Predictors of mortality after admission to pediatric intensive care unit in oncohematologic patients without history of hematopoietic stem cell transplantation: a single center experience.

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List of Abbreviations

Abbreviation	Full term or phrase
AKI	Acute Kidney Injury
CRRT	Continuous Renal Replacement Therapy
DIC	Disseminated Intravascular Coagulation
ECMO	Extracorporeal Membrane Oxygenation
HFOT	High Flow Oxygen Therapy
HFOV	High Frequency Oscillatory Ventilation
HSCT	Hematopoietic Stem Cell Transplantation
KDIGO	Kidney Disease Improving Global Outcomes
MOF	Multiple Organ Failure
MV	Mechanical Ventilation
NIV	Non-Invasive mechanical Ventilation
PaO2/FiO2	Arterial partial Oxygen Pressure/ Fraction of Oxygen
PARDS	Pediatric Acute Respiratory Distress Syndrome
PICU	Pediatric Intensive Care Unit
PIM3	Pediatric Index of Mortality Score 3

Abstract

Background: Pediatric oncohematologic patients are a high-risk population for clinical deterioration that might require a Pediatric Intensive Care Unit (PICU) admission. Several studies described outcomes and mortality predictors for patients post hematopoietic stem cell transplantation (HSCT), but fewer data exist regarding the category of non-HSCT patients.

Procedure: All oncohematologic non-HSCT patients ≤18 years requiring a PICU-admission from 1998 to 2015 in our tertiary-care academic-hospital were retrospectively evaluated by means of the Pediatric-Hematology-Oncology-Unit database and the Italian-PICUs-Data-Network (TIPNet) database. We assessed the relation between demographic and clinical characteristics and 90-day-mortality after PICU-admission.

Results: Of 3750 hospitalized oncohematologic patients, 3238 were non-HSCT and 63 (2%) of them were admitted to PICU. Patients were mainly affected by hematological malignancies (70%) and mostly were in the induction-therapy phase. The main reasons for admission were respiratory failure (40%), sepsis (25%) and seizures (16%). The median PICU-stay was 5 days (range 1-107). The mortality-rate at PICU-discharge was 30%, at 90-days was 35%. Fifty-five percent of deaths happened in the first two days of the PICU-stay. Cardiac arrest ($p=0.007$), presence of disseminated intravascular coagulation (DIC, $p=0.007$) and acute kidney injury (AKI) at PICU-admission ($p<0.001$) and during PICU-stay ($p=0.021$) were significant predictors of mortality at multivariate analysis. Respiratory failure and mechanical ventilation were not associated with mortality.

Conclusions: A relatively small percentage of non-HSCT patients required a PICU-admission, but the mortality-rate is still high. Hemodynamic instability, DIC and AKI, but not respiratory failure, were significant predictors of mortality.

Introduction

In the last few decades the outcome of pediatric oncohematologic patients affected by malignant or non-malignant diseases has improved due to potentially curative chemotherapy protocols, increased biological knowledge and innovative treatments such as the hematopoietic stem cell transplantation (HSCT). [1-3] HSCT is a well-known risk factor for mortality for this category of patients.[2,4-6] However, the oncohematologic disease itself and the intensity of the chemotherapy or radiotherapy can lead, independently of HSCT treatment, to severe complications and life-threatening conditions which may require intensive care treatment. To date, several studies have addressed the need for intensive care in pediatric oncohematologic patients [4,7-16] or specifically in HSCT-patients, [5,6,17-22] showing a high risk of mortality especially for patients who need mechanical ventilation.[5,17,18,20,22] Conversely, fewer studies have focused so far on outcomes and mortality predictors in the overall category of oncohematologic patients without a history of HSCT (non-HSCT). [6,23]

The main purpose of the present study was to describe the need for Pediatric Intensive Care Unit (PICU) admission and the related outcome of pediatric patients affected by oncohematologic diseases without a history of HSCT. A further purpose was to investigate the predictive factors of mortality in this category of patients.

Methods

Design of the study, setting and population

We performed a single-center observational retrospective study at Padua's University Hospital evaluating data from October 1998 to April 2015. All oncohematologic patients who had been hospitalized in the Pediatric Hematology-Oncology Clinic and had required a PICU-admission because of complications or life-threatening conditions were included in the study. We considered the following exclusion criteria: patients who received at least one HSCT before PICU-admission, PICU-admissions only related to post-operative monitoring or procedural sedation, patients with

central nervous system tumors (because of the completely different clinical characteristics and outcome, as previously reported)[5] patients >18 years of age. Patients who were already declared "do not resuscitate" before PICU-admission were excluded.

Padova Children's Hospital is an academic tertiary-care hospital receiving about 7000 inpatients/year. Its Hematology-Oncology Clinic received approximately 750 inpatients/year (160 new cancer diagnosis/year) and 1050 outpatients/year. Padova PICU is a high specialized unit and ECMO-center receiving about 400-450 inpatients/year.

The Pediatric Hematology-Oncology Clinic is a high-dependency unit, offering the following supports: dopamine inotropic support up to 3 mcg/kg/min, HFOT with FiO2 up to 60% and furosemide continuous infusion. The use of these supports is always accompanied by a daily PICU consult.

Data collection

Information has been collected by means of the Italian-PICUs-Data-Network (TIPNet) database, the Pediatric-Hematology-Oncology local database and patients' clinical charts. The TIPNet database is a database accessed only by users, developed by the Italian Society of Neonatal and Pediatric Anesthesia and Intensive Care (SARNePI) with the aim of monitoring and improving PICUs activities (www.tipnet.cineca.it). Both databases received the Institutional Review Board approval, which included the authorization to perform retrospective evaluations without any further approvals. As requested by our Institutional policies, an informed written consent authorizing the anonymous collection of data has been collected for each patient. The following data have been registered: age at time of PICU-admission, gender, underlying disease, treatment phase at the moment of PICU-admission, time from onset of the underlying disease to PICU-admission, time of the PICU-stay. At the moment of PICU-admission, we considered the following variables: main cause of admission, use of ventilation support as High Flow Oxygen Therapy (HFOT), presence

and severity of Pediatric Acute Respiratory Distress Syndrome (PARDS), arterial partial Oxygen Pressure/Fraction of O2 (PaO2/FiO2 ratio), inotropic drugs administration before PICU-admission, presence and severity of fluid overload, presence of septic shock, presence of Disseminated Intravascular Coagulation (DIC), presence of hepatic failure, presence and severity of Acute Kidney Injury (AKI), presence of Multiple Organ Failure (MOF), Pediatric Index of Mortality score 3 (PIM 3). Regarding the PICU-stay, we analyzed: use of HFOT, use of Non-Invasive mechanical Ventilation (NIV) or invasive Mechanical Ventilation (MV) for a period of time longer than 6 hour, use of High Frequency Oscillatory Ventilation (HFOV), presence and severity of PARDS, PaO2/FiO2 ratio, length of mechanical ventilation, use of inhaled nitric oxide, presence of sepsis and septic shock, use and number of inotropic drugs, episode of cardiac arrest requiring cardio-pulmonary resuscitation, presence of DIC, presence of infections, presence of hepatic failure, presence and severity of AKI and need for continuous renal replacement therapy (CRRT), presence of MOF and need for Extracorporeal Membrane Oxygenation (ECMO). As for patients with more than one admission, we considered the second admission as the same PICU-course if it happened within 24 hours of the PICU discharge. If not, we described the multiple admissions as descriptive data but, for the univariate and multivariate analysis, we consider only the first PICU-admission for each patient. As the main outcome measures, we evaluate the length of PICU-stay, the mortality at PICU-discharge and the mortality at 90 days of PICU-admission.

Definitions and Classifications

We classified the underlying disease as hematologic disease (acute lymphoblastic leukemia, acute myeloid leukemia, lymphoma, other hematologic malignancies, non-malignant diseases) or solid tumor. For the statistical evaluation, we also explored the following categorization: "hematologic/non-hematologic disease" and "neoplastic/non-neoplastic disease". We evaluated AKI based on kidney disease improving global outcomes (KDIGO) staging.[24] Fluid balance was

assessed using fluid overload calculation.[25] PARDS was defined according to the Pediatric Acute Lung Injury Consensus Conference's definition.[26] We considered "septic shock" when the patient showed fever, CRP >10 mg/dl and need for inotropic drugs.[27] For the definition of "organ failure" we adopted the TIPNet database definitions approved by a national consensus conference (available at www.tipnet.cineca.it). MOF was defined as the contemporary involvement of ≥ 2 organs. PIM 3 was calculated according to the current definition (in patients with admission before year 2013, PIM3 was retrospectively calculated).[28,29]

Statistical analysis

All statistical analyses were performed using the R statistical software (version 3.0.2) and the SAS statistical program (SAS-PC, version 9.3; SAS Institute Inc., Cary, NC, USA). Descriptive data were reported in terms of absolute frequencies and percentages for qualitative data. Quantitative data were described in terms of median values and minimum/maximum values due to their non-Gaussian distribution. The log-rank test was used to assess the difference in the 90-day cumulative probability of survival after PICU-admission based on the characteristics of the patients at the time of PICU-admission. Factors with p value <0.1 at univariate analysis were then included in a multivariate analysis using the Cox proportional hazards model. The Pearson Chi squared and Fisher exact test were used to compared PICU-stay characteristics between survivors and non-survivors. A logistic regression model including all the PICU-stay variables with p value <0.1 at univariate analysis was then used for the multivariate analysis. MOF was excluded from the final model because of its redundancy with AKI and hepatic failure. PIM3 was excluded because of its nature of predictive-score including multiple factors that could be redundant with the other variables. To assess differences over time, the same analyses were independently performed for the cohort of patients admitted in the period 1999-2008 (n =33) and for the cohort of patients admitted over the period of 2009-2015 (n =30). Statistical significance was set at a p-value <0.05.

Results

Incidence and characteristics of PICU admission

Of 3750 oncohematologic hospitalized pediatric patients, 3238 (86%) were non-HSCT patients and 63 (2% of them) required a PICU-admission because of complications or life-threatening conditions. Demographic, clinical features and main diagnoses of patients are summarized in Table 1. Nine (14%) of the 63 patients had 2 PICU-admissions over the course of the study, for a total number of 72 PICU-admissions (1% of the total 7263 PICU admissions over the course of the study) and a median of 3 admissions per year (range 0-8). The median time from the diagnosis of the underlying disease to PICU-admission was 56 days (range 0-1495 days). The main cause of PICU-admission was acute respiratory failure (n=29/72, 40%), largely due to infection (52% of cases) or secondary to direct complications of the underlying condition. In 7/72 admissions (10%), the patient was already on HFOT. In 20/72 admissions (28%) the patient met the criteria for PARDS (mild or moderate in 65%, severe in the remaining 35%). Sepsis related diagnosis ~~or septic shock~~ represented the reason for admission in 18/72 cases (25%) and were primarily caused by fungal infections (7/18 cases). Seizures were the reason for admission in 11/72 cases (16%) and were mainly due to direct neurologic involvement of the disease and thrombotic or hemorrhagic complications. Less frequent causes of admission were AKI (3/72, 4%), acute pancreatitis (3/72, 4%) heart failure (3/72, 4%), cardiac arrest (2/72, 3%), anaphylaxis (2/72, 3%) and severe hypertension (1/72, 2%). In 12 of 72 admissions (17%), patients presented a PIM3 $\geq$0.2. Regardless of the main cause of admission, 31/72 cases (43%) presented with signs of septic shock at admission and 18/72 (25%) presented with DIC. Forty cases (55%) patients were already receiving a circulatory support with at least one inotropic drug. Twelve cases (17%) presented with a fluid overload >10%. About one fourth of cases (21/72, 29%) presented with signs of AKI at admission, severe (KDIGO 3) in 33% of them. Twenty-two cases (31%) presented with hepatic failure. MOF

126 was registered in 40/72 admissions (56%).

127

128 *Characteristics of PICU--stay*

129 During PICU-stay, 37 (59%) patients required mechanical ventilation and 33 of them were
130 intubated. Two patients (3%) required HFOV; the same two patients required inhaled nitric oxide
131 therapy. Twenty-six patients (41%) met the criteria for PARDS. Half of the patients (32/63, 51%)
132 met the criteria for sepsis during the PICU course, whereas 44% the criteria for septic shock. All
133 patients presenting with signs of septic shock already met the criteria at PICU-admission. Twenty-
134 three (36%) had DIC. Thirty-seven (59%) patients required inotropic support during PICU-course:
135 57% required one inotropic drug, 22% two and the other 21% three or more. Thirteen patients
136 (21%) had at least one episodes of cardiac arrest requiring cardio-pulmonary resuscitation. Two
137 patients required a venous-arterial ECMO-support following an episode of cardiac arrest. One of
138 them survived, the second one died within 90-days of PICU-admission. With regards to organ
139 failure, 20 (32%) patients had hepatic failure, 18 (28%) AKI and 37 (59%) MOF. Five patients
140 presenting with AKI (25%) required CRRT treatment.

141

142 *Outcome*

143 The median duration of PICU-stay was 5 days (range 1-107). Twenty-two out of 63 patients (35%,
144 Figure 1) died within 90 days of PICU-admission, showing an overall 90-day cumulative survival
145 probability of 65% (95% CI 53-77%). Mortality at PICU-discharge was 30% (19/22 patients).
146 There was no significant difference in the mortality-rate between the cohort admitted in the period
147 1998-2008 and the cohort admitted in the period 2009-2015 (30% vs 40%, p=0.42). Among non-
148 survivors, 55% died within two days of PICU-stay, 73% within seven days (Figure 1). Half of the
149 patients (11/22, 50%) died from infections, such as sepsis or severe pneumonia, 18% (4/22 patients)
150 from hemorrhagic complications and 32% (7/22 patients) from underlying disease direct

complications (disease relapse or complication of a disease which never reached a remission).

Factors associated with 90-day mortality

In the univariate analysis regarding variables related to PICU-admission and 90-day mortality (Table 1), PIM3≥0.2, the presence of AKI and AKI-severity were significantly associated with 90-day mortality ($p=0.037$; $p<0.001$ and $p<0.001$ respectively). In the univariate analysis regarding variables related to PICU-stay, factors significantly associated with 90-day mortality were: the presence and severity of AKI ($p=0.001$; $p=0.002$), the presence of DIC ($p<0.001$), the administration of >2 inotropic drugs ($p=0.018$), an episode of cardiac arrest ($p=0.001$), the presence of hepatic failure ($p=0.045$) and MOF ($p=0.008$) (Table 2). The association of Aspergillus infection with mortality was at the limit of statistical significance ($p=0.055$).

In multivariate analyses, the only variable at PICU-admission confirmed as a predictor of mortality was the presence of AKI ($p <0.001$) (Table 3). PICU-stay factors confirmed as predictors of mortality were cardiac arrest ($p=0.007$), the presence of AKI ($p=0.021$) and the presence of DIC ($p= 0.007$, Table 4).

The same multivariate model applied to the two temporal-cohorts confirmed AKI at admission as a predictor of mortality for both cohorts ($p=0.040$ and $p=0.05$). PICU-stay factors identified as predictors of mortality were cardiac arrest for the cohort 1998-2008 ($p=0.014$) and DIC for the cohort 2009-2015 ($p=0.031$) (Supporting Information File 1).

Discussion

Pediatric oncohematologic patients are a high-risk population for rapid clinical deterioration, due to multiple factors such as the severity of the underlying condition, the toxicity of interventions and the associated immunosuppression. Several studies over the last decade aimed to identify the major risk and predictive factors for PICU-admission and outcome.[4-23] However, the majority of the

studies evaluated only HSCT-patients [5,6,17-22] or included HSCT-patients in the cohort of oncologic patients.[4,7-16] HSCT is a well-known independent risk factor for both PICU-admission and mortality, increasing the risk for infections, hemodynamic instability and pulmonary failure.[2,4-6] Our retrospective tertiary-care-center study extensively evaluated the non-HSCT cohort, with the aim of evaluating the specific needs and predictive factors of this category of patients.

In our sixteen-year experience, we demonstrated that approximately 2% of the hospitalized oncohematologic patients without a history of HSCT required a PICU-admission because of complications or life-threatening conditions. Our report showed a lower incidence rate of PICU-admission compared to previously reported data (range 2.5%-44.3%).[2-4,22] However, some issues have to be taken into consideration: first of all, some of these studies also included non-critically ill patients who required procedures or therapy-infusions.[8,15] Moreover, the criteria for PICU-admission are different among centers: in our center, especially in the final years of the study, the first care of a critical oncologic patient, such as HFOT or dopamine infusion, can be started in the Pediatric Hematology and Oncology Unit, in cooperation with the PICU-team. Finally, the majority of these studies evaluated only HSCT-patients or included HSCT-patients in the cohort of oncologic patients.[4-22]

In our sample, the main cause of PICU-admission was acute respiratory failure, as found in previous studies,[9,12,16,23] mainly caused by infection or the underlying condition. One third of patients met the criteria for PARDS and required invasive MV or NIV. Nevertheless, neither the presence nor the severity of respiratory failure at PICU-admission or during PICU-course were significantly predictive for 90-day mortality. These data differ from that reported in the past for cohorts of oncologic patients[2,3,11,14-16] and for HSCT-patients.[17,18,20,22] For example, a recent multicenter study by Rowan MC et al. described a high rate of PARDS in HSCT-patients, with the vast majority being severe and requiring HFOV.[21] Certainly, new ventilation techniques and strategies allowed a significant improvement of ventilated patients' outcome over time, as reported

in Tamburro et al.[6], but we also believe that the non-HSCT cohort is a completely different population compared with HSCT-patients, with less susceptibility to severe lung disease. We may speculate that non-HSCT patients could present a lower level of inflammation compared to HSCT-patients. Conversely, the resources for the lung healing could be higher, since the HSCT patients frequently present with a HSCT-related non-infectious pulmonary complication with variable degree of reversibility.[30]

An interesting result of our study was that more than 40% of patients presented with septic shock at time of PICU-admission and were already receiving an inotropic support, reflecting both a prompt intervention towards sepsis but also possibly pointing out the need to better and earlier identify patients who require an immediate PICU-admission. Despite the fact that septic shock did not reach a statistical significance as a predictor of mortality, in contrast with what was previously reported,[10,14,15] some correlated conditions such as the hemodynamic instability and the presence of DIC were identified by the multivariate analysis, confirming its central role in defining the prognosis for this population. Moreover, cardiac arrest was confirmed as a significant predictor of mortality, supporting what was previously reported.[31,32] Organ failure represented another important issue, since more than half of patients presented MOF at admission and a similar percentage during PICU-course. MOF was associated with mortality in the univariate analysis, as previously reported.[1,14,15,23] The presence of AKI during PICU-stay reached the statistical significance confirming current knowledge about critically ill patients and in particular about oncologic ones.[7,9,23,33] On the contrary, AKI at admission has not been previously reported as a predictor of mortality for oncologic patients.

In our population a relevant percentage of patients (35%) died within 90 days of the PICU-admission, mirroring the percentages previously reported by literature.[3,8,9,10,13,23] The underlying disease and the phase of treatment did not seem to be associated with 90-day mortality in our analysis. In particular, the presence of leukemia or lymphoma was not significantly associated with

226 a worse outcome, differently from what was reported by Zinter et al. and Meyer et al. [4,13] but
227 confirming the report of Dursun et al.[14] However, the small sample size of our study could have
228 affected this result and only larger studies are actually able to clarify this issue. Interestingly, we
229 found that a significant percentage of patients died in the first 48 hours after PICU-admission and a
230 good number of patients who presented the predictors of mortality during PICU-course
231 (hemodynamic instability, DIC or AKI) were already presenting them at time of admission. Based
232 on this result we may speculate, again, that the outcome of our cohort could have been affected by
233 the time of PICU-admission and that an earlier PICU-admission should be considered for this
234 category of patients, likely with the help of appropriate tools of risk-evaluation.
235 An appropriate useful tool is represented by the Pediatric Early Warning Score (PEWS), recently
236 demonstrated as a valid risk-measure to improve the identification of oncohematologic patients who
237 need intensive care treatments. [34,35,36,37]
238 Our study certainly has some limitations: the retrospective design inevitably implicates missing-
239 data and recall biases. The possibility to start the first care as HFOT or dopamine infusion out of
240 PICU could affect our study as a selection bias. The single-center setting and the relatively small
241 sample of patients requiring a PICU-admission reduce the statistical power and the possibility to
242 perform a reliable inference for the whole pediatric population. The study period is relatively long
243 and could be affected by modification of guidelines and clinical practice, even if the statistical
244 analysis in the two temporal-cohorts confirmed our results for both periods. Nevertheless, we think
245 that our study reported important data regarding the non-HSCT population, drawing attention to its
246 susceptibility to sepsis and hemodynamic instability and underlying the specific intensive care
247 needs of this category of patients.
248
249 **Conclusions**
250 A relatively small percentage of non-HSCT oncohematologic pediatric patients required a PICU-

admission, but the mortality rate is still high, especially in the first days after admission. The main causes of admission were respiratory failure, sepsis and seizures. The presence of hemodynamic instability, DIC and renal failure, but not the presence of respiratory failure or need for mechanical ventilation, represented significant predictors of mortality. Further strategies for early identification of these factors and the accurate timing of PICU-admission are strongly needed to optimize care.

Conflict of interest statement: The authors declare that there is no conflict of interest.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures and Tables

FIGURE 1 Cumulative 90-day mortality of non-HSCT oncohematologic patients who required PICU admission.

TABLE 1 Univariate predictors of 90-day mortality at PICU admission (n=63 patients).

TABLE 2 Univariate predictors of 90-day mortality during PICU stay (n=63 patients).

TABLE 3 Multivariate predictors of 90-day mortality at PICU admission (n=63 patients).

TABLE 4 Multivariate predictors of 90-day mortality during PICU stay (n=63 patients).

SUPPORTING INFORMATION FILE 1 Supplemental univariate and multivariate analyses during periods 1999-2008 (n=33) and 2009-2015 (n=30).

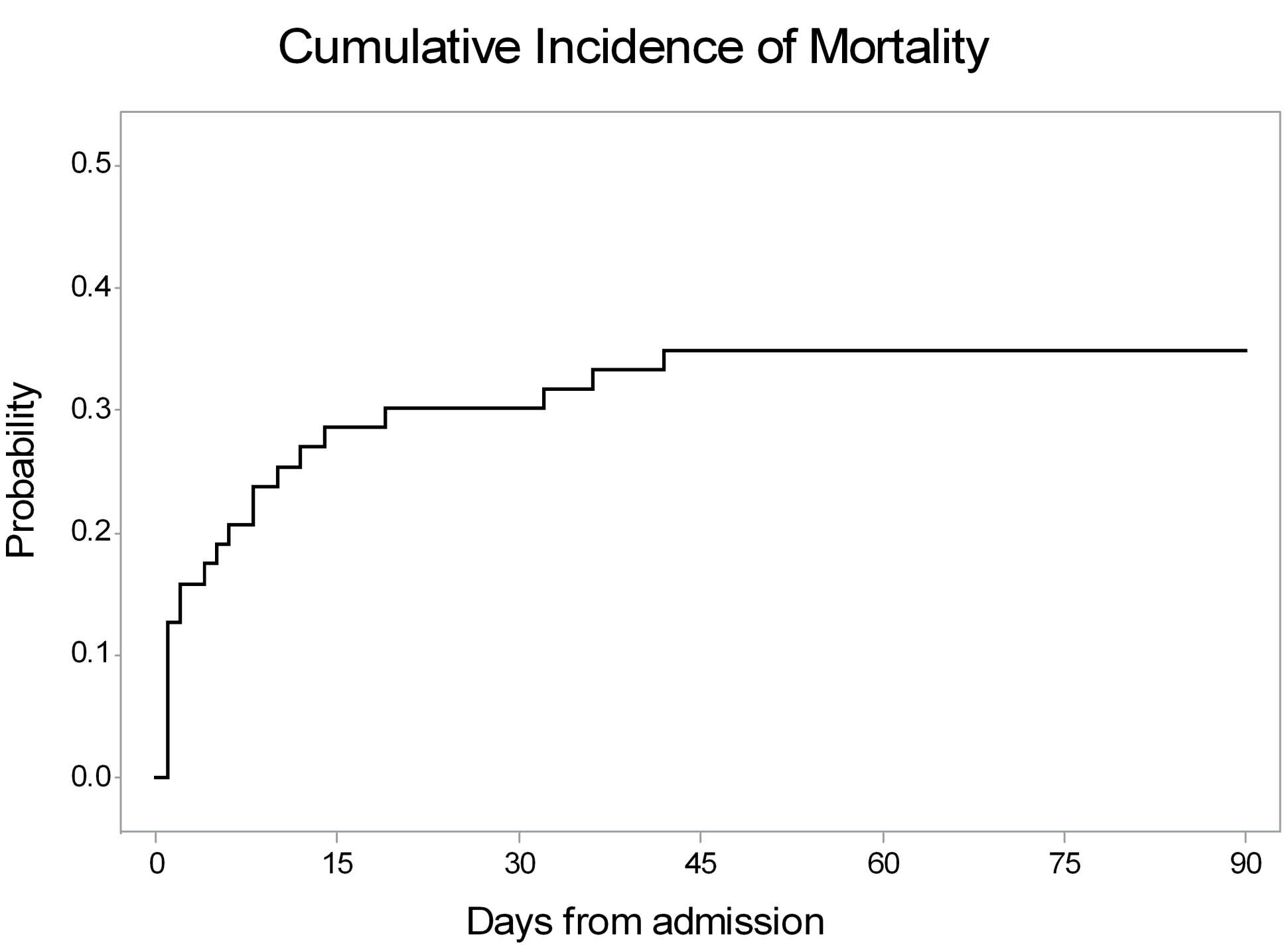
Cumulative Incidence of Mortality
Probability
0.5
0.4
0.3
0.2
0.1
0.0
0
15
30
45
60
75
90
Days from admission

TABLE 1 Univariate predictors of 90-day mortality at PICU admission (n=63 patients).

	N (n tot=63)	Non-survivors n=22 n (%)	Survivors n=41 n (%)	Cumulative probability of 90-day survival (CI 95%)	p value
Gender					
Male	38 (60%)	13 (34%)	25 (66%)	65.8% (52.3-82.7)	0.943
Female	25 (40%)	9 (36%)	16 (64%)	64.0% (47.7-85.9)	
Age*					
≤ 6.6 years	32 (51%)	11 (34%)	21 (66%)	65.3% (51.0-84.3)	0.954
> 6.6 years	31 (49%)	11 (35%)	20 (65%)	64.5% (49.7-83.8)	
Underlying disease					
ALL	22 (35%)	7 (32%)	15 (68%)	68.2% (51.3-90.7)	
AML+MDS	10 (16%)	5 (50%)	5 (50%)	50.0% (26.9-92.9)	
HL	2 (3%)	0 (0%)	2 (100%)	-	0.752
NHL	10 (16%)	4 (40%)	6 (60%)	60.0% (36.2-99.5)	
Solid tumor	15 (24%)	5 (33%)	10 (67%)	66.7% (46.6-95.3)	
Hematological non-malignant diseases	4 (6%)	1 (25%)	3 (75%)	75.0% (42.6-100)	
Group of diagnosis					
Hematologic disease	47 (75%)	17 (36%)	30 (64%)	63.8% (51.5-79.2)	0.577
Non-hematologic disease	16 (25%)	5 (31%)	11 (69%)	68.7% (49.4-95.7)	
Group of diagnosis					
Neoplastic disease	59 (94%)	21 (36%)	38 (64%)	64.4% (53.5-77.9)	0.742
Non-neoplastic disease**	4 (6%)	1 (25%)	3 (75%)	75.0% (42.6-100)	
Treatment phase					
No-therapy	6 (10%)	1 (17%)	5 (83%)	83.3% (58.3-100)	
Induction	36 (57%)	12 (33%)	24 (67%)	66.7% (52.9-84.0)	0.472
Consolidation	11 (17%)	3 (27%)	8 (73%)	72.7% (50.6-100)	
Reinduction	2 (3%)	1 (50%)	1 (50%)	50.0% (12.5-100)	
Maintenance	8 (13%)	5 (62%)	3 (38%)	37.5% (15.3-91.7)	
HFOT	7 (11%)	4 (57%)	3 (43%)	42.9% (18.2-100)	0.313
PARDS	20 (32%)	9 (45%)	11 (55%)	55.0% (37.0-81.8)	0.175
PARDS severity					
Mild	2 (3%)	1 (50%)	1 (50%)	50.0% (12.5-100)	
Moderate	11 (17%)	5 (46%)	6 (54%)	54.5% (31.8-93.6)	0.587
Severe	7 (11%)	3 (43%)	4 (57%)	57.1% (30.0-100)	
PaO2/FiO2***					
>300	14 (33%)	5 (36%)	9 (64%)	64.3% (43.5-95.0)	
201-300	4 (9%)	1 (25%)	3 (75%)	75.0% (42.6-100)	0.885
101-200	17 (39%)	6 (35%)	11 (65%)	64.7% (45.5-91.9)	
<100	8 (19%)	3 (38%)	5 (62%)	62.5% (36.5-100)	
Inotropic Drugs	37 (59%)	14 (38%)	23 (62%)	62.2% (48.3-79.9)	0.592
Fluid overload					
1-5%	12 (19%)	4 (33%)	8 (67%)	66.7% (44.7-99.5)	
5-10%	11 (17%)	2 (18%)	9 (82%)	81.8% (61.9-100)	0.646
>10%	12 (19%)	5 (42%)	7 (58%)	58.3% (36.2-94.1)	
Septic shock	28 (44%)	13 (46%)	15 (54%)	53.6% (37.9-75.6)	0.060
DIC	18 (29%)	7 (39%)	11 (61%)	61.1% (42.3-88.3)	0.601
Hepatic failure	20 (32%)	7 (35%)	13 (65%)	65.0% (47.1-89.7)	0.918
AKI	17 (27%)	12 (71%)	5 (29%)	29.4% (14.1-61.4)	<0.001
AKI Severity					
KDIGO 1	6 (9%)	4 (67%)	2 (33%)	33.3% (10.8-100)	
KDIGO 2	5 (8%)	4 (80%)	1 (20%)	20.0% (3.5-100)	<0.001
KDIGO 3	6 (9%)	4 (67%)	2 (33%)	33.3% (10.8-100)	
MOF	36 (57%)	15 (42%)	21 (58%)	58.3% (44.3-76.9)	0.169
PIM 3					
<0.2	51 (81%)	15 (29%)	36 (71%)	70.6% (59.1-84.3)	0.037
≥0.2	12 (19%)	7 (58%)	5 (42%)	41.7% (21.3-81.4)	

Legend: AKI: Acute Kidney Injury, ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; DIC: Disseminated Intravascular Coagulation; HL: Hodgkin Lymphoma; HFOT: High Flow Oxygen Therapy; MDS: Myelodysplastic Syndrome; NHL: Non-Hodgkin Lymphoma; PaO2/FiO2: arterial partial Oxygen Pressure/Fraction of Oxygen; PARDS: Pediatric Acute Respiratory Distress Syndrome; PIM 3: Pediatric Index of Mortality score 3. *The cut-off value is the median of the distribution. ** Patients were affected by genetic Hemophagocytic Lymphohistiocytosis (n=1), acquired Hemophagocytic Lymphohistiocytosis (n=1), Omenn Syndrome (n=1), Aplastic Anemia (n=1) ***Twenty missing observations.

TABLE 2 Univariate predictors of 90-day mortality during PICU stay (n=63 patients).

	N (n tot=63)	Non-survivors n=22 n (%)	Survivors n=41 n (%)	p value
HFOT	7 (11%)	3 (43%)	4 (57%)	0.687
NIV	11 (17%)	4 (36%)	7 (64%)	1
Invasive MV	33 (52%)	13 (39%)	20 (61%)	0.435
HFOV	2 (32%)	1 (50%)	1 (50%)	1
MV	37 (59%)	14 (38%)	23 (62%)	0.562
PARDS	26 (41%)	11 (42%)	15 (58%)	0.421
PARDS Severity Mild Moderate Severe	 4 (6%) 13 (21%) 9 (14%)	 2 (50%) 5 (38%) 4 (44%)	 2 (50%) 8 (62%) 5 (56%)	0.666
PaO2/FiO2* >300 201-300 101-200 <100	 10 (23%) 9 (21%) 17 (40%) 7 (16%)	 2 (20%) 5 (56%) 5 (30%) 3 (43%)	 8 (80%) 4 (44%) 12 (70%) 4 (57%)	0.372
iNO	2 (3%)	1 (50%)	1 (50%)	1
Sepsis	32 (51%)	14 (44%)	18 (56%)	0.188
Septic shock	28 (44%)	13 (46%)	15 (54%)	0.113
Inotropic drugs	37 (59%)	15 (41%)	22 (59%)	0.296
Number of inotropic drugs 1 2 3 4	 21 (33%) 8 (13%) 5 (8%) 3 (5%)	 7 (33%) 2 (25%) 4 (80%) 2 (67%)	 14 (67%) 6 (75%) 1 (20%) 1 (33%)	0.146
Number of inotropic drugs ≤2 >2	 55 (87%) 8 (13%)	 16 (29%) 6 (75%)	 39 (71%) 2 (25%)	0.018
Cardiac arrest	13 (21%)	10 (77%)	3 (23%)	<0.001
DIC	23 (36%)	15 (65%)	8 (35%)	<0.001
Aspergillosis	9 (14%)	6 (67%)	3 (33%)	0.055
Hepatic failure	20 (32%)	11 (55%)	9 (45%)	0.045
AKI	18 (29%)	12 (67%)	6 (33%)	0.001
AKI severity KDIGO 1 KDIGO 2-3	 2 (3%) 16 (25%)	 1 (50%) 11 (69%)	 1 (50%) 5 (32%)	0.002
CRRT	5 (8%)	3 (60%)	2 (40%)	0.333
MOF	37 (59%)	18 (49%)	19 (51%)	0.008
ECMO	2 (3%)	1 (50%)	1 (50%)	1

Legend: AKI: Acute Kidney Injury; CRRT: Continuous Renal Replacement Therapy; DIC: Disseminated Intravascular Coagulation; ECMO: Extracorporeal Membrane Oxygenation; HFOT: High Flow Oxygen Therapy; HFOV: High Frequency Oscillatory Ventilation; MOF: Multi-Organ Failure; MV: Mechanical Ventilation; NIV: Non-Invasive Ventilation; iNO: inhaled Nitrogen Oxide; PaO2/FiO2: arterial partial Oxygen Pressure/Fraction of Oxygen; PARDS: Pediatric Acute Respiratory Distress Syndrome. *Twenty missing observations.

TABLE 3 Multivariate predictors of 90-day mortality at PICU admission (n=63 patients).

Variable	Estimate	OR (95% CI)	SE	p value
Septic shock	0.617	1.85 (0.78-4.39)	0.439	0.160
AKI	1.475	4.37 (1.85-10.31)	0.438	<0.001

Legend: AKI: Acute Kidney Injury; OR: Odd Ratio; SE: Standard Error.

TABLE 4 Multivariate predictors of 90-day mortality during PICU stay (n=63 patients).

Variable	Estimate	OR (95% CI)	SE	p value
Hepatic failure	-0.498	0.608 (0.11-3.42)	0.882	0.572
Cardiac arrest	2.696	14.820 (2.1 – 105.7)	1.002	0.007
Aspergillosis	0.475	1.608 (0.22-11.62)	1.009	0.638
AKI	1.828	6.220 (1.32-29.39)	0.792	0.021
DIC	2.276	9.736 (1.87-50.74)	0.842	0.007

Legend: AKI: Acute Kidney Injury, DIC: Disseminated Intravascular Coagulation; OR: Odd Ratio; SE: Standard Error.

SUPPORTING INFORMATION FILE 1

Supplemental Table 1.1. Univariate predictors of 90-day mortality at PICU admission for patients admitted by December 2008 (n=33 patients).

	Total	90-day mortality		Cumulative probability of survival (CI 95%)	p value
		Yes, n. (%)	No, n. (%)		
Gender					
Male	23	7 (30.4%)	16 (69.6%)	69.6% (53.1-91.2)	0.991
Female	10	3 (30.0%)	7 (70.0%)	70.0% (46.7-100)	
Age*					
≤ 6.6 years	16	4 (25.0%)	12 (75.0%)	75.0% (56.5-99.5)	0.523
> 6.6 years	17	6 (35.3%)	11 (64.7%)	64.7% (45.5-91.9)	
Underlying disease					
ALL	10	2 (20.0%)	8 (80.0%)	80.0% (58.7-100)	
AML+MDS	8	4 (50.0%)	4 (50.0%)	50.0% (25.0-100)	
HL	2	0 (0.0%)	2 (100%)	-	0.346
NHL	6	3 (50.0%)	3 (50.0%)	50.0% (22.5-100)	
Solid tumor	7	1 (14.3%)	6 (85.7%)	85.7% (63.3-100)	
Hematological non-malignant disease	0	-	-	-	
Group of diagnosis					
Hematologic disease	25	9 (36.0%)	16 (64.0%)	64.0% (47.7-85.9)	0.216
Non-hematologic disease	8	1 (12.5%)	7 (87.5%)	87.5% (67.3-100)	
Group of diagnosis					
Neoplastic disease	33	10 (30.3%)	23 (69.7%)	-	-
Non-neoplastic disease	0	-	-	-	
Treatment phase					
No-therapy	5	1 (20.0%)	4 (80.0%)	80.0% (51.6-100)	
Induction	18	5 (27.8%)	13 (72.2%)	72.2% (54.2-96.2)	0.629
Consolidation	6	3 (50.0%)	3 (50.0%)	50.0% (22.5-100)	
Reinduction	0	-	-	-	
Maintenance	4	1 (25.0%)	3 (75.0%)	75.0% (42.6-100)	
HFOT					
No	32	10 (31.3%)	22 (68.7%)	68.7% (54.4-86.8)	0.541
Yes	1	0 (0.0%)	1 (100%)	100% (100-100)	
PARDS					
No	22	5 (22.7%)	17 (77.3%)	77.3% (61.6-96.9)	0.105
Yes	11	5 (45.5%)	6 (54.5%)	54.5% (31.8-96.9)	
PARDS severity					
No PARDS	22	5 (22.7%)	17 (77.3%)	77.3% (61.6-96.9)	
Mild	0	-	-	-	0.096
Moderate	8	3 (37.5%)	5 (62.5%)	62.5% (36.5-100)	
Severe	3	2 (66.7%)	1 (33.3%)	33.3% (6.7-100)	
PaO2/FiO2**					
>300	10	3 (30.0%)	7 (70.0%)	70.0% (46.7-100)	
201-300	3	1 (33.3%)	2 (66.7%)	66.7% (30.0-100)	0.976
101-200	8	2 (25.0%)	6 (75.0%)	75.0% (50.3-100)	
<100	3	1 (33.3%)	2 (66.7%)	66.7% (30.0-100)	
Inotropic Drugs					
No	10	3 (30.0%)	7 (70.0%)	70.0% (46.7-100)	0.989
Yes	23	7 (30.4%)	16 (69.6%)	69.6% (53.1-91.2)	

Fluid overload					
0	17	7 (41.2%)	10 (58.8%)	58.8% (39.5-87.6)	
1-5%	5	2 (40.0%)	3 (60.0%)	60.0% (29.3-100)	0.313
5-10%	7	1 (14.3%)	6 (85.7%)	85.7% (63.3-100)	
>10%	4	0 (0.0%)	4 (100%)	100% (100-100)	
Septic shock					
No	17	4 (23.5%)	13 (76.5%)	76.5% (58.7-99.5)	0.322
Yes	16	6 (37.5%)	10 (62.5%)	62.5% (42.8-91.4)	
DIC					
No	23	7 (30.4%)	16 (69.6%)	69.6% (53.1-91.2)	0.970
Yes	10	3 (30.0%)	7 (70.0%)	70.0% (46.7-100)	
Hepatic failure					
No	24	8 (33.3%)	16 (66.7%)	66.7% (50.2-88.5)	0.538
Yes	9	2 (22.2%)	7 (77.8%)	77.8% (54.9-100)	
AKI					
No	25	5 (20.0%)	20 (80.0%)	80.0% (65.8-97.3)	0.018
Yes	8	5 (62.5%)	3 (37.5%)	37.5% (15.3-91.7)	
AKI Severity					
No AKI	25	5 (20.0%)	20 (80.0%)	80.0% (65.8-97.3)	
KDIGO 1	2	0 (0.0%)	2 (100%)	100% (100-100)	0.003
KDIGO 2	3	2 (66.7%)	1 (33.3%)	33.3% (6.7-100)	
KDIGO 3	3	3 (100%)	0 (0.0%)	0.0%	
MOF					
No	16	4 (25.0%)	12 (75.0%)	75.0% (56.5-99.5)	0.443
Yes	17	6 (35.3%)	11 (64.7%)	64.7% (45.5-91.9)	
PIM 3					
<0.2	28	8 (28.6%)	20 (71.4%)	71.4% (56.5-90.3)	0.545
≥0.2	5	2 (40.0%)	3 (60.0%)	60.0% (29.3-100)	

Legend: AKI: Acute Kidney Injury, ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; DIC: Disseminated Intravascular Coagulation; HL: Hodgkin Lymphoma; HFOT: High Flow Oxygen Therapy; MDS: Myelodysplastic Syndrome; NHL: Non-Hodgkin Lymphoma; PaO2/FiO2: arterial partial Oxygen Pressure/Fraction of Oxygen; PARDS: Pediatric Acute Respiratory Distress Syndrome; PIM 3: Pediatric Index of Mortality score 3. *The cut-off value is the median of the distribution in the entire sample. **Nine missing observations.

Supplemental Table 1.2. Univariate predictors of 90-day mortality at PICU admission for patients admitted since January 2009 (n=30 patients).

	Total	90-day mortality		Cumulative probability of survival (CI 95%)	p value
		Yes, n. (%)	No, n. (%)		
Gender					
Male	15	6 (40.0%)	9 (60.0%)	60.0% (39.7-90.7)	0.896
Female	15	6 (40.0%)	9 (60.0%)	60.0% (39.7-90.7)	
Age*					
≤ 6.6 years	16	7 (43.8%)	9 (56.2%)	56.2% (36.5-86.7)	0.615
> 6.6 years	14	5 (35.7%)	9 (64.3%)	64.3% (43.5-95.0)	
Underlying disease					
ALL	12	5 (41.7%)	7 (58.3%)	58.3% (36.2-94.1)	
AML+MDS	2	1 (50.0%)	1 (50.0%)	50.0% (12.5-100)	
HL	0	-	-	-	0.920
NHL	4	1 (25.0%)	3 (75.0%)	75.0% (42.6-100)	
Solid tumor	8	4 (50.0%)	4 (50.0%)	50.0% (25.0-100)	
Hematological non-malignant	4	1 (25.0%)	3 (75.0%)	75.0% (42.6-100)	
Group of diagnosis					
Hematologic disease	22	8 (36.4%)	14 (63.6%)	63.6% (46.4-87.3)	0.709
Non hematologic disease	8	4 (50.0%)	4 (50.0%)	50.0% (25.0-100)	
Group of diagnosis					
Neoplastic disease	26	11 (42.3%)	15 (57.7%)	57.7% (41.5-80.2)	0.614
Non neoplastic disease	4	1 (25.0%)	3 (75.0%)	75.0% (42.6-100)	
Treatment phase					
No-therapy	1	0 (0.0%)	1 (100%)	100% (100-100)	
Induction	18	7 (38.9%)	11 (61.1%)	61.1% (42.3-88.3)	0.084
Consolidation	5	0 (0.0%)	5 (100%)	100% (100-100)	
Reinduction	2	1 (50.0%)	1 (50.0%)	50.0% (12.5-100)	
Maintenance	4	4 (100%)	0 (0.0%)	0.0%	
HFOT					
No	24	8 (33.3%)	16 (66.7%)	66.7% (50.2-88.5)	0.5248
Yes	6	4 (66.7%)	2 (33.3%)	33.3% (10.8-100)	
PARDS					
No	21	8 (38.1%)	13 (61.9%)	61.9% (44.3-86.6)	0.770
Yes	9	4 (44.4%)	5 (55.6%)	55.6% (31.0-99.7)	
PARDS severity					
No PARDS	21	8 (38.1%)	13 (61.9%)	61.9% (44.3-86.6)	
Mild	2	1 (50.0%)	1 (50.0%)	50.0% (12.5-100)	0.662
Moderate	3	2 (66.7%)	1 (33.3%)	33.3% (6.7-100)	
Severe	4	1 (25.0%)	3 (75.0%)	75.0% (42.6-100)	
PaO2/FiO2**					
>300	4	2 (50.0%)	2 (50.0%)	50.0% (18.8-100)	
201-300	1	0 (0.0%)	1 (100%)	100% (100-100)	0.865
101-200	9	4 (44.4%)	5 (55.6%)	55.6% (31.0-99.7)	
<100	5	2 (40.0%)	3 (60.0%)	60.0% (29.3-100)	
Inotropic Drugs					
No	16	5 (31.3%)	11 (68.7%)	68.7% (49.4-95.7)	0.324
Yes	14	7 (50.0%)	7 (50.0%)	50.0% (29.6-84.4)	

Fluid overload					
0	11	4 (36.4%)	7 (63.6%)	63.6% (40.7-99.5)	
1-5%	7	2 (28.6%)	5 (71.4%)	71.4% (44.7-100)	0.625
5-10%	4	1 (25.0%)	3 (75.0%)	75.0% (42.6-100)	
>10%	8	5 (62.5%)	3 (37.5%)	37.5% (15.3-91.7)	
Septic shock					
No	18	5 (27.8%)	13 (72.2%)	72.2% (54.2-96.2)	0.064
Yes	12	7 (58.3%)	5 (41.7%)	41.7% (21.3-81.4)	
DIC					
No	22	8 (36.4%)	14 (63.6%)	63.6% (46.4-87.3)	0.374
Yes	8	4 (50.0%)	4 (50.0%)	50.0% (25.0-100)	
Hepatic failure					
No	19	7 (36.8%)	12 (63.2%)	63.2% (44.8-89.0)	0.748
Yes	11	5 (45.5%)	6 (54.5%)	54.5% (31.8-93.6)	
AKI					
No	21	5 (23.8%)	16 (76.2%)	76.2% (60.0-96.8)	0.002
Yes	9	7 (77.8%)	2 (22.2%)	22.2% (6.5-75.4)	
AKI Severity					
No AKI	21	5 (23.8%)	16 (76.2%)	76.2% (60.0-96.8)	
KDIGO 1	4	4 (100%)	0 (0.0%)	0.0%	<0.001
KDIGO 2	2	2 (100%)	0 (0.0%)	0.0%	
KDIGO 3	3	1 (33.3%)	2 (66.7%)	66.7% (30.0-100)	
MOF					
No	11	3 (27.3%)	8 (72.7%)	72.7% (50.6-100)	0.284
Yes	19	9 (47.4%)	10 (52.6%)	52.6% (34.4-80.6)	
PIM 3					
<0.2	23	7 (30.4%)	16 (69.6%)	69.6% (53.1-91.2)	0.028
≥0.2	7	5 (71.4%)	2 (28.6%)	28.6% (8.9-92.2)	

Legend: AKI: Acute Kidney Injury, ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; DIC: Disseminated Intravascular Coagulation; HL: Hodgkin Lymphoma; HFOT: High Flow Oxygen Therapy; MDS: Myelodysplastic Syndrome; NHL: Non-Hodgkin Lymphoma; PaO2/FiO2: arterial partial Oxygen Pressure/Fraction of Oxygen; PARDS: Pediatric Acute Respiratory Distress Syndrome; PIM 3: Pediatric Index of Mortality score 3. *The cut-off value is the median of the distribution in the entire sample. **Eleven missing observations.

Supplemental Table 2.1 Multivariate predictors of 90-day mortality at PICU admission for patients admitted by December 2008 (n=33 patients).

Variable	Estimate	OR (95% CI)	SE	p value
Septic shock	0.414	1.51 (0.41- 5.56)	0.664	0.534
AKI	1.307	3.69 (1.03-13.23)	0.651	0.045

Legend: AKI: Acute Kidney Injury, PIM 3: Pediatric Index of Mortality score 3; OR: Odd Ratio; SE: Standard Error.

Supplemental Table 2.2. Multivariate predictors of 90-day mortality at PICU admission for patients admitted since January 2009 (n=30 patients).

Variable	Estimate	OR (95% CI)	SE	p value
Septic shock	1.201	3.32 (0.98-11.26)	0.623	0.054
AKI	1.804	6.07 (1.77-20.82)	0.629	0.004

Legend: AKI: Acute Kidney Injury, PIM 3: Pediatric Index of Mortality score 3, OR: Odd Ratio; SE: Standard Error.

Supplemental Table 3.1. Univariate predictors of 90-day mortality during PICU stay for patients admitted by December 2008 (n=33 patients).

	Total	90-day mortality		p value
		Yes, n. (%)	No, n. (%)	
HFOT				
No	33	10 (30.3%)	23 (69.7%)	-
Yes	0	-	-	
NIV				
No	29	9 (31.0%)	20 (69.0%)	1
Yes	4	1 (25.0%)	3 (75.0%)	
IV				
No	20	6 (30.0%)	14 (70.0%)	1
Yes	13	4 (30.8%)	9 (69.2%)	
HFOV				
No	33	10 (30.3%)	23 (69.7%)	-
Yes	0	-	-	
PARDS				
No	16	3 (18.8%)	13 (81.2%)	0.259
Yes	17	7 (41.2%)	10 (58.8%)	
PARDS				
No	16	3 (18.8%)	13 (81.2%)	0.270
Mild	1	1 (100%)	0 (0.0%)	
Moderate	11	4 (36.4%)	7 (63.6%)	
Severe	5	2 (40.0%)	3 (60.0%)	
PaO2/FiO2*				
>300	6	1 (16.7%)	5 (83.3%)	0.424
201-300	5	3 (60.0%)	2 (40.0%)	
101-200	11	3 (27.3%)	8 (72.7%)	
<100	2	1 (50.0%)	1 (50.0%)	
iNO				
No	33	10 (30.3%)	23 (69.7%)	1
Yes	0	-	-	
Sepsis				
No	16	4 (25.0%)	12 (75.0%)	0.708
Yes	17	6 (35.3%)	11 (64.7%)	
Septic shock				
No	17	4 (23.5%)	13 (76.5%)	0.465
Yes	16	6 (37.5%)	10 (62.5%)	
Inotropic drugs				
No	12	3 (25.0%)	9 (75.0%)	0.710
Yes	21	7 (33.3%)	14 (66.7%)	
Number of inotropic drugs				
0	12	3 (25.0%)	9 (75.0%)	0.904
1	14	4 (28.6%)	10 (71.4%)	
2	3	1 (33.3%)	2 (66.7%)	
3	2	1 (50.0%)	1 (50.0%)	
4	2	1 (50.0%)	1 (50.0%)	

Number of inotropic drugs ≤2 >2	 29 4	 8 (27.6%) 2 (50.0%)	 21 (72.4%) 2 (50.0%)	0.567
Cardiac arrest No Yes	 27 6	 5 (18.5%) 5 (83.3%)	 22 (81.5%) 1 (16.7%)	0.005
DIC No Yes	 23 10	 4 (17.4%) 6 (60.0%)	 19 (82.6%) 4 (40.0%)	0.035
Aspergillosis No Yes	 29 4	 7 (24.1%) 3 (75.0%)	 22 (75.9%) 1 (25.0%)	0.073
Hepatic failure No Yes	 21 12	 4 (19.0%) 6 (50.0%)	 17 (81.0%) 6 (50.0%)	0.114
AKI No Yes	 24 9	 5 (20.8%) 5 (55.6%)	 19 (79.2%) 4 (44.4%)	0.090
AKI severity No KDIGO 1 KDIGO 2-3	 24 1 8	 5 (20.8%) 0 (0.0%) 5 (62.5%)	 19 (79.2%) 1 (100%) 3 (37.5%)	0.071
CVVH No Yes	 32 1	 9 (28.1%) 1 (100%)	 23 (71.9%) 0 (0.0%)	0.303
MOF No Yes	 14 19	 2 (14.3%) 8 (42.1%)	 12 (85.7%) 11 (57.9%)	0.131
ECMO No Yes	 33 0	 10 (30.3%) -	 23 (69.7%) -	-

Legend: AKI: Acute Kidney Injury; CVVH: Continuous Veno-Venous Hemofiltration; DIC: Disseminated Intravascular Coagulation; ECMO: Extracorporeal Membrane Oxygenation; HFOT: High Flow Oxygen Therapy; HFOV: High Frequency Oscillatory Ventilation; IV: Invasive Ventilation; MOF: Multi-Organ Failure; NIV: Non-Invasive Ventilation; iNO: inhaled Nitrogen Oxide; PaO2/FiO2: arterial partial Oxygen Pressure/Fraction of Oxygen; PARDS: Pediatric Acute Respiratory Distress Syndrome. *Nine missing observations.

Supplemental Table 3.2. Univariate predictors of 90-day mortality during PICU stay for patients admitted since January 2009 (n=30 patients).

	Total	90-day mortality		p value
		Yes, n. (%)	No, n. (%)	
HFOT				
No	23	9 (39.1%)	14 (60.9%)	1
Yes	7	3 (42.9%)	4 (57.1%)	
NIV				
No	24	9 (37.5%)	15 (62.5%)	0.660
Yes	6	3 (50.0%)	3 (50.0%)	
IV				
No	18	5(27.8%)	13 (72.2%)	0.136
Yes	12	7 (58.3%)	5 (41.7%)	
HFOV				
No	28	11 (39.3%)	17 (60.7%)	1
Yes	2	1 (50.5%)	1 (50.5%)	
PARDS				
No	21	8 (38.1%)	13 (61.9%)	1
Yes	9	4 (44.4%)	5 (55.6%)	
PARDS				
No	21	8 (38.1%)	13 (61.9%)	1
Mild	3	1 (33.3%)	2 (66.7%)	
Moderate	2	1 (50.0%)	1 (50.0%)	
Severe	4	2 (50.0%)	2 (50.0%)	
PaO2/FiO2*				
>300	4	1 (25.0%)	3 (75.0%)	1
201-300	4	2 (50.0%)	2 (50.0%)	
101-200	6	2 (33.3%)	4 (66.7%)	
<100	5	2 (40.0%)	3 (60.0%)	
iNO				
No	28	11 (39.3%)	17 (60.7%)	1
Yes	2	1 (50.0%)	1 (50.0%)	
Sepsis				
No	15	4 (26.7%)	11 (73.3%)	0.264
Yes	15	8 (53.3%)	7 (46.7%)	
Septic shock				
No	18	5 (27.8%)	13 (72.2%)	0.136
Yes	12	7 (58.3%)	5 (41.6%)	
Inotropic drugs				
No	14	4 (28.6%)	10 (71.4%)	0.284
Yes	16	8 (50.0%)	8 (50.0%)	
Number of inotropic drugs				
0	14	4 (28.6%)	10 (71.4%)	0.090
1	7	3 (42.9%)	4 (57.1%)	
2	5	1 (20.0%)	4 (80.0%)	
3	3	3 (100%)	0 (0.0%)	
4	1	1 (100%)	0 (0.0%)	

Number of inotropic drugs ≤2 >2	 26 4	 8 (30.8%) 4 (100%)	 18 (69.2%) 0 (0.0%)	0.018
Cardiac arrest No Yes	 23 7	 7 (30.4%) 5 (71.4%)	 16 (69.6%) 2 (28.6%)	0.084
DIC No Yes	 17 13	 3 (17.6%) 9 (69.2%)	 14 (82.4%) 4 (30.8%)	0.008
Aspergillosis No Yes	 25 5	 9 (36.0%) 3 (60.0%)	 16 (64.0%) 2 (40.0%)	0.364
Hepatic failure No Yes	 22 8	 7 (31.8%) 5 (62.5%)	 15 (68.2%) 3 (37.5%)	0.210
AKI No Yes	 21 9	 5 (23.8%) 7 (77.8%)	 16 (76.2%) 2 (22.2%)	0.013
AKI severity No KDIGO 1 KDIGO 2-3	 21 1 8	 5 (23.8%) 1 (100%) 6 (75.0%)	 16 (76.2%) 0 (0.0%) 2 (25.0%)	0.017
CVVH No Yes	 26 4	 10 (38.5%) 2 (50.0%)	 16 (61.5%) 2 (50.0%)	1
MOF No Yes	 12 18	 2 (16.7%) 10 (55.6%)	 10 (83.3%) 8 (44.4%)	0.058
ECMO No Yes	 28 2	 11 (39.3%) 1 (50.0%)	 17 (60.7%) 1 (50.0%)	1

Legend: AKI: Acute Kidney Injury; CVVH: Continuous Veno-Venous Hemofiltration; DIC: Disseminated Intravascular Coagulation; ECMO: Extracorporeal Membrane Oxygenation; HFOT: High Flow Oxygen Therapy; HFOV: High Frequency Oscillatory Ventilation; IV: Invasive Ventilation; MOF: Multi-Organ Failure; NIV: Non-Invasive Ventilation; iNO: inhaled Nitrogen Oxide; PaO2/FiO2: arterial partial Oxygen Pressure/Fraction of Oxygen; PARDS: Pediatric Acute Respiratory Distress Syndrome. *Eleven missing observations.

Supplemental Table 4.1. Multivariate predictors of 90-day mortality during PICU stay for patients admitted by December 2008 (n=33 patients).

Variable	Estimate	OR (95% CI)	SE	p value
Hepatic failure	0.332	1.394 (0.10-19.31)	1.341	0.804
Cardiac arrest	4.017	55.538 (2.28-1351.5)	1.629	0.014
Aspergillosis	1.544	4.684 (0.21-104.5)	1.584	0.330
AKI	1.994	7.342 (0.53-102.7)	1.346	0.139
DIC	1.921	6.830 (0.40-117.9)	1.453	0.186

Legend: AKI: Acute Kidney Injury, DIC: Disseminated Intravascular Coagulation, OR: Odd Ratio; SE: Standard Error.

Supplemental Table 4.2. Multivariate predictors of 90-day mortality during PICU stay for patients admitted since January 2009 (n=30 patients).

Variable	Estimate	OR (95% CI)	SE	p value
Hepatic failure	-0.952	0.386 (0.03-5.3)	1.336	0.476
Cardiac arrest	1.657	5.244 (0.38-71.6)	1.333	0.214
Aspergillosis	0.020	1.020 (0.07-15.69)	1.394	0.989
AKI	2.183	8.875 (0.85-92.21)	1.194	0.068
DIC	2.488	12.034 (1.25-115.5)	1.154	0.031

Legend: AKI: Acute Kidney Injury, DIC: Disseminated Intravascular Coagulation; OR: Odd Ratio; SE: Standard Error.