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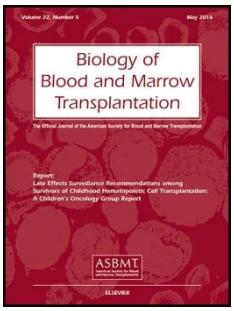

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Author: Marta Pillon, Angela Amigoni, Annaelena Contin, Manuela Cattelan, Elisa Carraro, Emiliana Campagnano, Manuela Tumino, Elisabetta Calore, Antonio Marzollo, Chiara Mainardi, Maria Paola Boaro, Marta Nizzero, Andrea Pettenazzo, Giuseppe Basso, Chiara Messina

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Risk factors and outcomes related to Pediatric Intensive Care Unit admission after Hematopoietic Stem Cell Transplantation: a single centre experience

Pillon Marta*, MD,1, Amigoni Angela*, MD,2, Contin Annaelena, MD,1, Cattelan Manuela, PhD,3, Carraro Elisa, BS,1, Campagnano Emiliana, MD,2, Tumino Manuela, MD,1, Calore Elisabetta, MD,1, Marzollo Antonio, MD,1, Mainardi Chiara, MD,1, Boaro Maria Paola, MD,1, Nizzero Marta, MD, 1, Pettenazzo Andrea, MD,2, Basso Giuseppe, MD,1, Messina Chiara, MD,1.

1. Pediatric Hematology and Oncology, Department of Woman's and Child's Health, University-Hospital of Padua

2. Pediatric Intensive Care Unit, Department of Woman's and Child's Health, University-Hospital of Padua

3. Department of Statistical Sciences, University of Padua

*first co-authors

Corresponding author:

Marta Pillon
Pediatric Hematology and Oncology, Department of Women's and Children's Health, University of Padua, Via Giustiniani 3, Padua 35128, Italy.
Phone: +39-049 8213579 ; Fax: +39-049 8213510;
e-mail : marta.pillon@unipd.it.

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Bone marrow transplantation; hematopoietic stem cell transplantation; mortality; outcome; pediatric intensive care unit; risk factors.

Abstract

To describe incidence, causes and outcomes related to pediatric intensive care unit (PICU) admission for patients undergoing hematopoietic stem cell transplantation (HSCT). To investigate risk factors predisposing to PICU admission and prognostic factors in terms of patient survival. From October 1998 to April 2015, 496 children and young adults (0-23 years) underwent transplantation in the HSCT Unit. Among them, 70 (14.1%) were admitted to PICU. The 3-year cumulative incidence of PICU admission was 14.3%. The main causes of PICU admission were: respiratory failure (36%), multiple organ failure (16%) and septic shock (13%). The overall 90-day cumulative probability of survival after PICU admission was 34.3% (95% CI 24.8-47.4). In multivariate analysis, risk factors predisposing to PICU admission were: allogeneic HSCT (vs autologous HSCT, p=0.030) and second or third HSCT (p=0.018). Characteristics significantly associated with mortality were: mismatched HSCT (p=0.011), relapse of underlying disease before PICU admission (p<0.001), acute respiratory distress syndrome at admission (p=0.012), hepatic failure at admission (p=0.021), need for invasive ventilation during PICU course (p<0.001). Our data indicate which patients have a high risk for PICU admission after HSCT and for dismal outcomes after PICU stay. These findings may provide support for the clinical decision-making process on the opportunity of PICU admission for severely compromised patients after HSCT.

Highlights

- We studied a cohort of 496 children undergoing HSCT in a single center.

- The 3-year cumulative incidence of PICU admission was 14.3%.

- Risk factors for PICU admission were allogeneic HSCT and second or third HSCT.

- 90-day probability of survival after PICU admission for HSCT was 34.3%.

- Relapse, mismatched HSCT, lung or hepatic failure were associated with mortality.

Introduction

Hematopoietic stem cell transplantation (HSCT) represents the only viable treatment option for selected children with malignant and non malignant disorders, even though this procedure may lead to severe complications often requiring admission to the pediatric intensive care unit (PICU). However, undergoing HSCT is confirmed to be a risk factor for mortality amongst this subset of patients (1, 2). Recent studies have reported that outcomes for these patients have improved over the course of years due to PICU technical advances (e.g. non invasive ventilation [NIV] and high flow oxygen therapy [HFOT]) and to the amelioration of supportive treatment during HSCT (1, 3-6). Nevertheless, the mortality rate is still high, especially when invasive ventilation (IV) and continuous renal replacement therapy (CRRT) are needed and many ethical and end-of-life challenges regarding the appropriateness of using intensive care resources for this population exist (5-8). Data regarding outcomes and risk factors associated with mortality in PICU are needed in order to establish the optimal clinical management of severely compromised patients after HSCT. The aim of our study was to describe incidence, causes and outcomes related to PICU admission of patients undergoing transplantation in the HSCT Unit of University-Hospital of Padua. We investigated risk factors predisposing to PICU admission and prognostic factors associated with mortality in patients transferred to PICU.

Materials and Methods

Design of the study and population. We retrospectively reviewed the clinical records of all patients affected by oncologic and hematologic disorders undergoing HSCT in the pediatric HSCT Unit of University-Hospital of Padua, between October 1998 and April 2015. According to our institutional protocol, initial intensive supportive measures were established in the HSCT Unit: non invasive monitoring (pulse oximetry and electrocardiogram), 6-hourly fluid balance monitoring, central venous pressure determination, HFOT, inotropic treatment with dopamine and continuous morphine infusion. PICU admission criteria were the need for invasive or more frequent monitoring (such as

continuous invasive arterial pressure monitoring), for positive pressure ventilation, or for a second inotropic drug. We considered all of the patients admitted to our departmental PICU after the initiation of conditioning for HSCT, with the following exclusion criteria: PICU admission for post-operative monitoring or procedural sedation and planned PICU admission for stem cell infusion in patients at risk (i.e. for age less than 1 year or affected by severe congenital immunodeficiency). In accordance with the Declaration of Helsinki, parents and children/adolescents, when able to understand, were asked to sign the informed consent for transplant procedure, data collection and analysis.

Data collection. Data were collected from the HSCT Unit database and from the TIPnet database (www.tipnet.cineca.it) of our PICU and for each patient we considered: sex, age at HSCT, underlying disease, date and number of HSCT, status of disease at HSCT, total body irradiation (TBI), type of donor, relapse, date of death or of last follow-up.

As for children admitted to PICU, we gathered further data about HSCT including: donor/recipient human leukocyte antigen (HLA) matching; occurrence of acute graft versus host disease (aGvHD) (9) or chronic GVHD (cGvHD); engraftment for polymorphonuclears and platelets; veno-occlusive disease (VOD)(10). In addition, data collected at PICU admission were: date and cause of PICU admission; Pediatric Index of Mortality Score 3 (PIM 3) (11); PaO2/FiO2 ratio; presence of fluid overload (FO) (12); presence of infections or viral reactivations; use of HFOT, dopamine administration before PICU admission. Data collected at admission or anytime during PICU stay included the presence of: pediatric acute respiratory distress syndrome (PARDS) (13), septic shock (14), acute kidney injury (AKI) with KDIGO staging (15), hepatic failure, or multiple organ failure (MOF) defined as the involvement of >2 organs. Regarding PICU stay, the following data were recorded: need for NIV, HFOT, IV, high frequency oscillatory ventilation (HFOV), inhaled nitric oxide, external cardiac massage, or CRRT; maximum number of vasoactive amines simultaneously administered; occurrence of aspergillosis; date of discharge; cause of death.

Definitions. We classified the underlying disease in two groups: hematological disorders (acute lymphoblastic or myeloid leukemia, lymphoma, other hematological malignancies, non malignant disorders) and solid tumors. The status of disease at the time of stem cells infusion was classified as "complete remission" (CR) when the disease was in morphologic, instrumental or molecular CR; as "presence of disease" in the other cases. Donor/recipient were considered "HLA mismatched" if < 5/6 for bone marrow transplants and peripheral blood stem cell transplants, and < 4/6 for cord blood transplants; the HLA analysis was based on high resolution genotyping. The day of the stem cells infusion was conventionally considered "day 0". Neutrophil engraftment was defined as a neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days, platelet engraftment as a platelet count $\geq 50 \times 10^9$/L for 7 consecutive days independently of platelet transfusions. The definition of "organ failure" was based on the criteria of the TIPnet database, approved by a national consensus conference (available at www.tipnet.cineca.it).

Statistical analysis. All statistical analyses were performed using the R statistical software, release 3.2.3 (16). First, characteristics of patients requiring and not requiring PICU admission were compared: all patients entered the study at the first day of the conditioning regimen for their first HSCT. Univariate analysis of risk factors for PICU admission was conducted using Pearson χ^2 test, Fisher exact test or Mann Whitney U test. Gray's test was applied to compare the 3-year cumulative incidence of PICU admission in allogeneic and autologous HSCT. The competing-risks regression model of Fine and Gray was applied in the multivariate analysis (17). Then, survival probability and risk factors for patients admitted to PICU were investigated: the Kaplan-Meier estimate of the 90-day cumulative probability of survival after PICU admission was calculated and the 95% confidence intervals (CI) were computed using the Greenwood formula. The log-rank test was used to assess differences in the characteristics of patients before or at the time of PICU admission. The risk factors were then included in a multivariate analysis using the Cox proportional hazards model. The independence between parameters collected during PICU course and the state (dead/alive) of patients 90 days after PICU admission was evaluated through the Pearson χ^2 test and Fisher exact

test. A logistic regression model was used for the multivariate analysis of these variables. A p-value <0.05 was considered statistically significant.

Results

Incidence and causes of PICU admission. 496 patients were included in this study: 284 males (57.3%) and 212 females (42.7%). Among them, 465 received one HSCT, 29 patients two HSCT and 2 patients three HSCT, for a total of 529 HSCT procedures. The median age at the first transplant was 8.3 years (range 0.2-23.6 years). Overall, 70 patients were admitted to PICU: 60/465 (12.9%) after their first HSCT, 8/29 (27.6%) after their second HSCT, and 2/2 (100%) after their third transplant; the 3-year cumulative incidence of admission was 14.3% (95% CI: 11.1%-17.4%). Regarding patients admitted to PICU, 56/70 (80%) were admitted once, 14/70 (20%) patients required 2 or more admissions, for a total number of 92 PICU admissions. The number of HSCT performed and the number of PICU admissions per year are shown in Figure 1. Forty-six out of 70 patients (65.7%) were admitted to PICU within 3 months from their last HSCT. Median time from stem cell infusion to the first admission was 49 days, ranging from -6 days (two patients admitted during conditioning) to 3 years. All of the 7 children admitted later than 12 months after the HSCT were affected by cGVHD. The causes for the 92 PICU admissions are reported in Table 1. The median length of PICU stay was 7 days (range: 1-81 days).

Outcome of patients requiring PICU admission. Amongst the 70 children admitted to PICU, 30 (42.9%) died in the PICU during their first admission, after a median time of 10 days (range, 1-78 days). Sixteen more patients died after PICU discharge, but within 90 days from PICU admission: 8/16 (50%) were readmitted to PICU. The overall 90-day cumulative probability of survival after PICU admission was 34.3% (95% CI 24.8-47.4%). Thirteen more patients died during follow-up, but later than 90 days from PICU admission. Globally, 20 out of 59 patients had presence of the underlying disease at the time of death. The causes and the timing of death were reported in Table 2. Overall, at last follow-up, 11 out of 70 patients admitted to PICU (15.7%) were alive and in CR

from the underlying disease. In comparison, amongst the 426 patients not requiring PICU admission, 320 (75.1%) were alive at last follow up.

Risk factors associated with PICU admission. The results of the univariate and multivariate analysis of clinical features and transplant associated factors at first PICU admission are shown in Table 3. In univariate analysis, the characteristics associated with PICU admission were: underlying hematological disease, undergoing more than one HSCT, allogeneic HSCT and the use of TBI. In multivariate analysis, a 3.13-fold increased risk of being admitted to the PICU was observed for children undergoing allogeneic HSCT, as compared with autologous HSCT (CI: 1.115-8.80; p=0.03), and a 2.02-fold increased risk for patients undergoing second or third HSCT, as compared with first HSCT (CI: 1.13-3.60; p=0.018).

Risk factors associated with 90-day survival after PICU admission. In Table 4 are shown the univariate analysis' results on risk factors related to 90-day survival after PICU admission, considering HSCT features and clinical conditions at the time of admission. In Table 5 are reported the results of the univariate analysis concerning characteristics observed during PICU stay and associated with 90-day survival. In multivariate analysis, mismatched HSCT (HR 2.3, p=0.011), relapse before PICU admission (HR 4.76, p<0.001), PARDS (HR 2.51, p=0.012), and hepatic failure (HR 2.22, p=0.021) were risk factors observed at PICU admission significantly associated with a higher 90-day mortality (Table 6). Amongst the parameters analyzed during PICU stay, only the need for IV was confirmed to be a negative prognostic factor for 90-day PICU mortality (OR 16.98, p<0.001) in multivariate analysis (Table 6).

Discussion

In the last decades, improvements in the outcomes progressively widened the indications of HSCT to a large number of malignant and non-malignant diseases (18). However, many patients undergoing HSCT might develop complications requiring PICU admission. Despite the amelioration of intensive care support, the mortality rate of these patients remains high. The aim of

our study was to consider globally the clinical course of children requiring PICU admission after HSCT and to establish risk factors for mortality in order to help the clinician in deciding the best treatment approach for children experiencing organ failure after HSCT. In our cohort, the 3-year cumulative incidence of PICU admission after HSCT was 14.3%. This result lies in the lower range of published data that report a PICU admission rate between 10% and 40% (3-5, 7, 19-29). This result could be related to the stringent criteria we used to define PICU admission. The analysis of a well-defined population of severely affected patients resulted in a lower 90-day survival rate after PICU admission (34.3%) as compared with previous experiences (1, 3-5, 8, 19, 22, 30-32). Differently from other studies, we only included patients in life-threatening conditions and we excluded those admitted for postoperative monitoring or other non-urgent causes (4). Moreover, initial intensive supportive measures (such as HFOT and dopamine infusion) were started in the HSCT Unit, exclusively reserving PICU admission for patients requiring more invasive treatment or more frequent monitoring. Our data suggest that the use of initial intensive measures in the HSCT ward is feasible if a strong collaboration between the hematologist and the PICU physician is in place. Of note, in our series, the number of PICU admissions and the failure rate in PICU were stable over time, despite the increased number of HSCTs. This finding highlights that the progressive amelioration of invasive and non-invasive support therapies available in the PICU allows to cure patients in more critical conditions (1, 3, 5, 6, 28, 33, 34). We cannot compare the clinical severity of our population to other published series, because different mortality scores were reported (35, 36). In fact, each center adopts its own criteria of PICU admission that do not allow to standardize the timing of PICU transfer. At last follow-up, only 15.7% children requiring PICU admission after HSCT were alive as compared to 75.1% (320/426) of those not admitted to PICU. This result highlights the severe prognosis of transplanted children admitted to PICU, in line with PIM 3 score which considers transplanted children as a 'very high risk' population (11). For a better understanding of which transplanted patients categories were at higher risk for PICU admission and dismal outcomes, we analyzed separately risk factors for PICU admission and risk factors for

mortality. In multivariate analysis, we confirmed that allogeneic HSCT (vs autologous HSCT) and second or third HSCT were associated with a higher risk for PICU admission, as previously reported (3, 19-21). Conversely, these factors did not have a significant negative impact on survival, in disagreement with other studies (1, 4, 19). Relapse of underlying disease before PICU admission was the one factor showing the strongest association with unfavorable prognosis after PICU admission, with an almost 5-fold increase in mortality risk. In fact, all of the 13 patients relapsing before PICU admission died within one year after PICU admission: 10 (76.9 %) within 90 days, the other 3 died respectively 99, 133 and 267 days after PICU admission. In particular, 12 out of 46 children (26.1 %) that died within 90 days after PICU admission had presence of the underlying disease at the time of death, showing that relapse represents not only a major cause of death in this population, but also a failure of the transplant procedure, thus making any effort in terms of intensive support treatment vain. Other risk factors for death included mismatched donor HSCT, hepatic and respiratory failure at admission and need for IV during the PICU stay. These data are supported by previous findings and suggest that early hepatic or respiratory dysfunction may hamper the functions of other organs and lead to a more severe clinical course (1, 4, 5, 21, 23-27, 33, 34, 37, 38). The "gut-liver-lung axis of inflammation" hypothesis may provide the background to explain the clinical association between hepatic failure and idiopathic pulmonary syndrome-related death (39-41). In our series, children with PARDS either at admission or requiring IV displayed a very high mortality rate (91.7% and 88.9%, respectively), even higher than previously reported (3-7, 22, 31, 32). A possible explanation to it is the fact that patients with milder respiratory distress were treated with HFOT in the HSCT ward, whilst those admitted to PICU suffered from a more severe pulmonary dysfunction. This is in line with a recent study on PARDS in this population (35). Furthermore, our policy was to delay intubation and invasive ventilation as long as possible, employing this treatment option only in case of NIV failure. Surprisingly, the presence of aGvHD was not associated with dismal outcomes in our cohort (28, 29). The clear distinction provided so far of factors associated with PICU admission and factors associated with

mortality after PICU admission may prove particularly useful to the clinician. Risk factors for PICU admission may be important to inform patients and families when proposing the HSCT, whereas factors associated with mortality may be useful to decide whether the PICU admission might be not recommended (as for relapsed patients) and palliative care might be more suitable.

The limitations of our study are its single-centre design, its retrospective nature and its relatively small size. Nevertheless, its strong point is the wide set of variables considered, leading to significant conclusions about risk factors, clinical course and organ dysfunction patterns of transplanted patients requiring PICU admission. Moreover, our data contribute to the cumulative knowledge of this issue, offering the experience of our specific approach, based on admitting to PICU a selected population of severely affected patients.

Conclusions

In conclusion, our study describes outcomes and risk factors predicting dismal outcomes after PICU admission for transplanted patients (relapse of underlying disease, mismatched HSCT or lung or hepatic failure). These data are crucial in deciding whether a severely compromised patient may beneficiate more from either PICU admission or continuation of supportive and palliative care in the ward, thus providing better end-of-life care also through parental support. Our study supports the clinical decision-making and gives hematologists and intensivists new hints on how to cooperate even better, aiming to ameliorate outcomes of transplanted patients.

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Figure 1. The number of HSCT performed and the number of PICU admissions per year.

Table 1. Causes of Pediatric Intensive Care Unit admission (92 admissions)

Cause of PICU admission	n	%	Median time and range of PICU admission (days from last HSCT)

Respiratory failure	33	36	61 (6-1546)
Viral pneumonia (CMV, EBV, adenovirus, parainfluenza virus or combined)	9		39 (15-92)
Lobar pneumonia	5		15 (11-409)
Aspergillosis	5		185 (97-583)
Pediatric acute respiratory distress syndrome	4		117.5 (76-228)
Interstitial pneumonia	4		16.5 (16-61)
Bronchiolitis obliterans due to cGvHD	2		972 (398-1546)
Pulmonary oedema	1		463
Pneumotorax	1		270
Epiglottitis	1		6
Cellulitis	1		45
Organ failure	15	16	15 (3-403)
Multiple organ failure	13		16 (3-403)
Veno-occlusive disease	2		14.5 (14-15)
Septic shock	12	13	87.5 (1-494)
Neurological dysfunction	11	12	106 (-6-1132)
Coma	6		121.5 (43-1132)
Status epilepticus	4		69 (-6-134)
Posterior reversible encephalopathy syndrome	1		409
Acute kidney injury	9	10	23 (0-1102)
Hypovolemic shock	6	7	78.5 (39-208)
Hearth failure	5	5	166 (29-267)
Cardiogenic shock	2		201 (166-236)
Pericardial effusion	2		167 (67-267)
Ventricular arrhythmia with hypokalemia	1		29
Adverse drug reaction	1	1	47

Table 2. Causes of death, within 90 days after PICU admission and beyond 90 days after PICU admission.

Causes of death within 90 days after PICU admission (46 patients)	**n**	**%**	**Median time of death (range) (days after PICU admission)**
MOF	14	30.4	22.5 (2-78)
Relapse of underlying disease[a]	12	26.1	4 (2-63)
Respiratory failure	9	19.6	23 (6-45)
Septic shock	4	8.7	10 (4-28)
aGVHD or cGVHD	4	8.7	46.5 (11-54)
Disseminated aspergillosis	2	4.3	33 (18-48)
Heart failure	1	2.5	2
Causes of death beyond 90 days after PICU admission (13 patients)	**n**	**%**	**Median time of death (range) (days after PICU admission)**

Relapse of underlying disease[b]	8	61.5	220 (99-428)
MOF	1	7.7	147
Pulmonary aspergillosis	1	7.7	163
Septic shock	1	7.7	491
cGVHD	1	7.7	3491
Heart failure	1	7.7	3576

[a] Ten patients relapsed before PICU admission, 2 patients during PICU stay
[b] Three patients relapsed before PICU admission and died respectively 99, 133 and 267 days after PICU admission; 5 relapsed subsequently

Table 3. Clinical and transplant-related factors associated with Pediatric Intensive Care Unit admission (n=496patients)

	Total HSCT	PICU admission		Univariate analysis	Multivariate analysis		
		Yes (%)	No (%)	p-value	HR	95% CI	p-value
Gender							
Male	284	39 (13.7)	245 (86.3)	0.880			
Female	212	31 (14.6)	181 (85.4)				
Age at HSCT							
< median (8.26 years)	248	31(12.5)	217 (87.5)	0.367			
≥median	248	39 (15.7)	209 (84.3)				
Underlying disease							
Hematologic disease	344	61 (17.7)	283 (82.3)	<0.001	Rif.	0.319-3.29	0.970
Non hematologic disease	152	9 (5.9)	143(94.1)		1.02		
Status of disease at 1st HSCT							
Complete remission	283	43 (15.2)	240 (84.8)	0.505			
Presence of disease	213	27 (12.7)	186 (87.3)				
Conditioning regimen[a]							
Not including TBI	317	32 (10.1)	285 (89.9)	0.001	Rif.	0.785-2.24	0.290
Including TBI	179	38 (21.2)	141 (78.8)		1.33		
Type of HSCT							
Autologous	202	12 (5.9)	190 (94.1)	<0.001	Rif.	1.115-8.80	0.030
Allogeneic	294	58 (19.7)	236 (80.3)		**3.13**		
Number of HSCT							
1	465	60 (12.9)	405 (87.1)	0.006	Rif.	1.13-3.60	0.018
>1	31	10 (32.3)	21(67.7)		**2.02**		
Relapse after HSCT[b]							
Yes	134	13 (9.7)	121 (90.3)	0.116			
No	362	57 (15.7)	305 (84.3)				
Year of HSCT							
Before 2005	196	27 (13.8)	169 (86.2)	0.966			
After 2005	300	43 (14.3)	257 (85.7)				

PICU: pediatric intensive care unit; HR: hazard ratio; CI: interval of confidence; HSCT: hematopoietic stem cell transplantation; Rif: parameter of reference; [a]Use of TBI was considered at any HSCT. [b] For patients admitted to PICU, only relapse before PICU admission was considered

Table 4. Univariate analysis of risk factors associated with 90-day survival after Pediatric Intensive Care Unit admission: characteristics at the time of admission

	Total	N. of deaths (%)	Cumulative probability of survival (95% CI)	P-value
Gender				
Male	39	30 (76.9)	23.1 (13-40.9)	0.019
Female	31	16 (51.6)	48.4 (33.6-69.6)	
Age at HSCT				
<median (9,04 years)	35	22 (62.9)	37.1 (24.1-57.2)	0.698
≥median	35	24 (68.6)	31.4 (19.3-51.3)	
Underlying disease				
Hematologic disease	61	42 (68.9)	31.1 (21.4-45.2)	0.365
Non hematologic disease	9	4 (44.4)	55.6 (31-99.7)	
Conditioning				
Not including TBI	36	26 (72.2)	27.8 (16.4-47)	0.170
Including TBI	34	20 (58.8)	41.2 (27.6-61.5)	
Type of HSCT				
Autologous	10	4 (40)	60 (36.9-99.5)	0.164
Allogeneic	60	42 (70)	30 (20.4-44.2)	
HLA matching				
Matched/autologous	46	25 (54.3)	45.7 (33.3-62.6)	0.002
Mismatched	24	21 (87.5)	12.5 (0.4-36)	
No. of HSCT				
1	60	37 (61.7)	38.3 (27.8-52.8)	0.016
>1	10	9 (90)	10.0 (1.6-64.6)	
Year of HSCT				
Before 2005	25	13 (52)	48 (31.9-72.2)	0.158
After 2005	45	33 (73.3)	26.7 (16.4-43.3)	
Relapse before PICU admission				
Yes	13	10 (76.9)	23.1 (8.6-62.3)	0.018
No	57	36 (63.2)	36.8 (26.2-52.8)	
Polymorphonuclears engraftment*				
Yes	58	36 (62.1)	37.9 (27.3-52.7)	0.116
No	12	10 (83.3)	16.7 (0.05-59.1)	
Platelets engraftment*				
Yes	30	19 (63.3)	36.7 (22.9-58.7)	0.820
No	40	27 (67.5)	32.5 (20.8-50.8)	
aGvHD*				
No	51	32 (62.7)	37.3 (26.1-53.2)	0.271
Grade 1-2	7	6 (85.7)	14.3 (2.3-87.7)	
Grade 3-4	12	8 (66.7)	33.3 (15-74.2)	
cGvHD*				
No	61	42 (68.9)	31.1 (21.4-45.2)	
Limited	3	1 (33.3)	66.7 (30-100)	0.268
Extended	6	3 (50)	50 (22.5-100)	
VOD*				
Yes	7	5 (71.4)	28,6 (8.9-92.2)	0.791
No	63	41 (65.1)	34.9 (24.9-48.9)	
Presence of infection/viral reactivation*	50	37 (74)	26 (16.3-41.5)	0.021
Yes	20	9 (45)	55 (37-81.8)	
No				
PaO2/FiO2 ratio*				
>300	5	3 (60)	40 (13.7-100)	0.184
201-300	11	5 (45.5)	54.4 (31.8-93.6)	
101-200	19	11 (57.9)	42.1 (24.9-71.3)	
<100	35	27 (77.1)	22.9 (12.2-42)	
Presence of PARDS*				
Yes	24	22 (91.7)	8.3 (2.2-31.4)	0.003
No	46	24 (52.2)	47.8 (35.4-64.7)	

High flow oxygen therapy*				
Yes	8	6 (75)	25 (7.5-83)	0.926
No	62	40 (64.5)	35.5 (25.4-49.6)	
Dopamine administration*				
Yes	33	17 (51.5)	48.5 (34.1-68.9)	0.074
No	37	29 (78.4)	21.6 (11.7-39.9)	
Septic shock*				
Yes	47	24 (51.1)	27.7 (17.4-43.9)	0.300
No	23	12 (52.2)	47.8 (31.2-73.3)	
Fluid overload %*				
0	35	23 (65.7)	34.3 (21.7-54.2)	0.531
0-5	13	9 (69.2)	30.8 (13.6-69.5)	
5-10	12	9 (75)	25 (9.4-66.6)	
>10	10	5 (50)	50 (26.9-92.9)	
Acute kidney injury*				
No	36	26 (72.2)	27.8 (16.4-47)	
Grade 1	12	4 (33.3)	66.7 (44.7-99.5)	0.067
Grade 2	9	7 (77.8)	22.2 (6.6-75.4)	
Grade 3	13	9 (69.2)	30.8 (13.6-69.5)	
Hepatic failure*				
Yes	29	25 (86.2)	13.8 (5.6-34.3)	0.004
No	41	21 (51.2)	48.8 (35.6-66.8)	
MOF*				
Yes	47	32 (68.1)	31.9 (21-48.5)	0.301
No	23	14 (60.9)	39.1 (23.5-65.1)	

N.: number; CI: interval of confidence; HSCT: hematopoietic stem cell transplantation; HLA: human leukocyte antigen; aGvHD: acute graft versus host disease; cGvHD: chronic graft versus host disease; VOD: veno-occlusive disease; PaO2/FiO2: partial oxygen pressure/fraction of O2; PARDS: pediatric acute respiratory distress syndrome; MOF: multiple organ failure; *Characteristics evaluated at PICU admission.

Table 5. Univariate analysis of risk factors observed during Pediatric Intensive Care Unit stay associated with 90-day survival after PICU admission.

	Total	N. of patients alive within 90-days from PICU admission (%)	p-value
Presence of PARDS			
Yes	30	3 (10)	<0.001
No	40	21 (52.5)	
NIV			
Yes	28	4 (14.3)	0.336
No	52	20 (38.5)	
High flow oxygen therapy			
Yes	14	5 (35.7)	1
No	56	19 (33.9)	
Invasive ventilation			
Yes	45	5 (11.1)	<0.001
No	25	19 (76)	
HFOV			
Yes	12	2 (16.7)	0.197
No	58	22 (37.9)	
Use of nitric oxyde			
Yes	4	0 (0)	0.291
No	66	24 (36.4)	
Septic shock			
Yes	38	7 (18.4)	0.005
No	32	17 (53.1)	

Maximum No. of vasoactive amine administered			
0	14	7 (50)	
1	21	10 (47.6)	0.108
2	15	2 (13.3)	
3	19	5 (26.3)	
4	1	0 (0)	
External cardiac massage			
No	45	22 (48.9)	<0.001
Yes	25	2 (8)	
Acute kidney injury			
No	28	12 (42.9)	
Grade 1	4	2 (50)	0.055
Grade 2	9	5 (55.6)	
Grade 3	29	5 (17.2)	
CRRT			
Yes	24	4 (16.7)	0.034
No	46	20 (43.5)	
Hepatic failure			
Yes	43	8 (18.6)	0.001
No	27	16 (59.3)	
Aspergillosis			
Yes	15	1(6)	0.013
No	55	23 (41.8)	
MOF			
Yes	51	8 (15.7)	<0.001
No	19	16 (84.2)	

N.: number; PICU: pediatric intensive care unit; PARDS: pediatric acute respiratory distress syndrome; NIV: non invasive ventilation; HFOV: high frequency oscillatory ventilation; CRRT: continuous renal replacement therapy; MOF: multiple organ failure.

Table 6. Multivariate analysis of risk factors associated with 90-day mortality after Pediatric Intensive Care Unit admission

Variables at admission to PICU	**Estimate**	**HR**	**OR**	**SE**	**P-value**
Gender: male	0.193	1.21	-	0.365	0.607
Number of HSCT: >1	0.439	1.55	-	0.431	0.309
Matching HLA: mismatched	0.833	2.3	-	0.329	0.011
Relapse before PICU admission: yes	1.560	4.76	-	0.432	<0.001
Infection/viral reactivation at admission: yes	0.577	1.78	-	0.391	0.140
Presence of PARDS at admission: yes	0.920	2.51	-	0.366	0.012
Hepatic failure at admission: yes	0.797	2.22	-	0.344	0.021
PIM3	0.251	1.29	-	0.737	0.734
Variables during PICU stay	**Estimate**	**HR**	**OR**	**SE**	**P-value**

Invasive ventilation: yes	2.832	-	16.98	0.791	<0.001
Septic shock: yes	-0.804	-	0.45	0.742	0.278
CRRT: yes	-0.461	-	0.63	0.885	0.603
External cardiac massage: yes	0.972	-	2.64	0.966	0.314

PICU: pediatric intensive care unit; HR: hazard ratio; OR: odds ratio; SE: standard error; HSCT: hematopoietic stem cell transplantation; HLA: human leukocyte antigen; PARDS: pediatric acute respiratory distress syndrome; PIM3: Pediatric Index of Mortality Score; CRRT: continuous renal replacement therapy.