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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.


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.

**Key Words:** bone marrow transplantation; child; hematopoietic stem cell transplantation; mechanical ventilation; mortality; pediatric intensive care unit; stem cell transplantation

**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 α = 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 (5,927/24,564; 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 Infection Type 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 Underlying HSCT Indication 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% (35/159; 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...
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).

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

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Distributions, <em>n</em> (%)</th>
<th>Mortality, <em>n</em> (%)</th>
<th>OR of Mortality</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean, 9.1 ± 0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>701 (39.3)</td>
<td>117 (16.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1081 (60.7)</td>
<td>171 (15.8)</td>
<td>0.94 (0.73–1.21)</td>
<td>0.640</td>
</tr>
<tr>
<td><strong>Illness score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Index of Mortality-2 POD (median, 1; IQR, 0–5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PRISM-3 (median, 8; IQR, 3–13)</td>
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<tr>
<td>PRISM-3 POD (median, 2.6; IQR, 0.6–9.3)</td>
<td></td>
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</tr>
<tr>
<td><strong>Hematopoietic stem cell transplantation indication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid cancer</td>
<td>332 (18.6)</td>
<td>19 (5.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>111 (6.2)</td>
<td>9 (8.1)</td>
<td>1.42 (0.64–3.31)</td>
<td>0.372</td>
</tr>
<tr>
<td>Nonmalignant hematologic</td>
<td>226 (12.7)</td>
<td>35 (15.4)</td>
<td>3.02 (1.68–5.43)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
<td>170 (9.5)</td>
<td>33 (19.4)</td>
<td>3.97 (2.18–7.22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hematologic cancer</td>
<td>739 (41.5)</td>
<td>168 (22.7)</td>
<td>4.85 (2.96–7.94)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No infection</td>
<td>967 (54.3)</td>
<td>107 (11.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>815 (45.7)</td>
<td>181 (22.2)</td>
<td>2.30 (1.77–2.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>436 (24.5)</td>
<td>97 (22.2)</td>
<td>2.30 (1.70–3.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gram-positive bacterial</td>
<td>125 (7.0)</td>
<td>22 (17.6)</td>
<td>1.72 (1.04–2.84)</td>
<td>0.039</td>
</tr>
<tr>
<td>Gram-negative bacterial</td>
<td>159 (8.9)</td>
<td>35 (22.0)</td>
<td>2.27 (1.48–3.47)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Viral</td>
<td>355 (19.9)</td>
<td>101 (28.5)</td>
<td>3.20 (2.35–4.34)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fungal</td>
<td>163 (9.1)</td>
<td>55 (33.7)</td>
<td>4.09 (2.79–6.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No NIPPV, IPPV, RRT, or ECMO</td>
<td>829 (56.4)</td>
<td>16 (1.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>NIPPV without IPPV</td>
<td>129 (8.3)</td>
<td>6 (4.7)</td>
<td>2.48 (0.95–6.46)</td>
<td>0.103</td>
</tr>
<tr>
<td>IPPV</td>
<td>617 (34.6)</td>
<td>262 (42.5)</td>
<td>3.75 (22.3–63.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RRT</td>
<td>181 (11.9)</td>
<td>94 (51.9)</td>
<td>54.9 (30.9–97.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ECMO</td>
<td>4 (0.2)</td>
<td>4 (100)</td>
<td>–</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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.

*OR refers to each additional year of age.

*OR refers to each additional point of illness score.

*PRISM-3 and PRISM-3 POD *n* = 1753 due to missing PRISM-3 scores.

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

*NIPPP without IPPV *n* = 1559 due to some centers not collecting NIPPV.

*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.
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).

**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), \(p < 0.001\). 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; \(p < 0.001\)).

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

<table>
<thead>
<tr>
<th></th>
<th>Sepsis, n (%)</th>
<th>Gram-Positive, n (%)</th>
<th>Gram-Negative, n (%)</th>
<th>Viral, n (%)</th>
<th>Fungal, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hematopoietic stem cell transplantation indications(^a)</td>
<td>390 (24.7)</td>
<td>110 (7.0)</td>
<td>143 (9.1)</td>
<td>318 (20.2)</td>
<td>155 (9.8)</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>56 (16.9)</td>
<td>16 (4.8)</td>
<td>32 (9.6)</td>
<td>23 (6.9)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>15 (13.5)</td>
<td>4 (3.6)</td>
<td>9 (8.1)</td>
<td>20 (18.0)</td>
<td>8 (7.2)</td>
</tr>
<tr>
<td>Nonmalignant hematologic</td>
<td>51 (22.6)</td>
<td>11 (4.9)</td>
<td>20 (11.8)</td>
<td>77 (34.1)</td>
<td>17 (7.5)</td>
</tr>
<tr>
<td>PID</td>
<td>58 (34.1)</td>
<td>14 (8.2)</td>
<td>32 (18.8)</td>
<td>53 (31.2)</td>
<td>13 (7.6)</td>
</tr>
<tr>
<td>Hematologic cancer</td>
<td>210 (28.7)</td>
<td>65 (8.9)</td>
<td>50 (6.8)</td>
<td>145 (19.8)</td>
<td>108 (14.8)</td>
</tr>
</tbody>
</table>

ANOVA, \(p\) values\(^b\) 0.076 0.031 0.034 0.058 0.037

\(p\) Values represent ANOVA comparison of all five HSCT indications.

\(p\) 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 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

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

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

\( OR \) = 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.
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 sub-group 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


