Children admitted to a pediatric intensive care unit after hematopoietic stem cell transplantation: Analysis of survival and predictors of mortality

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ABSTRACT

Introduction: Hematopoietic stem cell transplantation (HSCT) in children is a procedure that is not exempt of severe complications. Admission to the pediatric intensive care unit (PICU) is associated with a high mortality rate. *Objectives*: To analyze survival and predictors of mortality among children who received a HSCT and were admitted to the PICU, and to develop a mortality prediction model in this population. *Materials and methods*: Retrospective review of children and adolescents who received a HSCT between January 1st, 2005 and December 31st, 2019 and were admitted to the PICU of a tertiary care teaching hospital.

Results: Out of 264 children receiving the transplant, 114 were admitted to the PICU. The overall mortality rate was 29 % (n = 34). The type of transplant, underlying disease, febrile neutropenia event, cytomegalovirus infection, respiratory failure, graft versus host disease (GVHD), myeloablative chemotherapy, and previous malnutrition were associated with higher mortality rates. In the multivariate analysis, GVHD (odds ratio [OR]: 2.23; 95 % confidence interval [CI]: 1.92-2.98), need for mechanical ventilation (OR: 2.47; 95 % CI: 1.39-5.73), alternative donor transplant (OR: 1.58; 95 % CI: 1.14-2.17), and previous malnutrition (OR: 1.78; 95 % CI: 1.22-3.89) were associated with a higher mortality rate.

Conclusion: In the studied population, 2 out of 3 children who received a HSCT and were admitted to the PICU survived. GVHD, mechanical ventilation, alternative donor transplant, and previous malnutrition were predictors of mortality.

Key words: *hematopoietic stem cell transplantation, graft versus host disease, malnutrition, mechanical ventilation.*

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a therapeutic procedure validated in pediatrics both for some types of cancer and other non-cancer diseases; and, in some cases, it is the only therapeutic tool.

Survival in this population ranges between 38 % and 71 %.[1-3] Such variability was mainly explained by the difference between centers that only performed autologous transplants and others that included a high number of unrelated allogeneic grafts.

In the past decade, several studies have analyzed large cohorts of children admitted to the PICU after receiving a HSCT. Pre-transplant conditions and underlying diseases (solid tumors, severe congenital immunodeficiencies, and metabolic disorders, among others) have been associated with a poor post-transplant clinical course, although other hypotheses contrast with these statements and focus the discussion on the type of transplant (autologous, related and unrelated allogeneic).[4-7]

Several reports since 1999 to date have highlighted that associated morbidity and mortality have decreased considerably in the last decades due to the use of reduced-toxicity conditioning regimens, changes in immunosuppression regimes, and improved support treatment.[8-10] However, the risk of transplant-related mortality still exists: GVHD, both in its acute and chronic forms, is the leading risk

factor, followed by infections.[11,12] In line with the above, prediction scores such as the Pediatric Early Warning Score for Pediatric Oncology and the Early Warning and Assessment Scale (*Escala de Valoración y Alerta Temprana*, EVAT) have been developed, which allow to explore methods for the early identification of patients at a high risk for clinical deterioration and thus initiate an early management.[8,13,14]

In Argentina, several prediction scores for cohorts of children with HSCT have been analyzed;[15] however, there are currently no studies revealing the course of this pediatric population admitted to the PICU. For this reason, we decided to perform an analysis of a retrospective cohort of patients admitted to the PICU in order to offer additional evidence in this area of interest.

OBJECTIVES

The objectives of this study were to analyze survival and mortality-related factors in children admitted to the PICU after receiving a HSCT and develop a mortality prediction model in this population.

MATERIALS AND METHODS

This was a descriptive and observational study analyzing a retrospective cohort of children and adolescents younger than 16 years who received a HSCT and required critical care between January 1st, 2005 and December 31st, 2019 at Hospital Universitario Austral, province of Buenos Aires, Argentina.

This is a tertiary care center where HSCTs are performed in patients from Argentina and neighboring countries from Latin America. Its PICU is classified as a level-3 unit, with 450 admissions of critically-ill patients per year.

Inclusion criteria: children older than 1 month and younger than 16 years who received a HSCT and were admitted to the PICU, with a length of stay of more than 24 hours.

Exclusion criteria: children with a length of PICU stay of 24 hours or less.

The PICU admission criteria were need for mechanical ventilation (invasive or non-invasive), vasoactive support, and renal replacement therapy (continuous hemofiltration and hemodialysis). Patients' data were entered into a specifically designed database. The primary condition leading to HSCT was classified as "cancer" or "non-cancer disease".

The variables included were age, sex, mortality at PICU discharge, days of PICU stay and total hospital stay, pediatric index of mortality 2 (PIM2),[16] type of transplant (autologous, HLA-identical related allogeneic, unrelated or haploidentical allogeneic), conditioning regimen, need for non-invasive and invasive mechanical ventilation, vasopressor and inotropic use, need for renal support therapy, and extracorporeal membrane oxygenation (ECMO).

Transplant-related data were recorded, which included the type of transplant, the source of stem cells, donor's characteristics, and the chemotherapy conditioning regimen.

Sepsis documented by 2 blood cultures, malnutrition before PICU admission (Z-score < 2 for weight percentile), cytomegalovirus (CMV) viremia confirmed by polymerase chain reaction (PCR) or viral load, multiple organ failure (MOF), febrile neutropenia, acute GVHD, respiratory failure defined as an oxygenation index (OI) ≥ 6[17,18] (see definitions in the *Annex*).

The statistical analysis was performed with the Stata® 8.0 software. Continuous data were described as mean +/- standard deviation (SD) or median and interquartile range (IQR); variables were compared using Student's or Wilcoxon's tests. Categorical data were expressed as proportions and percentages, and were compared using the χ^2 test or Fisher's test. A *p* value < 0.05 was considered significant. After the initial univariate analysis based on variable significance, a multivariate logistic regression analysis was performed to assess the association of each regressor with the outcome variable, which was "mortality".

The effects of confounders and their interaction were controlled using a logistic regression. Risk measures, with their corresponding 95 % confidence intervals, were used. A mortality prediction model was developed and its calibration and discrimination power were analyzed to assess its performance using the Hosmer-Lemeshow test and an under the curve analysis for sensitivity and specificity.

Based on the cited bibliography which reported a mortality rate ranging between 31 % and 71 %,[1-3] an expected mortality rate of 57 %[1] was assumed as reference with a 0.05 type I error. Therefore, it was concluded that a sample consisting of 106 patients was required for a power of 90 %.

The study was approved by the Institutional Review Board (IRB) of the School of Biomedical Sciences of Universidad Austral, certified by the Central Ethics Committee of the Ministry of

Health of the Province of Buenos Aires, on May 26th, 2017 (File N° CIE17-019). No informed consent was included. Study data were coded and stored in a specifically designed database. Only the researchers and IRB members could access the database. It is worth noting that the study was conducted in a vulnerable population (minors) and that this is an observational study with no potential damage for patients, except for data confidentiality, which was protected as explained above.

RESULTS

A total of 264 transplants were performed in the study period. Among these patients, 118 required PICU admission; 4 of them had a stay of less than 24 hours, so they were excluded from the study. The final analysis included 114 children (*Table 1*).

Among them, 19 children (17 %) received an autologous (AUT) transplant, 38 (33 %) received a HLA-identical related allogeneic (RA) transplant, whereas 57 (50 %) received alternative donor transplants. This last group included haploidentical transplants (14) and unrelated allogeneic transplants of cord blood (21), peripheral blood (7), and bone marrow (15).

The mortality rate of patients admitted to the PICU was 29 % (n = 34). Among them, 2 received an AUT transplant; 9, a RA transplant; and 23, an alternative donor transplant.

Sepsis was the most common cause for PICU admission, present in 68 % of cases (n = 77) with causative microorganism isolation in 64 patients, followed by respiratory failure in 22 % of admitted patients (n = 26). However, of the 114 admitted patients, 39 % (n = 45) developed respiratory failure requiring invasive mechanical ventilation at some point of their stay. *Table 1* describes the characteristics of the population.

The univariate analysis highlighted that alternative donor transplant, cancer, male sex, febrile neutropenia, CMV viremia, MOF, need for invasive mechanical ventilation, GVHD, previous myeloablative chemotherapy, and pre-transplant malnutrition were associated with increased mortality (*Table 2*).

The multivariate analysis showed a statistically significant association between mortality and GVHD (OR: 2.23; 95 % CI: 1.92-2.98), invasive mechanical ventilation (OR: 2.47; 95 % CI: 1.39-5.73), alternative donor transplant (OR: 1.58; 95 % CI: 1.14-2.17), and previous malnutrition (OR: 1.78; 95 % CI: 1.22-3.89) (*Table 3*). This

model showed optimal discrimination capacity when assessed with an area under the curve for sensitivity and specificity of 0.83 (*Figure 1*).

A mortality rate ranging between 31 % and 71% was reported in the bibliography;[1-3] therefore, an expected mortality rate of 57 %[1] was assumed as reference with a 0.05 type I error. The power of this study sample for a 29 % incidence (95 % CI: 21.6-39.1) is higher than 90 %. In addition, the recording of 34 events in the outcome variable (mortality) has allowed to include 4 variables in the multiple logistic regression model.

TABLE 1. *Characteristics of the study population*

Characteristics of the population	N = 114
Autologous transplant	19
Related allogeneic transplant	42
Alternative donor transplant	53
Age in years*	10 (1-19)
Age in months*	
< 24	45 (41 %)
24-60	33 (31 %)
> 60	31 (28 %)
Sex	
Male	63 (55%)
Female	51 (45%)
Pediatric index of mortality 2 (PIM2)*	12 (0.33-70.47)
Days elapsed since HSCT until PICU admission	21 (14-68)
Length of hospital stay (days)*	24 (3-21)
Length of PICU stay (days)*	9 (3-29)
Mortality of patients admitted to the PICU	34 (29 %)
Diagnoses	
Cancer	
Acute lymphoblastic leukemia	30
Acute myeloid leukemia	30
Aplastic anemia	16
Solid tumors	24
Non-cancer disease	
Metabolic disorder	9
Immunodeficiency	2
Storage disease	3
Pre-HSCT malnutrition	42 (37 %)
Myeloablative chemotherapy before PICU admission	48 (42 %)
Invasive mechanical ventilation	45 (39 %)
Sepsis	77 (68 %)

* Median, (interquartile range [Pc25-75]).
HSCT: hematopoietic stem cell transplantation;
PICU: pediatric intensive care unit.

DISCUSSION

In the studied population, the mortality rate at the PICU is low (29 %). Similarly to other series, GVHD, the need for invasive mechanical ventilation, alternative donor transplant, and previous malnutrition were risk factors for mortality.[2,3]

Different studies have focused on studying risk factors in this vulnerable pediatric population. It is worth mentioning a 7-year series with 240 children admitted to the PICU.[7] This series concluded that the underlying disease, post-HSCT infections, the type of chemotherapy, and the need for mechanical ventilation were associated with a higher mortality rate. In the same study, after conducting the multivariate analysis, the authors considered GVHD as the main predictor of MOF. In addition, they mention that, if the lung was the first affected organ, this is considered an independent predictor of elevated mortality. Another large study including 128 PICUs from 26 countries concludes that the mortality rate is four times higher in units admitting patients with HSCT. In this report, sepsis was the most important concurrent cause, although the susceptibility of developing mechanical ventilation-associated pneumonia is also emphasized.[14]

Viral, bacterial, and *Pneumocystis carinii* infections are included among 90 % of causes for PICU admission. The main factor associated with increased mortality among these patients was the use of invasive mechanical ventilation.[2,19,20] In this regard, it is worth mentioning a study that included 260 patients admitted to the PICU after HSCT. Results show a 48 % survival rate at discharge among children who required invasive mechanical ventilation. They also point out that, among patients requiring more than 1 event of invasive ventilatory support (extubation failure or scheduled re-intubations with invasive ventilation), survival dropped to 35 %.[4]

Probably, the main contribution of this study is offering additional evidence about previous malnutrition as a predictor of mortality after removing confounders in the multivariate analysis.

Children tend to develop malnutrition after very long chemotherapy treatments, intercurrent febrile neutropenia events with long hospital

TABLE 2. *Univariate analysis*

Variables	OR	95 % CI	P
Cancer	3.24	2.79-5.34	0.01
Alternative donor transplant	2.12	1.87-4.07	0.02
Febrile neutropenia	2.13	1.23-9.33	0.04
Age < 24 months	1.24	0.42-5.98	0.05
Male sex	1.75	1.02-2.67	0.03
CMV infection (viremia)	1.52	1.37-1.73	0.01
Multiple organ failure	2.01	1.65-4.70	0.00
Graft versus host disease	1.47	1.89-4.78	0.02
Invasive mechanical ventilation	2.34	1.17-5.23	0.03
Pre-HSCT malnutrition	2.56	1.32-12.05	0.045
Myeloablative chemotherapy before PICU admission	0.65	2.26-7.07	0.01

OR: odds ratio; *P*: *P* value; CMV: cytomegalovirus;
HSCT: hematopoietic stem cell transplantation; PICU: pediatric intensive care unit.

TABLE 3. *Multivariate logistic regression analysis (mortality prediction model)*

Risk factors	OR	95 % CI	P
Graft versus host disease	2.23	1.92-2.98	0.03
Alternative donor transplant	1.58	1.14-2.17	0.04
Malnutrition	1.78	1.22-3.89	0.02
Invasive mechanical ventilation	2.47	1.39-5.73	0.01

OR: odds ratio; CI: confidence interval.

stays or during transplant induction with myeloablative conditioning regimens. A recent study conducted in Nicaragua with a large number of cancer patients has demonstrated that malnutrition is prevalent among children with cancer living in non-industrialized Latin American countries. In this study, children with malnutrition at the time of cancer diagnosis had a higher morbidity rate during treatment, a higher risk for treatment dropout, and a lower survival rate.[19]

It is well known that malnutrition has an influence on treatment delay (chemotherapy cycles), an increased risk of infections, delayed wound and eschar healing, a lower quality of life, and reduced tolerance or response to HSCT.[21]

In line with the results of our study, other groups observed the importance of malnutrition in the course of children with cancer, suggesting that nutritional recovery interventions in groups with high risk factors before transplant may improve morbidity and mortality. In this way, simple nutritional interventions will have a high cost-benefit relation, reducing the toxic effects of

chemotherapy and pre-transplant conditioning regimens, which results in an improved survival rate.[2,21,22]

It is necessary to mention that children with malnutrition who require mechanical ventilation have a higher risk for ventilator-associated pneumonia and difficulties for an optimal weaning, due to a defective skeletal-muscle pump. Delayed weaning from mechanical ventilation results in longer PICU stays and, therefore, more complications.[3,20,22,23]

The strength of this study lies in the 15-year analysis of a cohort of 264 patients in a single HSCT center. An analysis of concurrent variables was done to compare the results with previous bibliographic evidence and thus produce a report on this vulnerable population in Argentina.

All children included in this study were subjected to international quality and patient safety policies, with laminar flow units, double door sealing, negative pressure, drug preparation in the oncology pharmacy, institutional epidemiological surveillance controls and daily discussions with specialists in oncology

FIGURE 1. *Sensitivity and specificity curve of the mortality prediction model*
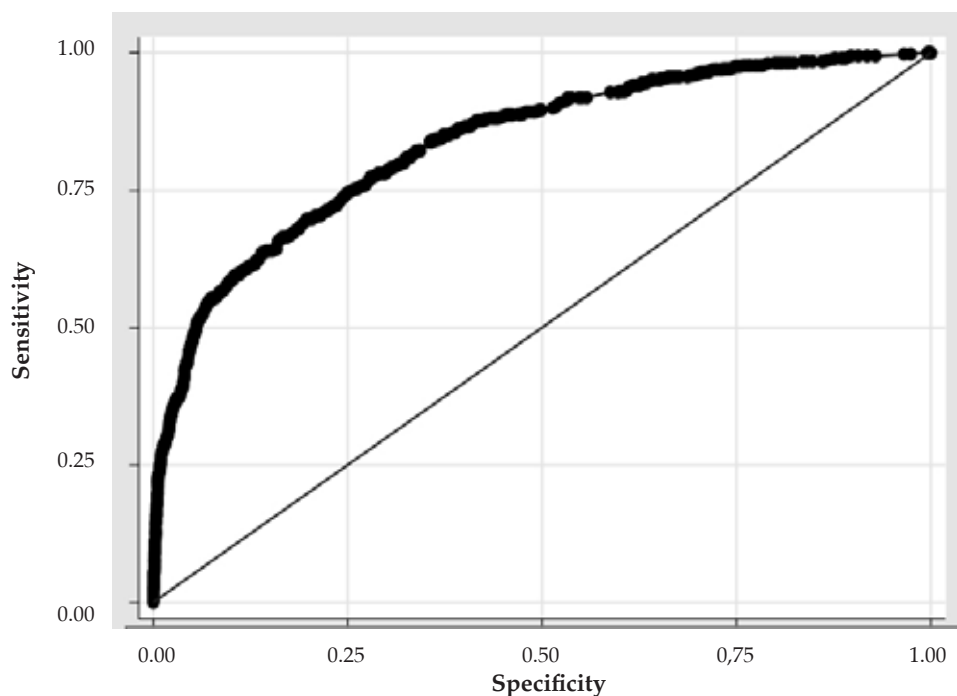
Area under the ROC curve = 0.8355

AUC 0.83 (95 % CI: 0.79-0.84)

and infectious diseases, nursing, respiratory physical therapy, and pediatric intensive care. These factors helped to mitigate potential biases that may occur in patients treated at different facilities or referred after the start of induction with conditioning chemotherapy. The analyzed data are relevant to know the care provided to this pediatric population in the critical care unit, considering the risks of the procedure, the high proportion of unrelated transplants, and associated GVHD.

Nevertheless, a weakness of this study is that it was conducted in a single center, since it does not reflect the variability and validity of a multicenter study. Therefore, the findings of the prediction model should be verified in another pediatric population admitted to the PICU after HSCT for an external validation.

CONCLUSIONS

In the studied population, 2 out of 3 children who have received a HSCT and have been admitted to the PICU survive. GVHD, the need for invasive mechanical ventilation, alternative donor transplant, and previous malnutrition were predictors of mortality. ■

Acknowledgments

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ANNEX

Definitions

- **Pediatric index of mortality 2** (PIM2): scale defining the baseline risk of each patient admitted to the pediatric intensive care unit, based on clinical and lab scores.[16]

- **Graft versus host disease** (GVHD): the impact of graft rejection by the host, resulting in tissue damage. Some of the most commonly affected organs are the skin, gastrointestinal system, and lungs. It is due to interaction between the host's innate and adaptive immunity, the inflammatory response with cytokine release, the interaction with the human leukocyte antigen (HLA) system and the response to conditioning chemotherapy, and pre- and post-transplant immunosuppression. According to the time of progression, it is classified into hyperacute GVHD (first week after transplant), acute GVHD (7-100 days after transplant), and chronic GVHD (100 days to 3 years after transplant).[2]

- **Multiple organ failure** (MOF): failure of 2 or more organs or systems (respiratory, cardiovascular, hematological, hepatic, and renal systems, among others). The higher the number of organs involved, the higher the patient's mortality rate. The dysfunction of each organ or system is defined based on clinical and lab parameters that show their function.[18]

- **Febrile neutropenia**: development of fever in a patient with neutropenia, defined as oral temperature ≥ 38 °C (rectal measurement is contraindicated) and neutrophil count < 500 cells/mm^3 or < 1000 cells/mm^3 with a decline between two consecutive counts.[4]

- **Respiratory failure**: according to the Pediatric Acute Lung Injury Consensus Conference (PALICC), it is defined based on the oxygenation index, which is calculated as the quotient of the fraction of inspired oxygen (in percent) and partial pressure of oxygen in blood (mmHg) multiplied by the mean airway pressure. Based on this index, a value ≥ 6 is defined as moderate to severe failure.[17]

- **Myeloablative treatment**: defined as pre-transplant chemotherapy consisting of a regimen generally used for autologous transplants and applicable to other transplants depending on the underlying diagnosis, leading to bone marrow ablation.[8]

- *Reduced-intensity conditioning* (RIC): pre-transplant reduced-intensity conditioning regimen not tending towards bone marrow ablation.[8]