

# Children admitted to PICU after Hematopoietic stem cell transplantation: A predictive model of mortality

## Abstract

**Introduction:** Hematopoietic stem cell transplantation (HSCT) in children is associated with severe complications that need admission to critical care units. Mortality in this group of patients remains high with reported survival that ranges between 38 and 71%.

**Goals:** To analyze the predictive factors of mortality of pediatric patients who received HSCT and were admitted to the pediatric intensive care unit (PICU)

**Material and methods:** Retrospective review and analysis of a population of children and adolescents who underwent hematopoietic stem cell transplantation from 12/01/2008 to 11/30/2018 and were admitted to the pediatric intensive care unit (PICU) of a university hospital.

**Results:** Of 248 patients subjected to the analysis, 109 patients were admitted. Overall mortality was 29% (n=32). After univariate analysis, the type of transplant (unrelated), baseline disease (malignant vs non-malignant), febrile neutropenia, cytomegalovirus (CMV) infection, multiorgan failure, respiratory failure, graft versus host disease (GVHD), conditioning regimen with myeloablative chemotherapy and pre-transplant malnutrition were associated with higher mortality. After the Multivariate Analysis of Logistic Regression, the variables GVHD (OR 2, 23 95% CI: 1.92 a 2, 98), need of mechanical ventilation (OR 2.47, 95% CI 1.39 a 5.73) unrelated allogeneic transplants (OR 1.58, 95% CI 1.14 a 2.17) and previous malnutrition (OR: 1.78, 95% CI 1,223-3.89) were statistically associated with mortality.

**Conclusion:** In our population two of three children receiving HSCT and admitted to PICU survived. Graft vs. host disease, need of mechanical ventilation, unrelated transplantation and previous malnutrition were predictors of mortality.

**Keywords:** hematopoietic stem cell transplantation, predictive model of mortality, unrelated transplantation, graft versus host disease, previous malnutrition, mechanical ventilation.

Volume 9 Issue 4 - 2019

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**Received:** July 24, 2019 | **Published:** August 16, 2019

**Abbreviations:** HSCT, Hematopoietic stem cell transplantation; PICU, pediatric intensive care unit; GVHD, graft versus host disease; CMV, Cytomegalovirus; MOF, Multiorgan failure; UAT, received unrelated allogeneic transplants; RAT, received related allogeneic transplants; AT, received autologous transplants; PIM 2, pediatric index of mortality 2.

## Introduction

Hematopoietic stem cell transplantation is used as a lifesaving therapy for a diversity of pediatric diseases. The procedure is associated with considerable mortality; however, better conditioning regimens and better supportive treatments have reduced the non-relapse mortality and more neoplastic and non-neoplastic conditions are now considered for transplantation. Despite these advances in treatments and techniques, HSCT remains a therapy associated with significant morbidity and mortality with patients often requiring treatment in a PICU. Septic shock and respiratory and multiple organ failure are common associated with admission and mortality

in PICU. In the last decade studies have been published<sup>1-4</sup> showing a progressive improvement in survival with aggressive critical care management.<sup>5-7</sup>

On the other hand is very important to know the controversial questions about the appropriateness of using intensive care resources for this population. Many studies have analyzed the survival of children undergoing HSCT and admitted to critical care units, with a survival range between 38 and 71%.<sup>6-9</sup> The proportion of autologous, related, unrelated or haploidentical transplants performed at each center, the initial diagnoses and the condition at admission to PICU can explain these differences in survival. The aim of this study was to retrospectively analysis at all pediatric patients admitted to our PICU post-HSCT over the last 16 years regarding the outcomes and predictors of mortality.

## Objective

To analyze the predictive factors of mortality of pediatric patients admitted to Pediatric intensive Care Unit after HSCT.

## Design

Analysis of a retrospective cohort.

## Material and methods

This is a retrospective review and analysis of a population of children and adolescents younger than 16 years who received HSCT and needed admission to PICU between 12/01/2008 and 11/30/2018. The hospital is a tertiary university center that offers HSCT for patients from Argentina and neighboring Latin-American countries. All patients who received an HSCT were recorded in the HSBC database, and the PICU admission is determined on a case-by-case basis between the intensive care and HSBC teams. The HSBC ward provides high dependency monitoring. Patients are transferred to the PICU when additional support is required (mechanical ventilation, inotropic support, dialysis, ECMO). Patients with HSCT that needed admission to intensive care were identified from the PICU database. In addition, the pediatric HSCT database was analyzed to crosscheck the information and avoid losing patients. Inclusion criteria were admission to the PICU for at least 24 hours after HSCT for any reason in patients under the age of 16 years. The underlying primary condition that led to the HSCT was classified as oncologic disease and non-oncologic disease. The exclusion criteria was the lack of complete data that we needed collect in the database. Detailed data was collected regarding gender, age, hospital and PICU length of stay, time from HSCT to PICU admission, Pediatric Index of Mortality 2 (PIM2) score, need of invasive and non-invasive ventilation, use of vasopressor/inotropes, use of renal support therapy. Vital signs, laboratory results and therapeutic interventions were collected during the 24-hour period following PICU admission. Details about date of transplant, type of transplant, source of cells and type of conditioning regimen were collected for all patients.

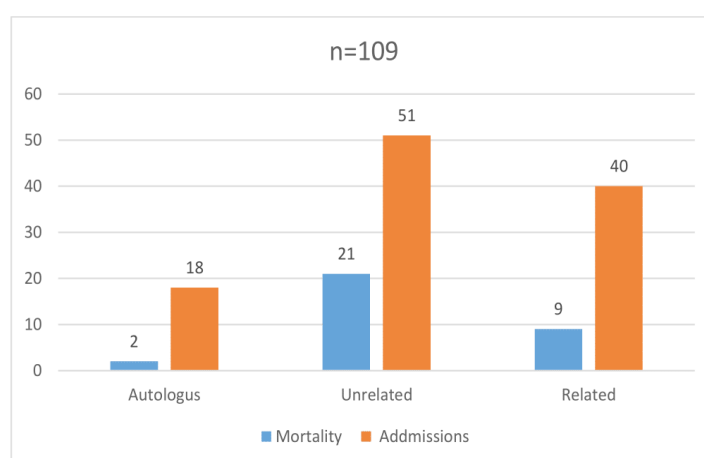
In addition we also evaluated presence of sepsis (blood culture +), previous malnutrition (<2 Z-Score weight percentile), cytomegalovirus (CMV) viremia, multiorgan failure (MOF) and graft versus host disease (GVHD).

Patients were assigned to the study cohort and were codified with a number to relate each patient with the principal outcomes.

The outcome analyzed was survival at hospital discharge. Statistical analysis was performed using Stata 8.0 (California, USA). Continuous data were expressed as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQ). According to verification of the normal standard population distribution, the samples were compared using the Student's t-test or Wilcoxon test. Categorical data were expressed as proportions and compared using the X<sup>2</sup> test or Fisher's test. A p value <0.05 was considered significant. For the initial comparison between groups we used the Chi Square test. A univariate analysis was used to screen for possible risk factors, setting the p value at 0.20 significance level for entry in the multiple regression model. A multivariate logistic regression was then conducted to predict the incidence of mortality and to evaluate the association of each of the regressor variables with the outcome variable (mortality). A p value of less than 0.05 was considered significant. A logistic regression allowed to control the effects of the confounding variables and the interactions between them. A predictive model of mortality was elaborated and was tested for its performance. The study was approved by the Institutional Review Board (IRB). Need for informed consent was waived.

## Results

A total of 48 pediatric bone marrow transplants were performed during the study period. Of 121 admissions data of 9 patients were excluded because the admission was less than 24 hours in duration such as to facilitate a procedure (vascular line insertion) and 3 date missed in the collection. Of these, 109 needed admission to the pediatric intensive care. (Table 1) Of the population admitted to PICU, 51 (47%) received unrelated allogeneic transplants (UAT), 40 (37%) received related allogeneic transplants (RAT), and 18 (16%) received autologous transplants (AT). Median time from HSCT to admission was 23 days (IQR,14-68), median PIM2 scores were 12(IQR,0.33-70,47) The median age was 10 years (IQR,12 months - 19 years) and the median stay in PICU was 11 days (IQR, 3 -29). When considering type of transplant, 84% of UAT, 65 % of RAT and 47% of AT needed admission to the PICU. Mortality of patients admitted to PICU was 29% (n=32). Of these patients, 2 (6%) received an autologous transplant, 9 (28%) a related transplant and 21 (66%) an unrelated transplant. PICU mortality in relation to type of transplant is described in Figure 1.



**Figure 1** Mortality and type of transplant admitted to PICU.

**Table 1** Population characteristics

Population characteristics	N=109
Autologus Transplant	18
Allogenic Related Transplant	40
Allogenic Unrelated Transplant	51
Age in years*	10; 1-19
<b>Age in months*</b>	
< 24 months	45 (41%)
24 -60 months	33 (31%)
> 60 months	31 (28%)
<b>Sex</b>	
Male	60 (55 %)
Female	49 (45 %)
PIM 2 Score*	12(0.33-70.47)
Days from HSCT to admission	23 (14-68)
Length of hospital stay (days)*	25 (3-121)
Length of PICU stay (days)*	11 (3-29)
Mortality Patients needing PICU	32 (29%)
<b>Diagnoses</b>	
<b>Oncologic Disease</b>	
Acutelymphoblastic Leukemia	28
Acute Myeloid Leukemia	30
Medullary Aplasia	16
Solid Tumors	22
<b>Non-oncologic Disease</b>	
Metabolic Diseases	9
Immunodeficiencies	2
Thesaurismosis	2
Previous Malnutrition	38(35%)
Mioloablative treatment before admission	48(44%)
Mechanical Ventilation	43 (39%)
Sepsis	74 (68%)

\*Median/Interquartile range (p25-75).

When evaluating cause of admission to the PICU, the most frequent cause was sepsis in 68% of the admissions (n =74) with 86 % of microbiological rescue (63 opportunities) followed by respiratory failure with oxygenation index (OI) of more than 6 in 22% of the admissions (n=24). However, of the total population of patients admitted to PICU, 39% (n=43) developed respiratory failure needing positive pressure ventilation at any moment of the stay. After univariate analysis, the type of transplant (unrelated), oncologic disease, male gender, febrile neutropenia, cytomegalovirus (CMV) viremia, multiorgan failure (MOF), need of mechanical ventilation, graft versus host disease (GVHD), conditioning regimen with myeloablative chemotherapy and pre-transplant malnutrition were associated with higher mortality (Table 2). After the Multivariate Analysis of Logistic Regression, the variables GVHD (OR 2,23 95% CI: 1.92 a 2,98), need of mechanical ventilation ( OR 2.47,95% CI 1.39 a 5.73), unrelated allogeneic transplants (OR 1.58, 95% CI 1.14 a 2.17) and previous malnutrition (OR: 1.78, 95% CI 1,223-3.89) were

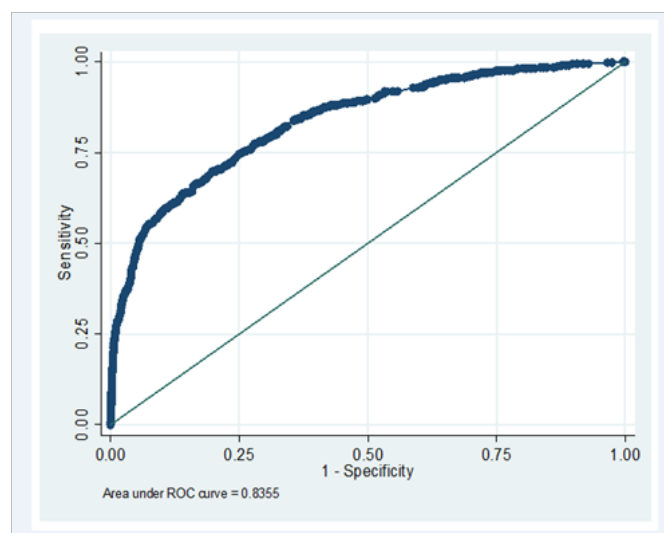
statistically associated with mortality (Table 3). Performance of the model was evaluated with the ROC curve (Figure 2) that showed an area under the curve (AUC) of 0.83 revealing an optimal capacity for discrimination (Figure 2).

**Table 2** Univariate analysis

Variables	OR	IC95%	P
Oncologic disease	3.24	1c:2.798-5.34	0.014
Febrile neutropenia	2.139	1.239-9.337	0.041
Age < 24months	1.24	0.429-5.981	0.05
Male	1.752	1.0292-2.678	0.038
CMV infection (Viremia)	0.525	0.374-1.735	0.019
Multiorgan failure (MOF)	2.017	1.654-4.701	0.003
Graft versus host disease (GVHD)	1.478	1.892-4.782	0.021
Need of mechanical ventilation	2.34	1.17-5.23	0.034
Previous malnutrition	2.56	1.324-12.05	0.045
Mioloablative treatment	0.651	2.261-7.071	0.011

**Table 3** Multivariate logistic regression analysis predictive model of mortality in PICU

Risk factors	OR	IC 95%	P
GVHD	OR 2.23	1.92-2.98	0.031
Unrelated transplantation	OR: 1.58	1.14-2.17	0.045
Malnutrition	OR 1.78	1.223- 3.89	0.02
Mechanical Ventilation	OR 2.47	1.39-5.73	0.01



**Figure 2** Performance of the model was evaluated with the ROC curve.

## Discussion

Patients receiving hematopoietic stem cell transplantation frequently need critical care given the high incidence of associated complications. During the last decade, numerous studies have analyzed large cohorts of patients admitted to the PICU after HSCT. Pre-transplantation conditions mainly related to the severity of the underlying disease

(solid tumors, severe congenital immunodeficiency and metabolic disorders) have been associated with worse complications, however, other studies contrast this hypothesis by disregarding the importance of the underlying disease and focusing the discussion on the type of transplantation (autologous, allogeneic related and unrelated).<sup>8,9</sup> Beyond the importance of the underlying disease, different analysis have observed that intensive cardiopulmonary support during the management of HSCT patients in PICU improves outcomes.<sup>9,10</sup> The current trend to develop risk predictive scores, like the Pediatric Early Warning Score for Pediatric Oncology and HSTC patients, has explored methods for early identification of clinical deterioration in this high-risk population.<sup>11</sup>

Based on our population and references from studies, we constructed a database in order to analyze the variables that represent a risk of morbidity and mortality in this group of children. After univariate analysis, we observed that the type of transplantation (unrelated), underlying disease (malignant vs. non-malignant), febrile neutropenia, cytomegalovirus (CMV) infection, multiorgan failure, respiratory failure, graft versus host disease (GVHD), conditioning regime and pre-transplant malnutrition were associated with higher mortality. With this analysis and evaluating the interactions between variables, confounding effects and probable bias, we carried out a multivariate analysis to construct a predictive model of mortality, which revealed that graft versus host disease, need of mechanical ventilation, unrelated transplant and previous malnutrition were statistically associated with mortality.

Children in our country frequently develop signs of malnutrition after several prolonged treatments with chemotherapy, or during the induction to transplant when very myeloablative chemotherapy, which conspires against the nutritional status, is used. Recently, a large study in Nicaragua showed that malnutrition is often prevalent in children with cancer who live in resource-limited countries. In this study, children with malnutrition at the moment of cancer diagnosis experienced increased treatment-related morbidity, abandoned therapy more frequently and had inferior event-free survival.<sup>12</sup> Beyond its effect on survival, malnutrition in pediatric oncology patients is associated with treatment delays, increased risk of infection, impaired wound healing, lower quality of life and inferior treatment tolerance and response including bone marrow transplantation.<sup>12-15</sup> In concordance with our findings, other groups have described the importance of malnutrition in the outcome of oncologic patients, suggesting that targeted nutritional interventions for high-risk groups as pre-transplantation states can improve morbidity and mortality. Simple cost-effective nutritional interventions could potentially diminish the effects of toxicity, thereby leading to improved results.<sup>12</sup> On the other hand, when stays are long as with unrelated transplants, or in the presence of infections and other intercurrents, children can suffer acute malnutrition that increases the risks and represents a serious obstacle for their definitive recovery.<sup>16</sup> Malnourished children who need mechanical ventilation are at a higher risk of developing ventilator-associated pneumonia and difficulties during the ventilation weaning because of a deficient muscular pump.<sup>7,17</sup> Delays in the exit of MV leads to a longer stay in critical care and more complications.<sup>18,19</sup>

Although malnutrition in our population was almost 35%, less myeloablative chemotherapy regimens during the last years together with an aggressive enteral and parenteral nutritional scheme as from the beginning of the conditioning regime could reduce its incidence. This is an interesting point to evaluate in future studies. Other risk

factors have been described in different studies. A series of 240 children admitted to PICU during 7 years showed that the underlying disease, post-transplant infectious and the type of chemotherapy predicted need of mechanical ventilation, which in turn was associated with high mortality. In the same study, after multivariate analysis, the authors concluded that the presence of acute graft-versus-host disease was a strong predictor of multiorgan failure, and if the lung was the first organ of failure, it became an independent predictor of high mortality (89). A large study involving 128 PICUs in 26 countries concluded that history of hematopoietic cell transplant was associated with a four-fold increased odds of hospital mortality, with sepsis as the most important cause. These patients were more likely to have different types of hospital-acquired infections including ventilator-associated pneumonia.<sup>10</sup>

Respiratory failure after HSCT is frequent. Viral, bacterial and pneumocystis carinii infections are described as responsible of up to 90% of the admissions to critical care.<sup>7,15,19,20</sup> The main factor associated with increased mortality in these patients is the use of invasive mechanical ventilation. Another single-center study of 206 pediatric patients that needed intensive care post HSCT, describes that invasive mechanical ventilation had a 48% survival to PICU discharge and if these patients needed mechanical ventilation more than once, the survival rate was 36% (16). When noninvasive ventilation can be used, compared to invasive ventilation, mortality decreases by one third (4, 5). On the other hand, when acute respiratory failure is combined with other failing organs, survival rates decrease significantly and can be less than 5%.<sup>4, 20</sup> In our study, 43 patients needed mechanical ventilation (39%) with a mortality of 48% (n=20). The elevated proportion of UAT may explain this mortality because all of the patients with UAT that needed mechanical ventilation died whereas mortality of AT and RAT that needed mechanical ventilation was 46%. Therefore, the important factor of mortality in this group is UAT with a significative association.

Other factors reported as predictors of poor prognosis include renal replacement therapy, graft versus host disease, age at transplant, bacterial pneumonia, sepsis PIM2 score and UAT.<sup>4,5,7,20-21</sup> Patients receiving UAT are at greater risk of complications like GVH and infections. Our study is a 10-year analysis of a cohort of 248 patients of a single hematopoietic stem-transplant center. All children were cared according to international quality and safety policies in units with laminar flow, double door sealing, and drug preparation in cancer pharmacy, institutional epidemiological surveillance and daily rounds with oncologists, nurses, pharmacists, microbiologists and intensive care pediatricians. These factors contribute to reduce possible biases that may be present when patients belong to several institutions; however, it is also a weakness, as it does not offer the variability of multicentric studies.

Although this predictive model of mortality was evaluated to verify its reliability, it should be tested in another population of transplanted children admitted to critical care for external validation. Different to other studies, we observed a determinant behavior of the variable nutrition.

## Conclusions

In our population two of three children receiving HSCT and admitted to PICU survived. Graft vs. host disease, need of mechanical ventilation, unrelated transplantation and previous malnutrition were predictors of mortality.



## Acknowledgments

None.

## Conflicts of interest

The authors declared there is no conflict of interest.

## Funding

None.

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