Mortality in Patients with Leukemia and Lymphoma Urgently Admitted to the PICU: Secondary Analysis of Data from a Cluster Randomized Controlled Trial

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Abstract

Objectives were to describe the severity of illness in patients with leukemia or lymphoma urgently admitted to pediatric intensive care and explores the risk factors for mortality. A secondary analysis was performed of prospectively collected data from a cluster-randomized controlled trial in 21 children's hospitals from 2011 to 2015. Eligible patients were urgently admitted to intensive care and had a diagnosis of leukemia or lymphoma. Associations with intensive care mortality (primary outcome) were determined with multivariable generalized estimating equation with a logit link, accounting for clustering by site. Associations with time to intensive care mortality (secondary outcome) were determined with multivariable proportional hazards models. A total of 109 patients were included, age 115 (interquartile range [IQR] 42, 168) months and intensive care length of stay was 3 (IQR 2, 6) days. During the first hour in intensive care 36 (33%) were ventilated, and during intensive care 45 (41.3%) had at least 1 technology day. Day 1 Pediatric Logistic Organ Dysfunction (PELOD) score was $\geq$ 20 in 37 (33.9%), Pediatric Index of Mortality 2 mortality risk was $>$ 10% in 35 (32.1%), and Children's Resuscitation Intensity Scale (RISC) was $\geq$ 3 (late admission to intensive care) in 32 (31.7%). Intensive care mortality was 20/109 (18.3%); with intensive care stay $\geq$ 20 days mortality was 51%. Previous urgent pediatric intensive care unit (PICU) admission, mechanical ventilation, and day 1 PELOD score were associated with higher PICU mortality. Mechanical ventilation, day 1 PELOD score, and late admission to the PICU (RISC $\geq$ 2) were associated with time to death. Patients with leukemia and lymphoma urgently admitted to intensive care had mortality of 18.3%, an improvement from historical cohorts. Risk factors were not accurate enough to make individual patient care decisions.

Keywords

- pediatric critical care
- pediatric intensive care
- leukemia
- lymphoma
- mortality
- oncology

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Introduction

Up to 40% of children with cancer are admitted to a pediatric intensive care unit (PICU) during their treatment course with published ICU mortality of 27.8%, much higher than the average PICU mortality rate of 2.5 to 5%.[1–4] Patients with hematologic cancers, including leukemia and lymphoma, experience higher PICU admission illness severity, higher rates of infection, and increased mortality compared to those with solid organ cancers.[2] Despite advances in intensive care technologies, PICU mortality for oncology patients has remained consistently high over recent decades.[1]

The lack of recent prospective multicenter data sets has limited the determination of potential changes in, and predictors of PICU mortality in this vulnerable population. This is necessary to improve decision-making and counseling for patients with leukemia and lymphoma who may benefit from admission to the PICU. To that end, we leveraged the database of prospectively collected variables from the Evaluating Processes of care and Outcomes of Children in Hospital (EPOCH) cluster-randomized controlled trial (RCT). The objectives of this study were to describe the technologic support, organ dysfunction, and PICU mortality in patients with leukemia or lymphoma who were urgently admitted to the PICU, and to explore the risk factors for mortality in these patients.

Methods

We performed a secondary analysis of prospectively collected data from a cluster-RCT of 144,539 patient discharges aged from 37 weeks gestational age to 18 years who were admitted to one of the 21 participating hospitals.[5] Enrollment in the EPOCH RCT was initiated on February 28, 2011 and ended on June 21, 2015.[5] The 21 hospitals in EPOCH were located in Belgium, Canada, England, Ireland, Italy, New Zealand, and the Netherlands. These hospitals had a range of pediatric services including cardiopulmonary bypass (12/21), solid organ transplantation (12/21), and bone marrow transplantation (10/21). All hospitals had pediatric trainee physicians and continuous in-house physician staffing. The hospitals were affiliated with a university in 19/21, had an emergency department in 20/21, and had $\geq$ 200 beds (excluding PICU beds) in 3/21.

Eligible patients for this study were those urgently admitted to the PICU who had a diagnosis of leukemia or lymphoma. Of all urgent PICU admissions, 121 (3.9%) had a hematology-oncology diagnosis; in order to maintain some homogeneity of the cohort included in this study, we chose to limit the analysis to leukemia or lymphoma (i.e., hematologic-oncology, $n = 109$), and not include the small numbers of other heterogeneous diagnoses. Urgent PICU admission was defined as (1) transfer to the PICU within 6 hours of the transfer decision from an eligible inpatient unit or (2) transfer initiated while an eligible patient was in the operating room. The time the PICU admission was initiated was defined as the time when the PICU admission is confirmed, or confirmed as a "definite possibility following surgery" in cases where postoperative care in the PICU might not be required. This was determined prospectively by review of chart notes and discussion with involved staff if necessary. This definition was based on reasoning by the EPOCH Steering Committee that if there was $\geq$ 6 hours for transfer to PICU, the patient was more likely an elective admission and not urgently requiring PICU level of care. The primary outcome was PICU mortality and the secondary outcome was time to death in the PICU.

In this cluster-RCT patients urgently admitted to the PICU had information collected prospectively on the study case report form, and this data was obtained from the EPOCH study data set. Data included demographic (e.g., age, admission category, and type of ward) and clinical information including peri-PICU admission technology used (defined to include invasive mechanical ventilation, high-frequency oscillatory ventilation [HFOV], inhaled nitric oxide [iNO], dialysis, and extracorporeal membrane oxygenation [ECMO]), on each patient that was urgently admitted to the PICU, as shown in ►**Tables 1** and **2**. Severity of illness scores calculated included the Pediatric Logistic Organ Dysfunction (PELOD) score, Pediatric Index of Mortality 2 (PIM2) score, and the Children's Resuscitation Intensity Scale (RISC).[6–8] The RISC score reflects the intensity of interventions proximate to the time of admission to the PICU (positive pressure ventilation, intubation, vasoactive support, high-volume resuscitation, cardiopulmonary resuscitation [CPR], ECMO, or death prior to transfer or within 1 hour of transfer to the PICU). Late admission to the PICU was defined as a RISC score $\geq$ 2, which included positive pressure ventilation, intubation, CPR, vasoactive drug infusion, at least 60 mL/kg volume boluses, or death in the 12 hours prior to PICU admission, or intubation, CPR, ECMO, or death within 1 hour of admission to PICU. The RISC score was obtained for those patients who met the EPOCH study clinical deterioration event definition, and therefore were not available for those urgently admitted to the PICU from the operating room (i.e., missing in 8 [7.3%] patients).

Statistical Analysis

Data from the last PICU admission for 109 patients with leukemia or lymphoma were included in the analyses. Variables were described using counts and percentages for categorical data, and median (interquartile range [IQR]) for continuous variables. The study's primary outcome was PICU mortality and determination of independent predictors of this outcome. The secondary outcomes included evaluation of time to death in PICU and determination of predictors of this outcome and description of the severity of illness in patients.

Primary Outcome

First, demographic and clinical variables were compared between survivors and nonsurvivors using Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher's exact tests (as appropriate) for categorical variables. Patients were categorized as having one or more previous urgent PICU admission(s), and the main analyses used the last admission per patient.

Table 1 Demographic and clinical characteristics of patients with leukemia or lymphoma urgently admitted to the pediatric intensive care unit

	Missing (%)	Overall	Died	Survived	*p*
n (%)		109 (100)	20 (18.3)	89 (81.7)	–
Age, mo		115 [42, 168]	110 [40, 159]	116 [44, 172]	0.748
Randomized to BedsidePEWS		30 (27.5%)	8 (40.0%)	22 (24.7%)	0.269
Admission occurred during the intervention period (vs. the run-in period)		76 (69.7%)	17 (85.0%)	59 (66.3%)	0.169
≥ 1 previous admission		14 (12.8%)	7 (35.0%)	7 (7.9%)	0.0038
Admission diagnostic category[a]					0.144
Cardiovascular/vascular/ cardiac		28 (25.7%)	3 (15.0%)	25 (28.1)	
Gastrointestinal		3 (2.8%)	2 (10.0%)	1 (1.1%)	
Genitourinary		1 (0.9%)	1 (5.0%)	0 (0.0%)	
Oncology/hematology		25 (22.9%)	5 (25.0%)	20 (22.5%)	
Metabolic/endocrine		2 (1.8%)	0 (0.0%)	2 (2.2%)	
Neurological		3 (2.8%)	1 (5.0%)	2 (2.2%)	
Other		2 (1.8%)	0 (0.0%)	2 (2.2%)	
Respiratory		45 (41.3%)	8 (40.0%)	37 (41.6%)	
Type of hospital ward	5.5				0.787
Medical		43 (41.7%)	9 (50.0%)	34 (40.0%)	
Surgical		1 (1.0%)	0 (0.0%)	1 (1.2%)	
Both		42 (40.8%)	6 (33.3%)	36 (42.4%)	
Other		17 (16.5%)	3 (16.7%)	14 (16.5%)	
Scope of hospital ward	6.4				0.205
General		8 (7.8%)	0 (0.0%)	8 (9.5%)	
Subspecialized		72 (70.6%)	16 (88.9%)	56 (66.7%)	
Both		22 (21.6%)	2 (11.1%)	20 (23.8%)	
Off-service patient (vs. home service patient)	6.4	2 (2.0%)	0 (0.0%)	2 (2.4%)	0.999
Recovery from surgery or procedure		7 (6.4%)	2 (10.0%)	5 (5.6%)	0.610
PIM2 score		–2.77 [–3.03, –1.77]	–1.76 [–2.93, –0.05]	–2.85 [–3.06, –1.97]	0.0056
PIM2 mortality risk (%)		5.9% [4.5, 14.5]	14.6% [5.0, 48.6]	5.4% [4.4, 12.2]	0.0064
PIM2 mortality risk category					0.058
0–5%		46 (42.2%)	5 (25.0%)	41 (46.1%)	
5.1–10%		28 (25.7%)	4 (20.0%)	24 (27.0%)	
> 10%		35 (32.1%)	11 (55.0%)	24 (27.0%)	
PELOD PICU day 1		11 [2, 20]	22 [11, 31]	11 [1, 20]	0.00015
PELOD PICU day 1 category					0.0034
< 10		28 (25.7%)	1 (5.0%)	27 (30.3%)	
10–19		44 (40.4%)	6 (30.0%)	38 (42.7%)	
≥ 20		37 (33.9%)	13 (65.0%)	24 (27.0%)	
PELOD whole PICU admission		20 [10, 22]	32 [22, 50]	11 [10, 21]	< 0.0001
PELOD whole PICU admission category					< 0.0001
< 10		19 (17.4%)	0 (0.0)	19 (21.3%)	
10–19		34 (31.2%)	0 (0.0)	34 (38.2%)	
≥ 20		56 (51.4%)	20 (100.0%)	36 (40.4%)	

(*Continued*)

Table 1 (*Continued*)

	Missing (%)	Overall	Died	Survived	*p*
RISC score	7.3				0.022
1		69 (68.3%)	10 (55.6%)	59 (71.1%)	
2		4 (4.0%)	1 (5.6%)	3 (3.6%)	
3		4 (4.0%)	1 (5.6%)	3 (3.6%)	
4		21 (20.8%)	3 (16.7%)	18 (21.7%)	
5		1 (1.0%)	1 (5.6%)	0 (0.0%)	
6		2 (2.0%)	2 (11.1%)	0 (0.0%)	

Abbreviations: BedsidePEWS, Bedside Paediatric Early Warning System; PELOD, Pediatric Logistic Organ Dysfunction, range from 0 to 70; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2; RISC, Children's Resuscitation Intensity Scale.
[a]Admission category was provided with the instruction to "please indicate the main reason for ICU admission."

Table 2 Outcome characteristics of patients with leukemia or lymphoma urgently admitted to the pediatric intensive care unit

	Missing (%)	Overall	Died	Survived	*p*
n (%)		109 (100%)	20 (18.3%)	89 (81.7%)	–
PICU length of stay, d		3 [2, 6]	4 [2, 7]	3 [2, 6]	0.356
PICU length of stay category					0.412
≤ 3 d		62 (56.9%)	9 (45.0%)	53 (59.6%)	
4–7 d		27 (24.8%)	6 (30.0%)	21 (23.6%)	
≥ 8 d		20 (18.3%)	5 (25.0%)	15 (16.9%)	
Mechanical ventilation at any time during the first hour in PICU		36 (33.0%)	13 (65.0%)	23 (25.8%)	0.0019
Mechanical ventilation days		0 [0, 2]	2 [1, 5]	0 [0, 1]	< 0.0001
Mechanical ventilation days category					< 0.0001
0		67 (61.5%)	3 (15.0%)	64 (71.9%)	
1–7		30 (27.5%)	14 (70.0%)	16 (18.0%)	
≥ 8		12 (11.0%)	3 (15.0%)	9 (10.1%)	
Nitric oxide days		0 [0, 0]	0 [0, 0]	0 [0, 0]	0.021
≥ 1 Nitric oxide days		8 (7.3%)	4 (20.0%)	4 (4.5%)	0.036
Dialysis days		0 [0, 0]	0 [0, 2]	0 [0, 0]	< 0.0001
≥ 1 dialysis days		13 (11.9%)	9 (45.0%)	4 (4.5%)	< 0.0001
ECMO days		0 [0, 0]	0 [0, 0]	0 [0, 0]	0.035
≥ 1 ECMO days		1 (0.9%)	1 (5.0%)	0 (0.0%)	0.183
HFOV days		0 [0, 0]	0 [0, 0]	0 [0, 0]	0.097
≥ 1 HFOV days		4 (3.7%)	2 (10.0%)	2 (2.2%)	0.153
Sum of technology days[a]		0 [0, 3]	4 [2, 9]	0 [0, 1]	< 0.0001
≥ 1 Technology day		45 (41.3%)	19 (95.0%)	26 (29.2%)	< 0.0001
Mechanical ventilation-free days[b]	16.5	28 [24, 28]	0 [0, 1]	28 [27, 28]	< 0.0001
Mechanical ventilation-free days category[b]	16.5				< 0.0001
0–7		14 (15.4%)	12 (100.0%)	2 (2.5%)	
8–14		1 (1.1%)	0 (0.0%)	1 (1.3%)	
15–21		5 (5.5%)	0 (0.0%)	5 (6.3%)	
22-28		71 (78.0%)	0 (0.0%)	71 (89.9%)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; PICU, pediatric intensive care unit.
[a]Technology days: the sum of mechanical ventilation, nitric oxide, ECMO, and dialysis days.
[b]Ventilation-free days are from the first urgent PICU admission to 28 days afterward. All other values are for the most recent urgent PICU admission if there were multiple urgent admissions.

To estimate the association with PICU mortality, variables were included in univariable generalized estimating equations (GEEs) with a logit link, and accounting for clustering by site using an exchangeable correlation matrix, if they had a p-value of < 0.1 and had $> 5\%$ of patients in each category on the initial univariate analysis (►**Table 1**).

To estimate independent associations with PICU mortality, multivariable GEE with a logit link, accounting for clustering by site using an exchangeable correlation matrix, were used, including variables that had p-value of < 0.05 in the univariable GEE. Due to collinearity, in each multivariable model only one of PELOD or PIM2 could be included.

Secondary Outcome

Time to death in the PICU was evaluated using Kaplan–Meier curves, with patients censored at discharge from the PICU. Using the same process as described above, univariable and multivariable proportional hazards models were used to estimate associations between variables and time to death. Due to collinearity, in each multivariable model only one of PELOD or RISC could be included; PIM2 was not included as it failed to meet the proportional hazards assumption.

Ethics

This EPOCH substudy was approved by the Human Research Ethics Board at the Hospital for Sick Children, Toronto, Canada; Approval REB # 1000062622.

Results

Description of the Patients

There were 127 urgent admissions to PICU in 109 individual patients in 17 pediatric centers during the study period, including 95 patients with one, 12 with two, 1 with three, and 1 with five admissions. Both patients with 3 and 5 urgent admissions survived to PICU discharge, and 5 of 12 (42%) with two urgent admissions survived to PICU discharge. Using only the last admission per patient, 109 individual patients were included for the remainder of the analyses. There were 20 PICU deaths, and these were associated with withdrawal of life support in 11, limitation of therapy in 4, and failed resuscitation in 5.

Patient characteristics according to mortality are shown in ►**Tables 1** and **2**. The 109 patients had a median (IQR) age of 115 (IQR 42, 168) months and a median (IQR) PICU length of stay of 3 (IQR 2, 6) days with 20 (18.3%) staying at least 8 days. Most were admitted to hospital for respiratory (45, 41.3%) or cardiovascular (28, 25.7%) indications. During the first hour in the PICU, 36 (33%) were mechanically ventilated, and over the entire PICU stay 42 (38.5%) were mechanically ventilated. During the course of PICU admission 45 (41.3%) had at least 1 technology day, including any of mechanical ventilation, iNO 8 (7.3%), ECMO 1 (0.9%), or dialysis 13 (11.9%).

Severity of illness scores included day 1 PELOD score ≥ 20 in 37 (33.9%) (and during the whole PICU admission 56 [51.4%] had PELOD score ≥ 20), and PIM2 mortality risk $> 10\%$ in 35 (32.1%) patients. Most patients had a low RISC score of 1 (none of the interventions during that period, 69 [68.3%]), and the other 32 (31.7%) had a RISC score indicating late admission to the PICU. Interventions provided in the 12 hours before PICU and the first hour of PICU included positive pressure ventilation in 4 (4%), intubation in 5 (5%), vasoactive infusion or at least 60 mL/kg intravenous volume in 22 (21%), and CPR or ECMO in 2 (2%). Mortality in the PICU occurred in 20/109 (18.3%) patients.

Clinical Characteristics Associated with Mortality (Univariate Analysis)

Variables describing technology use, especially various measures of use of mechanical ventilation (e.g., continuous and categorical descriptions of mechanical ventilation days and mechanical ventilation-free days), were associated with mortality. For example, mechanical ventilation at any time during the first hour in PICU occurred in 65% of patients who died compared with 26% of patients who survived ($p = 0.002$). Few patients were treated with ECMO (0.9%), HFOV (3.7%), iNO (7.3%), or dialysis (11.9%). Even so, use of iNO or dialysis, and technology days (the sum of mechanical ventilation, iNO, ECMO, and dialysis days) were associated with mortality. In addition, having had at least one previous urgent PICU admission was associated with mortality.

Continuous and categorical severity of illness scores were also associated with mortality. Patients who died had higher PIM2 score and mortality risk, PELOD score on day 1 and through the whole PICU admission, and RISC score ≥ 2.

Some variables were notable for lack of association with mortality. This included age, whether the patient site was randomized to using Bedside Paediatric Early Warning System or not, whether urgent PICU admission occurred after the start of the study period, and descriptions of admission diagnostic category and patient care service.

Independent Predictors of Mortality (Multivariate Analysis)

Based on the above results, categorical variables considered in logistic GEE of ICU mortality were: need for mechanical ventilation, one or more previous urgent PICU admissions, day 1 PELOD score, PIM2 mortality risk, and RISC score ≥ 2 (i.e., late admission to PICU). Upon multivariable logistic regression analysis, one or more previous urgent PICU admissions, at least one mechanical ventilation day, and day 1 PELOD score were associated with higher PICU mortality (►**Table 3**).

Time to Death in PICU

For patients who stayed in the PICU for at least 20 days, the probability of survival was 49% (►**Fig. 1**). Categorical variables considered in proportional hazards models for time to death were need for mechanical ventilation, one or more previous urgent PICU admissions, day 1 PELOD score, PIM2 mortality risk, and RISC score ≥ 2 (i.e., late admission to PICU). Variables were entered into univariate and multiple proportional hazards models for time to death in those patients remaining in PICU (►**Table 4**). Mechanical ventilation, day 1 PELOD score, and RISC score ≥ 2 were associated

Table 3 Logistic GEE regressions of risk factors for PICU mortality in patients with leukemia or lymphoma urgently admitted to the PICU

	Univariable		Multivariable 1		Multivariable 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
≥ 1 Previous PICU admission	6.51 (1.56, 27.2)	0.0101	8.37 (2.67, 26.2)	0.00027	3.55 (0.61, 20.6)	0.158
≥ 1 Mechanical ventilation day	13.3 (3.49, 50.6)	0.00015	10 (1.29, 77.9)	0.0276	7.66 (2.35, 25)	0.00072
Day 1 PELOD score ≥ 20	5.03 (1.28, 19.8)	0.0209	11.7 (1.97, 69.8)	0.00686		
PIM2 mortality risk ≥ 10 %	3.57 (1.12, 11.4)	0.0309			1.59 (0.61, 4.12)	0.344
RISC ≥ 2	1.92 (0.67, 5.43)	0.222				

Abbreviations: CI, confidence interval; GEE, generalized estimating equation; OR, odds ratio; PELOD, Pediatric Logistic Organ Dysfunction; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2; RISC, Children's Resuscitation Intensity Scale.

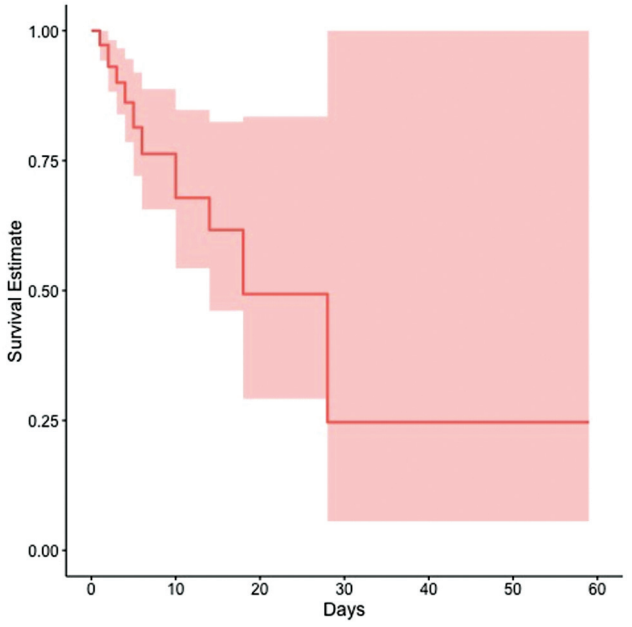

Fig. 1 Kaplan–Meier PICU survival estimates for patients with leukemia or lymphoma urgently admitted to the PICU. Probability of survival at day 5 was 0.81 (95% confidence interval [CI] 0.71, 0.91), at day 10 was 0.68 (95% CI 0.53, 0.91), at day 15 was 0.62 (95% CI 0.44, 0.80), and at day 20 was 0.49 (95% CI 0.23, 0.75). PICU, pediatric intensive care unit.

with time to death on univariate analysis, and remained statistically significant in multivariable models. PIM2 mortality risk did not meet the proportional hazards assumption and could not be included.

Discussion

The main findings from this study include the following. First, PICU mortality of 109 patients with leukemia or lymphoma urgently admitted to PICU was 18.3%. Second, risk factors for mortality on univariate analysis were technology use, particularly mechanical ventilation, severity of illness scores, and previous urgent PICU admission(s). Third, on multivariable logistic regressions, risk factors for mortality were mechanical ventilation, day 1 PELOD score, and previous urgent PICU admission. Fourth, the longer a patient stayed in PICU, the higher the hazard of mortality, with risk factors associated with time to death including mechanical ventilation, day 1 PELOD score, and admission RISC ≥ 2 (late admission to PICU).

A number of retrospective cohort studies have been conducted to identify risk factors associated with mortality in this population. In a review of studies reporting prognosis of all PICU admissions, Faraci et al found mechanical ventilation, number of dysfunctional organs, need for renal replacement therapy, and pediatric risk of mortality score to be the most commonly identified risk factors associated with lower PICU survival.[9] These findings were echoed in a more recent

Table 4 Proportional hazards models for time to mortality in patients with leukemia or lymphoma urgently admitted to the PICU

	Univariable		Multivariable 1		Multivariable 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
≥ 1 Previous PICU admission	1.52 (0.57, 4.06)	0.3999				
≥ 1 Mechanical ventilation day	4.42 (1.23, 15.85)	0.0226	4.77 (1.36, 16.79)	0.0149	4.68 (1.28, 17.17)	0.0199
Day 1 PELOD score ≥20	5.34 (1.89, 15.07)	0.00155	5.85 (2.06, 16.63)	0.00092		
PIM2 mortality risk ≥10 %[a]						
RISC ≥ 2	4.36 (1.56, 12.19)	0.00507			4.36 (1.57, 12.11)	0.0047

Abbreviations: CI, confidence interval; OR, odds ratio; PELOD, Pediatric Logistic Organ Dysfunction; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2; RISC, Children's Resuscitation Intensity Scale.
[a]Did not meet the proportional hazards assumption.

systematic review of 31 observational studies over 30 years (up to March 2017) of children with cancer admitted to the PICU, identifying need for mechanical ventilation, inotropic support, or renal replacement therapy as risk factors significantly associated with mortality.[1] Severity scores were not recorded in enough studies to analyze.[1] Sepsis and acute respiratory failure remain the most common causes for admission to the PICU in children with oncologic disease.[3,10–14] The lower ICU mortality that has been found in adult patients with cancer over the last several decades had not been confirmed in pediatric patients.[1,15]

In our cohort, mortality was lower than in the recent systematic review of children with cancer admitted to a PICU (18.3% compared to 27.8% [95% confidence interval [CI] 23.7, 31.9]).[1] Our study may reflect a trend toward improved PICU mortality for pediatric patients with cancer over recent years. Other possible reasons for our lower mortality include different selection criteria (i.e., we only included patients urgently admitted to the PICU), focus on only those with cancer due to leukemia or lymphoma, and inclusion of PICUs capable of complex technological interventions. Nevertheless, while the mortality of 18.3% is higher than general PICU admissions, it is encouraging that intensive care for this population of children is certainly not futile. Compatible with our finding of better survival than in historical cohorts, a recent retrospective registry study from 36 children's hospitals found that, over the time period 2012 to 2021, PICU oncology patient admissions steadily increased, markers of acuity increased (e.g., invasive mechanical ventilation, ECMO, multiple vasoactive agents), yet in the second 5-year period hospital mortality decreased with adjusted odds ratio 0.82 (95% CI 0.75, 0.90; $p < 0.001$).[16] That study was limited by retrospective design, use of International Classification of Diseases codes and billing codes to define diagnosis and management, including a broad range of diagnoses (e.g., any oncologic diagnosis, postoperative admissions), lack of PICU acuity and detailed oncology information, and analysis based on hospitalizations rather than individual patients.[16]

Risk factors for PICU mortality in our cohort included mechanical ventilation, day 1 PELOD score, and prior urgent PICU admission. Previous studies have outlined "number of organ failures" as being associated with PICU mortality.[9] Severity scores had not been sufficiently studied to allow for analysis in the recent systematic review; however, that risk factors for mortality included mechanical ventilation, inotropic support, and renal replacement therapy suggested severity of illness captured by PELOD score may be important.[1] Mechanical ventilation reflects an important organ dysfunction that was associated with mortality. Our finding that mortality was associated with previous urgent ICU admission was novel and likely indicates a failure to respond to ongoing treatments.

It is important to note that these risk factors are not accurate enough to be used at the bedside to make individual patient decisions. For example, mortality rates in those having mechanical ventilation was 17/42 (40.5%), mechanical ventilation for at least 8 days was 3/12 (25.0%), mechanical ventilation during the first hour in PICU was 13/36 (36.1%), day 1 PELOD score $\geq$ 20 was 13/37 (35.1%), PELOD score $\geq$ 20 at any point during PICU stay was 20/56 (35.7%), PIM2 mortality risk $>$ 10% was 11/35 (31.4%), RISC of $\geq$ 2 or $\geq$ 3 was 8/32 (25.0%) or 7/28 (25.0%), at least 1 technology day was 19/45 (42.2%), and having at least one previous urgent PICU admission was 7/14 (50.0%). The two patients having had 3 and 5 previous urgent PICU admissions survived to PICU discharge. These mortality rates are much higher than average PICU mortality rates, but are not sufficient to make definitive individual prognostic statements.

The major strength of this study is that we used prospectively collected data in a large multicenter cohort from a well-conducted published cluster-RCT. There are several limitations of this study. Only urgent admissions to PICU were included, limiting generalization to all PICU admissions for leukemia or lymphoma. Some data that may be important for prognosis were not collected, including inotrope requirements, specific organ scores within PELOD, diagnosis of sepsis, neutropenia, timing during cancer therapy, disease status and stage, contents of and response to chemotherapy, hematopoietic stem cell transplantation, and type of leukemia or lymphoma.[1,17,18] Some of the variables collected occurred only rarely, for example, neurological diagnosis (2.8%), recovery from a surgical procedure (6.4%), ECMO (0.9%), HFOV (3.7%), iNO (7.3%), and RISC over 4 (3%), preventing their inclusion in the multiple regression models (we included only variables occurring in at least 5% of survivors and nonsurvivors). The lower mortality in our cohort than in previous cohorts may be due to general improvements in oncology and ICU care over time; however, we cannot be more specific given the limitations in our data set. The data not available in our data set makes comparison to previously published cohorts tenuous. Finally, we used prospectively collected observational data and therefore the associations found may not be cause-effect relationships.

Conclusion

PICU mortality for patients with leukemia and lymphoma urgently admitted to PICU remained high in our cohort, at 18.3%. This represents an improvement from historical cohorts, which may be due to general improvement in oncology and ICU care over time. As this was a secondary analysis of data recorded in the EPOCH cluster RCT, we do not have the detailed data available that would be necessary to definitively show improved mortality with time. Patients requiring mechanical ventilation, with day 1 PELOD scores $\geq$ 20, and having had previous urgent PICU admission were more likely to die, indicating higher severity of illness on admission to PICU and ongoing lack of response to treatment. These findings may be helpful in risk stratification of this medically fragile population. We caution that none of the risk factors were accurate enough to make individual patient care decisions. Future study with more fine-grained patient data (e.g., patient oncological course, presenting illness, and specific therapies) is required before accurate individual prognostication can be made.

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Conflict of Interest
C.P. is a named inventor of the Bedside Paediatric Early Warning System and has shares in a decision support company in part owned by SickKids that was established to commercialize the Bedside Paediatric Early Warning System. All other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1 Wösten-van Asperen RM, van Gestel JPJ, van Grotel M, et al; POKER (PICU Oncology Kids in Europe Research group) research consortium. PICU mortality of children with cancer admitted to pediatric intensive care unit a systematic review and meta-analysis. Crit Rev Oncol Hematol 2019;142:153–163
2 Zinter MS, DuBois SG, Spicer A, Matthay K, Sapru A. Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. Intensive Care Med 2014;40(10):1536–1544
3 Rosenman MB, Vik T, Hui SL, Breitfeld PP. Hospital resource utilization in childhood cancer. J Pediatr Hematol Oncol 2005;27(06):295–300
4 Heneghan JA, Pollack MM. Morbidity: changing the outcome paradigm for pediatric critical care. Pediatr Clin North Am 2017;64(05):1147–1165
5 Parshuram CS, Dryden-Palmer K, Farrell C, et al; Canadian Critical Care Trials Group and the EPOCH Investigators. Effect of a Pediatric Early Warning System on all-cause mortality in hospitalized pediatric patients: the EPOCH randomized clinical trial. JAMA 2018;319(10):1002–1012
6 Leteurtre S, Martinot A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet 2003;362(9379):192–197
7 Slater A, Shann F, Pearson GPaediatric Index of Mortality (PIM) Study Group. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003;29(02):278–285
8 Parshuram CS, Dryden-Palmer K, Farrell C, et al; Canadian Critical Care Trials Group. Evaluating processes of care and outcomes of children in hospital (EPOCH): study protocol for a randomized controlled trial. Trials 2015;16:245
9 Faraci M, Bagnasco F, Giardino S, et al. Intensive care unit admission in children with malignant or nonmalignant disease: incidence, outcome, and prognostic factors: a single-center experience. J Pediatr Hematol Oncol 2014;36(07):e403–e409
10 Rr P, Tan EEK, Sultana R, et al. Critical illness epidemiology and mortality risk in pediatric oncology. Pediatr Blood Cancer 2020; 67(06):e28242
11 Caballero M, Faura A, Margarit A, et al. Outcomes for paediatric acute leukaemia patients admitted to the paediatric intensive care unit. Eur J Pediatr 2022;181(03):1037–1045
12 Dalton HJ, Slonim AD, Pollack MM. MultiCenter outcome of pediatric oncology patients requiring intensive care. Pediatr Hematol Oncol 2003;20(08):643–649
13 Tamburro RF, Barfield RC, Shaffer ML, et al. Changes in outcomes (1996-2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation. Pediatr Crit Care Med 2008;9(03):270–277
14 Hallahan AR, Shaw PJ, Rowell G, O'Connell A, Schell D, Gillis J. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. Crit Care Med 2000;28(11): 3718–3721
15 Shimabukuro-Vornhagen A, Böll B, Kochanek M, Azoulay É, von Bergwelt-Baildon MS. Critical care of patients with cancer. CA Cancer J Clin 2016;66(06):496–517
16 Rogerson CM, Rowan CM. Critical care utilization in children with cancer: U.S. Pediatric Health Information System Database cohort 2012–2021. Pediatr Crit Care Med 2024;25(01):e52–e58
17 Meyer S, Gottschling S, Biran T, et al. Assessing the risk of mortality in paediatric cancer patients admitted to the paediatric intensive care unit: a novel risk score? Eur J Pediatr 2005;164(09): 563–567
18 Ranta S, Broman LM, Abrahamsson J, et al. ICU admission in children with acute lymphoblastic leukemia in Sweden: Prevalence, outcome, and risk factors. Pediatr Crit Care Med 2021;22 (12):1050–1060