Original Article

Risk Factors for Mortality in Asian Children Admitted to the Paediatric Intensive Care Unit after Haematopoietic Stem Cell Transplantation

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Abstract

Introduction: This study aimed to investigate the risk factors associated with mortality in haematopoietic stem cell transplant (HSCT) patients admitted to our paediatric intensive care unit (PICU) over an 8-year period. Materials and Methods: A retrospective chart review was conducted of all HSCT patients requiring PICU admission at our centre (a tertiary care university hospital in Singapore) from January 2002 to December 2010. Chief outcome measures were survival at the time of PICU discharge and survival at 6 months after initial PICU admission. Results: Ninety-eight patients underwent HSCT during this period; 18 patients (18%) required 24 PICU admissions post-HSCT. The overall survival to PICU discharge was 62.5%. Of those who survived discharge from the PICU, 33% died within 6 months of discharge. Non-survivors to PICU discharge had a higher incidence of sepsis (89% vs 33%, *P* = 0.013) and organ failure as compared to survivors (cardiovascular failure 100% vs 20%, *P* = 0.0003; respiratory failure 89% vs 20%, *P* = 0.002; and renal failure 44% vs 7%, *P* = 0.047). Mortality rates were higher in patients requiring mechanical ventilation (70% vs 14%, *P* = 0.010) and inotropic support (70% vs 14%, *P* = 0.010). Mortality in all patients with renal failure requiring haemodialysis (n = 4) was 100%. Presence of 3 or more organ failures was associated with 80% mortality (*P* = 0.003). Conclusion: Sepsis, multiple organ failure and the need for mechanical ventilation, inotropes and especially haemodialysis were associated with increased risk of mortality in our cohort of HSCT patients.

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Key words: Bone marrow transplantation, Outcome, Prognostic factors

Introduction

Haematopoietic stem cell transplantation (HSCT) is well recognised as a definitive treatment in both malignant and certain non-malignant conditions and its use has increased significantly over time. It is, however, associated with high risks of morbidity and mortality, often necessitating admission to a paediatric intensive care unit (PICU). Once admitted to PICU, the prognosis tends to be guarded.

Several published studies seem to suggest that outcomes for paediatric HSCT patients requiring intensive care have generally shown improvement over the years.[1-5] A review by Naeem et al[1] looking at literature published between 1994 to 2004 suggests an improvement in the survival of HSCT patients requiring ICU transfer (both adult and paediatric patients) from 1998 onwards. The reported percentage of paediatric ICU patients surviving to hospital discharge or long-term survival rose from 9% to 11% prior to 1998, to 27% to 28% thereafter. Possible factors contributing to this encouraging outcome trend include use of less toxic preparative regimens, use of recombinant haematopoietic growth factors, use of mobilised blood cells rather than marrow, improved recognition of impending clinical deterioration and earlier escalation of treatment and transfer to ICU, as well as overall improved facilities in healthcare settings. Within the ICU, protective strategies for acute lung injury and early goal-directed therapy for sepsis have also likely contributed to improved survival for this patient population.

However, the question remains as to whether this reported improvement is real, or a result of better triage decisions

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regarding ICU transfer, resulting in patients with a better chance of recovery being transferred to the ICU more often and those with little chance being allowed to die in less invasive settings. Indeed, a meta-regression analysis on PICU mortality trends in children post-HSCT by van Gestel et al[6] reveals that characteristics of ICU-admitted patients have significantly changed over time, and after correcting for this, an improvement in ICU survival over time was less evident.

Several studies have looked at the risk factors influencing outcomes for this group of patients, in order to aid prognostication and parental counselling. Well known factors associated with increased mortality during PICU stay include allogeneic HSCT, respiratory, cardiovascular and neurologic failure, hepatotoxicity, multi-organ system failure, gross haemorrhage, graft-versus-host disease, the need for mechanical ventilation, need for renal replacement therapy (haemodialysis, ultrafiltration, or a combination), higher APACHE and oncological Pediatric Risk of Mortality (O-PRISM) scores at PICU transfer and higher Pediatric Risk of Mortality (PRISM) scores on the day of intubation.[7-20]

However, almost all of these studies have been conducted in the Western population, and a search of existing literature revealed only 1 paper by Cheuk DK et al[21] in which the study population was Asian. The objective of our study was to investigate the risk factors associated with mortality in our local Asian population of paediatric HSCT patients requiring admission to the PICU, with the aim of achieving a descriptive analysis of these risk factors in our local context.

Materials and Methods

A retrospective 8-year chart review was conducted of all HSCT patients admitted to our PICU located within a tertiary university hospital in Singapore from 2002 to 2010. Paediatric patients who had undergone HSCT for any reason, including non-malignant disease, were identified from a pre-existing HSCT database. Those admitted to the PICU had their medical records reviewed to collect data on their demographics, characteristics, medical complications, details of therapy, interventions, PICU acuity scores (O-PRISM[13] and PRISM-III[16] scores) and outcomes.

Patients admitted to the PICU for routine postoperative monitoring, and those HSCT patients who were admitted more than a year after their transplant, were excluded. The primary outcome variables were survival at the time of PICU discharge and survival at 6 months after initial PICU admission.

Sepsis and organ system failures were defined based on the 'International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics' as described by Goldstein et al.[22]

The relationship between mortality and specific morbidity variables was analysed using SPSS software. Fisher's exact t-test was used to examine the significance of the association between categorical variables, with the Mann-Whitney U test used to compare median mortality risk scores between groups. This study was approved by our hospital institutional review board, with waiver of the need for informed consent.

Results

Ninety-eight patients underwent HSCT during this period, with 18 patients (18%) requiring 24 PICU admissions, as 6 patients were readmitted a second time. Fourteen out of 18 (78%) patients survived their first PICU admission. Of the 14 survivors, 6 were readmitted to PICU within the next 6 months. Of this group, only 1 (17%) survived the readmission to PICU. The overall survival to PICU discharge was 62.5% (15 out of 24 admissions). The overall survival rate of this population within 6 months of PICU admission was 50% (9 out of 18). Patient characteristics are summarised in Table 1.

Bone marrow transplant (BMT) was the most common type of transplant performed (40% of all transplants). Only 1 patient received autologous stem cell rescue (ASCR) for neuroblastoma. One patient had an underlying diagnosis of beta-thalassaemia major and received both cord blood and peripheral blood stem cell transplant from her younger brother in the same sitting, while the other patient with acute myeloid leukaemia (AML) with secondary juvenile myelomonocytic leukaemia (JMML) received first a peripheral blood stem cell transplant (PBSCT) from his mother, but as there was only 20% engraftment of his mother's cells, he went on to receive a BMT from a matched unrelated donor. No statistically significant differences in survival outcome could be found with regard to type of transplant or conditioning regimes used.

The frequency of occurrence of sepsis was higher among non-survivors than survivors (89% vs 33%, $P = 0.013$) (Table 1). Sepsis included bacterial, fungal and viral sepsis, and in a number of patients, more than 1 organism was isolated. The most frequently isolated organism was *Pseudomonas aeruginosa*. Other bacteria isolated were *Klebsiella pneumoniae*, *Acinetobacter baumanii*, and *Stenotrophomonas maltophila*. Fungal agents isolated were *Candida tropicalis*, *Aspergillus* and *Pneumocystis jiroveci*. Virus isolates included *Cytomegalovirus*, *Herpes simplex* virus, *Varicella-zoster* virus and *Parainfluenza Type 3*. Organisms isolated from those who died versus those who survived were similar.

The type of organ system failures occurring among non-survivors versus survivors to PICU discharge is shown in Table 1. Non-survivors had a higher incidence of

Table 1. Characteristics of Children Admitted to Paediatric Intensive Care Unit (PICU) after Haematopoietic Stem Cell Transplant and PICU Mortality

Demographics	Total	Non-Survivors	Survivors	*P* Value
Number of patients	18	9	9	-
Number of admissions	24	9	15	-
Gender				
Male	10	3	7	0.153
Female	8	6	2	0.153
Ethnicity				
Chinese	13	7	6	1.000
Malay	3	1	2	1.000
Vietnamese	2	1	1	1.000
Median age at PICU admission	9	5	8.5	0.138
Range	(1 – 16)	(1.5 – 16)	(1 – 16)	
Median day post-transplant of PICU admission	47	44	60	0.411
Range	(6 – 267)	(22 – 180)	(6 – 267)	
Median Pediatric Risk of Mortality III (PRISM-III) score at 24 h from PICU admission	18 (0 – 51)	20.5	17	0.150
Median Oncological-Pediatric Risk of Mortality (O-PRISM) score at 24 h from PICU admission	21 (2 – 49)	27.5 (17 – 49)	13 (2 – 29)	0.002
Primary diagnosis				
Acute myeloid leukaemia	6	3	3	1.000
Acute lymphoblastic leukaemia	5	2	3	1.000
Aplastic anaemia	2	1	1	1.000
Beta thalassaemia major	2	1	1	1.000
Leucocyte adhesion defect	1	1	-	1.000
CD40 ligand deficiency	1	-	1	1.000
Neuroblastoma	1	1	-	1.000
Type of transplant				
Bone marrow transplant	8	3	5	0.637
Umbilical cord blood transplant	6	4	2	0.620
Peripheral blood stem cell transplant	5	3	2	1.000
Autologous stem cell rescue	1	1	-	1.000
Conditioning regimes				
Myeloablative	15	7	8	1.000
Non-myeloablative/reduced intensity conditioning	3	2	1	1.000
Total body irradiation	4	1	3	0.577
Grade 4 graft vs host disease	2	2	0	0.471
Failure of engraftment	5	3	2	1.000
Occurrence of sepsis	13	8	5	0.013
Type of organ system failures				
Cardiovascular	12	9	3	0.0003
Respiratory	11	8	3	0.002
Neurological	8	4	4	0.412
Haematological	18	7	11	1.000
Renal	5	4	1	0.047
Hepatic	3	2	1	0.533
Therapeutic interventions used				
Mechanical ventilation	10	7	3	0.010
Inotropes	10	7	3	0.010
Haemodialysis	4	4	0	0.012
None	12	2	10	0.089

PICU: Paediatric intensive care unit

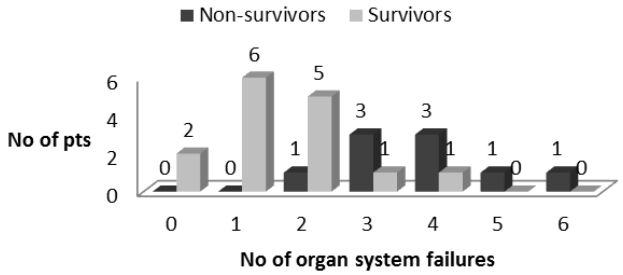

Fig. 1.Chart showing the comparison of the number of organ system failures among non-survivors versus survivors to PICU discharge. Data presented as number of patients in each group.

cardiovascular, respiratory and renal failure as compared with survivors. Pulmonary disease (in particular acute respiratory distress syndrome [ARDS]) was a frequent cause of mortality, featuring in at least 5 out of 9 (56%) mortalities. The number of organ system failures occurring among non-survivors versus survivors to PICU discharge is shown in Figure 1. An increased risk of mortality was associated with increasing number of organ system failures, with 3 or more organ failures associated with 80% mortality ($P = 0.003$).

The types of therapeutic interventions required by both non-survivors and survivors to PICU discharge are shown in Table 1. Mortality rates were significantly higher in patients requiring mechanical ventilation (70% vs 14%, $P = 0.010$) and inotropic support (70% vs 14%, $P = 0.010$) compared to those who did not require these interventions. Mortality in all patients with renal failure requiring haemodialysis was 100%. All 4 non-survivors who required haemodialysis also required both mechanical ventilation and inotropic support.

Of the 10 admissions for which mechanical ventilation was necessary, only 1 was on bilevel positive airway pressure (BiPAP) before being converted to conventional ventilation, followed by high frequency oscillation ventilation (HFOV). Eight had acute respiratory distress syndrome (ARDS), of which 2 had mild ARDS, 4 had moderate ARDS, and 2 had severe ARDS. ARDS was defined as per the 'Berlin Definition' published in 2012.[23] The 4 key diagnostic criteria as per this definition are that of acute onset, meaning onset over 1 week or less, presence of bilateral opacities consistent with pulmonary oedema and detected on computed tomography or chest radiograph, PaO_2/FIO_2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) <300mmHg with a minimum of 5 cm H_20 positive end-expiratory pressure (or continuous positive airway pressure), and "must not be fully explained by cardiac failure or fluid overload" in the physician's best estimation using available information (an "objective assessment", meaning an echocardiogram in most cases, should be performed if there is no clear risk factor present like trauma or sepsis). ARDS is further classified as mild, moderate or severe based on the degree of hypoxemia (mild: 200 mmHg $<PaO_2/FIO_2 \leq 300$ mmHg, moderate: 100 mmHg $<PaO_2/FIO_2 \leq 200$ mmHg, and severe: $PaO_2/FIO_2 \leq 100$ mmHg). The remaining 2 patients requiring mechanical ventilation did not have underlying lung parenchymal lung disease—1 was intubated for airway protection for status epilepticus, and the other for airway obstruction. The median duration of mechanical ventilation was 10.5 days (range, 12 hours to 37 days) among non-survivors, and 7 days (range, 4.5 days to 11 days) among survivors ($P = 1.000$).

The median length of PICU stay was 10.5 days (range, 0.5 days to 37 days) among non-survivors compared to 2.5 days (range, 1 day to 12 days) among survivors ($P = 0.318$). The median duration post-transplant for non-survivors at the time of death was day +63 (range, +23 to +181).

The primary reason for PICU admission among non-survivors and survivors to PICU discharge is shown in Table 2. Respiratory distress featured as the main reason for PICU admission among both survivors and non-survivors.

Discussion

In our centre, 18% of the transplanted population required PICU admission with an overall survival to PICU discharge of 62.5%, and a 6-month survival rate of 50%. This data

Table 2. Primary Reason for PICU Admission among Non-Survivors and Survivors to PICU Discharge

Primary Reason for PICU Admission	Non-Survivors n = 9 (37.5%)	Survivors n = 15 (62.5%)	*P* Value
Respiratory distress	4 (17%)	7 (29%)	1.000
Pneumonia	2	2	0.615
Pulmonary haemorrhage	2	1	0.533
Upper airway obstruction	-	2	0.511
Diaphragmatic splinting	-	2	0.511
Neurologic changes	2 (8%)	3 (12.5%)	1.000
Altered mental state	2	-	0.130
Recurrent seizures	-	1	1.000
Status epilepticus	-	2	0.511
Haemodynamic compromise	2 (8%)	3 (12.5%)	1.000
Cardiogenic shock	-	-	1.000
Septic shock	1	2	1.000
Haemorrhagic shock	1	1	1.000
Others	1 (4%)	2 (8%)	1.000

PICU: Paediatric intensive care unit

suggests improved survival rates compared to previously published studies.[1,4,7,12,24,25] This might be due to the fact that many of these studies looked at data from the 1990s, whereas our study period was more recent (from 2002 to 2010), by which time significant advances in ICU care have occurred; additionally, lower thresholds for ICU transfer in our institution may have contributed to earlier supportive care and better outcomes.

Objective assessments of severity of illness assist with prognostication in the PICU; as such, several scoring systems and probability models predicting mortality risks in the PICU have been developed over the years. These include the Pediatric Risk of Mortality-III (PRISM-III) score by Pollack MM et al[16] as well as the newer O-PRISM score by Schneider et al.[13,14]

In our study, the O-PRISM score served as a more accurate predictor of outcome than the PRISM-III score, when computed at 24 hrs from the time of admission. A 24-hour O-PRISM score of ≥30 was strongly associated with mortality in our study population. This is higher than what has been reported in previous studies in paediatric cohorts post-HSCT, which showed increased mortality in patients with O-PRISM scores ≥10 points.[14,15] In our study, all non-survivors had O-PRISM scores >10 points, however, a fairly large proportion of survivors (73%) also had O-PRISM scores >10 points. This potentially suggests better survival rates in our institution for the same severity of illness as quantified by the O-PRISM score; however, interpretation of this data is limited by our small sample size and possibly different patient characteristics as compared to other institutions. Threshold scores for predicting mortality may need to be individualised to each institution, due to factors such as variations in practice involving triage and time to intervention.

The reasons for admission to our PICU were similar to those described in other studies, most notably respiratory compromise.[24] The risk factors associated with mortality in our study population also mirror several previous studies on this topic conducted in Western populations. These include the presence of sepsis,[8,19] cardiovascular failure,[7,8] respiratory failure,[7,8,12,19,21,24,26] renal failure,[10-13,15,19,21,24] multi-organ failure involving ≥3 organs,[7,8,21] the need for mechanical ventilation,[4,7,8,12,15,20,21,24] inotropic support,[8,27] and haemodialysis.[10,11,19] That an increased number of organ system failures is associated with a proportionally increased risk of mortality is not surprising, as multi-organ system failure is well recognised to correlate with severity of complications and attendant poor outcome.

In our study, all 4 patients requiring haemodialysis died, and all 4 of these patients also required both mechanical ventilation and inotropic support. Most studies have found the need for mechanical ventilation and/or haemodialysis in paediatric stem cell transplant patients to be a poor prognostic factor for survival. In a study by Rajasekaran S et al,[10] only 1 out of 29 allogeneic haematopoietic stem cell transplantation patients who underwent haemodialysis survived beyond 6 months. Survival rates in stem cell transplant patients requiring both mechanical ventilation and haemodialysis have been dismal. Rossi et al[12] reported only 1 of 8 patients surviving after receiving both haemodialysis and mechanical ventilation. Both Jacobe et al[20] and Keenan et al[28] reported no survivors in patients receiving both therapies.

High grade graft versus host disease (GvHD),[7,9] allogeneic transplant[7,9] and neurologic deterioration[8,12] were associated with increased mortality in other studies. In our cohort of patients, while 2 out of 9 non-survivors had grade IV GvHD, none of the survivors did, though the difference was not statistically significant. Our small sample size with small numbers of patients in each subgroup likely precluded detection of any statistically significant differences in outcomes with regard to these risk factors.

The main limitation of our study is the small sample size, hence data such as mortality rates obtained from our cohort of patients may not be comparable to mortality rates in much larger patient cohorts abroad, with potentially very different patient characteristics. Nonetheless, our study serves to characterise this patient population in our local context and we hope to be able to prospectively assess mortality predictors to aid prognostication in our local patient population in future studies.

Conclusion

Sepsis, multiple organ failure (particularly ≥3 organ system failures) and the need for mechanical ventilation, inotropes and haemodialysis were associated with increased risk of mortality in our cohort of HSCT patients. Awareness of these risks will assist in appropriate prognostication and counselling for this group of critically ill patients and their families.

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