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Variables Affecting Mortality in Hematopoietic Stem Cell Transplanted Patients Requiring Admission to Pediatric Intensive Care

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Abstract

Introduction: Mortality is high for pediatric patients undergoing allogeneic Hematopoietic Stem Cell Transplantation (HSCT) who require admission to the Pediatric Intensive Care Unit (PICU).

Objective: The primary objective of this study was to describe and analyze risk factors for PICU admission in patients undergoing allogeneic HSCT and to investigate the factors associated with a poorer prognosis. Secondary objectives were to determine clinical characteristics, reasons for admission, and evolution of admitted patients, and evolution parameters associated with a poor prognosis.

Design: Observational, retrospective, descriptive, analytical study. Between 2008 and 2017, 132 allogeneic HSCT interventions were performed at Hospital de Santa Creu i Sant Pau (Barcelona) in 112 patients, 54 (48.2%) of whom (accounting for 68 transplants) required PICU admission. Data was evaluated on patient demographics, HSCT, and health status on PICU admission and during PICU stay.

Results: The overall actuarial survival rate was 41.7% at 12 years. Of the 54 patients who required PICU admission, the main reasons were respiratory failure (41.1%), followed by neurological (22.7%) or hemodynamic (21.2%) disorders, and kidney (6.0%) or liver (6.0%) failure. Admission was associated with an infectious process in 71.2% of cases.

On PICU admission, the univariate analysis showed significantly increased weight (p=0.007), creatinine (p=0.007), bilirubin (p<0.001), and international normalized ratio (p<0.001) values, and a significantly decreased glomerular filtration rate (p<0.001). Lower survival was associated with the O-PRISM (p=0.018), pSOFA (p=0.018), PELOD (p=0.010), and PIM-3 (p=0.015) prognostic scale scores, the SatO2/FiO2 ratio (p=0.004), and the need for invasive (p=0.010) or non-invasive (p=0.021) mechanical ventilation. Greater mortality was associated with vasoactive support (p=0.01), inotropic support (p=0.03), and maximum acute kidney injury (KDIGO-3) (p=0.036). Significant in the multivariate analysis for PICU admission were the O-PRISM (OR=8.162, p=0.004) and KDIGO-3 (OR=6.008, p=0.036) scores.

During PICU stay, significantly higher mortality was associated with the need for mechanical ventilation (invasive, p<0.001; non-invasive, p=0.001; high-frequency, p<0.001) and administration of inhaled nitric oxide (p<0.001). A poor prognosis was associated with pneumonia (p=0.036), acute respiratory distress syndrome (p<0.001), pneumothorax (p=0.028), pulmonary hemorrhage (p=0.008), cardiac massage (p<0.001), inotropic/vasoactive support (p<0.001), septic shock (p=0.008), hemorrhagic shock (p<0.001), and arrhythmias (p<0.001). Acute kidney injury (p=0.002), dialysis (p<0.001), a low Glasgow Coma Scale (GCS) score (p<0.001), and cerebral hemorrhaging (p=0.028) were associated with increased mortality. Significant in the multivariate analysis for PICU stay were infection (OR=9.284, p=0.017) and a low GCS score (OR=10.704, p=0.001).

Conclusion: Our findings can help identify which allogeneic HSCT patients have a higher risk of mortality on PICU admission and during PICU stay. Identifying patients at greater risk can contribute to slowing the progression of critical illness while still reversible, and even to adjusting procedures and avoiding medication overuse during PICU stay.

Keywords: Stem cell transplantation; Pediatric intensive Care; Prognostic factors

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Introduction

Hematopoietic Stem Cell Transplantation (HSCT) is a highly specialized medical procedure in which hematopoietic precursor cells are administered to a recipient patient with the intention of repopulating and replacing their hematopoietic system. Worldwide each year, HSCT offers disease-free survival potential to some 2,500 children with malignant and non-malignant pathologies [1]. However, between 17% and 40% of patients require admission to the Pediatric Intensive Care Unit (PICU) due to complications [2,3]. In the last decade, several studies have been conducted of HSCT patients admitted to the PICU with the aim of identifying the main risk factors and their predictive values [4-7].

The primary objective of this study was to describe and analyze risk factors for PICU admission in patients undergoing allogeneic HSCT and to investigate the factors associated with a poorer prognosis. Secondary objectives were to determine clinical characteristics, reasons for admission, and evolution of admitted patients, and evolution parameters associated with a poorer prognosis.

Methods

We designed an observational, retrospective, descriptive, analytical study, based on reviewing 11 years of medical records for all pediatric patients who underwent allogeneic HSCT in Hospital Santa Creu i Sant Pau (HSCSP; Barcelona) and who required admission to the PICU. Between 2008 and 2017, 132 allogeneic HSCT interventions were performed in 112 patients, 54 (48.2%) of whom required PICU admission. Patients admitted after undergoing surgery or any other intervention were excluded from the study. Data was evaluated on patient demographics, HSCT, and health status on PICU admission and during PICU stay. Table 1 reports demographic and transplant-related characteristics of the 54 patients admitted to the PICU who underwent 68 transplants in total. By sex, 30 were boys (55.6%) and 24 (44.4%) were girls, mean age at diagnosis was 3.12 years (1 month to 15.84 years), and mean age at transplantation was 5.47 years (3 months to 19.32 years).

Results

Overall survival at 12 years was 41.7%. Almost half (48.2%, n=54) of the patients who underwent HSCT required PICU admission (on 68 occasions). Reasons for PICU admission, associated with an infectious process in 71.2% of cases, were respiratory failure (41.1%), followed by neurological disorders (22.7%), hemodynamic disorders (21.2%), kidney failure (6.0%), and liver failure (6.0%). The univariate analysis revealed that patients on PICU admission showed significantly increased weight (p=0.007), creatinine (p=0.007), bilirubin (p<0.001), and International Normalized Ratio (INR) (p<0.001) values, and a significantly reduced Glomerular Filtration Rate (GFR) according to the Schwartz formula (p<0.001).

Table 2 summarizes scores for various prognostic scales on PICU admission. Mean prognostic scale scores were significantly lower for survivors than for non-survivors: Oncological Pediatric Risk of Mortality (O-PRISM) (p=0.018), Pediatric Sequential Organ Failure Assessment (pSOFA) (p=0.018), Pediatric Organ Logistic Dysfunction (PELOD) (p=0.010), and Pediatric Index of Mortality-3 (PIM-3) (p=0.015).

Table 3 compares PICU admission survivors and non-survivors in terms of demographic and analytical variables, transplant-related characteristics, and complications. Respiratory variables associated with lower survival were the oxygen saturation/fraction of inspired oxygen ($tSatO_2/FiO_2$) ratio (p=0.004) and the need for invasive (p=0.010) or non-invasive (p=0.021) mechanical ventilation. Other variables associated with mortality were the need for vasoactive support (p=0.01) and maximum Acute Kidney Injury (AKI), i.e., Kidney Disease Improving Global Outcomes (KDIGO) stage 3 (p=0.036).

Table 1: Demographic and transplant-related characteristics of 54 patients (68 HSCT interventions) admitted to PICU.

Age	Median	3.12 y
	Range	1 m - 15.84 y
Sex	Male	30 (55.6%)
	Female	24 (44.4%)
Underlying disease	Malignant Hematologic Solid tumor	34 (63%) 33 1
	Non-malignant Primary immunodeficiency Aplasia Hemoglobinopathies Inborn errors of metabolism	20 (37%) 10 3 2 5
Transplant type	Unrelated HLA matched HLA mismatched	49 (72.1%) 36 13
	Related HLA matched HLA mismatched or haploidentical	19 (27.9%) 6 13
Pre-processing	Non-myeloablative Myeloablative None	54 13 1
HSCT complications	Mucositis Grade I-II Grade III-IV	48 (70.5%) 21 27
	Graft syndrome	23 (33.8%)
	Veno-occlusive liver disease Mild-moderate Severe-very severe	14 (20.6%) 9 5
	Hemorrhagic cystitis Grade I-II Grade III Grade IV	14 (20.6%) 3 5 6
	Thrombotic microangiopathy	6 (8.8%)
	Reversible posterior leukoencephalopathy	2 (2.9%)
	Acute graft-versus-host disease Grade I-II Grade III-IV	46 (67.2%) 15 32
HSCT results	Total chimerism Partial chimerism Neutrophil engraftment	49 (72%) 6 (8.8%) Mean (SD) 18.61 (6.90) days

Table 2: Prognostic scale scores on PICU admission.

pSOFA		**PIM-3 (%)**	
Mean (SD)	5.67 (3.20)	Mean (SD)	14.81 (13.90)
Median (IQR)	5.00 (3.00-8.00)	Median (IQR)	10.15% (7.7-17.0)
PELOD		**PELOD-2**	
Mean (SD)	12.89 (9.14)	Mean (SD)	5.55 (3.04)
Median (IQR)	11.0 (9-20.25)	Median (IQR)	5.00 (4-7)
PRISM-3		**O-PRISM**	
Mean (SD)	16.17 (5.93)	Mean (SD)	12.97 (7.98)
Median (IQR)	17.00 (13-20)	Median (IQR)	11.5 (7-17)

IQR: Interquartile Range; O-PRISM: Oncological Pediatric Risk of Mortality; PELOD: Pediatric Logistic Organ Dysfunction; PIM: Pediatric Index of Mortality; PRISM: Pediatric Risk of Mortality; pSOFA: Pediatric Sequential Organ Failure Assessment Score; SD: Standard Deviation

Table 3: PICU survivors and non-survivors: Comparison of demographic and analytical variables, transplant-related characteristics, and complications.

Variable		PICU survivors	PICU non-survivors	p
Demographics	Age on HSCT (median, y)	9.07	6.45	0.108
	Weight (median, kg)	34.15	25.45	0.370
	Weight gain difference on PICU admission (median, kg)	0.77	1.95	**0.020**
Baseline analytics	Creatinine (median, umol/L)	45	41	0.075
	GFR (median, mL/min/1.73m^2)	105.2	106.36	0.755
	INR (median)	1.05	1.08	0.436
	Bilirubin (median, umol/L)	9	6	0.602
Transplant characteristics	HLA mismatched	17	23	0.391
	Haploidentical	5	6	0.733
	Myeloablative	2	11	0.060
HSCT complications	Acute GVHD Grade I-II Grade III-IV	13 3 10	26 9 17	0.256 0.714 0.714
	Hemorrhagic cystitis	8	6	0.102
	Thrombotic microangiopathy	2	4	1.00
	Graft syndrome	12	11	0.234
	Reversible posterior leukoencephalopathy	0	2	0.518
	Veno-occlusive liver disease Mild-moderate Severe-very severe	6 3 3	7 5 2	0.536 0.592 0.592

GFR: Glomerular Filtration Rate; GVHD: Graft-Versus-Host Disease; HLA: Human Leukocyte Antigen; HSCT: Hematopoietic Stem Cell Transplant; INR: International Normalized Ratio

Table 4 and 5 compare survivors and non-survivors on PICU admission and during PICU stay, respectively.

Significant in the multivariate analysis on PICU admission were O-PRISM (OR=8.162, p=0.004) and KDIGO-3 (OR=6.008, p=0.036).

The univariate analysis associated significantly higher mortality during PICU stay with the need for mechanical ventilation (invasive, p<0.001; non-invasive, p=0.001; high-frequency, p<0.001) and inhaled Nitric Oxide (NO) administration (p<0.001). A poorer prognosis was associated with pneumonia (p=0.036), Acute Respiratory Distress Syndrome (ARDS) (p<0.001), pneumothorax (p=0.028), and pulmonary hemorrhage (p=0.008). Also associated with a poorer prognosis were cardiac massage (p<0.001), inotropic/vasoactive support (p<0.001), septic shock (p=0.008), hemorrhagic shock (p<0.001), and arrhythmias (p<0.001), as well as AKI (p=0.002) and dialysis (p<0.001). A low Glasgow Coma Scale (GCS) score (p<0.001) and cerebral hemorrhaging (p=0.028) were associated with increased mortality.

Significant in the multivariate analysis were infection during PICU stay (OR=9.284, p=0.017) and a low GCS score (OR=10.704, p=0.001).

Of the 54 patients admitted to the PICU, 38 were discharged as survivors (70.4%).

Statistical analysis

Categorical variables are reported as numbers and percentages, and quantitative variables as mean and Standard Deviation (SD) values. For ordinal variables and quantitative variables that clearly deviated from normality, median and Interquartile Range (IQR) values are reported. Categorical variables were compared by means of contingency tables, and the chi-square or Fisher's exact test was used for inferential testing. Analysis of Variance (ANOVA) was implemented for quantitative variables, and ordinal variables were tested using the nonparametric Mann-Whitney U test. Statistical significance was set to 0.05 and the statistical analysis was performed with IBM-SPSS software (V22.2).

Discussion

Pediatric patients undergoing HSCT may develop complications requiring admission to the PICU. In our hospital over 11 years, 132 allogeneic HSCT interventions were performed in 112 patients, composed of 30 boys and 24 girls, with a mean age of 5.47 years at transplantation. Of that cohort, 54 (48.2%) required PICU admission, a percentage broadly similar to the 17% to 40% reported in the literature [2,8].

We found that age at transplantation influenced prognosis, which was poorer for older patients, although not to a significant degree. Chima et al. [9] reported a higher mean age for non-survivors than survivors, although the difference was also not statistically significant. Overall actuarial survival of our series of patients was 41.7%, for an average follow-up of 12.35 years. The literature indicates that survival has improved, from 15% in the 1990s to 70% in 2020 [11], probably due to improved conditioning and inoculum handling, early infection detection, and early treatment. Study heterogeneity needs to be taken into account when comparing survival rates, however, as some series include autologous transplants, while others do not rate transfers to other hospitals for end-of-life care as deaths [5,8,10]. In our hospital, all patients requiring treatment adjustments remain in the PICU as long as necessary, whatever the outcome.

We found significant weight gain in patients on PICU admission, and also found that weight gain was greater for survivors. This would suggest that weight gain before PICU admission may act as a protective factor, and may be related to a better response to depletion treatment.

In transplanted patients with ARDS, Zinter et al. [12] related a

Table 4: PICU admission comparison between survivors and non-survivors in terms of key variables.

Variable		PICU survivors	PICU non-survivors	p
Prognostic scale	pSOFA	6.50	4.50	**0.018**
	PELOD	13	10	**0.010**
	PELOD-2	6.00	4.50	0.169
	O-PRISM	14.50	10	**0.018**
	PIM-3	13.00	8.75	**0.015**
	PRISM-3	18.00	14.50	0.075
Respiratory	$SatO_2/FiO_2$ (median)	215	346	**0.004**
	Non-invasive mechanical ventilation	10	3	**0.010**
	Invasive mechanical ventilation	9	3	**0.021**
	High-flow cannulas	16	14	0.135
	High-frequency ventilation	2	0	0.176
	Inhaled NO	3	0	0.072
Haemodynamic	CVP (median)	9.50	9.00	0.42
	$SatVO_2$ (median)	67.90	70.25	0.91
	Vasoactive support	10	3	**0.01**
	Inotropic score (median)	34.50	5.00	**0.003**
	Arterial hypertension	25	15	0.445
Kidney	AKI KDIGO-1 KDIGO-2 KDIGO-3	11 3 2 6	11 8 2 1	0.435 0.331 1.00 **0.036**
	Dialysis	4	1	0.154
	Furosemide	17	17	0.58
Metabolic	Insulin	5	4	0.47
Neurological	GCS alteration	15	15	0.32
	GCS (median)	14	15	0.27
	Seizures	3	8	0.33
Infection	Infection	22	24	0.278
	Virus	17	15	0.135
	Bacteria	9	9	0.577
	Fungi	4	3	0.443
	Septic shock	5	3	0.269

AKI: Acute Kidney Injury; CVP: Central Venous Pressure; GCS: Glasgow Coma Scale; NO: Nitric Oxide; O-PRISM: Oncological Pediatric Risk of Mortality; PELOD: Pediatric Logistic Organ Dysfunction; PIM: Pediatric Index of Mortality; PRISM: Pediatric Risk of Mortality; pSOFA: Pediatric Sequential Organ Failure Assessment; $SatO_2/FiO_2$: Arterial Oxygen Saturation/Oxygen Concentration Ratio; SatVO2: Central Venous Oxygen Saturation; KDIGO: Kidney Disease Improving Global Outcomes

positive fluid balance on the third day of admission with increased mortality. As far as we could determine, however, the literature has no studies that analyze weight gain and positive fluid balance on PICU admission.

Prognostic scores for our patients on PICU admission indicated great severity, and the non-survivors had significantly higher scores than the survivors. Studies that have analyzed prognostic scores on PICU admission include Schneider et al. [13], who showed that O-PRISM scores above 10 were associated with increased mortality, Balit et al. [8], who found statistically different PELOD and PRISM-3 scores for non-survivors (mean PELOD and PRISM-3 values of 11 and 12, respectively) compared to survivors, and Zinter-Logan et al. [11], who reported a mean PRISM III score of 9. The PIM-3 score for our patients was associated with an estimated mortality of 14.81%. Note, however, that PIM-3 underestimates mortality for this type of patient, as demonstrated by studies that report poor PIM-3 score performance in predicting mortality in transplanted patients [6,14].

In the univariate analysis, clinical and analytical characteristics were found to be significantly related to increased mortality. PICU admission respiratory variables associated with a significant increase in mortality were the $SatO_2/FiO_2$ ratio, the need for invasive mechanical ventilation, and the need for non-invasive mechanical ventilation. The main respiratory conditions experienced by our patients were pulmonary oedema without myocardial dysfunction, followed by ARDS, and pneumonia. Pneumonia, ARDS, pneumothorax, and pulmonary hemorrhage, but not non-cardiogenic pulmonary oedema, modified the mortality risk. Rowan et al. [3] reported mortality of 40% to 77% for a cohort of 222 patients who met ARDS criteria, and no difference in the $SatO_2/FiO_2$ ratio between survivors and non-survivors. ARDS incidence of 33% in our patients was associated with 85% mortality and, in contrast with Rowan et al. [3], we found significant differences in the $SatO_2/FiO_2$

Table 5: PICU stay comparison between survivors and non-survivors in terms of key variables.

Variable		PICU survivors	PICU non-survivors	p
Respiratory	Invasive mechanical ventilation	26	7	**<0.001**
	Non-invasive mechanical ventilation	19	10	**0.001**
	High-flow cannulas	15	17	0.619
	High-frequency ventilation	15	1	**<0.001**
	Inhaled NO	11	1	**<0.001**
	$SatO_2/FiO_2$ (median)	89.5	323	**0.004**
	Days on respiratory support (median)	17.5	5	**0.005**
Respiratory disorders	Pneumonia	13	8	**0.036**
	ARDS	19	3	**<0.001**
	Bronchiolitis obliterans	6	3	0.153
	Pulmonary edema	13	17	1.00
	Pneumothorax	4	0	**0.028**
	Pulmonary hemorrhage	7	1	**0.008**
Hemodynamic	Cardiac massage	13	0	**<0.001**
	Vasoactive/inotropic support	23	6	**<0.001**
	Inotropic score (median)	60.00	16.00	0.131
	Days on inotropic support (median)	22	7	0.101
Hemodynamic disorders	Cardiogenic shock	5	2	0.125
	Septic shock	11	4	**0.008**
	Hemorrhagic shock	16	1	**<0.001**
	Pericardial effusion	5	7	1.00
	Arrhythmias	14	3	**<0.001**
Kidney	AKI KDIGO-1 KDIGO-2 KDIGO-3	24 1 4 19	18 5 6 7	**0.002** 0.068 0.281 **0.011**
	Dialysis	19	8	**<0.001**
	Days on dialysis	13	16	0.979
Metabolic	Insulin	16	11	**0.026**
	Days on insulin (median)	11.5	3	**0.05**
Neurological	GCS (median)	3	14	**<0.001**
	CNS infection	7	4	0.182
	Seizures	5	7	1.00
	Convulsive status	2	2	1.00
	Cerebral hemorrhage	4	0	**0.028**
	Reversible posterior leukoencephalopathy	2	4	1.00
Infection	Infection	28	30	**0.017**
	Virus	27	21	**<0.001**
	Bacteria	20	14	**0.007**
	Fungi	14	7	**0.008**
	Septic shock	14	4	0.001

AKI: Acute Kidney Injury; ARDS: Acute Respiratory Distress Syndrome; CNS: Central Nervous System; GCS: Glasgow Coma Scale; NO: Nitric Oxide; $SatO_2/FiO_2$: Arterial Oxygen Saturation/Oxygen Concentration Ratio; KDIGO: Kidney Disease Improving Global Outcomes

ratio between survivors and non-survivors. Intubation was required in 50% of our PICU admissions and was associated with a survival rate of 61%. The literature reports similar survival rates (63% to 75%) when mechanical ventilation was necessary, and mortality rates of 60.4% and 68.8% for intubated patients [3,15,16].

The need for vasoactive or inotropic support, whether on PICU admission or during PICU stay, was associated with significantly increased mortality in our patients. Previous studies have reported hemodynamic instability on PICU admission to be a risk factor for increased mortality [17]. Balit et al. [8] reported that 50% of the patients in their series required vasoactive or inotropic support on PICU admission and associated this with a significant increase in mortality.

The incidence of post-HSCT kidney failure has been reported as ranging between 0% and 60% depending on the series [18,19]. The main contributing factors are the type of chemotherapy, fluid overload, and activation of the systemic inflammatory cascade by the procedure [20,21]. The extent of kidney damage, and especially grade 3 AKI, has been associated with transplant-related mortality [22,23]. For our patients, we found that maximum AKI (KDIGO-3) on PICU admission significantly increased mortality. Strategies for early diagnosis of initial AKI stages are essential to minimizing kidney toxicity and improving prognosis. One such strategy is cystatin C monitoring, as it provides important information regarding vascular, hemodynamic, or toxic injury in PICU admissions before oliguria develops [24,25]. Cystatin C has been reported to be a better marker than creatinine for detecting AKI in critically ill children [26].

The reported incidence of Central Nervous System (CNS) disorders associated with HSCT varies widely, from 1.6% to 59% [27,28]. In our series, 15 patients (13.39%) admitted to the PICU presented a neurological complication, mainly an altered level of consciousness or seizures. Of the patients admitted for other reasons, 31 (47%) experienced a GCS score below 8, and a low GCS score was associated with a significant increase in mortality risk in both our univariate and multivariate studies. Of other neurological complications, we especially highlight cerebral hemorrhage, due to its seriousness; none of the 4 patients in our series who experienced cerebral hemorrhaging survived. Thus, although the number of patients was low, cerebral hemorrhage was significantly associated with increased mortality in the univariate analysis.

Cerebral vascular complications, which occur in 3.8% to 8.8% of patients who undergo HSCT, most often manifest in the pre-implantation or early post-implantation period [29]. The most common bleeding complications are subdural hematomas, often associated with refractory thrombocytopenia [30], and intraparenchymal hemorrhaging, associated with severe Graft-Versus-Host Disease (GVHD) [31]. Another neurological complication is Posterior Reversible Encephalopathy Syndrome (PRES), which accounts for around 75% of neurological PICU admissions [32]. In our series, of 6 patients who experienced PRES, 4 recovered completely at the neurological level on withdrawal of the triggering factor, and 2 died due to other causes.

CNS infections are complications related to immunosuppression, GVHD, or both. The most common organisms are *Aspergillus*, *Candida*, *Toxoplasma gondii*, *Cytomegalovirus* (CMV), Varicella-zoster virus, Human Herpesvirus (HHV) types 1 and 6, adenovirus, John Cunningham virus, and *Listeria* or tuberculosis bacterial infections [33]. In our series, in patients undergoing haploidentical transplantation with T-lymphocyte depletion, the dominant pathogen was HHV-6, with the typical clinical manifestations of anterograde amnesia, temperature control disorders, alterations in mental status, headache, and altered consciousness. Other pathogens isolated in the CNS of our patients were Epstein-Barr virus (EBV), CMV, and toxoplasma.

Opportunistic CNS infections are often fatal, so any suggestive neurological symptoms should be treated early on [34]. The clinical success of HSCT is influenced by the morbidity associated with viral, bacterial, and fungal infections. The most frequent post-transplant viral infections are CMV (22% to 24%), EBV (22% to 32%), adenovirus (25% to 50.4%), and HHV-6 (around 30%) [35]. Bacteremia, with an incidence of 20% to 30%, is frequent during HSCT, especially early on [36]. In most studies, gram-positive bacteria have been identified more frequently than gram-negative bacteria, although rates of resistant enterococci and gram-negative bacteria, associated with higher mortality, are increasing [37].

In relation to infections in our series, viral infection was detected in 87.9% of our patients, mainly CMV, followed by HHV-6, and EBV. The incidence of bacterial infections (especially those caused by gram-negative bacilli) was 51.5%, and of fungal infections was 31.8% (most frequently yeast fungi, 57.1%), while a single patient presented a parasitic infection. In the univariate analysis, viral, bacterial, and fungal infections were significantly associated with increased mortality, corroborating the results of other studies [38], while, according to the multivariate analysis, viral infection increased mortality ninefold. Infectious complications in transplant patients requiring PICU admission have been reported to increase mortality, stay, and duration of mechanical ventilation, so early diagnosis and treatment are crucial for these patients [15].

Regarding limitations of this study, as a single-center retrospective study investigating only patients undergoing allogeneic HSCT, our results cannot be generalized to all hemato-oncology patients. Further studies are therefore needed with larger cohorts of patients from multiple centers.

In conclusion, in this study we investigated mortality risk for allogeneic HSCT patients on PICU admission and during PICU stay. For PICU admission, we found that O-PRISM, pSOFA, PELOD, and PIM-3 scores predicted patient evolution, and that a low $SatO_2/FiO_2$ ratio, mechanical ventilation, vasoactive support, and AKI (KDIGO-3) were associated with significantly increased mortality. As for PICU stay, we found that mechanical ventilation, NO administration, inotropic/vasoactive support, AKI, a low GCS score, and infection (especially viral infection) were associated with significantly increased mortality.

Our findings should help identify HSCT patients at greater risk of complications, and also contribute both to slowing the progression of critical illness while still reversible and even to adjusting procedures and avoiding medication overuse during PICU stay.

Ethical Considerations

All patients and/or family members granted their informed consent in writing. The study complies with the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee.

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