scale clinical test of this scoring system; the results verified its usefulness in assessment of the severity of disease. Some researchers evaluated the relationship between the Pediatric risk of mortality score (PRISM) and PCIS, the results showed that these two scoring system has good correlation. So we think that PCIS is an objective, convenient test adapts to a rapid assessment of pediatric

| Variable | $P$ |
|----------|-----|
| Donor (related/unrelated) | 0.11 |
| Myeloablative/nonmyeloablative | 0.14 |
| Underlying disease (malignant/nonmalignant) | 0.35 |
| Gender (male/female) | 0.64 |
| Mechanical ventilation | 0.03 |
| Pediatric critical illness score | 0.02 |
| Respiratory failure | 0.50 |
| Renal replacement | 0.90 |
| Vasoactive agent | 0.05 |
| aGVHD | 0.79 |
| BUN | 0.19 |
| Lactate | 0.07 |
| Types of supportive therapies | 0.04 |

### Table 4

| Variable | $P$ |
|----------|-----|
| Gender (male/female) | 0.216 |
| Underlying disease: malignant/nonmalignant | 0.895 |
| Preconditioning: myeloablative/nonmyeloablative | 2.032 |
| Donor (related/unrelated) | 0.035 |
| aGVHD (Y/N) | 0.069 |
| MV (Y/N) | 5.11 |
| Renal replacement (Y/N) | 0.016 |
| Vasoactive agent (Y/N) | 4.668 |

| Y: yes; N: no |

### Table 5

| Variable | $P$ |
|----------|-----|
| Donor (related/unrelated) | 0.11 |
| Myeloablative/nonmyeloablative | 0.14 |
| Underlying disease (malignant/nonmalignant) | 0.35 |
| Gender (male/female) | 0.64 |
| Mechanical ventilation | 0.03 |
| Pediatric critical illness score | 0.02 |
| Respiratory failure | 0.50 |
| Renal replacement | 0.90 |
| Vasoactive agent | 0.05 |
| aGVHD | 0.79 |
| BUN | 0.19 |
| Lactate | 0.07 |
| Types of supportive therapies | 0.04 |

### Table 6

| Variable | $P$ |
|----------|-----|
| Mechanical Ventilation | 0.06 |
| Pediatric critical illness score | 0.04 |
| Vasoactive agent | 0.05 |
| Types of supportive therapy | 0.05 |
critical ill patients. In this study when the PCIS was less than 90, for every 10 points the score was below 90 the odds ratio of death increased 4.2 times (OR = 4.24, 95% CI 1.30-13.79).

Conclusions
Pediatric allogeneic hematopoietic stem cell transplantation recipients who requiring PICU treatment had high mortality. The PCIS was an independent prognostic factor for these patients.

Abbreviations
AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; GVHD, graft-versus-host disease; HPS, Hemophagocytic syndrome; HSCT, hematopoietic stem cell transplantation; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndromes; MPS, mucopolysaccharidosis; NHL, Non-Hodgkin’s Lymphoma; NPD, Niemann-Pick disease; PICS, pediatric critical illness score; PICU, pediatric intensive care unit; PIM, Pediatric intensive care unit mortality; PRISM, Pediatric risk of mortality score; SCID, severe combined immunodeficiency disease

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Authors’ contributions
J.C. participated in the design of the study; Y.W., B.R.L., C.Y.L., J.M.W., C.J.L. participated in the treatment of patients; K.A. collected the clinical data, performed the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
The Institutional Review Board at the Shanghai Children’s Medical Center approved the study protocol. We have uploaded the informed Consent Form which has reviewed by our ethics committee as attachment. All patients’ legal guardians signed the informed consent form when patients were admitted to hospital.

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