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New Insights Into Multicenter PICU Mortality Among Pediatric Hematopoietic Stem Cell Transplant Patients*

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Objectives: Over 2,500 children undergo hematopoietic stem cell transplantation in the United States each year, and up to 35% require PICU support for life-threatening complications. PICU mortality has dropped from 85% to 44%, but interpretation is confounded by significant cohort heterogeneity. Reports conflict regarding outcomes for patients with different underlying hematopoietic stem cell transplantation indications, and the burden of infectious complications for these patients has not been evaluated. We aim to describe infections, critical care interventions, and mortality for pediatric hematopoietic stem cell transplantation patients requiring PICU admission.

Design: A retrospective multicenter cohort analysis.

Setting: One hundred twelve centers in the Virtual PICU Systems database, January 1, 2009, to June 30, 2012.

Patients: A total of 1,782 admissions for patients who are 21 years old or younger with prior hematopoietic stem cell transplantation.

Interventions: None.

Measurements and Main Results: Pediatric Index of Mortality-2, Pediatric Risk of Mortality-3, transplant indication, infections, interventions, and mortality were recorded from admission through PICU death or discharge. Pediatric hematopoietic stem cell transplantation patients comprised 0.7% of all PICU admissions (1,782/246,346), which resulted in 16.2% mortality compared with 2.4% mortality for non–hematopoietic stem cell transplantation admissions (odds ratio, 7.8; 95% CI, 6.8–8.8; $p < 0.001$). Mortality for admissions with underlying hematologic malignancy (22.7%) was similar to that of admissions with primary immunodeficiency (19.4%; $p = 0.41$) but significantly greater than admissions with underlying nonmalignant non–primary immunodeficiency hematologic disease (15.4%; $p = 0.020$), metabolic disorder (8.1%; $p < 0.001$), or solid malignancy (5.7%; $p < 0.001$). Infection was documented in 45.7% of admissions with 22.2% mortality; viral and fungal mortality were 28.5% and 33.7%, respectively. Invasive positive pressure ventilation and renal replacement therapy were used in only 34.6% and 11.9% of admissions, with mortality of 42.5% and 51.9%, respectively.

Conclusions: PICU mortality for pediatric hematopoietic stem cell transplantation patients may be as low as 16.2% but higher for those receiving intubation (42.5%) or replacement therapy (51.9%). Hematologic malignancy and primary immunodeficiency had greater risk for mortality than other transplant indications. Greater understanding of other risk factors affecting mortality and the need for critical care support is needed. (*Crit Care Med* 2015; 43:1986–1994)

Over 2,500 children undergo hematopoietic stem cell transplantation (HSCT) in the United States each year for an increasingly broad set of life-threatening diseases (1). Posttransplant PICU admission is required for 17–35% of these patients (2–5). In the last 30 years, reported PICU mortality for this population has dropped impressively from over 85% to below 44% (2–4, 6–13), likely in part due to advances in reduced intensity conditioning, lung shielding for total body irradiation (TBI), human leukocyte antigen matching, infection prophylaxis, and mechanical ventilation (14, 15). However, the interpretation of this reduction in mortality is confounded by institutional variation in PICU admission criteria, heterogeneous transplant indications among cohorts, and lack of standardization of patients through illness severity scores such as the Pediatric Index of Mortality (PIM)-2 and Pediatric Risk of Mortality (PRISM)-3 (6, 16, 17). As a result, there is an active debate over whether and how much PICU mortality has decreased for these patients (6, 16, 18).

Of particular interest are the mortality rates for patients with different underlying transplant indications, as associated treatment regimens may mediate the progression of critical illness in the HSCT population (19, 20). Current reports conflict regarding which underlying conditions are associated with increased PICU mortality (4, 12). Also of interest are the rates and impact of different infections, which may vary by transplant indication due to relative immunodeficiency secondary to intensity of conditioning, type and source of donors, and graft processing such as T-cell depletion. Improved understanding of these risk factors may be used to create strategies to reduce morbidity and mortality, such as increased pre-PICU symptom surveillance (21), emphasis on early PICU admission (22, 23), and trials of early noninvasive positive pressure ventilation (NIPPV) and renal replacement therapy (RRT) (7, 24–26).

We undertook this study to analyze contemporary PICU mortality for pediatric HSCT patients in the Virtual PICU Systems (VPS) database, which represents the most comprehensive multicenter pediatric intensive care database available. We stratified our results by admission illness severity scores, underlying HSCT indication, infections, and use of mechanical ventilation and renal RRT in order to assess their impact on survival. We hypothesized that these factors would be strongly associated with PICU mortality in our cohort. The knowledge gained from this study will improve our understanding of the current state of critical care for pediatric HSCT patients. We anticipate that it will provide meaningful outcomes data to which future cohorts can be compared and will also identify high-risk populations within the pediatric HSCT cohort who may benefit from additional early and aggressive therapies.

MATERIALS AND METHODS

Design

We performed a retrospective multicenter cohort analysis involving 112 PICUs principally in the United States using the VPS database (VPS, LLC). VPS is the largest and most robust pediatric intensive care database to date and collects information regarding diagnoses, outcomes, and critical care interventions. As previously described, trained VPS analysts at each site collected patient data from PICU admission to PICU discharge, transfer, or death (11). Diagnoses assigned to each patient were identified by thorough review of attending physician documentation in the medical chart; some but not all sites additionally contributed *International Classification of Diseases,* 9th Edition (ICD-9) codes. This study was reviewed by our institutional review board and determined to be exempt, given that all patient information was de-identified prior to study team access.

Patients

We identified 192,956 patients who are 21 years old or younger accounting for a total of 246,346 PICU admissions between January 1, 2009, and June 30, 2012. From this group, HSCT patients were identified by querying diagnosis codes, indicating current or prior bone marrow transplant or hematopoietic stem cell transplant.

Outcome

PICU mortality was defined as death prior to PICU transfer or discharge.

Predictors

We queried PIM-2 score, PRISM-3 score, underlying HSCT indication, infections, and interventions for all patients. PIM-2 Probability of Death (POD) was calculated within the first hour of ICU contact (27). PRISM-3 raw scores and POD were calculated within the first 12 hours of admission (28, 29). Underlying HSCT indications were grouped as hematologic malignancy, solid malignancy, nonmalignant hematologic disease, primary immunodeficiency (PID), and metabolic disorders according to the Center for International Blood and Marrow Transplant Research (CIBMTR) data collection system (30). Gram-positive bacterial, Gram-negative bacterial, fungal, and viral infections were identified if listed in admission, progress, transfer, or discharge notes only; clinical, radiographic, and microbiologic data in support of these diagnoses were not available to the study team. A diagnosis of sepsis included patients with sepsis, severe sepsis, and septic shock, as neither clinician-applied guidelines nor ICD-9 codes have sufficient sensitivity and specificity to differentiate sepsis severity (31). NIPPV was defined as continuous or bilevel positive airway pressure without prior or subsequent endotracheal intubation. Invasive positive pressure ventilation (IPPV) was defined as endotracheal intubation with any mechanical ventilation. Renal RRT was defined as hemodialysis or continuous venovenous hemofiltration/hemodialysis. Extracorporeal membrane

oxygenation (ECMO) was defined as any extracorporeal life support. Documentation of infections, IPPV, and ECMO was mandatory at all centers. Due to center agreements, documentation of NIPPV and RRT was optional for 12.5% (223/1,782) and 14.8% (263/1,782) of respective admissions; analyses of these variables excluded centers not collecting these data. HSCT-related variables such as transplant type (autologous vs allogeneic), HLA match, conditioning regimen, and presence of complications including graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) were not documented in the database and could not be queried.

Statistics

The distributions of categorical variables were compared with Fisher exact tests and odds ratios (ORs) (32). Continuous variables were compared with t tests for normally distributed data and with Wilcoxon rank-sum tests otherwise. In order to discriminate which of PIM-2 POD, PRISM-3, or PRISM-3 POD predicted mortality best in our cohort, receiver operating characteristic area under the curves (ROC AUC) were created and compared with the Hanley method (33). In order to test how well the PRISM-3 POD was calibrated to predict mortality at low, medium, and high scores within our cohort, we used the Hosmer-Lemeshow goodness-of-fit test (34). To analyze the independent effect of our predictors on mortality, we used multivariable generalized estimating equation models with a logistic link function and clustered by site (35, 36). To analyze the effect of multiple admissions of the same patient, we used mixed effects models clustered by both site and patient. We examined estimated mortality ORs with 95% CIs and two-tailed p values based on robust SE estimates with a nominal significance level of $\alpha = 0.05$. All analyses were performed using STATA statistical software, version 13.1 (StataCorp, College Station, TX).

RESULTS

We identified 1,102 patients with HSCT accounting for 1,782 PICU admissions. This represents 1.6 admissions per HSCT patient and accounts for 0.7% of all PICU admissions (**Table 1**); 16.2% of admissions resulted in death (288/1,782), but due to multiple admissions of the same patient over the study period, 26.1% of patients died in the PICU during the study period (288/1,102). There was a trend toward increased mortality in patients with more than one PICU admission compared with those with only one PICU admission (105/361 vs 183/741; OR, 1.25; 95% CI, 0.94–1.67; $p = 0.125$). Mortality for HSCT admissions (288/1,782; 16.2%) had OR 3.2 (95% CI, 2.7–3.7; $p < 0.001$) compared with non-HSCT oncology admissions (536/9,420; 5.7%) and OR 7.8 (95% CI, 6.8–8.8; $p < 0.001$) compared with all non-HSCT admissions (5,927/244,564; 2.4%). Overall, HSCT admissions accounted for 4.6% of PICU deaths (288/6,215).

Mortality Discrimination and Calibration of the PIM-2 and PRISM-3

PIM-2 POD, PRISM-3, and PRISM-3 POD distributions were all nonparametrically skewed toward the low end of their distributions with medians of 1% (interquartile range

[IQR], 0–5%), 8 (IQR, 3–13), and 2.6% (IQR, 0.6–9.3%), respectively. The ROC AUCs for mortality were 0.70 (95% CI, 0.67–0.73), 0.73 (95% CI, 0.70–0.76), and 0.74 (95% CI, 0.71–0.77), respectively (**eFig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B307). Pairwise comparison showed that the PRISM-3 POD was superior to the PIM-2 POD in predicting the actual mortality observed in our dataset ($p = 0.019$). Although the PRISM-3 POD predicted mortality best of the three tools listed above, it was poorly calibrated to our dataset, both significantly underpredicting mortality at low scores and overpredicting mortality at high scores (chi-square = 584.8; degrees of freedom = 4; $p < 0.005$) (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B307).

Prevalence and Association of Underlying HSCT Indication on PICU Mortality

In comparison to 5.7% PICU mortality for admissions with solid malignancy (19/332), PICU mortality was higher for children with underlying hematologic malignancy (22.7%; 168/739; OR, 4.85; 95% CI, 2.96–7.94; $p < 0.001$) or PID (19.4%; 33/170; OR, 3.97; 95% CI, 2.18–7.22; $p < 0.001$), followed by those with nonmalignant hematologic disease (15.4%; 35/226; OR, 3.02; 95% CI, 1.68–5.43; $p < 0.001$) and metabolic disorders (8.1%; 9/111; OR, 1.42; 95% CI, 0.64–3.31; $p = 0.372$) (**Fig. 1**). There was no difference in mortality between admissions with hematologic malignancies and those with PID ($p = 0.412$) nor admissions with PID and nonmalignant hematologic disease ($p = 0.347$). There was no difference in mortality between admissions with severe combined immunodeficiency (SCID) and other forms of PID (18/90 vs 15/80; $p = 0.85$); 11.2% of admissions did not have an underlying HSCT indication identifiable in the database (199/1,782); their mortality was 12.1% (24/199). Five admissions had an underlying HSCT indication of systemic sclerosis; all survived. The aforementioned findings were upheld when adjusting for multiple admissions of the same patient (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B307).

Prevalence and Association of Infection Type on PICU Mortality

A total of 54.3% of admissions had no documented infection (967/1,782) and had PICU mortality of 11.1% (107/967). In comparison, admissions with at least one documented infection had 22.2% mortality (181/815; OR, 2.30; 95% CI, 1.77–2.98; $p < 0.001$). Gram-positive and Gram-negative infections were identified in 7.0% (125/1,782) and 8.9% (159/1,782) of admissions, with mortality of 17.6% (22/125; OR, 1.72; 95% CI, 1.04–2.84; $p = 0.039$) and 22.0% (35/19; OR, 2.27; 95% CI, 1.48–3.47; $p < 0.001$), respectively. Viral infections were identified in 19.9% of admissions (355/1,782), with 28.5% mortality (101/355; OR, 3.20; 95% CI, 2.35–4.34; $p < 0.001$). Mortality for admissions with adenovirus and cytomegalovirus (CMV) was 42% (29/68) and 32% (35/109), respectively ($p = 0.20$). Fungal infections were identified in 9.1% of admissions (163/1,782), with a mortality of

TABLE 1. Univariate Predictors of PICU Mortality for Hematopoietic Stem Cell Transplantation Patients (Total *n* = 1,782)

Predictor	Distributions, *n* (%)	Mortality, *n* (%)	OR of Mortality	*p*
Demographic				
Age[a] (mean, 9.1 ± 0.1)	–	–	1.02 (0.99–1.05)	0.162
Female	701 (39.3)	117 (16.7)	1	–
Male	1081 (60.7)	171 (15.8)	0.94 (0.73–1.21)	0.640
Illness score				
Pediatric Index of Mortality-2 POD[b] (median, 1; IQR, 0–5)	–	–	1.04 (1.02–1.06)	< 0.001
PRISM-3[c] (median, 8; IQR, 3–13)	–	–	1.12 (1.10–1.14)	< 0.001
PRISM-3 POD[c] (median, 2.6; IQR, 0.6–9.3)	–	–	1.04 (1.03–1.05)	< 0.001
Hematopoietic stem cell transplantation indication[d]				
Solid cancer	332 (18.6)	19 (5.7)	1	–
Metabolic disorder	111 (6.2)	9 (8.1)	1.42 (0.64–3.31)	0.372
Nonmalignant hematologic	226 (12.7)	35 (15.4)	3.02 (1.68–5.43)	< 0.001
Primary immunodeficiency	170 (9.5)	33 (19.4)	3.97 (2.18–7.22)	< 0.001
Hematologic cancer	739 (41.5)	168 (22.7)	4.85 (2.96–7.94)	< 0.001
Infection				
No infection	967 (54.3)	107 (11.1)	1	–
Any infection	815 (45.7)	181 (22.2)	2.30 (1.77–2.98)	< 0.001
Sepsis	436 (24.5)	97 (22.2)	2.30 (1.70–3.11)	< 0.001
Gram-positive bacterial	125 (7.0)	22 (17.6)	1.72 (1.04–2.84)	0.039
Gram-negative bacterial	159 (8.9)	35 (22.0)	2.27 (1.48–3.47)	< 0.001
Viral	355 (19.9)	101 (28.5)	3.20 (2.35–4.34)	< 0.001
Fungal	163 (9.1)	55 (33.7)	4.09 (2.79–6.00)	< 0.001
Interventions				
No NIPPV, IPPV, RRT, or ECMO[e]	829 (56.4)	16 (1.9)	1	–
NIPPV without IPPV[f]	129 (8.3)	6 (4.7)	2.48 (0.95–6.46)	0.103
IPPV	617 (34.6)	262 (42.5)	37.5 (22.3–63.1)	< 0.001
RRT[g]	181 (11.9)	94 (51.9)	54.9 (30.9–97.5)	< 0.001
ECMO	4 (0.2)	4 (100)	–	< 0.001

OR = odds ratio, POD = Probability of Death, IQR = interquartile range, PRISM = Pediatric Risk of Mortality, NIPPV = noninvasive positive pressure ventilation, IPPV = invasive positive pressure ventilation, RRT = replacement therapy, ECMO = extracorporeal membrane oxygenation.
[a]OR refers to each additional year of age.
[b]OR refers to each additional point of illness score.
[c]PRISM-3 and PRISM-3 POD *n* = 1753 due to missing PRISM-3 scores.
[d]Hematopoietic stem cell transplantation (HSCT) indication *n* = 1578 due to 199 patients with no documented HSCT indication and five patients with systemic sclerosis.
[e]No NIPPV, IPPV, RRT, or ECMO *n* = 1470 due to some centers not collecting all four interventions.
[f]NIPPV without IPPV *n* = 1559 due to some centers not collecting NIPPV.
[g]RRT *n* = 1519 due to some centers not collecting RRT.
Dashes indicate variable with continuous data (for distributions or mortality reports), or the reference variable for ORs.

33.7% (55/163; OR, 4.09; 95% CI, 2.79–6.00; *p* < 0.001). Mortality for admissions with *Aspergillus* and *Candida* infections was 40% (18/45) and 30.6% (15/49), respectively (*p* = 0.39). Sepsis was identified in 24.5% of admissions (436/1,782) with 22.2% mortality (97/436; OR, 2.30; 95% CI, 1.70–3.11; *p* < 0.001). Of note, HSCT admissions with infection had a higher mortality than non-HSCT admissions with infection (181/815 vs 1,010/26,011; OR, 7.07; 95% CI, 5.92–8.43; *p* < 0.001).
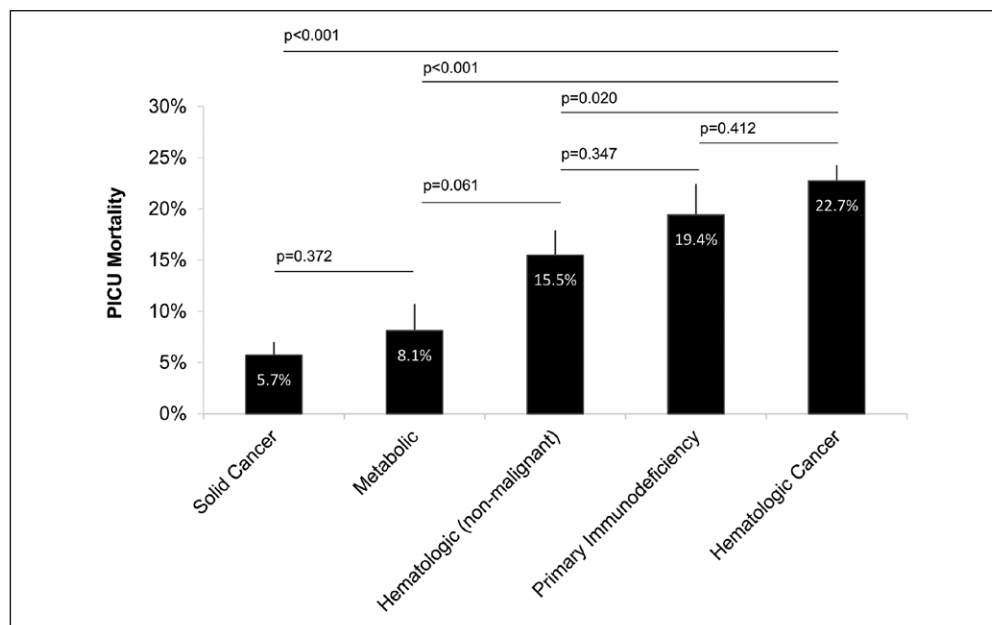
Figure 1. PICU mortality by hematopoietic stem cell transplantation indication. *Vertical lines* represent binomial SE. Analysis of variance with Bonferroni correction used to reject omnibus null hypothesis of no difference between groups with *p* < 0.001.

Compared with admissions for patients with hematologic malignancy, admissions for patients with PID were more likely to have Gram-negative infections (18.8% vs 6.8%; OR, 3.16; 95% CI, 1.96–5.11; *p* < 0.001) and viral infections (31.2% vs 19.8%; OR, 1.83; 95% CI, 1.26–2.66; *p* = 0.002), but admissions for patients with hematologic malignancy were more likely to have fungal infections (14.8% vs 7.6%; OR, 2.09; 95% CI, 1.15–3.81; *p* = 0.012) (**Table 2**). Our study was not powered to detect differences in pathogen-specific mortality among differing HSCT indications (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B307).

Prevalence and Association of Critical Care Interventions on PICU Mortality

A total of 56.4% of HSCT-related admissions did not use NIPPV, IPPV, RRT, or ECMO (829/1,470) and had mortality of 1.9% (16/829). In comparison, NIPPV without prior or subsequent IPPV was used in 8.3% of admissions (129/1,559) with 4.7% mortality (6/129, OR, 2.48; 95% CI, 0.95–6.46; *p* = 0.103). IPPV was used in 34.6% of admissions (617/1,782) with 42.5% mortality (262/617; OR, 37.5; 95% CI, 22.3–63.1; *p* < 0.001). RRT was used in 11.9% of admissions (181/1,519) with 51.9% mortality (94/181; OR, 54.9; 95% CI, 30.9–97.5; *p* < 0.001). ECMO was used in four patients, all of whom died (*p* < 0.001). There was no statistically significant difference in mortality among centers caring for more than 10 different intubated patients during the study period (*p* = 0.94). Of note, HSCT admissions using RRT had higher mortality than non-HSCT admission using RRT (94/181 vs 317/890; OR, 1.95; 95% CI, 1.42–2.70; *p* < 0.001).

Subgroup Analysis of Intubated Patients

Of admissions requiring intubation, 44.1% did not have a documented infection (272/617) and had a 35.3% mortality (96/272),

TABLE 2. Prevalence of Infection by Hematopoietic Stem Cell Transplantation Indication

	Sepsis, *n* (%)	Gram-Positive, *n* (%)	Gram-Negative, *n* (%)	Viral, *n* (%)	Fungal, *n* (%)
All hematopoietic stem cell transplantation indications[a]	390 (24.7)	110 (7.0)	143 (9.1)	318 (20.2)	155 (9.8)
Solid cancer	56 (16.9)	16 (4.8)	32 (9.6)	23 (6.9)	9 (2.7)
Metabolic disorder	15 (13.5)	4 (3.6)	9 (8.1)	20 (18.0)	8 (7.2)
Nonmalignant hematologic	51 (22.6)	11 (4.9)	20 (11.8)	77 (34.1)	17 (7.5)
PID	58 (34.1)	14 (8.2)	32 (18.8)	53 (31.2)	13 (7.6)
Hematologic cancer	210 (28.7)	65 (8.9)	50 (6.8)	145 (19.8)	108 (14.8)
ANOVA, *p* values[b]	0.076	0.031	0.034	0.058	0.037
PID vs hematologic cancer, *p* values[c]	0.162	0.881	< 0.001	0.002	0.012

PID = primary immunodeficiency, ANOVA = analysis of variance.

[a]Hematopoietic stem cell transplantation (HSCT) indication *n* = 1578 due to 199 patients with no documented HSCT indication and five patients with systemic sclerosis.

[b]*p* Values represent ANOVA comparison of all five HSCT indications.

[c]*p* Values compare PID patients with hematologic cancer patients.

There was no difference in rates of sepsis (*p* = 0.162) or Gram-positive infections (*p* = 0.881); however, PID admissions were more likely to have Gram-negative (*p* < 0.001) and viral infections (*p* = 0.002), and hematologic cancer patients were more likely to have fungal infections (*p* = 0.012).

whereas 55.9% had an infection (345/617) and had a 48.1% mortality (166/345; OR, 1.70; 95% CI, 1.23–2.36; $p = 0.001$) (**eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B307). In comparison to admissions without a documented infection, mortality was 38.5% for those with Gram-positive infection (20/52; OR, 1.15; 95% CI, 0.62–2.11; $p = 0.750$), 50% for those with Gram-negative infection (34/68; OR, 1.83; 95% CI, 1.07–3.14; $p = 0.036$), 53% for those with viral infection (96/180; OR, 2.10; 95% CI, 1.43–3.08; $p < 0.001$), and 58% for those with fungal infection (47/81; OR, 2.53; 95% CI, 1.53–4.21; $p < 0.001$). Mortality was 47.1% (89/189) for admissions with sepsis (OR, 1.63; 95% CI, 1.12–2.38; $p = 0.012$).

Of admissions requiring intubation, patients with underlying solid malignancy had 23.0% mortality (17/74). In comparison, patients with underlying hematologic malignancy or PID had mortalities of 54% (149/274; OR, 4.00; 95% CI, 2.21–7.22; $p < 0.001$) and 48% (33/69; OR, 3.07; 95% CI, 1.50–6.31; $p = 0.003$), respectively. Patients with nonmalignant hematologic disease had 35.5% mortality (33/93; OR, 1.84; 95% CI, 0.93–3.67; $p = 0.091$) and patients with metabolic disorders had 18.9% mortality (7/37; OR, 0.78; 95% CI, 0.29–2.10; $p = 0.807$). Mortality among intubated patients with hematologic malignancy or PID was not statistically different ($p = 0.35$).

Multivariable Analysis of Variables Associated With PICU Mortality

On multivariable analysis, underlying HSCT indication was independently associated with mortality after clustering by center and controlling for age, gender, admission PRISM-3 score, whether the patient had an infection, and whether the patient received IPPV (**Table 3**). In comparison with patients transplanted for underlying solid malignancy, patients had increased odds of mortality if they were transplanted for underlying hematologic malignancy (OR, 3.82; 95% CI, 2.18–6.69; $p < 0.001$) or PID (OR, 2.57; 95% CI, 1.35–4.89; $p = 0.004$). On multivariable analysis, admissions with PID did not have increased mortality relative to admissions with hematologic malignancy (OR, 0.67; 95% CI, 0.38–1.19; $p = 0.172$). The aforementioned findings were upheld when adjusting for multiple admissions of the same patient (**eTable 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B307).

DISCUSSION

In this study, we found that pediatric HSCT patients make up 0.7% of PICU admissions but account for 4.6% of PICU deaths; 16.2% of admissions resulted in PICU death, but mortality was significantly higher for patients requiring IPPV (42.5%) or RRT (51.9%) and patients with viral (28.5%) or fungal infections (33.7%). Compared with other HSCT indications, patients transplanted for underlying hematologic malignancy or PID have significantly higher PICU mortality even after controlling for admission illness severity and rates of infection.

First, our finding of 16.2% PICU mortality is the lowest reported mortality in a pediatric HSCT cohort to date; other

TABLE 3. Multivariable Predictors of PICU Mortality for Hematopoietic Stem Cell Transplantation Patients

	OR of Mortality	*p*
Age[a]	1.00 (0.98–1.03)	0.712
Gender	0.97 (0.74–1.26)	0.802
Pediatric Risk of Mortality-3[b]	1.06 (1.04–1.09)	< 0.001
Hematopoietic stem cell transplantation indication	—	—
Solid cancer[c]	1	—
Metabolic disorder	1.20 (0.50–2.84)	0.683
Nonmalignant hematologic	1.69 (0.86–3.32)	0.126
Primary immunodeficiency	2.57 (1.35–4.89)	0.004
Hematologic cancer	3.82 (2.18–6.69)	< 0.001
Infection	1.34 (0.92–1.94)	0.125
Invasive positive pressure ventilation	25.0 (13.6–45.8)	< 0.001

OR = odds ratio.
[a]OR refers to each additional year of age.
[b]OR refers to each additional point in Pediatric Risk of Mortality (PRISM)-3 raw score; PRISM-3 score was an independent predictor of mortality.
[c]Solid cancer is the reference group for hematopoietic stem cell transplantation indication; hematologic cancer and primary immunodeficiency were independent predictors of mortality.

recent reports have described 44–58% mortality (2, 4, 6, 7, 16). Comparison to historical cohorts is challenging due to varying PICU admission criteria, limited reporting of traditional illness severity scores, and the limited utility of these scores when applied to the pediatric HSCT population. We question the utility of comparing pediatric HSCT cohorts using illness severity scores such as the PRISM-3. The original PRISM-3 was derived from a general PICU population with likely few HSCT patients, had an ROC AUC of 0.95, and was well-calibrated to predict mortality at low, moderate, and high scores (29). In comparison, when we applied the PRISM-3 to our HSCT cohort, we found an ROC AUC of 0.74, significant underprediction of mortality at low scores, and overprediction of mortality at high scores. Nonetheless, in attempting to compare our cohort to historical cohorts in the literature, we found that the majority of cohorts used older scoring systems such as the PRISM-2 and the original PIM, which is an inherent challenge to improving and updating such scores over time. However, in comparison to a contemporary multicenter cohort with 52% PICU mortality, our median PIM-2 scores were lower for survivors (1% vs 7.4%) and nonsurvivors (4% vs 13.4%) (7), suggesting that decreased admission illness severity in our cohort is at least partially involved in our finding of low mortality. It is possible that a portion of those patients with low illness severity scores were admitted to the PICU as a precaution and would not have developed critical illness to the degree of patients in comparison cohorts. It is also possible that these

patients were admitted early in the course of critical illness and benefitted from therapies preempting the evolution of more severe pathophysiology. This study was not equipped to differentiate these possibilities.

Second, we found that patients transplanted for underlying hematologic cancer or PID had significantly higher mortality than those with underlying nonmalignant hematologic disease, metabolic disease, or solid cancer. This finding was independent of age, gender, PRISM-3 score, presence of infection, and use of IPPV, suggesting that the effect of the indication for HSCT on PICU mortality is robust and cannot be explained solely by intergroup differences in admission illness severity or infection rates. Previously published reports have shown conflicting results regarding which transplant indications are associated with higher PICU mortality (3, 4, 12). Although our finding of 19.4% PICU mortality for HSCT patients with underlying immunodeficiency is much lower than previous reports of 47–54% (3, 13), it is not statistically different from mortality of patients with underlying hematologic malignancies or nonmalignant hematologic disease. This finding is novel in strongly establishing these patients as a high-risk subgroup and could be related to infection at the time of HSCT or the use of high-dose chemotherapy in these very young children (37). The relationship between underlying HSCT indication and PICU mortality may be mediated by varying use of allogeneic transplantation, rates of GVHD, conditioning regimen intensity, and disease- and treatment-related toxicities, although these factors could not be assessed in this study. For example, it is likely that the low mortality rate for patients with underlying solid tumors is related to virtually all patients having received autologous transplantation. Although this could not be evaluated with the current dataset, CIBMTR administered Stem Cell Therapeutic Outcomes Database reinforce that the vast majority of transplants for solid tumors are autologous (38). Interestingly, the lower mortality rate in patients with underlying metabolic disorders, despite reliance on allogeneic transplantation, suggests that the low rates of TBI, high use of serotherapy, and low rates of pretransplant chemotherapy in these patients remain pertinent to PICU outcomes (39).

Third, our finding of 45.7% infection prevalence is interesting and suggests that a large portion of HSCT patients require intensive care for noninfectious complications of their primary disease or their transplant (40–42). Of note, this finding does not address the possibility that some patients might have had occult and undiagnosed infections. Our finding of 11.1% mortality in uninfected patients versus 22.2% mortality in infected patients suggests that infectious complications of transplant continue to be leading cause of mortality in the PICU. This finding persists when stratifying for only patients receiving IPPV (35.3% vs 48.1%). Unfortunately, we were unable to identify those patients with HSCT-related complications of GVHD and SOS, which could explain at least some of the mortality in the uninfected patients. Also of interest is our finding that viral infections are associated with greater mortality than bacterial infections. This was particularly true for adenovirus (42% mortality) and herpes viruses such as CMV

(32% mortality) and may relate to antiviral resistance or high rates of T-cell immune incompetence secondary to the intensity of the conditioning, use of serotherapy, underlying disease, and processing, such as T-cell depletion (43). Consistent with the literature, fungal infections had a strong association with mortality, although our finding of 33.7% mortality in fungal infections is lower than recent mortality reports of 41–58% in this population (44–47) and may suggest improvement from new antifungal agents and diagnostic tests (44). These results also show that hematologic cancer patients and PID patients have different infection patterns posttransplant, with hematologic patients at higher risk for fungal infections and PID patients at higher risk for Gram-negative and viral infections. Understanding of these differences may help target infection-prophylaxis strategies to those groups most susceptible to mortality from certain categories of organisms. The significantly higher infectious mortality in HSCT admissions compared with non-HSCT admissions (22.2% vs 3.9%) further supports the need for aggressive infection prevention and control. Interestingly, children with SCID at any age have recently been shown to have a significantly higher mortality if they are infected at the time of HSCT versus having never been infected or having their infection resolve by the time of HSCT (37). We were unable to address this in our current patient cohort.

Fourth, our finding of 42.5% mortality in patients using IPPV is comparable to recently published reports of 41–52% (3, 4, 7, 9) and our finding of 51.9% mortality in patients using RRT is slightly lower than recently published reports of 55–65% (3, 48, 49). This supports the recent literature, suggesting that overall PICU mortality may be decreasing for the most critically ill pediatric HSCT patients. However, mortality for admissions requiring RRT was significantly higher in HSCT patients than non-HSCT patients (51.9% vs 35.6%), which may suggest particularly detrimental effects of fluid overload and renal failure in the pediatric HSCT population compared to others. Interestingly, the rates of IPPV use (34.6%) in our study were much lower than historical cohorts (63–86%) (8, 12, 13, 50), which may suggest increased use of early proactive PICU admission and/or some success in halting critical illness progression such that IPPV was not needed. Noninvasive technologies such as NIPPV may assist in achieving this (25, 51, 52). In addition, our finding of 1.9% PICU mortality for those not using NIPPV, IPPV, RRT, or ECMO is quite low and suggests that there may be a practice trend to keep end-of-life do not resuscitate/do not intubate patients out of the PICU, particularly immediately prior to death (53). If true, this may have also contributed to our overall low mortality data by shunting HSCT patient deaths out of the PICU. Unfortunately, our finding of four of 1,782 admissions using ECMO with 100% mortality is discouraging and emphasizes the need for ECMO-use guidelines in this population, especially as outcomes appear to be dismal (54, 55).

There are several limitations to our study. First, we were unable to identify an HSCT indication for 11.1% of our patients, which may reflect incomplete diagnosis coding or database quality. Second, the VPS database did not have

information on transplant-related variables, including allogeneic versus autologous transplant, stem cell source, HLA match, conditioning regimen, or presence and staging of GVHD or clinical status at the time of HSCT. Lack of these data limits the scope of conclusions that can be drawn in this study and reinforces the need for record merging and sharing projects among databases. Third, this study does not capture mortalities that occurred outside of the PICU.

CONCLUSIONS

To conclude, this analysis represents the largest cohort of pediatric HSCT patients requiring PICU admission and demonstrates PICU mortality of 16.2%, which is significantly lower than previously reported. Of note, only 34.6% of our cohort required IPPV and only 54.3% had a documented infection. Mortality for pediatric HSCT patients in the PICU may be as low as 16.2% but remains higher for those receiving intubation (42.5%) or RRT (51.9%) and those with viral (28.5%) or fungal infections (33.7%). Greater understanding of other risk factors affecting mortality and the need for critical care support is needed. In order to accomplish this, a future direction will be to pair the VPS database with a database that captures HSCT-specific variables, such as that maintained by the CIBMTR.

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REFERENCES

1. Pasquini MC, Wang Z: Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2013. Available at: http://www.cibmtr.org/referencecenter/slidesreports/summaryslides. Accessed April 23, 2014

2. 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

3. Chima RS, Daniels RC, Kim MO, et al: Improved outcomes for stem cell transplant recipients requiring pediatric intensive care. *Pediatr Crit Care Med* 2012; 13:e336–e342

4. 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

5. Diaz MA, Vicent MG, Prudencio M, et al: Predicting factors for admission to an intensive care unit and clinical outcome in pediatric patients receiving hematopoietic stem cell transplantation. *Haematologica* 2002; 87:292–298

6. 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

7. van Gestel JP, Bierings MB, Dauger S, et al: Outcome of invasive mechanical ventilation after pediatric allogeneic hematopoietic SCT: Results from a prospective, multicenter registry. *Bone Marrow Transplant* 2014; 49:1287–1292

8. Jacobe SJ, Hassan A, Veys P, et al: Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. *Crit Care Med* 2003; 31:1299–1305

9. Kache S, Weiss IK, Moore TB: Changing outcomes for children requiring intensive care following hematopoietic stem cell transplantation. *Pediatr Transplant* 2006; 10:299–303

10. Bratton SL, Van Duker H, Statler KD, et al: Lower hospital mortality and complications after pediatric hematopoietic stem cell transplantation. *Crit Care Med* 2008; 36:923–927

11. 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

12. Aspesberro F, Guthrie KA, Woolfrey AE, et al: Outcome of pediatric hematopoietic stem cell transplant recipients requiring mechanical ventilation. *J Intensive Care Med* 2014; 29:31–37

13. Cole TS, Johnstone IC, Pearce MS, et al: Outcome of children requiring intensive care following haematopoietic SCT for primary immunodeficiency and other non-malignant disorders. *Bone Marrow Transplant* 2012; 47:40–45

14. Gooley TA, Chien JW, Pergam SA, et al: Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med* 2010; 363:2091–2101

15. Savani BN, Montero A, Wu C, et al: Prediction and prevention of transplant-related mortality from pulmonary causes after total body irradiation and allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; 11:223–230

16. van Gestel JP, Bollen CW, van der Tweel I, et al: Intensive care unit mortality trends in children after hematopoietic stem cell transplantation: A meta-regression analysis. *Crit Care Med* 2008; 36:2898–2904

17. McArthur J, Pettersen G, Jouvet P, et al; Pediatric Acute Lung Injury and Sepsis Investigators: The care of critically ill children after hematopoietic SCT: A North American survey. *Bone Marrow Transplant* 2011; 46:227–231

18. Leclerc F, Leteurtre S: Pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation: Do we do a better job? *Pediatr Crit Care Med* 2008; 9:334–335

19. Piñana JL, Martino R, Barba P, et al: Pulmonary function testing prior to reduced intensity conditioning allogeneic stem cell transplantation in an unselected patient cohort predicts posttransplantation pulmonary complications and outcome. *Am J Hematol* 2012; 87:9–14

20. Satwani P, Jin Z, Duffy D, et al: Transplantation-related mortality, graft failure, and survival after reduced-toxicity conditioning and allogeneic hematopoietic stem cell transplantation in 100 consecutive pediatric recipients. *Biol Blood Marrow Transplant* 2013; 19:552–561

21. Sefton G, McGrath C, Tume L, et al: What impact did a Paediatric Early Warning system have on emergency admissions to the paediatric intensive care unit? An observational cohort study. *Intensive Crit Care Nurs* 2015; 31:91–99

22. Parshuram CS, Duncan HP, Joffe AR, et al: Multicentre validation of the bedside paediatric early warning system score: A severity of illness score to detect evolving critical illness in hospitalised children. *Crit Care* 2011; 15:R184

23. Parshuram CS, Hutchison J, Middaugh K: Development and initial validation of the Bedside Paediatric Early Warning System score. *Crit Care* 2009; 13:R135

24. Pancera CF, Hayashi M, Fregnani JH, et al: Noninvasive ventilation in immunocompromised pediatric patients: Eight years of experience in a pediatric oncology intensive care unit. *J Pediatr Hematol Oncol* 2008; 30:533–538

25. Azoulay E, Alberti C, Bornstain C, et al: Improved survival in cancer patients requiring mechanical ventilatory support: Impact of noninvasive mechanical ventilatory support. *Crit Care Med* 2001; 29:519–525

26. Elbahlawan L, Morrison RR: Continuous renal replacement therapy in children post-hematopoietic stem cell transplantation: The present and the future. *Curr Stem Cell Res Ther* 2012; 7:381–387

27. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group: PIM2: A revised version of the Paediatric Index of Mortality. *Intensive Care Med* 2003; 29:278–285

28. Pollack MM, Ruttimann UE, Getson PR: Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16:1110–1116

29. Pollack MM, Patel KM, Ruttimann UE: PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med* 1996; 24:743–752

30. Center for International Blood and Marrow Transplant Research (CIB-MTR): Pre-transplant essential data form 2400, revision 4. Available at: http://www.cibmtr.org/DataManagement/DataCollectionForms/Documents/2400/Rev4.0/2400R4.0+.pdf. Accessed October 14, 2014

31. Weiss SL, Parker B, Bullock ME, et al: Defining pediatric sepsis by different criteria: Discrepancies in populations and implications for clinical practice. *Pediatr Crit Care Med* 2012; 13:e219–e226

32. Ludbrook J, Dudley H: Issues in biomedical statistics: Analysing 2 x 2 tables of frequencies. *Aust N Z J Surg* 1994; 64:780–787

33. Hanley JA, McNeil BJ: A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; 148:839–843

34. Hosmer DW, Lemeshow S: Applied Logistic Regression. New York, Wiley, 2000

35. Diggle PJ, Heagerty P, Liang K, et al: Analysis of Longitudinal Data. Oxford Statistical Science Series. 2002

36. Hardin J, Hilbe J: Generalized Estimating Equations. Oxford, Chapman and Hall/CRC, 2003

37. Pai SY, Logan BR, Griffith LM, et al: Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med* 2014; 371:434–446

38. Center for International Blood and Marrow Transplant, a contractor for the C.W. Bill Young Cell Transplantation Program operated through the U. S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau. Stem Cell Therapeutic Outcomes Database: U.S. Transplant Data by Disease Report. Available at: http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/data_by_disease/national.aspx. Accessed October 14, 2014

39. Boelens JJ, Aldenhoven M, Purtill D, et al; Eurocord; Inborn Errors Working Party of European Blood and Marrow Transplant Group; Duke University Blood and Marrow Transplantation Program; Centre for International Blood and Marrow Research: Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. *Blood* 2013; 121:3981–3987

40. Panoskaltsis-Mortari A, Griese M, Madtes DK, et al; American Thoracic Society Committee on Idiopathic Pneumonia Syndrome: An official American Thoracic Society research statement: Noninfectious lung injury after hematopoietic stem cell transplantation: Idiopathic pneumonia syndrome. *Am J Respir Crit Care Med* 2011; 183:1262–1279

41. Cooke KR, Yanik G: Acute lung injury after allogeneic stem cell transplantation: Is the lung a target of acute graft-versus-host disease? *Bone Marrow Transplant* 2004; 34:753–765

42. Yanik GA, Mineishi S, Levine JE, et al: Soluble tumor necrosis factor receptor: Enbrel (etanercept) for subacute pulmonary dysfunction following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2012; 18:1044–1054

43. Zinter MS, Levy ER, Gertz SJ: A review of pathogens causing lower respiratory tract infection in the pediatric hematopoietic stem cell transplant recipient. *J Pediatr Intensive Care* 2014; 3:115–132

44. Wattier RL, Dvorak CC, Hoffman JA, et al: A prospective, international cohort study of invasive mold infections in children. *J Pediatr Infect Dis Soc* 2014. Available at: http://jpids.oxfordjournals.org/content/early/2014/07/16/jpids.piu074.full. Accessed July 16, 2014

45. Dvorak CC, Steinbach WJ, Brown JM, et al: Risks and outcomes of invasive fungal infections in pediatric patients undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2005; 36:621–629

46. Hovi L, Saarinen-Pihkala UM, Vettenranta K, et al: Invasive fungal infections in pediatric bone marrow transplant recipients: Single center experience of 10 years. *Bone Marrow Transplant* 2000; 26:999–1004

47. Castagnola E, Cesaro S, Giacchino M, et al: Fungal infections in children with cancer: A prospective, multicenter surveillance study. *Pediatr Infect Dis J* 2006; 25:634–639

48. Flores FX, Brophy PD, Symons JM, et al: Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. *Pediatr Nephrol* 2008; 23:625–630

49. Rajasekaran S, Jones DP, Avent Y, et al: Outcomes of hematopoietic stem cell transplant patients who received continuous renal replacement therapy in a pediatric oncology intensive care unit. *Pediatr Crit Care Med* 2010; 11:699–706

50. Diaz de Heredia C, Moreno A, Olive T, et al: Role of the intensive care unit in children undergoing bone marrow transplantation with life-threatening complications. *Bone Marrow Transplant* 1999; 24:163–168

51. Wermke M, Schiemanck S, Höffken G, et al: Respiratory failure in patients undergoing allogeneic hematopoietic SCT–A randomized trial on early non-invasive ventilation based on standard care hematology wards. *Bone Marrow Transplant* 2012; 47:574–580

52. Zhan Q, Sun B, Liang L, et al: Early use of noninvasive positive pressure ventilation for acute lung injury: A multicenter randomized controlled trial. *Crit Care Med* 2012; 40:455–460

53. Ullrich CK, Dussel V, Hilden JM, et al: End-of-life experience of children undergoing stem cell transplantation for malignancy: Parent and provider perspectives and patterns of care. *Blood* 2010; 115:3879–3885

54. Di Nardo M, Locatelli F, Palmer K, et al: Extracorporeal membrane oxygenation in pediatric recipients of hematopoietic stem cell transplantation: An updated analysis of the Extracorporeal Life Support Organization experience. *Intensive Care Med* 2014; 40:754–756

55. Gow KW, Heiss KF, Wulkan ML, et al: Extracorporeal life support for support of children with malignancy and respiratory or cardiac failure: The extracorporeal life support experience. *Crit Care Med* 2009; 37:1308–1316