Received: 19 November 2024 | Revised: 30 January 2025 | Accepted: 20 February 2025

DOI: 10.1002/cncr.35818

ORIGINAL ARTICLE

Multilevel mortality risk factors among pediatric hematology-oncology patients with deterioration

Asya Agulnik MD, MPH[1] | Maricela Robles-Murguia MS, MSM[1] | Yichen Chen PhD[1] | Hilmarie Muñiz-Talavera PhD[1] | Linh Pham MS[1] | Angela Carrillo PhD[1] | Adolfo Cardenas-Aguirre MD[1] | Juliana Costa MD[1] | Alejandra Mendez Aceituno MD[1] | Carlos Acuña Aguirre MD[2] | Ana Berenice Aguilar Roman MD[3] | Shillel Yahamy Alvarez Arellano RN[4] | Leticia Aradi Andrade Sarmiento MD[5] | Daniela Arce Cabrera MD[6] | Erika Esther Blasco Arriaga MD[7] | Claudia María De León Gutiérrez MD[8] | Rosdali Diaz-Coronado MD[9] | Maria do Céu Diniz Borborema MD[10] | Mariana do Nascimento Othero Campacci MD[11] | Leticia Drumond Alberto MD[12] | Natalia Soledad Gonzalez MD[13] | Martha Herrera Almanza MD[14] | Valentine Jimenez Antolinez MD[15] | Merle Denisse Laffont Ortiz MD[16] | Laura Lemos De Mendonça E. Fontes MD[17] | Norma Araceli López Facundo MD[18] | Claudia Beatriz López Vázquez MD[19] | Idalia Margarita Lozano Lozano MD[20] | Jose Miguel Mijares Tobias MD[21] | Lupe Nataly Mora Robles MD[22] | Berenice Noriega Acuña MD[23] | Fernanda Paula Endo Marques MD[24] | Clara Krystal Pérez Fermín MD[25] | Monica Lorena Quijano Lievano RN[26] | Andreia Ribeiro Pereira Aguiar De Paula MD[24] | Ligia Rios MD[27] | Jocelyn Rivera MD[28] | Marcela Alejandra Sahonero MD[29] | Beatriz Salas Mendoza MD[30] | María Sánchez-Martín MD[31] | Jennifer Sepúlveda Ramírez RN[32] | Verónica Soto Chávez MD[33] | Daniela María Velásquez Cabrera MS[34] | Erika Elena Villanueva Hoyos MD[35] | Luz Yadira Zuñiga Quijano MD[36] | Meenakshi Devidas PhD[1] | Carlos Rodriguez-Galindo MD[1] | for the Escala de Valoracion de Alerta Temprana Study Group

Correspondence
Asya Agulnik, St. Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis, TN 38104, USA.
Email: asya.agulnik@stjude.org

Abstract

Background: Hospitalized pediatric hematology-oncology patients have frequent clinical deterioration events (CDEs) requiring intensive care unit (ICU) interventions

Funding information
National Cancer Institute, Grant/Award Number: 5P30CA021765; American Lebanese Syrian Associated Charities

and resulting in high mortality, particularly in resource-limited settings. This study identifies independent risk factors for CDE mortality in hospitals providing childhood cancer care in Latin America and Spain.

Methods: Centers implemented a prospective CDE registry, defined as unplanned transfer to a higher level of care, use of ICU-level interventions on the ward, or nonpalliative ward death. The authors analyzed registry data from April 2017 to December 2022. The primary outcome was CDEs mortality, defined as death occurring during ICU admission, <24 hours of ICU discharge, or end of ward-based ICU interventions. Multilevel modeling identified event-, patient-, and hospital-level independent risk factors for CDE mortality.

Results: Among 69 participating hospitals in 18 countries, 4134 CDEs were reported in 3319 pediatric hematology-oncology patients with an event mortality of 26.8% (1108 events). Of all CDEs, 33.7% used ICU interventions on the ward and 87.5% were transferred to a higher level of care. In multilevel modeling, significant independent risk factors for event mortality present at the start of deterioration included patient (disease relapse) and event (e.g., reason for hospital admission, use of ICU intervention on wards, abnormal lactate, platelets, or C-reactive protein, reason for deterioration, and number of organs with dysfunction); hospital factors were not significant predictors of mortality.

Conclusions: Hospitalized pediatric hematology-oncology patients with CDE have high mortality with significant variability across centers. Mortality, however, is largely driven by modifiable event-level factors, demonstrating the need for targeted interventions to improve survival.

KEYWORDS
clinical deterioration, intensive care, Latin America, pediatric oncology, resource-limited settings

INTRODUCTION

A third of childhood cancer deaths after starting treatment are due to treatment-related complications; in low- and middle-income countries, one in every 15 children with cancer experiences treatment-related mortality.[1] Children with cancer frequently develop critical illness,[2] with rates of critical complications increasing over time.[3] In high-resource settings, excellent outcomes for critically ill children with cancer are possible with coordinated, multidisciplinary supportive and critical care.[4] Over 90% of children with cancer, however, live in resource-limited settings.[5] Hospitals in these settings have variable access to material and human resources,[6,7] resulting in challenges managing critical illness in high-risk patients such as children with cancer.[8]

To improve outcomes for critically ill children with cancer, it is imperative to understand the presentation, mechanism, and risk factors for mortality among these patients. In high-resource settings, cancer type, severity of illness, and presence of infection are associated with mortality among critically ill children with cancer.[2,4] Data from resource-limited settings, however, are mostly limited to single-center studies, preventing generalization across settings and evaluation of center-level risk factors for mortality.[8] Additionally, children with cancer in resource-limited settings frequently develop critical illness outside of a formal intensive care unit (ICU) setting,[9,10] requiring a more inclusive definition to accurately evaluate factors contributing to mortality.

In 2017, the St. Jude Global Critical Care Program[11] worked with regional stakeholders in Latin America to develop Proyecto Escala de Valoracion de Alerta Temprana (EVAT), a multidisciplinary quality improvement collaborative to improve the care of children with cancer who develop critical illness.[12] As part this collaborative, hospitals implement a prospective quality improvement registry of clinical deterioration events, or events where hospitalized patients develop acute critical illness, occurring among children with cancer and other blood disorders in their hospitals. In 2021, preliminary analysis of the first year of registry data demonstrated modifiable risk for mortality, including higher severity of illness at event recognition and use of ICU-level interventions on the wards, but was limited by the relatively small number of collaborating centers.[10] The objective of this study is to expand on this preliminary analysis and describe multilevel risk factors for CDE mortality among hospitalized children with cancer in Latin America and Spain over 5 years.

MATERIALS AND METHODS

Study design and setting

This study is a retrospective analysis of data collected in a de-identified, prospective quality improvement registry of clinical deterioration events (CDEs) as part of Proyecto EVAT, a quality improvement collaborative to improve outcomes for children with cancer through implementation of a pediatric early warning system (PEWS) (Figures S1 and S2).[12,13] Methods of data collection are similar to those previously described[10,14] and briefly summarized below.

Centers are eligible to participate in Proyecto EVAT if they provide inpatient childhood cancer care and are primarily Spanish- or Portuguese-speaking; they are recruited through collaboration with St. Jude Global[15] or learning about the program from colleagues. Participating centers have a range of resources and hospital characteristics, with most identifying as resource-limited due to a range of resource challenges, including inadequate nursing and physician staffing, insufficient ICU resources, and patients with low socioeconomic, education, and nutritional status.

This study includes all registry data reported from April 1, 2017 (start of Proyecto EVAT) through December 31, 2022. All centers contributing data to the registry were included in analysis. Deterioration occurring in patients with limitations on escalation of care (do-not-resuscitate order or equivalent) was not considered CDEs and was not reported in the registry.

Data collection

Centers participating in Proyecto EVAT identify a local multidisciplinary leadership team to lead program activities. From the start the program, hospitals participate in a prospective de-identified quality improvement registry of CDEs among hospitalized children with cancer at and continue data collection through 18 months post-PEWS implementation.[16] For each CDE, a de-identified case report form is completed by the local site lead (Figure S3) and emailed to St. Jude, where it is entered into a REDCap database[17] by a bilingual clinical research associate. Registry data are routinely checked by St. Jude research staff for missing and incorrect values to assure data quality. The case report form documents characteristics of the deterioration event and patient oncologic history. In addition, site leads provide institutional data on hospital structure and resources for childhood cancer care. Each center is also classified by country income-level as per World Bank criteria.[18]

Definitions

CDE was used as an inclusive definition of the development of acute critical illness[9] and defined as an event in a hospitalized child with cancer or other blood disorder requiring (1) unplanned transfer to the ICU, (2) ICU-level intervention on the ward, or (3) ward death in a patient without limitations to escalation of care (do-not-resuscitate order or equivalent). ICU-level interventions were defined as invasive or noninvasive mechanical ventilation (CPAP [continuous positive airway pressure], BiPAP [bilevel positive airway pressure], ventilation through a tracheostomy, or intubation with mechanical ventilation), vasoactive infusions, or cardiopulmonary resuscitation (CPR). A CDE started when the patient first met criteria for CDE and ended at death, at time of ICU discharge, or end of ICU-level interventions on the ward; all events were followed to this time point. If ICU interventions were re-started and/or ICU re-admission occurred within 24 hours, this was considered as part of the same CDE. If ICU interventions and/or ICU re-admission was required more than 24 hours following CDE end, this was considered a new CDE and documented as a new entry in the registry. CDE mortality, or death during the deterioration event, was defined as a death occurring during ICU admission, while receiving ward-based ICU interventions, or within 24 hours of ICU discharge or end of ward-based ICU interventions.

The primary event was the first event experienced by the patient who met criteria for a CDE. Cardiac arrest was defined as CPR or primary event as death on the ward; cardiopulmonary arrest was a cardiac arrest or intubation/mechanical ventilation on the ward. Critical deterioration, a pragmatic standardized measure of late identification of deterioration and/or ICU transfer, was defined per the literature as an event requiring life-sustaining interventions (ICU interventions, transfer to a higher-level of care, or death) within 12 hours of event start.[19,20] For patients transferred from the ward during a CDE, higher-level-of care was defined as an ICU, emergency room, or other hospital area designed for critically ill patients. Data collected in the CDE registry documented events that occurred before, during, and after PEWS implementation at participating centers.[14] PEWS implementation included documentation of PEWS with every set of vital signs in the nursing flow-sheet of every hospitalized child with cancer as part of routine care.[12] Following PEWS implementation, the CDE case report form (Figure S2) included the highest PEWS documented in the medical record during the 24 hours before the start of deterioration; as a result, PEWS documentation was a proxy-measure of PEWS use in the patient's care during the deterioration event. As previously described, PEWS documentation was nearly 100% at centers using PEWS post-implementation with a high degree of accuracy.[14,16] As a result, CDEs without a documented PEWS represented those that occurred before PEWS implementation at the center and represented events during which PEWS was not used in patient care (rather than data missing from the medical record).

Laboratory values, including the lactate (mmol/L), C-reactive protein (CRP, mg/L), absolute neutrophil count (cells/μL), and platelet count ($\times 10^3$/mm), were recorded if collected as part of routine care within 24 hours of the start of the event. If multiple laboratory values were collected, the value closest to the start of the event was documented. Organ dysfunction and sepsis severity were defined by Goldstein et al.[21] criteria; Pediatric Index of Mortality 2 (PIM2) is a measure of severity of illness at the start of critical care and was defined using standard criteria.[22] Delay in identification of deterioration or transfer to the ICU was determined by the clinical team; for patients transferred to a higher level of care, the time waiting for a bed (hours) was also documented.

Statistical analysis

The primary outcome was CDE mortality. All CDEs during the study period occurring among patients with a pediatric hematology-oncology diagnosis with a documented event outcome (survival or death) were included in analysis. Each CDE was used as the unit of analysis. Descriptive statistics summarized CDE characteristics at the level of the event, patient, and center. Continuous variables were reported with median and interquartile range (IQR) and categorical variables were reported with frequency and percentages.

Minimum distance estimation was used to identify the optimal cut-point values from the receiver operating characteristic (ROC) curves.[23] The optimal cut-point values were used to convert continuous laboratory (lactate, neutrophils, platelets, CRP) to categorical (abnormal vs. not) variables.

Univariate analysis was conducted using Wilcoxon rank sum test and χ^2 test to compare event, patient, and hospital characteristics (Table S1 lists potential risk factors with descriptions). Potential confounding variables and collinearity were identified statistically through pairwise association or correlation analysis (χ^2 test or Spearman's rank correlation coefficient), and inclusion of variable was based on clinical appropriateness. Significant risk factors in univariate analyses were used to build a mixed-effects multi-level logistic regression model. Use of ICU interventions on the wards, ward cardiopulmonary arrest, and cardiac arrest were collinear; hence only use of ICU interventions on wards was included in the multilevel modeling. Multi-level modeling was conducted iteratively by adding event-level, patient-level, and hospital-level predictors to account for the hierarchical nesting of data. Intercept was included as a random effect to represent the variance of intercepts between event-level, patient-level, and hospital-level factors. Odds ratio was estimated on each level of the risk factor if it was categorical or estimated on one-unit change of the risk factor if it was continuous. Model performance was evaluated and compared by Akaike information criterion (AIC). Missing laboratory data represented resource-limitations (test not available) or clinical decision-making (test not used in the patients care) rather than a failure to document a collected value. Accordingly, laboratory data were not considered to occur at random but rather to be informative of resource availability and practices in resource-limited settings; hence missing laboratory values considered as a separate level for laboratory data. p values of $<.05$ were considered significant. Data was processed and analyzed using R, version 4.3.3 and SAS, version 9.4.

Human subjects

The Proyecto EVAT and the CDE registry was approved by the St. Jude institutional review board (IRB) as quality improvement; retrospective analysis of de-identified registry data was classified by the IRB as nonhuman subjects research with no consent required for data collection and analysis. All collaborating centers obtained institutional approval to participate in Proyecto EVAT; additional ethical review board approvals were obtained when needed per local standards.

RESULTS

Sample characteristics

Among 69 centers in 18 countries (Figure 1; Table S2 with center characteristics), 4290 clinical deterioration events were reported; 142 events among nonpediatric hematology-oncology (PHO) were excluded; an additional 14 events were excluded due to lack of documented CDE outcome. The final sample contained 4134 CDEs (range 3–405/center) among 3319 individual patients.

Table 1 describes event characteristics. Events started a median of 3.17 days (IQR, 0–181 days) after hospital admission. The most common primary event was unplanned transfer to the ICU (2756 of 4134, 67%). However, 33.7% (1392 of 4134 events) used at least one ICU-level intervention on the ward, and 53.7% (2218 of 4134 events) met criteria for critical deterioration. Ultimately, 87.5% (3619 of

FIGURE 1 Map of participating centers. This figure shows centers ($n = 69$ centers) participating in the prospective registry of clinical deterioration events included in this study. Numbers inside circle demonstrate number of participating centers in each listed country. Blue color demonstrates country income level (low-middle income, upper-middle income, or high-income) per World Bank criteria.[18]

TABLE 1 Characteristics of CDE.

Characteristic	Variable	No. (%), $n = 4134$
Primary CDE	Unplanned ICU transfer	2756 (67)
	Vasoactive on ward	895 (22)
	Mechanical ventilation on ward	374 (9)
	CPR on ward	90 (2)
	Ward death	18 (0.4)
	Missing	1
Service during event start	Oncology ward	3274 (79.2)
	Pediatric ward	192 (4.6)
	Transplant ward	535 (12.9)
	Oncology-intermediate ward (UNOP[a] only)	127 (3.1)
	Other	6 (0.2)
Ward ICU-level intervention	Any (vasoactive, mechanical ventilation, and/or CPR)	1392 (33.7)
	Vasoactive on ward[b]	1110 (26.9)
	Mechanical ventilation on ward[b]	577 (14.0)
	CPR on ward[b]	185 (4.5)
	None	2742 (66.3)
CDE	Yes	2218 (53.7)
	No	1916 (46.3)
Evaluated by ICU team on ward	Yes	3016 (73)
	No	1118 (27)
Transfer to a higher level-of-care (unit type)	No	515 (12.5)
	ICU	3105 (76.2)
	IMCU	367 (8.9)
	ED	132 (3.2)
	COVID area	3 (0.07)
	Other	10 (0.2)
	Missing	2

Abbreviations: CDE, clinical deterioration event; CPR, cardiopulmonary resuscitation; ED, emergency department; ICU, intensive care unit; IMCU, intermediate care unit.

[a]UNOP (Unidad Nacional de Oncologia Pediatrica) in Guatemala has a separate intermediate oncology ward that is managed as a ward hospital area, not an ICU, but is reported separately than their oncology ward.

[b]Event could have used more than one ICU-level intervention on wards.

4134 events) were transferred to a higher level of care. Of those not transferred (515 events) (Table S3), the most common documented reasons were lack of ICU space (34.3%) and not being considered sick enough to require ICU care (28%).

Of all CDEs, the median event duration was 4 days (IQR, 1.94–8.44) and hospital length of stay was a median of 34 days (IQR, 18–57). Among those transferred to a higher level of care ($n = 3619$), the ICU length-of-stay was a median of 4.22 days (IQR, 2.01–8.74). Among all CDEs, 56% required vasoactive infusions, 40% required mechanical ventilation, and 16% required CPR (Figure S4).

CDE mortality

Event mortality was 26.8% (1108 events; range, 0%–90% mortality/center); 479 (43.2%) of these occurred within 48 hours of event start. Mortality was highest among those who required ICU-level interventions (Figure S4). Among 515 events not transferred to a higher level of care, mortality was 37% (191 of 515). Of these deaths, 81.7% (156 of 191) occurred among events where the ICU declined admission, no ICU space was available, or the patient died before ICU bed availability (Table S3).

Multilevel risk-factors for CDE mortality

For laboratory values at the start of deterioration (lactate, platelets, neutrophils, and CRP), ROC curves were used to identify the optimal threshold for abnormal values conveying higher mortality risk (Figures S5–S8; Tables S4–S7). The same strategy was applied for hours waiting for an ICU bed (Figure S9; Table S8). Table S9 reports a summary of the final values used.

Univariate analysis for event-, patient-, and hospital-level risk factors for mortality present at the start of CDE are shown in Tables 2 and 3. Event-level risk factors were assessed at the start of deterioration ($n = 4134$, Table 2) and at time of transfer to a higher level of care for those transferred ($n = 3612$, Table S10). Notable significant risk factors for mortality in univariate analysis present at the start of deterioration included event (reason for hospital admission, use of ICU-level intervention on the ward, cardiopulmonary or cardiac arrest on the ward, lack of documented PEWS, abnormal lactate, platelets, neutrophils, or CRP, delay in event identification or ICU transfer, deterioration due to sepsis, respiratory, other cardiovascular, or neurologic dysfunction, and number of organs with dysfunction), patient (oncologic diagnosis and relapsed oncologic disease), and hospital (governance, type, lack of dedicated PHO unit, presence of department of quality and safety, type of physician responsible for ward care, type of ICU, number of hospital beds, and annual volume of PHO diagnoses) factors. Among those transferred to a higher level of care, additional significant event-level

TABLE 2 Univariate risk factors for CDE mortality (event-level factors—all patients, $n = 4134$).

Variable	Options	All events $N = 4134$	Mortality $N = 1108$	Survival $N = 3026$	Univariate p[a]
Reason for hospital admission, No. (%)	New or relapsed cancer	1832	573 (31.28)	1259 (68.72)	<.0001
	Scheduled admission	771	177 (22.96)	594 (77.04)	
	Acute admission	1501	348 (23.18)	1153 (76.82)	
	Other	28	10 (35.71)	18 (64.29)	
	Missing	2			
Any ward ICU interventions, No. (%)	No	2742	570 (20.79)	2172 (79.21)	<.0001
	Yes	1392	538 (38.65)	854 (61.35)	
Ward cardiopulmonary arrest, No. (%)	No	3522	723 (20.53)	2799 (79.47)	<.0001
	Yes	612	385 (62.91)	227 (37.09)	
Ward cardiac arrest, No. (%)	No	3915	906 (23.14)	3009 (76.86)	<.0001
	Yes	219	202 (92.24)	17 (7.76)	
Documented PEWS, No. (%)	No	1875	585 (31.20)	1290 (68.80)	<.0001
	Yes	2259	523 (23.15)	1736 (76.85)	
Abnormal lactate, No. (%)	0	1721	337 (19.58)	1384 (80.42)	<.0001
	1	1278	443 (34.66)	835 (65.34)	
	Missing	1135			
Abnormal platelets, No. (%)	0	2638	571 (21.65)	2067 (78.35)	<.0001
	1	1311	466 (35.55)	845 (64.45)	
	Missing	185			
Abnormal neutrophils, No. (%)	0	1766	379 (21.46)	1387 (78.54)	<.0001
	1	2145	640 (29.84)	1505 (70.16)	
	Missing	223			
Abnormal CRP, No. (%)	0	806	136 (16.87)	670 (83.13)	<.0001
	1	1836	462 (25.16)	1374 (74.84)	
	Missing	1492			
Delay in identifying the deterioration or ICU transfer, No. (%)	Yes	1219	430 (35.27)	789 (64.73)	<.0001
	No	2910	676 (23.23)	2234 (76.77)	
	Missing	5			
Patient's first CDE, No. (%)	No	858	208 (24.24)	650 (75.76)	.0631
	Yes	3276	900 (27.47)	2376 (72.53)	
Time of event start, No. (%)	Night	1534	409 (26.66)	1125 (73.34)	.9048
	Day	2600	699 (26.88)	1901 (73.12)	
Day of event start, No. (%)	Weekday	3135	838 (26.73)	2297 (73.27)	.8861
	Weekend	999	270 (27.03)	729 (72.97)	
Reason for deterioration, No. (%)[b]	Sepsis/septic shock	2510	713 (28.41)	1797 (71.59)	.0042
	Respiratory dysfunction	1603	607 (37.87)	996 (62.13)	<.0001
	Other CV dysfunction	985	376 (38.17)	609 (61.83)	<.0001
	Neurologic dysfunction	697	258 (37.02)	439 (62.98)	<.0001
	Hematologic dysfunction	182	60 (32.97)	122 (67.03)	.0665
	Metabolic dysfunction	96	11 (11.46)	85 (88.54)	.0009
	Renal dysfunction	58	13 (22.41)	45 (77.59)	.5415
	Tumor lysis syndrome	54	8 (14.81)	46 (85.19)	.0647
	Pancreatitis	38	6 (15.79)	32 (84.21)	.1752
	Hepatic dysfunction	22	10 (45.45)	12 (54.55)	.0820
	Other oncologic emergency	28	3 (10.71)	25 (89.29)	.0864
	Other	98	18 (18.37)	80 (81.63)	.0730
No. organs with dysfunction	Median [IQR]	1.00 [1.00–2.00]	3.00 [2.00–3.00]	1.00 [0.00–2.00]	<.0001

Abbreviations: CDE, clinical deterioration event; CRP-C, reactive protein; CV, cardiovascular; ICU, intensive care unit; IQR, interquartile range; PEWS, pediatric early warning system.

[a] p value comparing survivors and nonsurvivors.

[b] Event could have used more than one reason for deterioration.

TABLE 3 Univariate risk factors for CDE mortality (patient and hospital factors, $n = 4134$).

Level	Variable	Options	All events $N = 4134$	Mortality $N = 1108$	Survival $N = 3026$	Univariate p[a]
Patient	Age	Years, median [IQR]	8.7 [3.8–13.3]	8.5 [3.7–13.67]	8.7 [3.8–13.2]	.7559
	Sex, No. (%)	Male	2250	596 (26.49)	1654 (73.51)	.6677
		Female	1876	509 (27.13)	1367 (72.87)	
		Missing	8			
	Oncologic diagnosis, No. (%)	Heme malignancy	3087	843 (27.31)	2244 (72.69)	.0019
		Solid tumor	657	155 (23.59)	502 (76.41)	
		CNS tumor	227	49 (21.59)	178 (78.41)	
		Nonmalignant heme	162	61 (37.65)	101 (62.35)	
		Other	1	0 (0)	1 (100.00)	
	Leukemia in first induction, No. (%)	Yes	1531	444 (29.00)	1087 (71.00)	.1825
		No	1988	535 (26.91)	1453 (73.09)	
		Missing	36			
	Relapsed oncologic disease, No. (%)	Yes	743	246 (33.11)	497 (66.89)	<.0001
		No	3389	861 (25.41)	2528 (74.59)	
		Missing	2			
Hospital	Country income level, No. (%)	High income	324	73 (22.53)	251 (77.47)	.1164
		Lower middle income	339	100 (29.5)	239 (70.5)	
		Upper middle income	3471	935 (26.94)	2536 (73.06)	
	Hospital governance, No. (%)	Mixed (public/private)	1114	227 (20.38)	887 (79.62)	<.0001
		Private	637	112 (17.58)	525 (82.42)	
		Public	2383	769 (32.27)	1614 (67.73)	
	Hospital type, No. (%)	General (adults and pediatric)	933	279 (29.9)	654 (70.1)	<.0001
		Oncology (adults and pediatric)	937	236 (25.19)	701 (74.81)	
		Other (describe)	45	10 (22.22)	35 (77.78)	
		Pediatric multidisciplinary	1431	458 (32.01)	973 (67.99)	
		Pediatric oncology	671	87 (12.97)	584 (87.03)	
		Women's and children's	117	38 (32.48)	79 (67.52)	
	Separate PHO unit, No. (%)	Yes	3821	998 (26.12)	2823 (73.88)	.0007
		No (integrated with another unit)	313	110 (35.14)	203 (64.86)	
	Dept quality and safety, No. (%)	No	826	179 (21.67)	647 (78.33)	.0002
		Yes	3308	929 (28.08)	2379 (71.92)	
	Physician providing ward care, No. (%)	Pediatric hematologist-oncologist	2960	847 (28.61)	2113 (71.39)	<.0001
		Pediatric hematology-oncology fellow or trainee	36	11 (30.56)	25 (69.44)	
		Pediatrician	531	136 (25.61)	395 (74.39)	
		Other	607	114 (18.78)	493 (81.22)	
	Type of ICU, No. (%)	Pediatric oncology ICU	1030	144 (13.98)	886 (86.02)	<.0001
		Pediatric multidisciplinary ICU	2351	761 (32.37)	1590 (67.63)	
		Adult ICU	535	143 (26.73)	392 (73.27)	
		Other non-ICU	218	60 (27.52)	158 (72.48)	
	No. inpatient beds	Median [IQR]	187 [77–300]	200 [77–350]	187 [77–280]	.0030
	No. annual PHO diagnoses	Median [IQR]	110 [60–320]	110 [60–200]	150 [60–320]	.0022
	Patients/nurse on ward	Median [IQR]	5 [4–7]	5 [4–7]	5 [4–7]	.3452

Abbreviations: CNS, central nervous system; Dept, department; ICU, intensive care unit; IQR, interquartile range; PHO, pediatric hematology oncology.

[a]p value comparing survivors and nonsurvivors.

risk factors at the time of transfer included PIM2, ICU bed availability, presence of septic shock, type of higher level of care, longer time waiting for ICU bed, respiratory or hemodynamic support as reason for ICU transfer, and number of organs with dysfunction.

Multi-level modeling evaluated risk factors at the level of the event, patient, and hospital. The best model selected had an AIC of 3635.6 (Table S11). Significant independent risk factors for event mortality present at the start of deterioration ($n = 4134$) included event (reason for hospital admission, use of ICU intervention on wards, documented PEWS, abnormal lactate, platelets, or C-reactive protein, delay in identifying or managing deterioration, reason for deterioration, and number of organs with dysfunction) and patient (disease relapse) factors (Table 4). Hospital factors were not significant predictors of mortality. When evaluating risk factors present at the time of transfer to a higher level of care ($n = 3619$), again only event and patient factors were significant independent predictors of mortality (Table 4; Table S12).

DISCUSSION

In this study, we describe characteristics and outcomes of over 4000 clinical deterioration events (CDE) among hospitalized children with cancer and other blood disorders across 69 variably resourced centers in 18 countries. The definition of CDE describes the development of acute critical illness among hospitalized children with cancer, including at hospitals without formal ICUs.[9,10,14,24] Our findings highlight independent event- and patient-level risk factors for mortality present at the start of deterioration or at time of transfer to a higher level of care. Notably, hospital-level factors, including the structure, governance, pediatric oncology volume, and human and ICU resources, were not significant risk factors for mortality in multilevel analysis. These findings add further evidence to the importance of modifiable event-level factors (e.g., individual clinical decision-making, local clinical practices, and hospital systems-level processes) rather than fixed hospital characteristics (e.g., organization, governance, or resources) as important targets for interventions to reduce mortality among these high-risk patients.

All centers included in this study participate in Proyecto EVAT, a quality improvement collaborative to support PEWS implementation.[12] Registry data used in this analysis represent clinical deterioration that occurred before, during, and after PEWS implementation at these centers. Events with a documented PEWS occurred when PEWS was routinely used in patient care (after PEWS implementation), thus representing active PEWS use in the care of the deteriorating patient. In past work, we demonstrated multiple benefits of PEWS at the level of the patient, clinician, medical team, and institution,[25–33] including a significant reduction in clinical deterioration event mortality.[14] As expected, PEWS use was independently protective against mortality in this study, adding further evidence to support global use of PEWS in the care of all hospitalized children with cancer.

In addition to lack of PEWS use, this study identified other independent risk factors for mortality that can be leveraged to identify patients at high-risk death and who may benefit from early identification, timely ICU admission, and appropriate ICU-level interventions. Additionally, controlling for PEWS use, we identified modifiable clinical practices associated with mortality, such as use of ICU-level interventions on the ward, delay in identification or intervention for deterioration, long time waiting for an ICU bed (>3 hours), and late transfer to a higher level of care at a higher severity of illness (more organ dysfunction and high PIM2). Prior research from high-research settings have similarly identified late ICU transfer, defined as severity of illness and organ dysfunction or treatment delays, as risk factors for mortality among hospitalized PHO patients.[4,19,34–37] These practices represent important targets for novel interventions aimed to change clinical practice and further improve patient outcomes. Deterioration due to sepsis or septic shock had a protective effect on mortality, suggesting that global work to improve sepsis care, including guidelines for sepsis management in children,[38] has also impacted outcomes for children with cancer. Future work should target development of guidance on how to improve clinical management of neurologic and respiratory dysfunction, both independently associated with higher mortality in this study. Greater focus on management of patients at higher risk of mortality from deterioration, such as those with cancer relapse, is also needed. Finally, these findings highlight the importance of continuous quality improvement, including hospital-based outcomes registries and ongoing collection, review, and action based on local data,[39] as an integral component of improving outcomes for all hospitalized children.

Our finding that hospital-level factors were not associated with mortality is consistent with other studies showing hospital characteristics are less important to outcomes when controlling for other factors.[40] These findings, however, must be interpreted in the context of centers included in this study. Although inclusion of 69 centers in 18 countries enriches this analysis, most centers were in middle-income countries. Despite a range of resource limitations, ICU interventions were widely available to most critically ill patients. Although ICU resources varied, only five centers had no formal ICUs for PHO patients. Although included centers are representative of facilities providing childhood cancer care in Latin America, the impact of resources on mortality may be different in settings with no or very limited access to ICU-level interventions. Additionally, these findings do not account for center-level variables not explored in this analysis, such as medication availability and staff training. However, these findings emphasize that physical presence of ICUs and availability of ICU interventions does not guarantee their actual availability and appropriate use for children with cancer in real-world settings. A third of deterioration events used ICU-level interventions on the ward and one-fifth of events ultimately transferred to the ICU spent more than 3 hours waiting for an ICU bed. Among events not transferred to a higher level of care, over a third died, most due to lack of timely availability of ICU beds, highlighting global shortages in ICU infrastructure.[6] Even when ICU interventions were available and used, mortality was high, consistent with prior studies of children with cancer who require organ support.[2,8] These results demonstrate

TABLE 4 Significant risk factors for CDE mortality in multilevel model comparing survivors and nonsurvivors.

Variable (reference level)	OR (95% CI)[c]	p[c]
All CDEs (n = 4134)[a]		
Any ward ICU interventions (Ref: no)		
Yes	1.666 (1.354–2.051)	<.0001
New or relapsed cancer as reason for hospital admit (Ref: scheduled admission)		
New or relapsed cancer	1.644 (1.271–2.126)	.0002
Documented PEWS (Ref: no)		
Yes	0.8 (0.658–0.973)	.0255
Abnormal lactate (Ref: ≤2 mmol/L)		
>2 mmol/L	1.569 (1.282–1.92)	<.0001
Missing lactate	1.5 (1.152–1.954)	.0026
Abnormal platelets (Ref: ≥40 × 10^3/mm)		
<40 × 10^3/mm	1.568 (1.283–1.917)	<.0001
Abnormal C-reactive protein (Ref: ≤12.2 mg/L)		
>12.2 mg/L	1.693 (1.341–2.138)	.0005
Missing C-reactive protein	1.578 (1.219–2.042)	.0017
Delays in identifying the deterioration (Ref: no)		
Yes	1.306 (1.076–1.586)	.0069
Reason for deterioration (sepsis/septic shock) (Ref: no)		
Yes	0.743 (0.6–0.92)	.0064
Reason for deterioration (neurologic dysfunction) (Ref: no)		
Yes	1.594 (1.244–2.042)	.0002
Reason for deterioration (respiratory dysfunction) (Ref: no)		
Yes	1.723 (1.426–2.082)	<.0001
No. of organs with dysfunction at event start (unit change)	2.184 (2.001–2.384)	<.0001
Relapsed oncologic disease (Ref: no)		
Yes	1.742 (1.387–2.187)	<.0001
CDEs transferred to higher level of care (n = 3619)[b]		
New or relapsed cancer as reason for hospital admit (Ref: scheduled admission)		
New or relapsed cancer	1.33 (0.952–1.857)	.0094
Abnormal lactate (Ref: ≤2 mmol/L)		
>2 mmol/L	1.33 (1.029–1.719)	.0292
Missing lactate	1.662 (1.163–2.375)	.0053
Abnormal C-reactive protein (Ref: ≤12.2 mg/L)		
>12.2 mg/L	1.496 (1.12–1.999)	.0065
Missing lactate	1.491 (1.068–2.082)	.0189
Reason for deterioration (sepsis/septic shock) (Ref: no)		
Yes	0.499 (0.336–0.74)	.0006
PIM2 (unit change)	6.677 (3.766–11.838)	<.0001
Reason for ICU transfer (hemodynamic support) (Ref: no)		
Yes	1.36 (1.002–1.846)	.0489
No. of organs with dysfunction at transfer (unit change)	3.296 (2.96–3.67)	<.0001
Relapsed oncologic disease (Ref: no)		
Yes	1.831 (1.365–2.457)	<.0001

Note: Only variables significant in the multivariable model included in this table.

Abbreviations: CI, confidence interval; CDE, clinical deterioration event; ICU, intensive care unit; OR, odds ratio; PEWS, pediatric early warning system; PIM2, Pediatric Index of Mortality 2 score.

[a]See Table S11 for complete multi-level models for all CDEs (n = 4134).

[b]See Table S12 for complete multi-level models for CDEs transferred to higher level of care (n = 3619).

[c]ORs and p are reported for the significant level versus reference. See Tables S11 and S12 for type III test; p values are reported for the significant risk factors.

the need to look beyond simple availability of ICU resources to focus on improving timely and appropriate use of available resources in the care of children with cancer. They also highlight the need to move from identifying risk factors for mortality to interventional studies that support appropriate use of existing technologies and novel interventions to improve outcomes. Future work should leverage clinical and comparative effectiveness research to develop and compare different management interventions[41] for clinical deterioration and implementation science methods[42] to identify effective strategies to ensure their sustainable implementation in the care of all children with cancer globally. Additionally, we must develop new interventions, beyond PEWS,[14,27] to predict and prevent clinical deterioration in high-risk patients as a mechanism to avoid complications and reduce treatment-related mortality.

This study is strengthened by a large sample size of children with cancer who experienced clinical deterioration at diverse hospitals providing childhood cancer care in Latin America and Spain. This sample is representative of the diversity of PHO patients, including different ages, oncologic diagnoses, and disease stages, making these findings generally applicable to hospitalized children with cancer. The study's large sample size also facilitated inclusion of data-driven thresholds for lactate, platelets, neutrophils, and C-reactive protein at the start of deterioration that are associated with mortality in these patients. Although the expected dose–response is present across all variables, with higher mortality among more abnormal values, the identified thresholds differ from those in scoring systems developed for general pediatric patients (for example, the Phoenix pediatric sepsis criteria uses a lactate of >5 as higher risk).[43] These findings add further evidence that traditional risk-scoring systems developed in general pediatrics do not always perform well among children with cancer, emphasizing the need for future work to prospectively assess general pediatric tools and tailor them to these unique patients.[36,44] Additionally, this work highlights potential differences in risk factors for mortality among children with cancer who develop critical illness in high-resource versus resource-limited settings, where access to blood products, supportive medications, and ICU interventions are different.

This study has several limitations in addition to those discussed above. As an analysis of prospectively collected quality improvement registry data, it is limited by traditional challenges of this study design. Although centers prospectively identified clinical deterioration events, clinical details were retrospectively extracted from patient charts. Clinical data not available in these records, notably laboratory data not collected as part of patient care or not available at a given center, were missing from the registry. To address missing laboratory data, we used "missing" as a category in multilevel analysis; missing lactate and CRP were independent risk factors for mortality. Future work should prospectively collect clinical data to inform ongoing research. Centers included in this analysis represent hospitals managing children with cancer who participate in Proyecto EVAT, resulting in more centers from some countries (e.g., Mexico, 30 centers) compared to others (e.g., Guatemala, one center). This is due to differences in population size and structure of cancer care in these countries.[45] Our use of event-level rather than center-level analysis, and inclusion of center-level variables in the multivariable model, however, accounts for this potential bias. Finally, this study includes only hospitals in Latin America and Spain, most of which had access to formal ICUs or ICU-level interventions and all of which chose to join Proyecto EVAT. This may limit generalizability of findings beyond cancer care in these countries and to hospitals with more limited ICU-resources and less interest in collaborative quality improvement. Further work is needed to evaluate if risk factors for mortality for children with cancer experiencing clinical deterioration identified in this study are similar in other global regions and centers.

In conclusion, hospitalized children with cancer and other blood disorders who experience clinical deterioration in resource-limited settings frequently require ward-based ICU interventions and have high mortality, with significant variability in outcomes across centers. When controlling for event-, patient-, and hospital-level factors, this variability was not associated with hospital characteristics or resources to treat critical illness. Instead, mortality was driven by modifiable event-level factors, such as use of ICU-level interventions on the wards and late transfer to higher level of care. These findings highlight an urgent need for targeted contextually relevant interventions to promote appropriate, timely use of ICU-level interventions and, if available, early ICU transfer for children with cancer who develop critical illness to improve global survival among children with cancer.

AUTHOR CONTRIBUTIONS

Asya Agulnik: Conceptualization, funding acquisition, resources, methodology, writing–original draft, and writing–review and editing. **Maricela Robles-Murguia:** Project administration, data curation, validation, investigation, visualization, and writing–review and editing. **Yichen Chen:** Methodology, data curation, software, validation, formal analysis, investigation, writing–original draft, visualization, and writing–review and editing. **Hilmarie Muniz-Talavera:** Project administration, data curation, validation, investigation, and writing–review and editing. **Linh Pham:** Data curation, software, validation, formal analysis, investigation, visualization, and writing–review and editing. **Angela Carrillo:** Data curation, validation, investigation, and writing–review and editing. **Adolfo Cardenas-Aguirre:** Project administration, investigation, and writing–review and editing. **Juliana Costa:** Project administration, investigation, and writing–review and editing. **Alejandra Mendez Aceituno:** Investigation, project administration, and writing–review and editing. **Carlos Acuña Aguirre:** Investigation and writing–review and editing. **Ana Berenice Aguilar Roman:** Investigation and writing–review and editing. **Shillel Yahamy Alvarez Arellano:** Investigation and writing–review and editing. **Leticia Aradi Andrade Sarmiento:** Investigation and writing–review and editing. **Daniela Arce Cabrera:** Investigation and writing–review and editing. **Erika Esther Blasco Arriaga:** Investigation and writing–review and editing. **Claudia María De León Gutiérrez:** Investigation and writing–review and editing. **Rosdali Diaz-Coronado:** Investigation and writing–review and editing. **Maria do Céu Diniz Borborema:** Investigation and writing–review and

editing. **Mariana do Nascimento Othero Campacci:** Investigation and writing–review and editing. **Leticia Drumond Alberto:** Investigation and writing–review and editing. **Natalia Soledad Gonzalez:** Investigation and writing–review and editing. **Martha Herrera Almanza:** Investigation and writing–review and editing. **Valentine Jimenez Antolinez:** Investigation and writing–review and editing. **Merle Denisse Laffont Ortiz:** Investigation and writing–review and editing. **Laura Lemos De Mendonça E. Fontes:** Investigation and writing–review and editing. **Norma Araceli López Facundo:** Investigation and writing–review and editing. **Claudia Beatriz López Vázquez:** Investigation and writing–review and editing. **Idalia Margarita Lozano Lozano:** Investigation and writing–review and editing. **Jose Miguel Mijares Tobias:** Investigation and writing–review and editing. **Lupe Nataly Mora Robles:** Investigation and writing–review and editing. **Berenice Noriega Acuña:** Investigation and writing–review and editing. **Fernanda Paula Endo Marques:** Investigation and writing–review and editing. **Clara Krystal Pérez Fermín:** Investigation and writing–review and editing. **Monica Lorena Quijano Lievano:** Investigation and writing–review and editing. **Andreia Ribeiro Pereira Aguiar De Paula:** Investigation and writing–review and editing. **Ligia Rios:** Investigation and writing–review and editing. **Jocelyn Rivera:** Investigation and writing–review and editing. **Marcela Alejandra Sahonero:** Investigation and writing–review and editing. **Beatriz Salas Mendoza:** Investigation and writing–review and editing. **María Sánchez-Martín:** Investigation and writing–review and editing. **Jennifer Sepúlveda Ramírez:** Investigation and writing–review and editing. **Verónica Soto Chávez:** Investigation and writing–review and editing. **Daniela María Velásquez Cabrera:** Investigation and writing–review and editing. **Erika Elena Villanueva Hoyos:** Investigation and writing–review and editing. **Luz Yadira Zuñiga Quijano:** Investigation and writing–review and editing. **Meenakshi Devidas:** Methodology, data curation, supervision, writing–original draft, and writing–review and editing. **Carlos Rodriguez-Galindo:** Conceptualization, funding acquisition, resources, methodology, supervision, and writing–review and editing. All authors contributed to the interpretation of the findings, the editing of the article, and the approval of the final submitted version. All authors have access to all the data reported in this study.

AFFILIATIONS

[1]St. Jude Children's Research Hospital, Memphis, Tennessee, USA

[2]Hospital Dr Luis Calvo Mackenna, Santiago, Chile

[3]Hospital General de Zona #2 Nueva Frontera, OncoCREAN Tapachula Chiapas, Tapachula, Mexico

[4]Hospital General Con Especialidades Juan Maria De Salvatierra, La Paz, BCS, Mexico

[5]Hospital Pediatria Centro Médico Nacional Siglo XXI, Mexico City, Mexico

[6]Hospital Pediátrico de Sinaloa, Culiacán, Mexico

[7]Instituto Oncológico Nacional Solca Guayaquil, Guayaquil, Ecuador

[8]Unidad Nacional de Oncología Pediatrica, Guatemala, Guatemala

[9]Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

[10]Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil

[11]Grupo de Apoio ao Adolescente e à Criança com Câncer, Sao Paulo, Brazil

[12]Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[13]Sanatorio Allende, Cordoba, Argentina

[14]Hospital Infantil de Especialidades de Chihuahua, Chihuahua, Mexico

[15]Hospital Universitario Dr. José Eleuterio González, Monterrey, Mexico

[16]Hospital para el niño del instituto Materno infantil del Estado de México, Toluca, Mexico

[17]Hospital Martagão Gesteira, Salvador, Brazil

[18]Hospital Materno Infantil Del Issemym, Toluca, Mexico

[19]Hospital General León, León, Mexico

[20]Hospital San José, Monterrey, Mexico

[21]Hospital De Especialidades Del Niño Y La Mujer "Dr. Felipe Nuñez Lara", Querétaro, Mexico

[22]Hospital De Solca Cuenca, Cuenca, Ecuador

[23]Hospital de Especialidades Pediátricas Chiapas, Tuxtla, Gutiérrez, Mexico

[24]Hospital Infantil de Cancer de Barretos, Barretos, Brazil

[25]Hospital infantil regional Dr. Arturo Grullon, Santiago, Dominican Republic

[26]Clínica Imbanaco, Cali, Colombia

[27]Hospital Nacional Edgardo Rebagliati Martins, Lima, Perú

[28]Hospital Infantil Teletón de Oncología, Querétaro, Mexico

[29]Hospital de niños Santísima Trinidad de Córdoba, Córdoba, Argentina

[30]Hospital del niño Manuel Ascencio Villarroel, Cochabamba, Bolivia

[31]Hospital Universitario La Paz, Madrid, Spain

[32]Instituto Nacional de Cancerología-Bogotá, Bogotá, Colombia

[33]Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Guadalajara, Mexico

[34]Hospital Regional de Alta Especialidad del Bajío, León, Mexico

[35]Sociedad Oncológica Lucha contra el Cáncer (SOLCA), Quito, Ecuador

[36]Hospital Infantil de Morelia "Eva Samano de López Mateos", Morelia, Mexico

ACKNOWLEDGMENTS

We acknowledge the members of the Proyecto EVAT Steering Committee, Maria Puerto-Torres, and Samantha Hayes. This study was funded by the American Lebanese-Syrian Associated Charities (ALSAC) and the National Cancer Institute (5P30CA021765). These funders were not involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

Asya Agulnik reports grant and/or contract funding from the National Cancer Institute. Alejandra Méndez reports consulting fees from St. Jude Children's Research Hospital. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

De-identified data (including data dictionaries) that underlie the results reported in this article, as well as the study protocol, statistical

analysis plan, and analytic code, will be made available beginning 6 months and ending 5 years after article publication to researchers who provide a methodologically sound proposal that has been reviewed by the Proyecto EVAT Steering Committee to achieve the aims of the approved proposal. Proposals should be directed to Asya Agulnik. Data requestors will need to sign a data access agreement.

ORCID

Asya Agulnik https://orcid.org/0000-0001-8932-8181
Maricela Robles-Murguia https://orcid.org/0000-0002-1216-8930
Rosdali Diaz-Coronado https://orcid.org/0000-0002-1849-2256
Jocelyn Rivera https://orcid.org/0000-0002-5741-5640
María Sánchez-Martín https://orcid.org/0000-0002-0425-9883

REFERENCES

1. Ehrlich BS, McNeil MJ, Pham LTD, et al. Treatment-related mortality in children with cancer in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Oncol*. 2023;24(9):967-977. doi:10.1016/s1470-2045(23)00318-2
2. Wosten van-Asperen RM, van Gestel JPJ, van Grotel M, et al. 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. doi:10.1016/j.critrevonc.2019.07.014
3. 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(1):e52-e58. doi:10.1097/pcc.0000000000003380
4. 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. doi:10.1007/s00134-014-3389-2
5. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. *Lancet Oncol*. 2019;20(4):483-493. doi:10.1016/s1470-2045(18)30909-4
6. Muttalib F, González-Dambrauskas S, Lee JH, et al. Pediatric emergency and critical care resources and infrastructure in resource-limited settings: a multicountry survey. *Crit Care Med*. 2021;49(4):671-681. doi:10.1097/ccm.0000000000004769
7. Arias AV, Sakaan FM, Puerto-Torres M, et al. Development and pilot testing of PROACTIVE: a pediatric onco-critical care capacity and quality assessment tool for resource-limited settings. *Cancer Med*. 2023;12(5):6270-6282. doi:10.1002/cam4.5395
8. Gabela A, Wösten-van Asperen RM, Arias AV, et al. The burden of pediatric critical illness among pediatric oncology patients in low- and middle-income countries: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2024;203:104467. doi:10.1016/j.critrevonc.2024.104467
9. Arias AV, Lintner-Rivera M, Shafi NI, et al. A research definition and framework for acute paediatric critical illness across resource-variable settings: a modified Delphi consensus. *Lancet Glob Health*. 2024;12(2):e331-e340. doi:10.1016/s2214-109x(23)00537-5
10. Agulnik A, Cárdenas A, Carrillo AK, et al. Clinical and organizational risk factors for mortality during deterioration events among pediatric oncology patients in Latin America: a multicenter prospective cohort. *Cancer*. 2021;127(10):1668-1678. doi:10.1002/cncr.33411
11. St. Jude Global Critical Care Program. Accessed January 9, 2023. https://www.stjude.org/global/programs.html#cbb742cac15612dad552d4efee42ba66c8f4cedd92e83659dbb696ad9c912825=0
12. Agulnik A, Gonzalez Ruiz A, Muniz-Talavera H, et al. Model for regional collaboration: Successful strategy to implement a pediatric early warning system in 36 pediatric oncology centers in Latin America. *Cancer*. 2022;128(22):4004-4016. doi:10.1002/cncr.34427
13. Agulnik A, Forbes PW, Stenquist N, Rodriguez-Galindo C, Kleinman M. Validation of a pediatric early warning score in hospitalized pediatric oncology and hematopoietic stem cell transplant patients. *Pediatr Crit Care Med*. 2016;17(4):e146-e153. doi:10.1097/PCC.0000000000000662
14. Agulnik A, Muniz-Talavera H, Pham LTD, et al. Effect of paediatric early warning systems (PEWS) implementation on clinical deterioration event mortality among children with cancer in resource-limited hospitals in Latin America: a prospective, multicentre cohort study. *Lancet Oncol*. 2023;24(9):978-988. doi:10.1016/s1470-2045(23)00285-1
15. St. Jude Global. Accessed March 2, 2020. https://www.stjude.org/global.html
16. Agulnik A, Mendez Aceituno A, Mora Robles LN, et al. Validation of a pediatric early warning system for hospitalized pediatric oncology patients in a resource-limited setting. *Cancer*. 2017;123(24):4903-4913. doi:10.1002/cncr.30951
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
18. The World Bank. *Country Classification*. The World Bank. Accessed July 1, 2024. https://datahelpdesk.worldbank.org/knowledgebase/topics/19280-country-classification
19. Agulnik A, Gossett J, Carrillo AK, Kang G, Morrison RR. Abnormal vital signs predict critical deterioration in hospitalized pediatric hematology-oncology and post-hematopoietic cell transplant patients. *Front Oncol*. 2020;10:354. doi:10.3389/fonc.2020.00354
20. Bonafide CP, Roberts KE, Priestley MA, et al. Development of a pragmatic measure for evaluating and optimizing rapid response systems. *Pediatrics*. 2012;129(4):e874-e881. doi:10.1542/peds.2011-2784
21. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8. doi:10.1097/01.pcc.0000149131.72248.e6
22. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Med*. 2003;29(2):278-285. doi:10.1007/s00134-002-1601-2
23. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol*. 2006;163(7):670-675. doi:10.1093/aje/kwj063
24. Rosman SL, Karangwa V, Law M, Monuteaux MC, Briscoe CD, McCall N. Provisional validation of a pediatric early warning score for resource-limited settings. *Pediatrics*. 2019;143(5):e20183657. doi:10.1542/peds.2018-3657
25. Mirochnick E, Graetz DE, Ferrara G, et al. Multilevel impacts of a pediatric early warning system in resource-limited pediatric oncology hospitals. *Front Oncol*. 2022;12:1018224. doi:10.3389/fonc.2022.1018224
26. Agulnik A, Mora Robles LN, Forbes PW, et al. Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. *Cancer*. 2017;123(15):2965-2974. doi:10.1002/cncr.30664
27. Agulnik A, Johnson S, Wilkes R, Faughnan L, Carrillo A, Morrison R. Impact of implementing a pediatric early warning system (PEWS) in a pediatric oncology hospital. *Pediatr Qual Safe*. 2018;3(2):e065. doi:10.1097/pq9.0000000000000065

28. Agulnik A, Nadkarni A, Mora Robles LN, et al. Pediatric early warning systems aid in triage to intermediate versus intensive care for pediatric oncology patients in resource-limited hospitals. *Pediatr Blood Cancer*. 2018;65(8):e27076. doi:10.1002/pbc.27076
29. Agulnik A, Antillon-Klussmann F, Soberanis Vasquez DJ, et al. Cost-benefit analysis of implementing a pediatric early warning system at a pediatric oncology hospital in a low-middle income country. *Cancer*. 2019;125(22):4052-4058. doi:10.1002/cncr.32436
30. Graetz D, Kaye EC, Garza M, et al. Qualitative study of pediatric early warning systems' impact on interdisciplinary communication in two pediatric oncology hospitals with varying resources. *JCO Glob Oncol*. 2020;6:1079-1086. doi:10.1200/go.20.00163
31. Graetz DE, Giannars E, Kaye EC, et al. Clinician emotions surrounding pediatric oncology patient deterioration. *Front Oncol*. 2021;11:626457. doi:10.3389/fonc.2021.626457
32. Garza M, Graetz DE, Kaye EC, et al. Impact of PEWS on perceived quality of care during deterioration in children with cancer hospitalized in different resource-settings. *Front Oncol*. 2021;11:660051. doi:10.3389/fonc.2021.660051
33. Gillipelli SR, Kaye EC, Garza M, et al. Pediatric early warning systems (PEWS) improve provider-family communication from the provider perspective in pediatric cancer patients experiencing clinical deterioration. *Cancer Med*. 2022;12(3):3634-3643. doi:10.1002/cam4.5210
34. Flerlage T, Fan K, Qin Y, et al. Mortality risk factors in pediatric onco-critical care patients and machine learning derived early onco-critical care phenotypes in a retrospective cohort. *Crit Care Explor*. 2023;5(10):e0976. doi:10.1097/cce.0000000000000976
35. Soeteman M, Fiocco MF, Nijman J, et al. Prognostic factors for multi-organ dysfunction in pediatric oncology patients admitted to the pediatric intensive care unit. *Front Oncol*. 2023;13:1192806. doi:10.3389/fonc.2023.1192806
36. Rubnitz Z, Sun Y, Agulnik A, et al. Prediction of attributable mortality in pediatric patients with cancer admitted to the intensive care unit for suspected infection: a comprehensive evaluation of risk scores. *Cancer Med*. 2023;12(23):21287-21292. doi:10.1002/cam4.6709
37. Fausser JL, Tavenard A, Rialland F, et al. Should we pay attention to the delay before admission to a pediatric intensive care unit for children with cancer? Impact on 1-month mortality. A report from the French Children's Oncology Study Group, GOCE. *J Pediatr Hematol Oncol*. 2017;39(5):e244-e248. doi:10.1097/mph.0000000000000816
38. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med*. 2020;46(suppl 1):10-67. doi:10.1007/s00134-019-05878-6
39. Maas MR, Yang A, Muir MA, et al. Evaluating implementation of a hospital-based cancer registry to improve childhood cancer care in low- and middle-income countries. *Cancer Med*. 2024;13(17):e70125. doi:10.1002/cam4.70125
40. McKay V, Chen Y, Prewitt K, et al. Connecting clinical capacity and intervention sustainability in resource-variable pediatric oncology centers in Latin America. *Glob Implement Res Appl*. 2024;4(1):102-115. doi:10.1007/s43477-023-00106-2
41. Agulnik A, Mahadeo KM, Steiner ME, McArthur JA. Editorial: critical complications in pediatric oncology and hematopoietic cell transplant - how far we have come and how much further we must go. *Front Oncol*. 2023;13:1148321. doi:10.3389/fonc.2023.1148321
42. Woods-Hill CZ, Wolfe H, Malone S, et al. Implementation science research in pediatric critical care medicine. *Pediatr Crit Care Med*. 2023;24(11):943-951. doi:10.1097/pcc.0000000000003335
43. Sanchez-Pinto LN, Bennett TD, DeWitt PE, et al. Development and validation of the Phoenix criteria for pediatric sepsis and septic shock. *JAMA*. 2024;331(8):675-686. doi:10.1001/jama.2024.0196
44. Wolf J, Rubnitz Z, Agulnik A, Ferrolino J, Sun Y, Tang L. Phoenix sepsis score and risk of attributable mortality in children with cancer. *JAMA Netw Open*. 2024;7(6):e2415917. doi:10.1001/jamanetworkopen.2024.15917
45. Vásquez L, Fuentes-Alabi S, Benitez-Majano S, et al. Collaboration for success: the Global Initiative for Childhood Cancer in Latin America. *Rev Panam Salud Publica*. 2023;47:e144. doi:10.26633/rpsp.2023.144

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Agulnik A, Robles-Murguia M, Chen Y, et al. Multilevel mortality risk factors among pediatric hematology-oncology patients with deterioration. *Cancer*. 2025;e35818. doi:10.1002/cncr.35818