ORIGINAL CLINICAL REPORT

OPEN

Mortality Risk Factors in Pediatric Onco-Critical Care Patients and Machine Learning Derived Early Onco-Critical Care Phenotypes in a Retrospective Cohort

Tim Flerlage, MD[1]
Kimberly Fan, MD[2]
Yidi Qin, MSc[3]
Asya Agulnik, MD, MPH[4]
Anita V. Arias, MD[5]
Cheng Cheng, PhD[6]
Lama Elbahlawan, MD[7]
Saad Ghafoor, MD[8]
Caitlin Hurley, MD[9]
Jennifer McArthur, MD[10]
R. Ray Morrison, MD[11]
Yinmei Zhou, MSc[12]
H.J. Park, PhD[13]
Joseph A. Carcillo, MD[14]
Melissa R. Hines MD[15]

OBJECTIVES: To use supervised and unsupervised statistical methodology to determine risk factors associated with mortality in critically ill pediatric oncology patients to identify patient phenotypes of interest for future prospective study.

DESIGN: This retrospective cohort study included nonsurgical pediatric critical care admissions from January 2017 to December 2018. We determined the prevalence of multiple organ failure (MOF), ICU mortality, and associated factors. Consensus *k*-means clustering analysis was performed using 35 bedside admission variables for early, onco-critical care phenotype development.

SETTING: Single critical care unit in a subspeciality pediatric hospital.

INTERVENTION: None.

PATIENTS: There were 364 critical care admissions in 324 patients with underlying malignancy, hematopoietic cell transplant, or immunodeficiency reviewed.

MEASUREMENTS: Prevalence of multiple organ failure, ICU mortality, determination of early onco-critical care phenotypes.

MAIN RESULTS: ICU mortality was 5.2% and was increased in those with MOF (18.4% MOF, 1.7% single organ failure [SOF], 0.6% no organ failure; $p \leq 0.0001$). Prevalence of MOF was 23.9%. Significantly increased ICU mortality risk was associated with day 1 MOF (hazards ratio [HR] 2.27; 95% CI, 1.10–6.82; $p = 0.03$), MOF during ICU admission (HR 4.16; 95% CI, 1.09–15.86; $p = 0.037$), and with invasive mechanical ventilation requirement (IMV; HR 5.12; 95% CI, 1.31–19.94; $p = 0.018$). Four phenotypes were derived (PedOnc1–4). PedOnc1 and 2 represented patient groups with low mortality and SOF. PedOnc3 was enriched in patients with sepsis and MOF with mortality associated with liver and renal dysfunction. PedOnc4 had the highest frequency of ICU mortality and MOF characterized by acute respiratory failure requiring invasive mechanical ventilation at admission with neurologic dysfunction and/or severe sepsis. Notably, most of the mortality in PedOnc4 was early (i.e., within 72 hr of ICU admission).

CONCLUSIONS: Mortality was lower than previously reported in critically ill pediatric oncology patients and was associated with MOF and IMV. These findings were further validated and expanded by the four derived nonsynonymous computable phenotypes. Of particular interest for future prospective validation and correlative biological study was the PedOnc4 phenotype, which was composed of patients with hypoxic respiratory failure requiring IMV with sepsis and/or neurologic dysfunction at ICU admission.

KEY WORDS: multiple organ dysfunction syndrome; multiple organ failure; onco-critical care; pediatric critical care; sepsis

DOI: 10.1097/CCE.0000000000000976

KEY POINTS

Question: Will an agnostic machine learning approach identify additional or unique combinations of risk factors for ICU mortality in a single-center study of critically ill pediatric oncology patients to guide future prospective studies?

Findings: In this cohort study, we found that the development of multiple organ failure (MOF) and the need for invasive mechanical ventilation were associated with the highest risk of death. These findings were further demonstrated by the derivation of four early nonsynonymous phenotypes using an agnostic machine learning analytic approach. One phenotype, PedOnc4, was characterized by early MOF, particularly respiratory and neurologic failure, and had the highest risk of death.

Meaning: Based on the risk factors found and the derived early pediatric onco-critical care phenotypes, patients with respiratory failure requiring invasive mechanical ventilation and MOF with associated neurologic dysfunction and/or rapidly evolving sepsis at ICU admission (i.e., PedOnc 4) are of particular interest for future prospective studies.

Among critically ill pediatric patients, pediatric cancer and hematopoietic cell transplant (HCT) patients remain a high-risk group with reported mortality at least three times higher (and pooled mortality 10 times higher) than the general pediatric critical care population (1–14). Increases in mortality have been described in pediatric oncology patients with neutropenia, neurologic dysfunction, sepsis, and those who require critical care support resources, such as invasive mechanical ventilation (IMV), vasoactive support, and continuous renal replacement therapy (CRRT) (2, 4, 6, 7, 15–23). More recently, it has been shown that critically ill pediatric oncology patients with respiratory failure who receive noninvasive mechanical ventilation (NIV) or high-flow nasal cannula (HFNC) before IMV have higher mortality rates (17, 19, 24). Although respiratory failure has been further studied, there are little data describing the prevalence of and mortality from multiple organ failure (MOF), which is a well-known risk factor for ICU mortality in critically ill pediatric patients in general, specifically within critically ill pediatric oncology patient populations. Furthermore, pediatric oncology and HCT patients are often considered and reported as a homogenous group of patients in studies with similar risk factors for mortality to general pediatric patients who develop sepsis. However, pediatric oncology and HCT patients often develop critical illness secondary to etiologies other than sepsis, including chemotherapy, radiation, HCT conditioning, and associated morbidities, or the malignancy itself, which differentiates this group of patients from critically ill general pediatric patients (7, 8, 25–36). Furthermore, critical illness from these etiologies can frequently be indistinguishable from critical illness secondary to sepsis at presentation. Due to the known differences in critically ill pediatric oncology patients to critically ill general pediatric patients as well as the known, inherent heterogeneity of pediatric oncology patients, there is a need to evaluate pediatric oncology patients with and without sepsis separately from the general pediatric population to determine risk factors associated with mortality, particularly MOF, to better identify critically ill pediatric oncology patients who may benefit from early identification and intervention. Our aim was to determine risk factors associated with mortality in critically ill pediatric oncology patients to identify patient phenotypes of interest for future prospective studies using supervised and unsupervised statistical methodology. We hypothesized that an agnostic machine learning approach would identify additional individual risk factors or a combination of risk factors associated with ICU mortality in critically ill pediatric oncology patients.

MATERIALS AND METHODS

Study Population and Data Collection

This project, Defining the Burden of Multi-system Organ Failure in Critically Ill Hematology/Oncology Patients, was reviewed and approved by the St Jude Children's Research Hospital (SJCRH) institutional review board (number 20-0479) in accordance with institutional ethical standards and the Helsinki Declaration of 1975 for human experimentation. We performed a single-center, retrospective review of all medical admissions to the ICU from January 2017 to December 2018 of pediatric and young adult patients at SJCRH, a specialized hospital for hematology/oncology patients

with eight ICU beds and four step-down ICU beds. At SJCRH all patients that require more respiratory support than a binasal cannula or oxymask are admitted to the ICU. The pediatric early warning system (PEWS) is used at SJCRH as previously described (9, 37). ICU consultation is required for patients with PEWS score of five or greater per the algorithm previously published (37). ICU admissions were excluded if patients had underlying nonmalignant hematologic diagnosis (i.e., sickle cell disease, aplastic anemia, etc.), were admitted to the ICU postoperatively, or transferred from an outside ICU (**sFig. 1**, http://links.lww.com/CCX/B251). Patients with underlying immunodeficiencies (hemophagocytic lymphohistiocytosis and severe combined immunodeficiency syndrome) were included. Data for each admission, including patient demographics, organ function, infection, and critical care resource utilization, were recorded from the electronic medical record on ICU days 1 (admission), 3, 7, 14, and 28.

Acute organ failure was defined by criteria (Organ Failure Index; OFI) set forth by Carcillo et al (38, 39), which were adapted for pediatric oncology patients. For determination of OFI and severity of organ dysfunction (**sTable 1**, http://links.lww.com/CCX/B251), the most abnormal values within 24 hours of the time point of interest were used. Pediatric Risk of Mortality (PRISM) III was calculated using the most abnormal values for each data point within 12 hours of admission (40). Presence of acute organ failure was determined for cardiovascular, respiratory, renal, hepatic, hematologic, and neurologic systems. Severity of organ failure was determined for cardiovascular (vasoactive infusion score; [VIS]), respiratory (acute respiratory distress syndrome severity [ARDS]; per the Pediatric Acute Lung Injury Consensus Conference for IMV), and renal (Kidney Disease Improving Global Outcomes; KDIGO) systems (41–43). OFI was assigned, indicating the number of dysfunctional organ systems at each time point. MOF was defined as an OFI greater than or equal to 2 (44). Overall MOF was defined as the development of MOF at any of the time points (i.e., ICU day 1, 3, etc.). Systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis were defined using the criteria set by the International Pediatric Sepsis Consensus Conference (45). "Active infection" was defined as an ongoing infection based on previously positive fluid (urine, bronchial, respiratory, blood) cultures, polymerase chain reaction (PCR), etc., and/or findings on diagnostic imaging suggestive of infection before the time point of interest that the patient was receiving ongoing treatment or had continuing symptomology. "New infection" was defined as a new infection identified at the timepoint of interest based on positive fluid (urine, bronchial, respiratory, blood) cultures, PCR, etc., and/or findings on diagnostic imaging suggestive of infection. Neutropenia was defined as absolute neutrophil count less than or equal to 500 cells/mm^3.

Statistical Analysis

Due to concerns about multiple sampling and the potential effect on certain analyses, statistical analysis for hospital mortality, and demographic features (sex and race) was based on hospital admission (n = 324). All other analyses were based on ICU admission (n = 364). Each ICU admission was treated as an individual event. Basic descriptive statistics of the patient demographics, severity of illness, presence of infection, and neutropenia were compared in patients with or without MOF by the chi-square test for discrete variables and t test for continuous variables. Fisher exact test was used to compare the use of critical care resources for patients with or without MOF. Association of the development of types of organ failure, MOF, and/or progressive MOF with underlying diagnosis, presence of neutropenia, sepsis, SIRS, number of ICU admissions, and infection was determined using chi-square test. Association with ICU mortality and ICU length of stay and number of ICU admissions was determined using t test and chi-square testing, respectively. Univariate Cox proportional hazard modeling was used to determine the association of ICU mortality to ICU characteristics (all reported p values are two-sided; SAS 9.4; Cary, NC).

Selection of Clinical Variables and Machine Learning Approach. There were 48 variables present within 24 hours of admission available for clustering analysis (sFig. 1, http://links.lww.com/CCX/B251). Of these 48 variables, there were 35 variables that were used for further analysis based on less than 20% missingness and less than 0.6 correlation (**sTables 2** and **3** and **sFig. 2**, http://links.lww.com/CCX/B251). These included demographic variables, infection data, PRISM III score, vital

signs, presence of SIRS and sepsis criteria, length of neutropenia before ICU admission, presence of organ dysfunction, severity of organ dysfunction, laboratory values, need for positive pressure respiratory support, and presence of arterial line (**Table 3**; and sTables 2, 3, and **12**, http://links.lww.com/CCX/B251). Multivariate Imputation By Chained Equations was employed, then consensus *k*-means clustering models were used to derive computable phenotypes using the 35 variables described earlier (sFigs 1–**3**, http://links.lww.com/CCX/B251) and further validated using latent class analysis (LCA). Sensitivity analysis was performed using consensus *k*-means clustering on data from patients with single ICU admissions. Primary outcome was ICU mortality. Secondary outcomes were hospital mortality, day 1 MOF, ICU length of stay, ICU-free days, MV-free days, vasopressor-free days, and CRRT-free days. Intervention-free days were defined as the number of days a patient was alive and without the intervention in the 28 days after ICU admission, with 0 given for nonsurvivors. Therapeutic interventions between the four phenotypes were compared using the Fisher exact test. A detailed overview of statistical methods for derivation of phenotypes is available in **Supplementary Material** (http://links.lww.com/CCX/B251).

RESULTS

Description of Admissions, Demographics, and Severity of Illness

We reviewed 489 ICU admissions during our study period and excluded 125 for a total of 364 admissions from 324 unique patients (sFig. 1, http://links.lww.com/CCX/B251). There were 32 patients with multiple ICU admissions (n = 72) during the same hospitalization. The median age at ICU admission was 10.1 years (0.1–26.7) and there were more male patients (194/324; 59.9%; **Table 1**). Most prominent race was White (230/324; 71%) followed by Black (60/324; 18.5%). Most patients had an underlying diagnosis of leukemia/lymphoma without HCT (117/364; 32.9%) or received an HCT (112/364; 30.9%). The median PRISM III score at admission was 6 (0–33) with 55% (199/264) of admissions meeting SIRS criteria and 51% (187/364) meeting sepsis criteria at admission (Table 1).

Factors Associated With Mortality

ICU mortality rate was 5.2% (19/364; Table 1) and hospital mortality was 11.4% (37/324; Table 3). There was no difference in ICU mortality between all admissions (5.2%) and single admissions (5.1%; **sTable 10**, http://links.lww.com/CCX/B251). Causes of ICU mortality included disease progression (n = 9; 47.4%), septic shock with organ failure (n = 5; 26.3%), and progressive organ failure (n = 5; 26.3%). Most ICU deaths occurred in patients with MOF (16/19; 84.2%). Patients requiring more than one ICU admission in a single hospitalization (p = 0.01; **sTable 6**, http://links.lww.com/CCX/B251), as well as those with day 1 MOF (hazards ratio [HR] 2.27; 95% CI, 1.10–6.82; p = 0.03), had increased ICU mortality risk. MOF during ICU admission (HR 4.16; 95% CI, 1.09–15.86; p = 0.037) and requirement of IMV (HR 5.12; 95% CI, 1.31–19.94; p = 0.018; **Table 2**) were associated with the highest increased ICU mortality risk of the factors tested. Additional analyses identified higher maximum OFI (p < 0.0001) and the presence of MOF (p < 0.0001) as variables associated with ICU and hospital mortality (**sTable 7**, http://links.lww.com/CCX/B251). Furthermore, ICU mortality was significantly different in those with MOF (18.4%), single organ failure (1.7%), and no organ failure (0.6%; p < 0.0001) but ICU mortality was not associated with D1 neutropenia (p = 0.175; sTable 7, http://links.lww.com/CCX/B251).

Prevalence and Description of Multiple Organ Failure and Need for Invasive Mechanical Ventilation

MOF was present in 87 (23.9%) ICU admissions (Table 1). There was a significantly higher cumulative MOF frequency in patients presenting to the ICU with SIRS (73.6% vs 26.4%, p < 0.0001) and sepsis (71.3% vs 28.7%, p < 0.0001) with an overall higher median PRISM III score in MOF (9 [0–33] vs 5 [0–25] no MOF). Neutropenia at admission was not associated with the development of MOF. Bacterial infections were the most common of the identified infections (71.2%) on D1 of ICU stay (Table 1). Overall, 49.6% of patients with sepsis at admission developed MOF. Of the admissions in which MOF was diagnosed, the majority had an OFI of 2 (57/87, 65.5%) and only 4 of 87 (4.6%) had a maximum OFI of 5 (**sFig. 4*A***, http://links.lww.com/CCX/B251). Renal failure was

TABLE 1.
Patient and ICU Admission Characteristics

	Overall (*n* = 364)	MOF (*n* = 87)	No MOF (*n* = 277)	*p*
Demographic data				
Age (median; range)[a]	10.1 (0.1–26.7)	11.3 (0.5–22.1)	9.4 (0.1–26.7)	0.45
Sex	*n* = 324[b]	*n* = 83	*n* = 241	0.3
Male	194 (59.9)	54 (65.1)	140 (58.1)	
Female	130 (40.1)	29 (34.9)	101 (41.9)	
Race	*n* = 324[b]	*n* = 83	*n* = 241	0.62
White (including Hispanic)	230 (71.0)	57 (68.7)	173 (71.8)	
Black	60 (18.5)	18 (21.7)	42 (17.4)	
Asian/Pacific Islander	25 (7.7)	7 (8.4)	18 (7.5)	
Other or unknown	9 (2.8)	1 (1.2)	8 (3.3)	
Primary diagnosis by admission	*n* = 364[a]	*n* = 87	*n* = 277	0.21
Hematopoietic cell transplant	112 (30.9)	33 (37.9)	79 (28.5)	
Leukemia/lymphoma	117 (32.1)	31 (35.7)	86 (31.0)	
Solid tumor	75 (20.6)	13 (14.9)	62 (22.4)	
Neuro-oncology	50 (13.7)	8 (9.2)	42 (15.2)	
Immunodeficiency	10 (2.7)	2 (2.3)	8 (2.9)	
Severity of illness at admission				
Pediatric Risk of Mortality III (median; range)[a]	6 (0–33)	9 (0–33)	5 (0–25)	**< 0.0001**
Systemic inflammatory response syndrome[a]	*n* = 364	*n* = 87	*n* = 277	**< 0.0001**
Present	199 (54.7)	64 (73.6)	135 (48.7)	
Not present	165 (45.3)	23 (26.4)	142 (51.3)	
Sepsis[a]	*n* = 364	*n* = 87	*n* = 277	**< 0.0001**
Present	187 (51.4)	62 (71.3)	125 (45.1)	
Not present	177 (48.6)	25 (28.7)	152 (54.9)	
Infection at admission				
Active or ongoing infection	*n* = 296	*n* = 92	*n* = 204	
Bacterial	153 (51.7)	50 (54.3)	103 (50.5)	0.93
Viral	99 (33.4)	28 (30.4)	71 (34.8)	
Fungal	34 (11.5)	11 (12.0)	23 (11.3)	
Other	10 (3.4)	3 (3.3)	7 (3.4)	
New infection at ICU admission[a]	*n* = 151	*n* = 45	*n* = 106	
Bacterial	88 (58.3)	26 (57.8)	62 (58.5)	0.93
Viral	48 (31.8)	14 (31.1)	34 (32.1)	
Fungal	15 (9.9)	5 (11.1)	10 (9.4)	
Other	0 (0)	0 (0)	0 (0)	

(*Continued*)

TABLE 1. (*Continued*)
Patient and ICU Admission Characteristics

	Overall (*n* = 364)	MOF (*n* = 87)	No MOF (*n* = 277)	*p*
Neutropenia at admission	*n* = 322	*n* = 62	*n* = 260	
Neutropenia (*n* = 322)	152 (47.2)	30 (48.3)	122 (46.9)	0.098
Days neutropenic prior ICU admission (*n* = 152; median [range])	7 (0–176)	7 (0–176)	7 (0–78)	0.36
Critical care resources[a]				
Continuous renal replacement therapy (*n*, %)	10 (2.7)	8 (9.2)	2 (0.7)	**0.0002**
Mechanical ventilation	76 (20.9)	46 (52.9)	30 (10.8)	**< 0.0001**
Vasopressor	82 (22.5)	54 (62)	28 (10.1)	**< 0.0001**
Extracorporeal life support	1 (0.3)	1 (1.4)	0 (0)	0.24
ICU mortality[a]	19 (5.2)	16 (18.4)	3 (1.1)	**< 0.0001**

MOF = multiple organ failure.
[a]Values calculated using total ICU admissions (*n* = 364).
[b]Values calculated using total number of unique patients (*n* = 324).
Mechanical ventilation includes continuous positive airway pressure, bilevel positive airway pressure, invasive mechanical ventilation, Pediatric Risk of Mortality Score was calculated based on values after first 12 hr of ICU stay. Leukemia/lymphoma group includes leukemia, lymphoma, myelodysplastic disorders, posttransplant lymphoproliferative disorders; immunodeficiency includes hemophagocytic lymphohistiocytosis and severe combined immunodeficiency; multiple organ failure is defined as Organ Failure Index greater than or equal to two any time during ICU stay; neutropenia defined as absolute neutrophil count less than 500; length of neutropenia = time before ICU admission that patient was neutropenic.
Statistically signficant values are shown in boldface font.

TABLE 2.
Risk Factors for ICU Mortality

ICU Factors (*n* = 364)	Hazard ratio (95% CI)	*p*
Invasive mechanical ventilation (*n* = 67)	5.12 (1.31–19.94)	**0.02**
Noninvasive mechanical ventilation (*n* = 30)	0.36 (0.05–2.72)	0.32
Inotrope/vaso (*n* = 80)	1.3 (0.48–3.51)	0.36
CRRT; *n* = 10	1.86 (0.6–5.83)	0.28
MV + CRRT (*n* = 9)	1.88 (0.6–5.9)	0.28
MV + vaso (*n* = 34)	2.17 (0.77–6.12)	0.14
CRRT + vaso (*n* = 7)	1.95 (0.62–6.14)	0.26
MOF day 1 of ICU admission (*n* = 58)	2.74 (1.1–6.82)	**0.03**
MOF during ICU admission (*n* = 87)	4.16 (1.09–15.86)	**0.04**

CRRT = continuous renal replacement therapy, MOF = multiple organ failure, MV = mechanical ventilation, Vaso = vasopressor.
Univariate Cox's Proportional Hazard Model was used for this analysis; MV includes continuous positive airway pressure, bilevel positive airway pressure, and invasive MV.
Statistically signficant values are shown in boldface font.

the most common (115/364, 31.6%) organ dysfunction identified followed by cardiovascular failure (81/362, 22.2%; **sFig. 4*B***, http://links.lww.com/CCX/B251). There was a trend toward increasing severity of renal failure with longer durations of ICU admission (**sFig. 4*C***, http://links.lww.com/CCX/B251) as well as an increasing frequency of respiratory (from 9.3% on D1 to 56.3% on D28), renal (from 23.6% on

D1 to 37.5% on D28), and hepatic dysfunction (from 10.4% on D1 to 25% on D28) with increasing days of ICU stay (sFig. 4*B*, http://links.lww.com/CCX/B251). Patients with leukemia/lymphoma (31/117; 26.5%) or who had undergone HCT (33/112; 29.4%; **sTable 5**, http://links.lww.com/CCX/B251) had the highest prevalence of MOF development. Non-HCT leukemia/lymphoma patients accounted for the highest percentage of hepatic dysfunction (26/59, 44.1%; $p = 0.0014$), HCT patients accounted for the highest percentage of renal dysfunction (52/115, 45.2%; $p < 0.00001$), and CNS malignancy patients accounted for the highest percentage of neurologic dysfunction (11/31, 35.5%; $p = 0.0097$; sTable 5, http://links.lww.com/CCX/B251). HFNC was the most common respiratory support used (147/364; 40.4%) with NIV being used the least (30/364; 8.2%). The majority of admissions with MOF were supported with IMV. Risk of ICU death was higher in those requiring IMV versus NIV (Table 2). Overall ICU mortality in admissions requiring IMV was 16/67 (24%; 11/46 [24%] non-HCT patients; 5/21 [24%] HCT patients). In admissions requiring NIV and HFNC, mortality occurred in 1 of 30 (3.4%) and 2 of 147 (1.4%), respectively. Of those requiring IMV ($n = 67$), there was no difference in ICU mortality in patients who received IMV only compared to those who were supported using HFNC before IMV (HR 3; 95% CI, 0.84–11.37; $p = 0.1071$). However, NIV failure before IMV (4/67; 6%), while rare, was associated with increased ICU mortality (HR 6.3; 95% CI, 1.21–31.99; $p = 0.03$).

Early Onco-Critical Care Phenotypes

Derivation and Description of Phenotypes. Based on the derived *k*-means clustering models, there was a four-class model with the optimal fit with four early onco-critical care phenotypes (PedOnc1, 2, 3, and 4) identified. Consensus matrix plots and the relative change under the cumulative distribution curves implied little statistical gain by increasing to a five- or six-class model with penalty of overfitting (sFig. 3, http://links.lww.com/CCX/B251). A four-class model was verified to be optimal based on LCA (**sTable 4**, http://links.lww.com/CCX/B251). When comparing patient membership between consensus *k*-means groups and LCA groups, the adjusted rand index was low (0.156). To ensure that the patient overlap between both methods was not random, permutation analysis was performed and repeatedly showed an adjusted rand index < 0.156 suggesting that the patient overlap seen between consensus *k*-means and LCA is not due to random grouping. While overlap was relatively low between consensus *k*-means groups and LCA groups, both methods identified PedOnc 2 and PedOnc4 as a unique phenotypes with consensus *k*-means clustering better distinguishing PedOnc1 and 3 (**sTables 14** and **15** and **sFig. 5**, http://links.lww.com/CCX/B251). For a full description, see **Supplementary Detailed Statistical Methods** (http://links.lww.com/CCX/B251). In a sensitivity analysis, there was no significant difference in the outcomes of the four groups formed by *k*-means clustering of single admissions only ($n = 292$) (**sTables 8–11**, http://links.lww.com/CCX/B251). Additionally, there was a 96.92% matching rate between the four groups formed in analysis of single-admission patients and PedOnc1, 2, 3, 4 (**sFig. 6**, http://links.lww.com/CCX/B251). Based on the comparison between LCA and consensus *k*-means clustering as well as the sensitivity analysis performed using single ICU admission data, we proceeded with analysis of all ICU admissions ($n = 364$) using consensus *k*-means clustering.

In this analysis, characteristics were significantly different across all groups except for sex, severity of cardiovascular (CV) dysfunction, mean oxygen saturation, presence of schistocytes, and underlying diagnosis of immunodeficiency (**sTables 9** and **12**, http://links.lww.com/CCX/B251). PedOnc 3 included the largest group of ICU admissions (39.3%) and PedOnc 4 included the lowest number of ICU admissions (8%). PedOnc1 was exclusively composed of allogeneic HCT recipients with an underlying diagnosis of leukemia/lymphoma who predominantly developed renal dysfunction and had no IMV requirement (Table 3, **Fig. 1**; and sTable12, http://links.lww.com/CCX/B251). PedOnc2 was characterized by nonleukemia/lymphoma diagnoses with predominantly CNS dysfunction and viral infection. This phenotype was associated with the lowest severity of illness, inflammation, and mortality. PedOnc3 represented the largest group of ICU admissions in our study. Patients with this phenotype commonly had an underlying diagnosis of leukemia/lymphoma without prior HCT ($n = 94$), the highest occurence of SIRS and bacterial infection, and the highest respiratory rates (RR). PedOnc4 was not

TABLE 3.
Critical Care Factors and Outcomes of the Four Phenotypes

Characteristics	All	PedOnc1	PedOnc2	PedOnc3	PedOnc4
Number of patients, *n* (%)	364	83 (22.8)	108 (29.7)	143 (39.3)	30 (8.2)
Critical care factors					
MV, *n* (%)[a]	76 (20.9)	12 (14.5)	12 (11.1)	23 (16.1)	29 (96.7)[d,e,f]
CRRT, *n* (%)	10 (2.7)	2 (2.4)	1 (0.9)	5 (3.5)	2 (6.7)
Vasopressors/inotropes, *n* (%)[a,c]	82 (22.5)	20 (24.1)	6 (5.6)	42 (29.4)	14 (46.7)[d,e,f]
Day 1 multiple organ failure, *n* (%)[a]	58 (15.9)	13 (15.7)	7 (6.5)	25 (17.5)[e]	13 (43.3)[a,b,c]
ICU outcomes					
ICU mortality, *n* (%)[a]	19 (5.2)	3 (3.6)	3 (2.8)	6 (4.2)	7 (23.3)[d,e,f]
ICU length of stay, median (IQR)[a]	3 (2–7)	4 (2–10.5)	3 (2–5.25)	3 (2–5)	7.5(3–16.8)[e,f]
ICU-free days, median (IQR)[a]	25 (21–26)	24(17.5–26)[g]	25 (22–26)[g]	25 (23–26)[d,g]	15 (0–22)
MV-free days, median (IQR)[a]	25.4 (7.0)	26.3 (5.7)[g]	27.1 (4.1)[g]	25.6 (7.1)[g]	16.2 (10.4)
Vasopressor-free days, mean; SD[a]	26.3 (5.5)	26.1 (4.8)	27.7 (2.7)[d,f,g]	26.2 (5.5)	22.2 (10.4)
CRRT-free days, mean; SD[a]	27.6 (3.3)	27.3 (4.3)	28.0 (0.2)	27.7 (2.6)	26.1 (7.1)
Hospital outcomes	324	63	106	133	22
Hospital mortality, Single and last admissions, *n* (%)[b]	37 (11.4)	5 (7.9)	11 (10.4)	11 (8.3)	10 (45.5)[e,f,g]

CRRT = continuous renal replacement therapy, HSCT = hematopoietic stem cell transplant, IQR = interquartile range, MV = mechanical ventilation, phenotype = PedOnc.

[a]Comparisons across all four computable phenotypes were performed using the Kruskal-Wallis test, the χ^2 test, or the Fisher exact test (**Supplementary Tables 10** and **11**, http://links.lww.com/CCX/B251), $p < 0.05$ for all comparisons after adjustment. The variables in this table were log transformed for modeling.

[b]Comparisons across all four computable phenotypes were performed using the χ^2 test and adjusted modeling accounting for presence and number multiple admissions, $p < 0.05$ for all comparisons after adjustment (**Supplementary Table 4**, http://links.lww.com/CCX/B251).

[c]Vasopressor/inotropes include milrinone, epinephrine, norepinephrine, dopamine, vasopressin (shock dosing) drips. phenylephrine and dobutamine were not used in this cohort.

[d]The outcome characteristic of this computable phenotype is significantly higher than PedOnc1 ($p < 0.05$).

[e]The outcome characteristic of this computable phenotype is significantly higher than PedOnc2 ($p < 0.05$).

[f]The outcome characteristic of this computable phenotype is significantly higher than PedOnc3 ($p < 0.05$).

[g]The outcome characteristic of this computable phenotype is significantly higher than PedOnc4 ($p < 0.05$).

MV includes continuous positive airway pressure, bilevel positive airway pressure, and invasive MV.

associated with any predominant underlying diagnosis and was characterized by the highest occurence of ARDS with need for IMV at admission, need for sedation and arterial line placement, and MOF. Notably, PedOnc 3 and 4 had the highest frequency of MOF (Fig. 1). For detailed comparison, please see Table 3 and sTables 8, 9, and 12 (http://links.lww.com/CCX/B251) and the Detailed Descriptions of Phenotypes in **Supplementary Material** for more detail (http://links.lww.com/CCX/B251).

Phenotype Association with Outcomes, Critical Care Resources, and Therapeutics. Overall, PedOnc4 was associated with the highest ICU and hospital mortality, fewest ICU and MV-free days, and the highest need for vasopressor support (46.7%; Table 3; and sTable 9 [http://links.lww.com/CCX/B251]) and PedOnc2 was associated with the lowest mortality and had the highest vasopressor-free days. Most ICU deaths occurred within one week of ICU admission among patients exhibiting the PedOnc4 phenotype. In contrast, all other phenotypes showed an increasing number of deaths after 14 days of ICU stay (**Fig. 2**). Hospital mortality was significantly higher in PedOnc4 (45%) compared to PedOnc1–3 (7.9–10.4%; $p < 0.001$; Table 3). Causes of death for all mortality in PedOnc2 was disease progression whereas the cause of death was

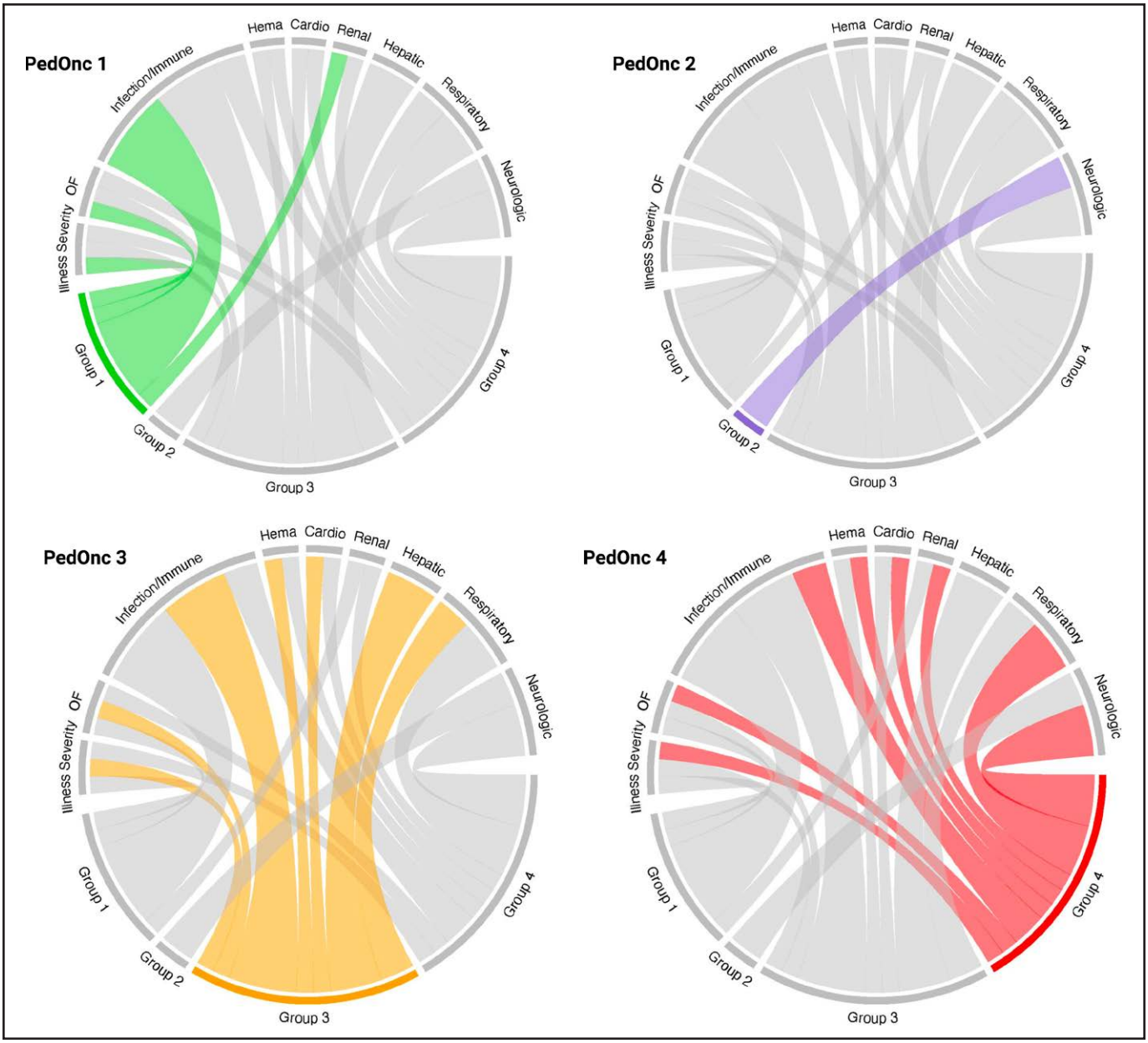

Figure 1. Cord plot of early onco-critical care phenotypes A. To aid in visualization of the presenting features of each phenotype, PedOnc1-4 are shown with different color ribbons connecting each phenotype to associated organ failures (*top of the circle falling to the right*) illness severity, and general organ failure (*on the right of the circle*). Cords connect the phenotype to the organ failure/severity of illness if the category group mean of the specific variable differs from the overall mean (Table 2) with oxygen saturation and Glasgow Coma Score (GCS) being lower and all other variables being higher. Illness severity = Pediatric Risk of Mortality III; systemic inflammatory response syndrome; infection/immune = length of neutropenia and presence of infection; hema = heme Organ Failure Index (OFI) and schistocytes; cardio = heart rate and CV = cardiovascular severity Renal = Renal severity; Hepatic = hepatic OFI, ALT = alanine aminotransferase, bilirubin respiratory = respiratory rate, oxygen saturation, respiratory severity, need for respiratory support; neurologic = CNS OFI and GCS.

reported as sepsis, MOF, and disease progression for PedOnc1, 3, and 4. The mode of death for patients in PedOnc4 was failure of maximum critical care support with redirection of care (5/7; 72%), failure of CPR (1/7; 14%), and irreversible cessation of neurologic dysfunction (1/7; 14%).

We further observed that mortality was associated with autologous HCT, higher RR, lower heart rate, and no respiratory support in PedOnc1; the presence of CNS failure, CNS malignancy, higher heart rate, lack of arterial line, and younger age in PedOnc2; higher bilirubin, longer neutropenia, higher KDIGO

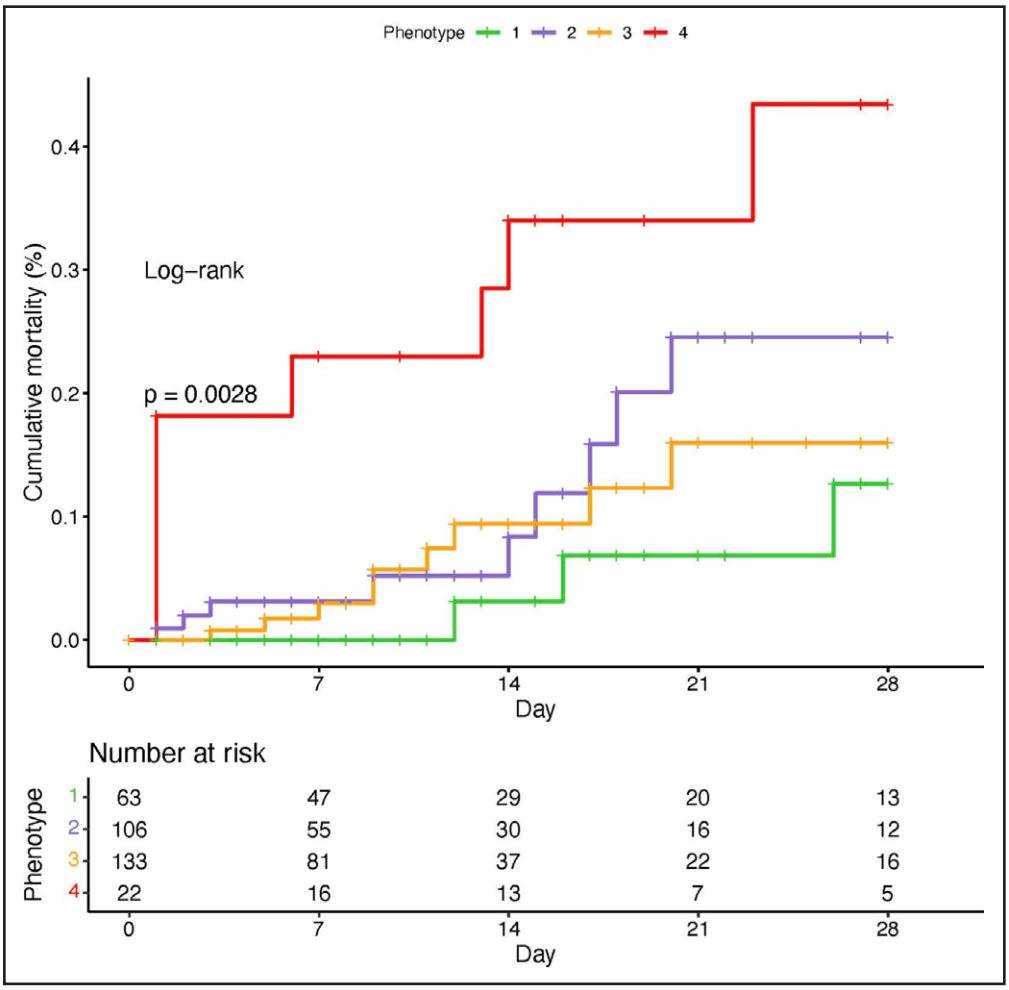

Figure 2. Early onco-critical care phenotypes and associated mortality ICU mortality are shown based on PedOnc phenotype with the highest mortality present in PedOnc4. This difference was statistically significant across all four phenotypes as well as pairwise comparison between all other phenotypes and PedOnc4. Most notably the majority of PedOnc4 deaths occurred early in ICU stay (≤ 7 d after ICU admission).

score and presence of schistocytes in PedOnc3; higher VIS, oxygen saturations, PRISM III, ARDS severity, age and KDIGO score, and presence of hematologic and CNS dysfunction, as well as lower Glasgow Coma Scale (GCS) in PedOnc4 (**sFig. 7**, http://links.lww.com/CCX/B251). Notably, on day 1 of ICU admission intubation and IMV initiation occurred at a low frequency in PedOnc1-3 (0/83, 0%; 4/109, 3.7%; 0/143, 0%, respectively); however, 28/30 (93.3%) of PedOnc4 patients were intubated for IMV initiation on day 1 of ICU admission. The reasons for intubation included hypoxic respiratory failure (11/28; 39%), neurologic failure (5/28; 18%), sepsis (1/28; 4%), upper airway obstruction (2/28; 7%), and intubation for emergent or semi-emergent procedures in a high-risk patient (i.e., pericardial effusion/tamponade, bronchoscopy; 9/28; 32%). Upon further evaluation of PedOnc4 pre-ICU admission characteristics, we found that more than half of inpatients (14/23; 61%) required oxygen therapy (BNC, blow-by oxygen, home bilevel positive airway pressure [BiPAP]) and 6 of 23 (26%) had CNS dysfunction before ICU admission. One-quarter of PedOnc4 patients (7/30; 24.1%) were directly admitted from outpatient areas or other institutions and most patients who were hospitalized before ICU admission did not meet criteria for an ICU consult before transfer. See Detailed Descriptions of Phenotypes in Supplementary Material (http://links.lww.com/CCX/B251). Usage of anti-cytokine therapy, corticosteroids, IVIG, and therapies for veno-occlusive disease (VOD) or thrombotic microangiopathy (TMA) differed significantly among the four derived phenotypes, with highest use in PedOnc1 and 4 (**sTable 13**, http://links.lww.com/CCX/B251).

DISCUSSION

It is well known that pediatric oncology patients are at high risk for mortality following ICU admission (33.5%; pooled weighted mortality, nonsurgical patients) (1–9). Previously, critically pediatric oncology patients have most commonly been studied as a subgroup of critically ill general pediatric patients or separately as a homogenous group. In this study, we sought to determine risk factors associated with increased mortality, including MOF, in a large cohort of pediatric oncology patients with critical illness using

supervised and agnostic (i.e., *k*-means cluster analysis) statistical approaches to identify patient phenotypes for future prospective evaluation.

In our cohort, ICU mortality was 5.2% which is much lower than previously described in critically ill pediatric oncology patients; however, it remains twice as high as the general pediatric critical care population (3, 40). The frequency of MOF in 23.9% of our ICU admissions is consistent with the widely variable findings from the general pediatric population of 6–57% in cohorts with similar severity of illness by PRISM III (36, 46–49). Consistent with previous reports in general pediatric patients, day 1 MOF and overall MOF were significantly associated with ICU mortality (36, 38, 50). Cardiovascular and renal failure were the most common organ failures observed. The frequency of cardiovascular failure was two times higher, and renal failure was ten times higher than the reported average frequency in general pediatric literature, suggesting that careful monitoring for evidence of both cardiovascular and renal dysfunction is warranted in these patients (36, 46). Respiratory failure with the need for IMV was the most significant risk factor for mortality, but mortality in both our oncology (24%) and HCT patients (24%) was about 50% lower than previously reported in pediatric HCT patients (60%) (17, 21). Like previous reports, failure of NIV before IMV, although rare in our cohort (6%), was associated with further increased mortality (19, 20), but the use of HFNC before IMV was not. Additionally, there was a significantly higher frequency of MOF in patients presenting to the ICU with SIRS or sepsis; however, one-third of patients with MOF did not present with sepsis or suspected infection, which highlights the need to evaluate sepsis and nonsepsis patients when studying critical illness and MOF in pediatric oncology patients.

In addition to validation of previously known risk factors for mortality, we identified four nonsynonymous early onco-critical care phenotypes with different clinical characteristics and outcomes that validated and expanded upon the known risk factors for mortality within critically ill pediatric oncology patients. These results are similar to previous work utilizing patient-level data with clustering methodology that identified four pediatric sepsis and critical care MOF phenotypes; however, our phenotypes had several distinctive features and associations with mortality (39, 47). Variable use of therapeutic agents, particularly anti-cytokine therapy, IVIG, steroids, and anti-TMA/VOD therapies suggests differing pathophysiology of organ dysfunction between groups. Overall, PedOnc1 and 2 represented groups with low mortality and, if organ dysfunction was present, only single organ dysfunction was noted. Importantly, the cause of death in PedOnc2 group was related to underlying disease progression; therefore, the reversal of organ failure in this group should target the underlying oncologic process. PedOnc4 was associated with a mortality five times higher than that of the other phenotypes. Based on ICU presentation, associated features with mortality, and timing of ICU death, PedOnc4 included patients with acute respiratory failure requiring IMV and MOF with associated neurologic dysfunction and/or rapidly evolving sepsis. These findings further confirm the significant association of increased mortality with acute respiratory failure with the need for IMV in critically ill pediatric oncology patients documented in this study, as well as in others, particularly when in combination with neurologic dysfunction and/or sepsis (5, 17, 19, 24). Pre-ICU admission findings for PedOnc4 suggest that close monitoring with possible escalation to ICU level care for changes in neurologic status accompanied by new or increased supplemental oxygen requirement may be warranted in pediatric oncology patients. However, intervention before ICU admission may be limited since many patients in PedOnc4 were directly admitted to the ICU or did not meet the criteria for ICU consultation. The limitation of possible pre-ICU intervention in PedOnc4 highlights the importance of the development of early ICU identification systems, like the computable early onco-critical phenotypes and further research to understand underlying potentially targetable biologic mechanisms, particularly in PedOnc4 patients or patients that require IMV at admission. Based on previous work (38, 51, 52), patients within this group may be at high risk for previously described empiric or a priori sepsis-related MOF phenotypes, such as immunoparalysis-associated MOF, thrombocytopenia-associated MOF, sequential-MOF, and macrophage activation syndrome, but validation of a priori sepsis-related MOF phenotypes and correlative biologic studies need to be performed within this patient population to further guide possible therapeutic interventions. Based on their associated mortality and reproducibility of this group with further validation methods (i.e., LCA), patients with the characteristics

of PedOnc4 (i.e., acute respiratory failure requiring IMV and MOF with associated neurologic dysfunction and/or sepsis) should be the focus of future studies of critically ill pediatric oncology patients.

Aside from limitations inherent to retrospective studies, there are several additional limitations to our study. First, this study included patients managed at a single center, thus treatment-related predisposition to organ failure following ICU admission may differ from that observed at other centers. Additionally, differences in organ failure definitions used in the literature make it difficult to compare our findings to other pediatric studies. Overall, the prevalence of MOF may have been underestimated in our patient population relative to other pediatric studies because we did not include cytopenia in the hematologic failure diagnosis. Similarly, a direct comparison of renal and CV dysfunction to other studies is challenging as these were different from than Proulx/Goldstein criteria (49). Our power to identify a significant association between certain interventions and mortality may be limited due to an overall small number of patients receiving specific interventions (i.e., CRRT). The phenotype derivation presented may be limited since patients were from a single center and some variables can be associated with practice variation from institution to institution, such as arterial line placement and decisions for initiation of IMV. In the same vein, it remains to be seen if the phenotypes derived are reproducible, particularly PedOnc1 and 3 because there was a significant overlap between these groups of patients when using other unsupervised methodology (i.e., LCA). Additionally, it is possible that the derived phenotypes are not representative of underlying biologic or pathophysiologic similarity but may be representative of groups of patients presenting at similar time points in their critical illness. Only further prospective validation and biologic studies can confirm the clinical significance of these early ICU phenotypes in pediatric oncology patients. Despite the limitations of our study, it is the first study of its kind to evaluate the prevalence of MOF and the risk factors of mortality using diverse statistical approaches within a large, heterogenous group of critically ill pediatric oncology patients.

CONCLUSIONS

Critically ill pediatric oncology patients remain an important patient population for future study due to their increased mortality risk compared to general pediatric patients. In this study, we verified that critically ill oncology patients are a heterogenous group with varying presentations and mortality risks by evaluating previously described risk factors which was further validated by the four derived nonsynonymous computable phenotypes. Development of MOF and need for IMV remain important risk factors for mortality within this group. Of the phenotypes identified in this study, PedOnc4 is of particular interest for future prospective validation with correlative biologic studies given its reproducibility, as well as associated increased risk of mortality in patients admitted to the ICU with this phenotype.

ACKNOWLEDGMENTS

We would like to thank Yvonne Avent and Kristen Ryan for their contributions to the data in this study.

1 *Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, TN,*

2 *Division of Critical Care, Department of Pediatrics, MD Anderson Cancer Center, Houston, TX.*

3 *Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.*

4 *Department of Global Medicine, St Jude Children's Research Hospital, Memphis, TN.*

5 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

6 *Division of Critical Care, Department Biostatistics, St Jude Children's Research Hospital, Memphis, TN.*

7 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

8 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

9 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

10 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

11 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

12 *Department of Biostatistics, St Jude Children's Research Hospital, Memphis, TN.*

13 *Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.*

14 *Division of Pediatric Critical Care, Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA.*

15 *Division of Critical Care, Department of Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Drs. Flerlage and Fan contributed equally to the article.

Drs. Flerlage, Hines, Qin, Carcillo, and Park analyzed the data. Drs. Flerlage, Hines, and Qin wrote the article. Drs. Fan and Hines collected the data. Drs. Qin, Park, Cheng, and Zhou, and all provided biostatistical support for the project. All authors reviewed, edited, and contributed to the article.

Funding was supported, in part, by grant R01GM108618 (to Dr. Carcillo PI, HJ Park CoI) from the National Institutes of General Medical Sciences, by 5U01HD049934-10S1 (to Dr. Carcillo) from the Eunice Kennedy Shriver *National Institutes of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, and the following cooperative agreements: U10HD049983, U10HD050096, U10HD049981, U10HD063108, U10HD63106, U10HD063114, U10HD050012, and U01HD049934.*

Dr. Hines receives research funding from Incyte for a clinical trial. Dr. Carcillo and Park are supported by a grant from the National Institutes of General Medical Sciences. Dr. Carcillo also receives funding from Eunice Kennedy Shriver *National Institutes of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services.*

For information regarding this article, E-mail: melissa.hines@stjude.org

Our data are available for sharing with permission from our institutional review board. Please contact the corresponding author with inquiries.

REFERENCES

1. Butt W, Barker G, Walker C, et al: Outcome of children with hematologic malignancy who are admitted to an intensive care unit. *Crit Care Med* 1988; 16:761–764
2. Raymakers-Janssen P, Lilien MR, Tibboel D, et al: Epidemiology and outcome of critically ill pediatric cancer and hematopoietic stem cell transplant patients requiring continuous renal replacement therapy: A retrospective nationwide cohort study. *Crit Care Med* 2019; 47:e893–e901
3. Zinter MS, DuBois SG, Spicer A, et al: Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014; 40:1536–1544
4. Fiser RT, West NK, Bush AJ, et al: Outcome of severe sepsis in pediatric oncology patients. *Pediatr Crit Care Med* 2005; 6:531–536
5. Rr P, Tan EEK, Sultana R, et al: Critical illness epidemiology and mortality risk in pediatric oncology. *Pediatr Blood Cancer* 2020; 67:e28242
6. Zinter MS, Dvorak CC, Spicer A, et al: New insights into multicenter PICU mortality among pediatric hematopoietic stem cell transplant patients. *Crit Care Med* 2015; 43:1986–1994
7. Zinter MS, Logan BR, Fretham C, et al: Comprehensive prognostication in critically ill pediatric hematopoietic cell transplant patients: results from merging the Center for International Blood and Marrow Transplant Research (CIBMTR) and Virtual Pediatric Systems (VPS) Registries. *Biol Blood Marrow Transplant* 2020; 26:333–342
8. Wosten-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
9. Agulnik A, Forbes PW, Stenquist N, et al: Validation of a pediatric early warning score in hospitalized pediatric oncology and hematopoietic stem cell transplant patients. *Pediatr Crit Care Med* 2016; 17:e146–e153
10. Bembea MM, Agus M, Akcan-Arikan A, et al: Pediatric Organ Dysfunction Information Update Mandate (PODIUM) contemporary organ dysfunction criteria: executive summary. *Pediatrics* 2022; 149(1 Suppl 1):S1–S12
11. Lindell RB, Gertz SJ, Rowan CM, et al; Sepsis PRevalence, OUtcomes, and Therapies Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: High levels of morbidity and mortality among pediatric hematopoietic cell transplant recipients with severe sepsis: insights from the Sepsis Prevalence, Outcomes, and Therapies International Point Prevalence Study. *Pediatr Crit Care Med* 2017; 18:1114–1125
12. Lindell RB, Nishisaki A, Weiss SL, et al: Risk of mortality in immunocompromised children with severe sepsis and septic shock. *Crit Care Med* 2020; 48:1026–1033
13. Ruth A, McCracken CE, Fortenberry JD, et al: Pediatric severe sepsis: Current trends and outcomes from the Pediatric Health Information Systems database. *Pediatr Crit Care Med* 2014; 15:828–838
14. Weiss SL, Fitzgerald JC, Pappachan J, et al; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med* 2015; 191:1147–1157
15. Elbahlawan L, West NK, Avent Y, et al: Impact of continuous renal replacement therapy on oxygenation in children with acute lung injury after allogeneic hematopoietic stem cell transplantation. *Pediatr Blood Cancer* 2010; 55:540–545
16. Lamas A, Otheo E, Ros P, et al: Prognosis of child recipients of hematopoietic stem cell transplantation requiring intensive care. *Intensive Care Med* 2003; 29:91–96
17. Rowan CM, McArthur J, Hsing DD, et al; Investigators of the Pediatric Acute Lung Injury and Sepsis Network: Acute respiratory failure in pediatric hematopoietic cell transplantation: A multicenter study. *Crit Care Med* 2018; 46:e967–e974
18. 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; 9:270–277
19. Lindell RB, Fitzgerald JC, Rowan CM, et al; National Emergency Airway Registry for Children (NEAR4KIDS) and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: The use and duration of preintubation respiratory support is associated with increased mortality in immunocompromised children with acute respiratory failure. *Crit Care Med* 2022; 50:1127–1137
20. Cater DT, Fitzgerald JC, Gertz SJ, et al: Noninvasive ventilation exposure prior to intubation in pediatric hematopoietic cell transplant recipients. *Respir Care* 2022; 67:1121–1128

21. Rowan CM, Smith LS, Loomis A, et al; Investigators of the Pediatric Acute Lung Injury and Sepsis Network: Pediatric acute respiratory distress syndrome in pediatric allogeneic hematopoietic stem cell transplants: A multicenter study. *Pediatr Crit Care Med* 2017; 18:304–309
22. Tamburro R: Pediatric cancer patients in clinical trials of sepsis: Factors that predispose to sepsis and stratify outcome. *Pediatr Crit Care Med* 2005; 6:S87–S91
23. Duncan CN, Lehmann LE, Cheifetz IM, et al; Pediatric Acute Lung Injury and Sepsis (PALISI) Network: Clinical outcomes of children receiving intensive cardiopulmonary support during hematopoietic stem cell transplant. *Pediatr Crit Care Med* 2013; 14:261–267
24. Rowan CM, Fitzgerald JC, Agulnik A, et al: Risk factors for noninvasive ventilation failure in children post-hematopoietic cell transplant. *Front Oncol* 2021; 11:653607
25. Cahill RA, Spitzer TR, Mazumder A: Marrow engraftment and clinical manifestations of capillary leak syndrome. *Bone Marrow Transplant* 1996; 18:177–184
26. Choi SJ, Lee KH, Lee JH, et al: Peri-engraftment clinical abnormalities following allogeneic hematopoietic cell transplantation: a retrospective review of 216 patients. *Bone Marrow Transplant* 2003; 32:809–813
27. Demaret P, Pettersen G, Hubert P, et al: The critically-ill pediatric hemato-oncology patient: epidemiology, management, and strategy of transfer to the pediatric intensive care unit. *Ann Intensive Care* 2012; 2:14
28. Kraguljac AP, Croucher D, Christian M, et al: Outcomes and predictors of mortality for patients with acute leukemia admitted to the intensive care unit. *Can Respir J* 2016; 2016:3027656
29. Schmid I, Stachel D, Pagel P, et al: Incidence, predisposing factors, and outcome of engraftment syndrome in pediatric allogeneic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2008; 14:438–444
30. Spitzer TR: Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2001; 27:893–898
31. Tryka AF, Godleski JJ, Fanta CH: Leukemic cell lysis pneumonopathy. A complication of treated myeloblastic leukemia. *Cancer* 1982; 50:2763–2770
32. Shah NN, Highfill SL, Shalabi H, et al: CD4/CD8 T-cell selection affects chimeric antigen receptor (CAR) T-cell potency and toxicity: Updated results from a phase i anti-CD22 CAR T-cell trial. *J Clin Oncol* 2020; 38:1938–1950
33. Fitzgerald JC, Weiss SL, Maude SL, et al: Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med* 2017; 45:e124–e131
34. Teachey DT, Lacey SF, Shaw PA, et al: Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Cancer Discov* 2016; 6:664–679
35. Teachey DT, Rheingold SR, Maude SL, et al: Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood* 2013; 121:5154–5157
36. Villeneuve A, Joyal JS, Proulx F, et al: Multiple organ dysfunction syndrome in critically ill children: clinical value of two lists of diagnostic criteria. *Ann Intensive Care* 2016; 6:40
37. Agulnik A JS, Wilkes R, Faughnan L, et al: Impact of Implementing a Pediatric Early Warning System (PEWS) in a pediatric oncology hospital. *Pediatr Qual Safety* 2018; 3:e065
38. Carcillo JA, Berg RA, Wessel D, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: A multicenter network assessment of three inflammation phenotypes in pediatric sepsis-induced multiple organ failure. *Pediatr Crit Care Med* 2019; 20:1137–1146
39. Qin Y, Kernan KF, Fan Z, et al: Machine learning derivation of four computable 24-h pediatric sepsis phenotypes to facilitate enrollment in early personalized anti-inflammatory clinical trials. *Crit Care* 2022; 26:128
40. Pollack MM, Dean JM, Butler J, et al: The ideal time interval for critical care severity-of-illness assessment. *Pediatr Crit Care Med* 2013; 14:448–453
41. Gaies MG, Gurney JG, Yen AH, et al: Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010; 11:234–238
42. Kellum JA LN, Aspelin P, Barsoum RS, et al: Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2:1–138
43. Emeriaud G, Lopez-Fernandez YM, Iyer NP, et al; Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) Group on behalf of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Executive Summary of the Second International Guidelines for the Diagnosis and Management of Pediatric Acute Respiratory Distress Syndrome (PALICC-2). *Pediatr Crit Care Med* 2023; 24:143–168
44. Weiss SL, Carcillo JA, Leclerc F, et al; Pediatric Organ Dysfunction Information Update Mandate (PODIUM) Collaborative: Refining the pediatric multiple organ dysfunction syndrome. *Pediatrics* 2022; 149(1 Suppl 1):S13–S22
45. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis: International Pediatric Sepsis Consensus Conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2–8
46. Bose SN, Greenstein JL, Fackler JC, et al: Early prediction of multiple organ dysfunction in the pediatric intensive care unit. *Front Pediatr* 2021; 9:711104
47. Sanchez-Pinto LN, Stroup EK, Pendergrast T, et al: Derivation and validation of novel phenotypes of multiple organ dysfunction syndrome in critically ill children. *JAMA Netw Open* 2020; 3:e209271
48. Tantalean JA, Leon RJ, Santos AA, et al: Multiple organ dysfunction syndrome in children. *Pediatr Crit Care Med* 2003; 4:181–185
49. Watson RS, Crow SS, Hartman ME, et al: Epidemiology and outcomes of pediatric multiple organ dysfunction syndrome. *Pediatr Crit Care Med* 2017; 18(3_suppl Suppl 1):S4–S16
50. Typpo KV, Petersen NJ, Hallman DM, et al: Day 1 multiple organ dysfunction syndrome is associated with poor functional outcome and mortality in the pediatric intensive care unit. *Pediatr Crit Care Med* 2009; 10:562–570
51. Hall MW, Knatz NL, Vetterly C, et al: Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome. *Intensive Care Med* 2011; 37:525–532
52. Reilly JP, Anderson BJ, Hudock KM, et al: Neutropenic sepsis is associated with distinct clinical and biological characteristics: A cohort study of severe sepsis. *Crit Care* 2016; 20:222