Risk Factors and Outcomes Related to Pediatric Intensive Care Unit Admission after Hematopoietic Stem Cell Transplantation: A Single-Center Experience

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

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Abstract

Objective: To describe incidence, causes and outcomes related to pediatric intensive care unit (PICU) admission of patients undergoing hematopoietic stem cell transplantation (HSCT). To investigate risk factors predisposing to PICU admission and prognostic factors in terms of patients' survival.

Design: Retrospective study.

Setting: Pediatric HSCT Unit and PICU of the University-Hospital of Padua.

Patients: From October 1998 to April 2015, 496 children and young adults (0-23 years) undergoing transplantation in the HSCT Unit. Amongst them, 70 (14.1%) were admitted to PICU of the same department.

Main results: The 3-year cumulative incidence of PICU admissions 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: undergoing allogeneic HSCT (p=0.030) and more than one 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 (IV) during PICU course (p<0.001).

Conclusions: 14.1% of children receiving HSCT developed complications which required PICU admission. The 90-day mortality was high, especially for patients relapsing before PICU admission, or undergoing allogeneic HSCT, or developing respiratory or hepatic failure at PICU admission, or needing IV during PICU stay. Admissions and outcomes remained stable over time, despite the advance of support treatments. Our data highlight the need for selecting groups of transplanted

patients who could benefit from current intensive treatment.

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Keywords

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

Highlights

- We studied children with blood marrow transplantation admitted to intensive care.
- Admission rate and outcomes were stable over time.
- 90-day probability of survival after admission was 34.3%: mortality was high.
- Risk factors were mismatched trasplant, lung or hepatic failure, relapse of disease.

Introduction

Hematopoietic stem cell transplantation (HSCT) often represents the only viable treatment option for malignant and non malignant pediatric diseases. However, this procedure can lead to severe complications often requiring admission to the pediatric intensive care unit (PICU). Moreover, amongst patients with oncologic and hematologic disorders, those receiving HSCT are at particular risk for unfavorable outcomes after PICU admission (1, 2). Recent studies have reported that outcomes for these patients have improved in the course of years thanks to PICU technical advances (e.g. non invasive ventilation [NIV] and high flow oxygen therapy [HFOT]) and to transplant-related procedures (1, 3-6). Nevertheless, the mortality rate is still high, especially when invasive ventilation (IV) and continuous renal replacement therapy (CRRT) are needed (7, 8). Many ethical and end-of-life challenges exist about the appropriateness of using intensive care resources for this

population, but recent data have been published showing a progressive improvement in survival adopting an aggressive critical care management (5, 6).

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 therefore 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 496 patients (0-23 years) affected by oncologic and hematologic disorders who underwent 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, or continuous morphine infusion. PICU admission criteria were the need for invasive or more frequent monitoring (such as continuous invasive arterial pressure monitoring), positive pressure ventilation, or a second inotropic drug. We considered all 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 at risk population (i.e. for age less than 1 year or affected by severe congenital immuno-deficiency). In accordance with the Declaration of Helsinki, parents and children/adolescents, when able to understand, were required to sign the informed consent for the transplant procedure and for data collection and analysis.

Data collection. Data were collected from the database of the HSCT Unit and from TIPnet database (www.tipnet.cineca.it) of our PICU and for each transplanted patient we considered: sex, age at

HSCT, underlying disease, date and number of HSCT, status of the disease at HSCT, use of total body irradiation (TBI) during conditioning regimen, type of donor, presence of relapse, date of death or last follow-up.

Regarding children admitted to PICU, we gathered data about HSCT, including: donor/recipient human leukocyte antigen (HLA) matching; occurrence of acute graft versus host disease (aGvHD) with Glucksberg grade (9) or chronic GVHD (cGvHD); engraftment for polymorphonuclears and platelets; veno-occlusive disease (VOD), according to MC Donald's criteria (10). In addition, detailed data were collected about PICU admission and course: date and cause of PICU admission; characteristics presented at admission, such as Pediatric Index of Mortality Score 3 (PIM 3) (11), PaO2/FiO2 ratio, fluid overload (FO) according to the weight formula (12), and presence of infections or viral reactivations; use of HFOT and/or dopamine administration before PICU admission; presence of organ dysfunction at admission or during PICU course, such as: pediatric acute respiratory distress syndrome (PARDS) according to the PALICC definition (13), septic shock defined according to previously published guidelines (14), acute kidney injury (AKI) with KDIGO staging (15), hepatic failure, or multiple organ failure (MOF) defined as the involvement of $\geq$2 organs); need of some support measures in the PICU: NIV, HFOT, IV, high frequency oscillatory ventilation (HFOV), inhaled nitric oxide, external cardiac massage, or CRRT; maximum number of vasoactive amines administered in the PICU; occurrence of aspergillosis in the PICU; date of discharge; cause of death when applicable.

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 no matched" if $\leq$ 5/6 for bone marrow transplants and peripheral blood stem cell transplants and $\leq$ 4/6 for cord blood

transplants; the HLA analysis was based on high resolution typing from 1998. The day of the stem cells infusion was conventionally considered the "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 independently of platelet transfusions for 7 consecutive days. The definition of "organ failure" was based on the criteria of the TIPnet database, approved by a national consensus conference (see 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 with PICU admission and without PICU admission were compared: 496 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. Among the 496 transplanted patients, 465 patients 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: 12.9% (60/465) after their first HSCT, 27.6% (8/29) after their second HSCT, and 100% after their third transplant; the 3-year cumulative incidence of admission of 14.3% (95% CI: 11.1%-17.4%). Regarding the patients admitted to PICU, 56/70 (80%) were admitted once, 14/70 (20%) patients had instead 2 or more admissions, for a total number of 92 PICU admissions. The median length of PICU stay was 7 days (range, 1-81 days). The risk of PICU admission was significantly higher for children undergoing allogeneic than for patients undergoing autologous HSCT, 20% (95% CI: 15.3%-24.7%) vs 6% (95% CI: 2.7%-9.3%), respectively ($p<0.001$). The number of HSCT per year and the PICU admissions are shown in Figure 1.

The causes of the 92 PICU admissions are reported in Table 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 the 7 children admitted later than 12 months after the HSCT were affected by cGVHD.

Outcome of PICU admission. Among 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 had no further PICU admission, 8 were readmitted to PICU. The overall 90-day cumulative probability of survival after PICU admission was 34.3% (95% CI 24.8-47.4%). The causes of death for these patients were MOF (n=14, 30.4%), relapse of underlying disease (12, 26.1%), respiratory failure (n=9, 19.6%), septic shock (n=4, 8.7%), aGVHD or cGVHD (n=4, 8.7%), disseminated aspergillosis (n=2, 4.3%), heart failure (n=1, 2.5%). Thirteen more patients died during follow-up, but later than 90 days from

PICU admission. Overall, at the last follow-up, 11 out of 70 patients (15.7%) were alive and in CR from the underlying disease. In comparison, among the 426 patients that did not need PICU admission, 320 (75.1%) were alive at the 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 reported in Table 2. In univariate analysis, the characteristics associated with PICU admission were: underlying hematological disease, undergoing more than one HSCT, the use of TBI, and allogeneic HSCT. In multivariate analysis, a 3.13-fold increased risk of being admitted to the PICU was observed for children who underwent allogeneic HSCT, compared with autologous HSCT (CI: 1.115-8.80; p=0.030), and a 2.02-fold increased risk for patients who underwent two or more HSCT, compared with one HSCT (CI: 1.13-3.60; p=0.018).

Risk factors associated with 90-day mortality from PICU admission. In Table 3 we reported the univariate analysis of the factors related with 90-day mortality from PICU admission, considering the features of the HSCT and the clinical condition at the time of PICU admission. The results of the univariate analysis of the characteristics observed during PICU stay and associated with a worse 90-day survival are reported in Table 4. Among the characteristics reported in Table 3, only no matched 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) at PICU admission, were significantly associated with a higher 90-day mortality in multivariate analysis (Table 5). Moreover, among the variables described in Table 4, only IV was confirmed to be a negative prognostic factor for 90-day PICU mortality in multivariate analysis (OR 16.98, p<0.001) (Table 5).

Discussion

In the last decades, the number of malignant and non malignant diseases successfully treated with HSCT has increased thanks to HSCT procedure improvement (18). However, many patients undergoing HSCT still develop complications that require PICU admission, related mortality

remaining high. The aim of our study was to consider the whole clinical course of children requiring PICU admission after HSCT. We underline the specific approach adopted in our Unit, that aimed to establish some initial intensive supportive measures in the HSCT Unit, reserving PICU admission only for patients that needed more invasive or more frequent monitoring. Therefore, our specific experience can be valuable as adding important findings to the cumulative knowledge of outcome of HSCT patients, when admitted to PICU. In our experience, the 3-year cumulative incidence of PICU admission after HSCT was 14.3%. This result lies in the lower range of the published data, proportion of patients admitted to PICU ranging from 10% to 40 % (3-5, 7, 19-29). Criteria used to define PICU admission in our series of patients were stringent and, diverging from other studies, we only admitted patients in life-threatening conditions, e.g. excluding those in need for postoperative monitoring (4). In our study period, the 90-day survival rate after PICU admission was 34.3%. Other experiences reported in literature show survival rates ranging from 30 to 75% (1, 3-5, 8, 19, 22, 30-32), thus locating our result in the lower bracket of the above-mentioned range, all due to the high stringency of our selection criteria. Particularly, an improving trend in prognosis over years was observed in some cohorts of patients, thanks to the progressive amelioration of invasive and non-invasive support therapies available in the PICU (1, 3, 5, 6, 28, 33, 34). In our series of patients, instead, not only the number of PICU admissions was stable over time, but also failures in PICU treatment were stable. A possible explanation is that some semi-intensive treatment approaches (such as HFOT and dopamine infusion) were adopted in the HSCT Unit; such procedures were, in fact, not followed by PICU admission. At the last follow-up, only 15.7% children undergoing PICU admission after HSCT were alive; instead, 75.1% (320/426) of those patients not needing any PICU admission were alive. This result highlights the severe prognosis of transplanted children admitted to PICU, in line with PIM 3 score which estimates the mortality risk of patients at PICU admission and considers transplanted children as a ‘very high risk’ population (11). In multivariate analysis, allogeneic HSCT was confirmed to be a predisposing factor for PICU

admission, as already reported (19-21), as well as undergoing more than one HSCT, according to Aspesberro et al. study (3). In contrary, these two factors did not have a significant negative impact on survival during PICU stay, in disagreement with other studies (1, 4, 19). Moreover, the presence of aGVHD at the time of admission, which has been reported as a risk factor for PICU stay-related mortality, was not associated with adverse outcomes in our cohort (28, 29). In our multivariate analysis, other factors displayed significantly negative impact on PICU-related survival rate. Primarily, relapse of underlying disease before PICU admission is strongly associated with unfavorable prognosis, with almost 5-fold increased incidence of mortality. In fact all the 13 patients with relapse before PICU admission died within an year after PICU admission, 10 (76.9 %) within 90 days, the other 3 died respectively 99, 133 and 267 days after PICU admission. Furthermore, twelve out of 46 children (26,1 %) that died within 90 days after PICU admission had presence of underlying disease at the time of death, showing that relapse is often the cause of death in this population. This finding shows relapse to represent a failure of the transplantation procedure, thus making any effort in terms of intensive support treatment vain. Also the use of mismatched donors - already known to be associated with a delayed immune recovery - turned out to be a risk factor for the 90-day mortality after PICU admission. Moreover, as for the effects of single organ dysfunction on patients' prognosis, hepatic and respiratory failure at admission and need for IV during the PICU stay came out to be associated with a higher mortality, in line with previous experiences (1, 4, 5, 21, 23-27, 33, 34, 35, 36). The main cause of death in our experience was MOF including cardiovascular and renal failure, but early hepatic or respiratory dysfunction may hamper the functions of other organs and lead to a more severe clinical course. Our results seem to be in line with the hypothesis of the "gut-liver-lung axis of inflammation" and to support the clinical linkage - pointed out by other authors (37-39) - between hepatic failure and idiopathic pulmonary syndrome-related death. In our series of patients, children with PARDS at admission or requiring IV had a very high mortality (91.7% and 88.9%, respectively). These percentages are

higher than the ones reported in other recent studies (3-7, 22, 31, 32). A possible explanation for this discrepancy is the fact that patients with milder respiratory distress were treated with HFOT in the HSCT ward and those admitted to PICU displayed more severe pulmonary dysfunction. Furthermore, our policy was to delay intubation and invasive ventilation as long as possible, targeting this treatment option only in case of other non invasive strategies failure. Our finding is important in considering whether early interventions for respiratory failure could be associated with a better outcome, as suggested by a recent study (6). This issue is actually under debate and further investigations are needed regarding the correct timing of admission to PICU and of starting NIV or IV.

The limitations of our study are its single-centre design, its retrospective nature and its small size. Despite this, 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 undergoing PICU admission. Moreover, we underline our contribution to the cumulative knowledge of this issue, offering the experience of our specific approach, based in reserving intensive supportive treatments only to the patients in critical conditions.

Conclusions

Amongst children and young adults undergoing HSCT, the cumulative incidence of PICU admission was 14.3%. Admission rate and outcomes were stable over time, despite the advanced support therapies available. For these patients mortality was high, especially in case of mismatched HSCT, of lung or hepatic failure, or of underlying disease relapse.

The knowledge of factors predisposing to PICU mortality is pivotal in redirecting patients whether to PICU admission- in case of critical conditions- or to continue supportive care in the ward, providing better end-of-life care, also permitting 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 transplanted patients' prognosis.

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Figure Legends

Figure 1. Description of the study population.

HSCT: hematopoietic stem cell transplantation; PICU: pediatric intensive care unit; pts: patients; MOF: multiple organ failure; cGVHD: chronic graft versus host disease.

Figure 2. Trend of admissions to Pediatric Intensive Care Unit and survival during the period 1st October 1998-30th April 2015.

PICU: pediatric intensive care unit; n.: number; HSCT: hematopoietic stem cell transplantation.

Figure 1

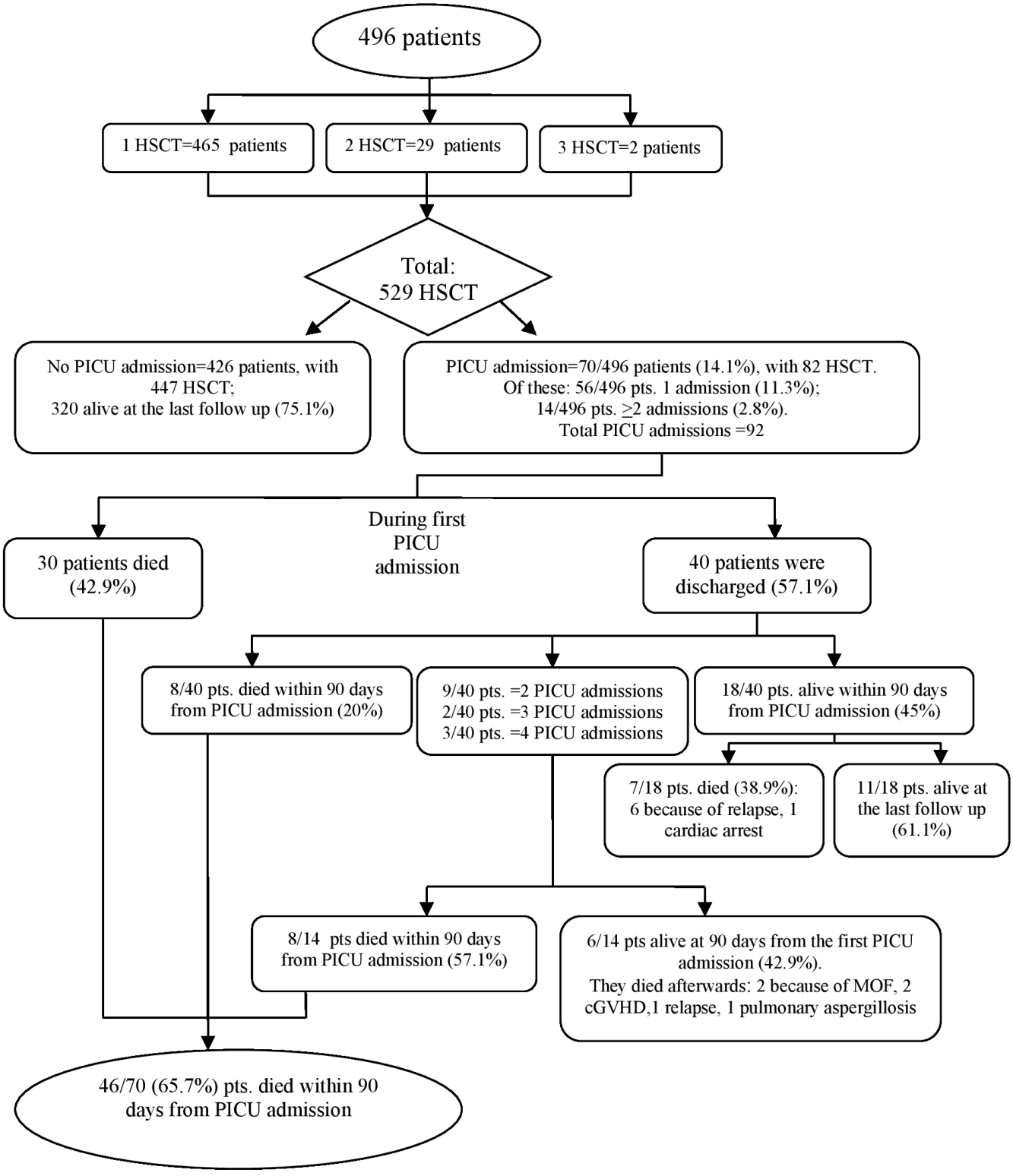
496 patients
1 HSCT=465 patients
2 HSCT=29 patients
3 HSCT=2 patients
Total:
529 HSCT
No PICU admission=426 patients, with 447 HSCT;
320 alive at the last follow up (75.1%)
PICU admission=70/496 patients (14.1%), with 82 HSCT.
Of these: 56/496 pts. 1 admission (11.3%);
14/496 pts. ≥2 admissions (2.8%).
Total PICU admissions =92
During first PICU admission
30 patients died (42.9%)
40 patients were discharged (57.1%)
8/40 pts. died within 90 days from PICU admission (20%)
9/40 pts. =2 PICU admissions
2/40 pts. =3 PICU admissions
3/40 pts. =4 PICU admissions
18/40 pts. alive within 90 days from PICU admission (45%)
7/18 pts. died (38.9%): 6 because of relapse, 1 cardiac arrest
11/18 pts. alive at the last follow up (61.1%)
8/14 pts died within 90 days from PICU admission (57.1%)
6/14 pts alive at 90 days from the first PICU admission (42.9%).
They died afterwards: 2 because of MOF, 2 cGVHD,1 relapse, 1 pulmonary aspergillosis
46/70 (65.7%) pts. died within 90 days from PICU admission

Figure 2

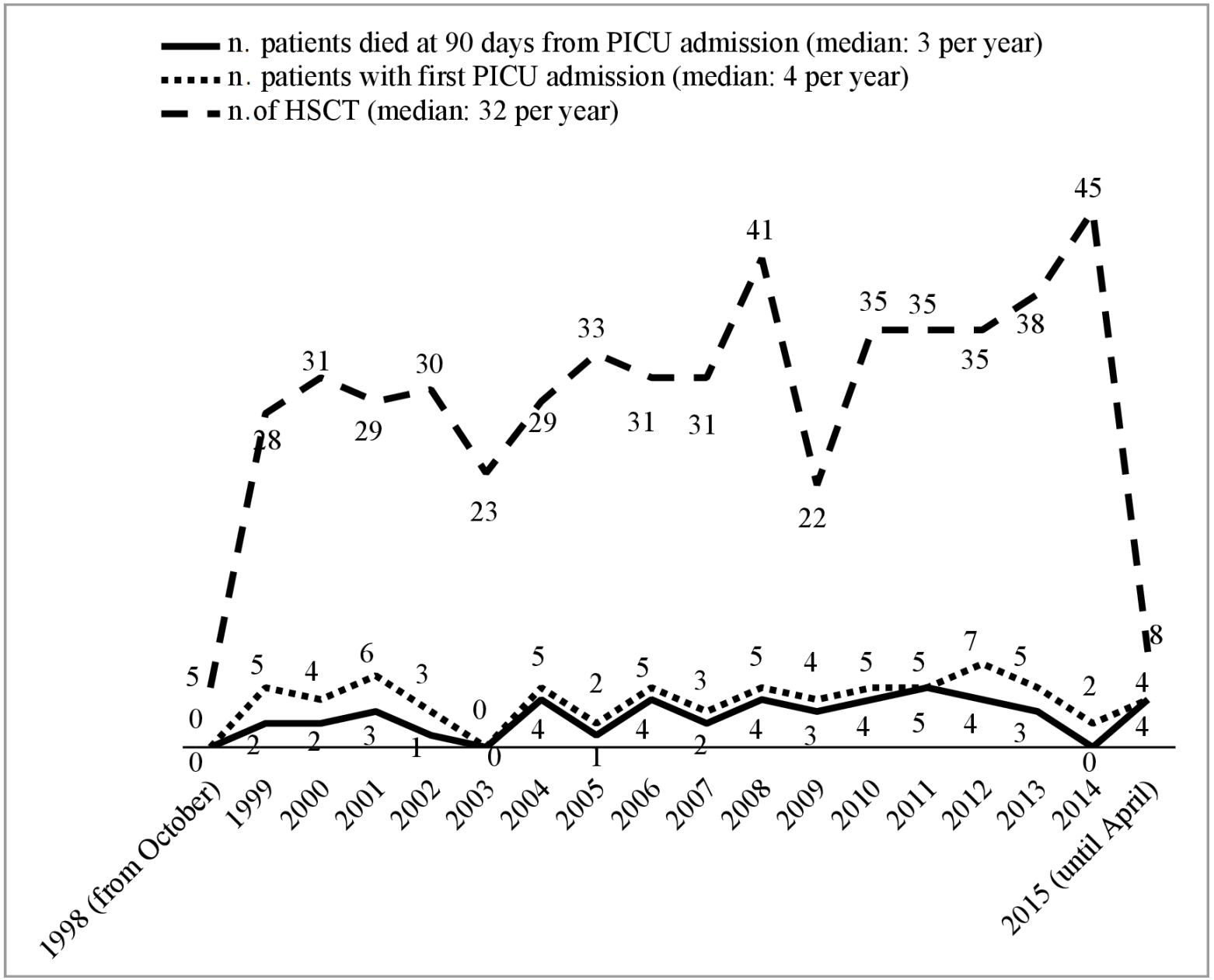
n. patients died at 90 days from PICU admission (median: 3 per year)
n. patients with first PICU admission (median: 4 per year)
n. of HSCT (median: 32 per year)
1998 (from October)
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015 (until April)
5
28
31
29
30
23
29
33
31
31
41
22
35
35
35
38
45
8
0
5
4
6
3
0
5
2
5
3
5
4
5
5
7
5
2
4
0
2
2
3
1
0
4
1
4
2
4
3
4
5
4
3
0
4

Table 1. Analysis of clinical and transplant factors associated with Pediatric Intensive Care Unit admission (n=496 transplanted patients)

	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]							
Without TBI	317	32 (10.1)	285 (89.9)	0.001	Rif.	0.785-2.24	0.290
With 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] It was considered if the patient underwent TBI in any of the HSCT that he received. [b] If the patient was admitted to PICU, it was considered the occurrence of relapse before PICU admission

Table 2. Univariate analysis of risk factors present associated with 90-day survival from Pediatric Intensive Care Unit admission: characteristics before and 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				
Without TBI	36	26 (72.2)	27.8 (16.4-47)	0.170
With 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)	
Matching HLA				
Matched/autologous	46	25 (54.3)	45.7 (33.3-62.6)	0.002
Non matched	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)	
Infections/reactivations*				
Yes	50	37 (74)	26 (16.3-41.5)	0.021
No	20	9 (45)	55 (37-81.8)	
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 flux 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
Grede 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: chronicGVHD; VOD: veno occlusive disease; PaO2/FiO2: partial oxygen pressure/fraction of O2; PARDS: acute respiratory distress syndrome; MOF: multiple organ failure; * Characteristics evaluated at PICU admission.

Table 3. Univariate analysis of risk factors observed during Pediatric Intensive Care Unit stay associated with 90-day survival from the 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
Grede 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: acute respiratory distress syndrome; NIV: non invasive ventilation; HFOV: high frequency oscillatory ventilation; CRRT: continuous renal replacement therapy; MOF: multiple organ failure.

Table 4. Multivariate analysis of risk factors associated with 90-day mortality from Pediatric Intensive Care Unit admission

Variables before or 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: unmatched	0.833	2.3	-	0.329	0.011
Relapse before PICU: yes	1.560	4.76	-	0.432	<0.001
Infections/reactivations 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
PIM 3	0.251	1.29	-	0.737	0.734
Variables during PICU stay	**Estimate**	**HR**	**OR**	**SE**	**P-value**
Invasive ventilation in PICU: yes	2.832	-	16.98	0.791	<0.001
Septic shock in PICU: yes	-0.804	-	0.45	0.742	0.278
CRRT in PICU: yes	-0.461	-	0.63	0.885	0.603
External cardiac massage in PICU: yes	0.972	-	2.64	0.966	0.314

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