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Pediatric Hematopoietic Cell Transplant Patients Who Survive Critical Illness Frequently Have Significant but Recoverable Decline in Functional Status

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A B S T R A C T

The number of pediatric hematopoietic cell transplant (HCT) patients who survive pediatric intensive care unit (PICU) admission is increasing, yet little is known about their functional morbidity after PICU discharge. We hypothesized that relative to control subjects, pediatric HCT patients who survive PICU admission would have greater rates of new functional morbidity at the time of PICU discharge and only some of these patients would return to their functional baseline by the end of the hospitalization. We performed a retrospective cohort study with secondary data analysis of the Trichotomous Outcomes in Pediatric Critical Care dataset. The pediatric HCT cohort was identified by querying International Classification of Diseases, 9th edition, diagnostic codes. A control group consisted of previously healthy patients matched 4:1 on age, sex, and illness severity, as estimated by the Pediatric Risk of Mortality (PRISM) score. We benchmarked our findings by comparing with a previously healthy group of children with lower respiratory tract infections. Functional impairment was measured by the Functional Status Scale, wherein new morbidity was defined as an increase of ≥3 points relative to the prehospital baseline. Relative to matched control subjects, HCT patients had similar admission PRISM scores ($P = .516$) but greater PICU mortality (12.9% [11/85] versus 6.2% [21/340], $P = .035$). However, among those who survived to PICU discharge, HCT patients had similar rates of *new* morbidity at PICU discharge (14.9% [11/74] versus 17.2% [55/319], $P = .622$) and similar rates of resolution of *new* morbidity by hospital discharge (54.5% [6/11] versus 60.0% [33/55], $P = .737$). Relative to the comparison group with lower respiratory tract infections, HCT patients had both greater admission PRISM scores ($P < .001$) and greater PICU mortality (12.9% [11/85] versus 1.6% [5/308], $P < .001$). However, among those who survived to PICU discharge, HCT patients again displayed similar rates of new morbidity at PICU discharge (14.9% [11/74] versus 22.1% [67/303], $P = .168$) as well as resolution of new morbidity by hospital discharge (54.5% [6/11] versus 71.6% [48/67], $P = .299$). For pediatric HCT patients PICU survival with new functional morbidity is as prevalent an outcome as PICU mortality. Although pediatric HCT patients have greater PICU mortality than age-, sex-, and PRISM-matched control subjects, they have similar rates of new functional morbidity at PICU discharge and similar resolution of new functional morbidity at hospital discharge. Future interventions focused on improving functional status in pediatric HCT survivors of critical illness are warranted.

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BACKGROUND

Critically ill pediatric hematopoietic cell transplant (HCT) patients have nearly 8 times greater odds for pediatric intensive care unit (PICU) mortality than do other critically ill children [1]. Studies suggest mortality rates of up to 16% per PICU admission, with significantly higher mortality for patients requiring invasive mechanical ventilation (42.5%) or renal replacement therapy (51.9%) [1,2]. Although trends suggest that mortality has decreased over time for these patients, historical comparisons are confounded by the increasingly heterogeneous cohorts, varied timing of PICU admission, and lack of illness severity standards that allow for controlled comparisons [3,4]. Nonetheless, as the number of pediatric HCT PICU survivors increases, it is becoming ever more important to assess a broad set of outcomes beyond PICU mortality.

Frameworks for assessing both functional status and health-related quality of life currently exist in pediatric critical care research and include metrics such as the Pediatric Overall Performance Category (POPC), the Pediatric Cerebral Performance Category (PCPC), and the Pediatric Quality of Life Inventory [5]. The Functional Status Scale (FSS) has been introduced as a more robust scale for assessing gradations of functional status over multiple domains [6]. Studies such as the Trichotomous Outcomes in Pediatric Critical Care (TOPICC) have applied the FSS in the general PICU population and have found that up to 36% of children demonstrate new functional impairment at the time of PICU discharge [7]. Additional studies demonstrate persistent functional impairment in 10% to 13% of PICU survivors when assessed at 2 years [8-14].

Among pediatric HCT patients who survive to PICU discharge, functional status decline at PICU discharge and at hospital discharge has not been assessed. However, 1 large study identified that pediatric HCT patients discharged from intensive care had similar 1-year survival and functional outcomes compared with pediatric HCT patients who did not require intensive care; this suggests that for many pediatric HCT patients, morbidity acquired during critical illness may be recoverable over time [15]. Therefore, we aimed to extend the growing body of knowledge on functional status changes after pediatric critical illness to the particularly vulnerable population of pediatric HCT patients to more fully characterize the breadth of significant clinical outcomes after critical illness in pediatric HCT patients.

METHODS

Study Design

We performed a retrospective cohort study using a secondary data analysis of the TOPICC dataset. The TOPICC study enrolled 10,078 patients younger than age 18 years who were admitted between December 4, 2011 and April 7, 2013 to 1 of 8 PICUs of the Collaborative Pediatric Critical Care Research Network. Where patients had multiple PICU admissions during a single hospital stay, the first PICU admission was used. Where patients had multiple PICU admissions during multiple hospital stays, the first PICU admission within the first hospital stay was used and the rest excluded.

Cohort

HCT recipients were identified within the TOPICC database by querying the following International Classification of Diseases, 9th edition (ICD-9) diagnosis codes: V42.81 (bone marrow replaced by transplant), V42.82 (peripheral stem cells replaced by transplant), 41.0 with all subcodes (bone marrow or hematopoietic stem cell transplant), 279.5 with all subcodes (graft-versus-host disease), and 996.85 (complications of transplanted bone marrow). For each patient we recorded age, sex, race, and ethnicity. We used the Pediatric Risk of Mortality (PRISM) score as a measurement of admission physiologic dysfunction (admission illness severity). The PRISM score weights vital sign and laboratory derangements within the first 4 hours of PICU admission according to their association with PICU mortality [16,17].

We also measured critical care resource utilization according to use of invasive mechanical ventilation, vasoactive infusions, and renal replacement therapy, including intermittent or continuous hemodialysis, hemofiltration, or hemodiafiltration. Because of the challenges of retrospectively ascertaining PICU admission indication from lists of diagnosis codes, we were unable to describe each patient's primary PICU admission indication.

Control Group

To account for varying demographics and admission illness severity, we matched each HCT patient to 4 non-HCT control patients of the same age group (<1 year, 1 to 4.99 years, 5 to 12.99 years, and 13 to 17.99 years), same sex, PRISM score within 2 points, and with no chronic medical conditions. In cases where an HCT patient had more than 4 possible control subjects, 4 control subjects were selected randomly using a computer-based random number generator. For 3 instances where 1 HCT patient had fewer than 4 possible control subjects, age- and sex-matched control subjects were selected according to patients with the next closest PRISM score.

Comparison Group

We anticipated that the matched control group would be heterogeneous in terms of PICU admission indication. Because patients with lower respiratory tract infections (LRTIs) compose a large portion of general PICU admissions [17] and 73% to 88% of pediatric HCT PICU admissions are indicated for LRTI and other types of respiratory failure [15,18-20], we identified a group of pediatric patients with LRTIs to serve as a useful clinical benchmark against which to compare the pediatric HCT population. The LRTI comparison group was identified by querying the TOPICC database for non-HCT patients with ICD-9 diagnosis codes 480 to 487, including all subcodes. We then excluded patients with any chronic medical condition as indicated on the original TOPICC case report form.

Measurements

The FSS measures 6 domains of daily function (mental status, sensory, communication, motor, feeding, and respiratory), each on a 5-point scale from normal function to very severe dysfunction, to produce a global assessment of no, mild, moderate, severe, or very severe impairment (total scores of 6 to 7, 8 to 9, 10 to 15, 16 to 21, and 22 to 30, respectively) [6]. In contrast, the POPC and the PCPC are abbreviated assessments scored from 1 to 5 that estimate global functioning as normal, mild disability, moderate disability, severe disability, or coma/vegetative [5]. In the TOPICC study the FSS, POPC, and PCPC were each measured at prehospital baseline, at PICU discharge, and at hospital discharge by review of medical records and discussion with bedside caregivers.

Outcomes

The primary outcome was the trichotomous outcome of mortality, survival with new functional morbidity, or survival without new functional morbidity, measured at PICU discharge and again at hospital discharge. New morbidity was defined as a change in FSS score ≥ 3 points relative to the prehospital baseline. The secondary outcome was the prevalence of moderate/severe functional status impairment, defined as FSS score ≥ 10, measured at the time of PICU discharge and again at hospital discharge.

Statistics

Distributions of categorical variables were described with percentages and compared with chi-square or Fisher exact tests. Distributions of continuous variables were described with median and interquartile ranges (IQRs) and compared with Wilcoxon rank sum tests. All tests are 2-sided.

RESULTS

Cohort

Of the 10,014 PICU admissions in the TOPICC database that were accompanied by ICD-9 codes, we identified 85 admissions for pediatric HCT patients (.8%); 340 admissions for previously healthy children matched 4:1 to HCT patients on age, sex, and PRISM score (3.4%); and 308 admissions for previously healthy children with LRTIs (3.1%) Characteristics of the HCT patients, the matched control group, and the LRTI comparison group are depicted in Table 1.

HCT Patients Compared with Matched Control Subjects

Relative to the matched control subjects, HCT patients had similar distribution of age, sex, race, ethnicity, and PRISM score, suggesting successful patient–control matching. However, HCT patients had worse baseline functional status

Table 1
Characteristics of Pediatric HCT Patients

	HCT Patients (n = 85)	Matched Control Group (n = 340)		LRTI Comparison Group (n = 308)	
	Value	Value	P	Value	P
Demographics					
Median age, yr (IQR)	7.1 (3.7-13.4)	7.9 (2.8-13.3)	.969	1.2 (.4-4.4)	**<.001**
Female	37 (43.5)	148 (43.5)	1.000	144 (46.8)	.598
Race			.430		.365
Black	14 (16.5)	73 (21.5)		68 (22.1)	
White	48 (56.5)	167 (49.1)		149 (48.4)	
Other/unknown	23 (27.1)	100 (29.4)		91 (29.6)	
Ethnicity			.145		.158
Hispanic/Latino	11 (12.9)	56 (16.5)		53 (17.2)	
Non-Hispanic/Latino	56 (65.9)	184 (54.1)		167 (42.5)	
Unknown	18 (21.2)	100 (29.4)		88 (22.4)	
PICU admission illness severity					
Median PRISM score (IQR)	5 (0-10)	4.5 (0-9)	.516	2 (0-5)	**<.001**
Median baseline functional status scores (IQR)					
FSS	7 (6-10)	6 (6-6)	**<.001**	6 (6-6)	**<.001**
POPC	3 (2-3)	1 (1-1)	**<.001**	1 (1-1)	**<.001**
PCPC	1 (1-2)	1 (1-1)	**<.001**	1 (1-1)	**<.001**
Baseline functional status class			**<.001**		**<.001**
No/mild impairment (FSS score < 10)	60 (70.6)	338 (99.4)		303 (98.4)	
Moderate/severe impairment (FSS score ≥ 10)	25 (29.4)	2 (.6)		5 (1.6)	
PICU supportive care					
At least 1 supportive therapy	47 (55.3)	140 (41.2)	**.019**	161 (52.3)	.621
Mechanical ventilation	31 (36.5)	125 (36.8)	.956	154 (50)	**.027**
Renal replacement therapy	5 (5.9)	8 (2.4)	.148	5 (1.6)	**.043**
Vasoactive infusions	30 (35.3)	74 (21.8)	**.010**	57 (18.5)	**.001**

Values are n (%), unless otherwise defined. Patients in the matched control group were matched 4:1 to HCT patients on age, sex, and PRISM score. Functional status represents prehospital baseline.
Bold indicates statistically significant comparisons.

on the FSS, POPC, and PCPC scores ($P < .001$) and more frequently used vasoactive infusions ($P = .010$) but had similar rates of invasive mechanical ventilation ($P = .956$) and renal replacement therapy ($P = .148$).

HCT Patients Compared with LRTI Comparison Group

Relative to the LRTI comparison group, HCT patients had similar distribution of sex, race, and ethnicity but were older ($P < .001$); had worse baseline functional status on the FSS, POPC, and PCPC scores ($P < .001$); had higher PICU admission illness severity as assessed by the PRISM score ($P < .001$);

and had more frequently used renal replacement therapy ($P = .027$) and vasoactive infusions ($P = .001$) but less frequently used invasive mechanical ventilation ($P = .027$).

Change in Functional Status Between PICU Admission and PICU Discharge

Longitudinal changes in functional status of the 85 pediatric HCT patients are illustrated in Figure 1. At PICU discharge 63 maintained their functional baseline (ΔFSS score < 3), 11 developed new impairment (ΔFSS score ≥ 3), and 11 died. There was no statistically significant difference in rates of PICU
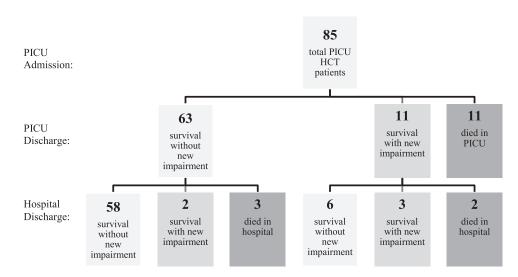

Figure 1. Trichotomous longitudinal outcomes of pediatric HCT patients admitted to the PICU. New impairment defined as increase in FSS score of at least 3 points relative to prehospital baseline.

Table 2
Outcomes of Pediatric HCT Patients

	HCT Cohort (n = 85)	Matched Control Group (n = 340)		LRTI Comparison Group (n = 308)	
	Value	Value	P	Value	P
PICU discharge					
Median functional status scores (IQR)					
FSS	8.5 (6-11)	6 (6-8)	**<.001**	7 (6-8)	**.002**
POPC	3 (2-4)	2 (1-2)	**<.001**	2 (1-2)	**<.001**
PCPC	1 (1-3)	1 (1-1)	**<.001**	1 (1-1)	**<.001**
Functional class			**<.001**		**<.001**
No/mild impairment (FSS score < 10)	46 (54.1)	270 (79.4)		262 (85.1)	
Moderate/severe impairment (FSS score ≥ 10)	28 (32.9)	49 (14.4)		41 (13.3)	
Dead	11 (12.9)	21 (6.2)		5 (1.6)	
Functional status change			.159		**.034**
No new impairment (ΔFSS score < 3)	63 (74.1)	264 (77.6)		236 (76.6)	
New impairment (ΔFSS score ≥ 3)	11 (12.9)	55 (16.2)		67 (21.8)	
Dead	11 (12.9)	21 (6.2)		5 (1.6)	
Hospital discharge					
Median functional status scores (IQR)					
FSS	8 (6-10)	6 (6-7)	**<.001**	6 (6-6)	**<.001**
POPC	3 (2-4)	2 (1-2)	**<.001**	1 (1-2)	**<.001**
PCPC	1 (1-4)	1 (1-1)	**<.001**	1 (1-1)	**<.001**
Functional class			**<.001**		**<.001**
No/mild impairment (FSS score < 10)	45 (52.9)	296 (87.1)		284 (92.2)	
Moderate/severe impairment (FSS score ≥ 10)	24 (28.2)	21 (6.2)		18 (5.8)	
Dead	16 (18.8)	23 (6.8)		6 (1.9)	
Functional status change (n, %)			.001		**<.001**
No new impairment (ΔFSS score < 3)	64 (75.3)	295 (86.8)		283 (91.9)	
New impairment (ΔFSS score ≥ 3)	5 (5.9)	22 (6.5)		19 (6.2)	
Dead	16 (18.8)	23 (6.8)		6 (1.9)	

Values are n (%), unless otherwise defined. Functional status change at PICU discharge and at hospital discharge are relative to the prehospital baseline. Functional class and functional status change at PICU discharge and at hospital discharge were compared as ordered trichotomous categorical variables.
Bold indicates statistically significant comparisons.

death among patients with moderate/severe baseline impairment versus patients no/mild baseline impairment versus (16.0% [4/25] versus 11.7% [7/60], *P* = .724). Similarly, among those discharged alive from the PICU, there was no statistically significant difference in the development of new functional impairment among patients with moderate/severe baseline impairment versus no/mild baseline impairment (9.5% [2/21] versus 17.0% [9/53], *P* = .718).

Change in Functional Status Between PICU Discharge and Hospital Discharge

Of 63 HCT patients discharged from the PICU at their functional baseline, 58 were discharged from the hospital at their functional baseline (ΔFSS score < 3), 2 were discharged from the hospital with new morbidity (ΔFSS score ≥ 3), and 3 died in the hospital. Of the 11 HCT patients discharged from the PICU with new functional impairment, 6 were discharged from the hospital with recovery to their functional baseline, 3 were discharged from the hospital with persistent new morbidity, and 2 died in the hospital. Of the 3 patients discharged from the hospital with persistent new morbidity relative to baseline, the first had persistent deficits in communication, motor skills, and mental function; the second had persistent deficits in feeding and motor function; and the third had persistent deficits in feeding and respiratory function.

There was a nonsignificant trend toward greater hospital death among HCT patients discharged from the PICU with new functional impairment versus HCT patients discharged from the PICU at their baseline functional status (18.2% [2/11] versus 4.8% [3/63], *P* = .157). Post hoc power analysis indicates that a sample size of 325 HCT patients requiring PICU admission would be necessary to demonstrate statistical significance for this difference in hospital mortality between

those who survived PICU admission with versus without new functional morbidity (chi-square test, α = .05, β = .2). In comparison with *new* functional impairment, there was no difference in hospital death among HCT patients with moderate/severe impairment at PICU discharge versus HCT patients with no/mild impairment at PICU discharge (10.7% [3/28] versus 4.3% [2/46], *P* = .360).

Comparison of HCT Patients versus Control Subjects at PICU Discharge

At the time of PICU discharge, HCT patients had greater mortality than both matched control subjects (12.9% [11/85] versus 6.2% [21/340], *P* = .035) and the LRTI comparison group (12.9% [11/85] versus 1.6% [5/308], *P* < .001; Table 2). Among patients who survived to PICU discharge, HCT patients also had higher FSS scores at that time than the matched control subjects (median 8.5 [IQR, 6 to 11] versus 6 [IQR, 6 to 8], *P* < .001) and the LRTI comparison group (median 8.5 [IQR, 6 to 11] versus 7 [IQR, 6 to 8], *P* = .002) and had greater prevalence of moderate-to-severe functional impairment than the matched control subjects (37.8% [28/74] versus 15.4% [49/319], *P* < .001) and the LRTI comparison group (37.8% [28/74] versus 13.5% [41/303], *P* < .001). Among patients who survived to PICU discharge, HCT patients displayed similar rates of *new* morbidity at PICU discharge relative to matched control subjects (14.9% [11/74] versus 17.2% [55/319], *P* = .622) and the LRTI comparison group (14.9% [11/74] versus 22.1% [67/303], *P* = .168).

Comparison of HCT Patients versus Control Subjects at Hospital Discharge

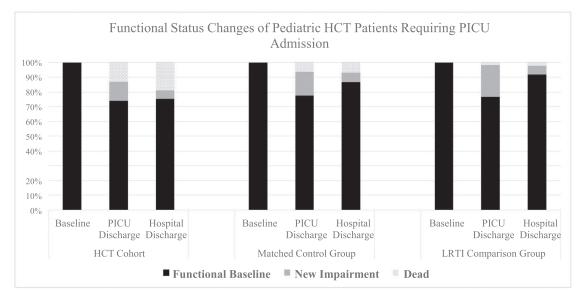At the time of hospital discharge the HCT cohort again had greater hospital mortality than both the matched control

Figure 2. Functional status changes of pediatric HCT patients requiring PICU admission. New impairment defined as increase in FSS score of at least 3 points relative to prehospital baseline.

subjects (18.8% [16/85] versus 6.8% [23/340], *P* < .001) and the LRTI comparison group (18.8% [16/85] versus 1.9% [6/308], *P* < .001; Figure 2). Among patients who survived to hospital discharge, HCT patients also had higher FSS scores at that time than did the matched control subjects (median 8 [IQR, 6 to 10] versus 6 [IQR, 6 to 7], *P* < .001) and the LRTI comparison group (median 8 [IQR, 6 to 10] versus 6 [IQR, 6 to 6], *P* < .001); they also had greater prevalence of moderate-to-severe functional impairment than did the matched control subjects (34.7% [24/69] versus 6.6% [21/317], *P* < .001) and the LRTI comparison group (34.7% [24/69] versus 6.0% [18/302], *P* < .001). Among patients who survived to PICU discharge, HCT patients had similar rates of *new* morbidity at hospital discharge when compared with matched control subjects (7.2% [5/69] versus 6.9% [22/317], *P* = .928) and the LRTI comparison group (7.2% [5/69] versus 6.3% [19/302], *P* = .787). Among patients discharged from the PICU with *new* morbidity, pediatric HCT patients displayed similar rates of resolution of new morbidity at hospital discharge relative to matched control subjects (54.5% [6/11] versus 60.0% [33/55], *P* = .737) and the LRTI comparison group (54.5% [6/11] versus 71.6% [48/67], *P* = .299).

DISCUSSION

This study adds to a growing body of knowledge regarding functional outcomes of pediatric HCT patients who survive critical illness. First, we identified that the group of HCT patients discharged from the PICU with new functional morbidity is equally as large as the group of HCT patients who do not survive PICU admission. This finding suggests a clinically relevant outcome that has to date received little formal investigation and may be an appropriate target for interventional trials. Second, we identified that although HCT patients are more likely to die in the PICU, those who survive have similar rates of new morbidity at PICU discharge and similar rates of resolution of new morbidity at hospital discharge when compared with matched control subjects. This suggests that a subset of pediatric HCT survivors of critical illness may have reversible functional status decline at PICU discharge and might benefit from interventions to improve

functional status. Third, we identified a high-risk group of PICU survivors: HCT patients with new functional morbidity at PICU discharge appeared to have greater risk of hospital mortality than did HCT patients discharged from the PICU at their functional baseline.

Prevalence of New Functional Morbidity after PICU Discharge

This study identifies a large subgroup (12.9%) of pediatric HCT patients who survive critical illness but acquire new functional morbidity that is evident at the time of PICU discharge. This subgroup constitutes as many patients as those who die from critical illness, suggesting that the outcome of survival with new functional morbidity is not only clinically relevant but significantly prevalent. Previous studies assessing functional status at PICU discharge have been performed in non-HCT cohorts and identify functional impairment in up to 36% of children at the time of PICU discharge [8-14]. Our findings are novel, because assessment of functional status at PICU and hospital discharge in pediatric HCT patients has not been undertaken before. A growing number of studies report significant long-term morbidity in survivors of critical illnesses such as acute respiratory distress syndrome [21-24]. Although our study did not follow patients beyond hospital discharge, Duncan et al. [15] found that 1-year survival and organ function tests in pediatric HCT survivors of critical illness were similar to those of pediatric HCT patients who did not require intensive care. This suggests that for pediatric HCT survivors of critical illness, ongoing recovery from critical illness–related decline in functional status is indeed possible. Currently, the Center for International Blood and Marrow Transplant Research, the National Institutes of Health, the Pediatric Blood & Marrow Transplant Consortium, and the European Group for Blood and Marrow Transplantation have recommended following all pediatric HCT patients for long-term cardiopulmonary, renal, and multiorgan toxicity as well as for neurodevelopmental outcomes and health-related quality of life [25-27]. Based on the results of this study, we advocate for close long-term monitoring for functional deficits in

pediatric HCT survivors of critical illness who do not regain their baseline functional status.

Resolution of New Functional Morbidity Between PICU Discharge and Hospital Discharge

This study also suggests that although pediatric HCT patients who survive to PICU discharge have greater rates of moderate/severe impairment, they have similar rates of *new* functional impairment when compared with matched control subjects and a general group of nonchronically ill children with LRTI. Given the well-established higher risk of PICU mortality among pediatric HCT patients, one might expect that pediatric HCT patients would have a higher risk of new morbidity and perhaps lower rates of resolution of new morbidity. Although survival without new morbidity, survival with new morbidity, and nonsurvival are a single continuum of outcomes, the ability to avert escalation along this continuum likely varies among different patient groups. We therefore speculate that because of lower functional morbidity at baseline, the matched control subjects and LRTI comparison group may have been better able to survive critical illness, resulting in discharge with new morbidity, whereas pediatric HCT patients may have been less able to survive critical illness, limiting the number of survivors with new functional morbidity in favor of more nonsurvivors.

Interestingly, although matched on PRISM score, the HCT group had greater usage of vasoactive infusions than did the matched control subjects. This may suggest that pediatric HCT patients have different underlying pathobiology of critical illness, they may have more rapid and severe progression of critical illness beyond the 4-hour PRISM observation window, or different physician management strategies with respect to treating multiorgan failure in critically ill pediatric HCT patients versus matched control subjects. However, the 12.9% mortality of pediatric HCT PICU patients in our study is comparable with other large studies and is consistent with an international trend toward decreasing PICU mortality of pediatric HCT patients over time [1,3,19,28]. The reasons for decreasing PICU mortality in this population may include improvements in transplant conditioning regimens, infection surveillance, and treatment of post-transplant complications as well as a bias toward more frequent admissions with lower illness severity; nonetheless, as the number of pediatric HCT survivors of critical illness grows, the need to follow survivors for short- and long-term morbidity will become increasingly important [29-33].

In addition to having similar rates of new functional impairment at PICU discharge, pediatric HCT patients discharged from the PICU with new functional impairment were as likely to be discharged from the hospital with resolution of the new functional impairment as were the matched control subjects and the LRTI comparison group. This suggests that a portion of pediatric HCT survivors of critical illness have the potential to make significant functional recovery after critical illness; hence, the full spectrum of rehabilitative services, including physical, occupational, and speech therapy where appropriate, should be considered to maximize chances of functional recovery [34,35].

Patients at High Risk for Future Death or Disability

This study identifies a particularly high-risk subgroup of pediatric HCT survivors of critical illness that merit close attention for persistent or progressive comorbidities. The long-term clinical outcomes of pediatric HCT patients who survive critical illness but develop new functional morbidity remain

unknown, particularly with respect to survivors of mechanical ventilation. With our cohort of 85 pediatric HCT patients, we demonstrated a nonsignificant trend toward worsened hospital survival rates among pediatric HCT patients discharged from the PICU with versus without new functional morbidity (18.2% [2/11] versus 4.8% [3/63], $P = .157$). Post hoc sample size calculations indicate that a sample size of 325 HCT patients requiring PICU admission is necessary to demonstrate statistical significance for this difference in hospital mortality between those who survive PICU admission with versus without new functional morbidity (chi-square test, $\alpha = .05$, $\beta = .2$). Therefore, we advocate for continued assessment of functional status in pediatric HCT patients who survive critical illness. Future interventions aimed at early and aggressive medical and rehabilitative intervention where appropriate may be particularly impactful in reducing subsequent morbidity and mortality in this high-risk cohort of PICU survivors.

Study Strength and Weakness

Our study has several strengths. First, the proportion of HCT patients in this PICU cohort (.8%, 85/10,014) is consistent with the proportion of HCT patients in our previous study of greater than 100 PICU admissions in the Virtual Pediatric Systems database (.6%, 1,102/192,956) [1]. This suggests external validity of this dataset with respect to the larger Virtual Pediatric Systems dataset, which does not document functional status scores. Second, this study benefits from rigorous application of the FSS by trained assessors with checks of inter-rater reliability. Third, our study assesses functional status at precritical illness baseline, at PICU discharge, and at hospital discharge, allowing longitudinal characterization of functional status changes throughout the course of critical illness and in-hospital recovery.

Our study has several weaknesses. First, because of the complexity of multiple diagnostic codes in a retrospective analysis, we were unable to assign each patient a primary reason for PICU admission. Second, our study lacked granular data on HCT characteristics commonly associated with adverse clinical outcomes, such as underlying disease, donor type and HLA match, conditioning regimen, and post-transplant toxicities including graft-versus-host disease. Importantly, PRISM score alone may not be adequately suitable to approximate illness severity in pediatric HCT patients; incorporation of transplant-specific risk-factors such as those described above may allow more precise prognostication of mortality risk [36,37]. Third, our study included only the first PICU admission for each patient during the study interval and therefore does not directly address functional outcomes after iterative episodes of critical illness. Future studies that combine transplant- and critical care–specific data are needed to better delineate subgroups of pediatric HCT patients at high risk for both mortality and new or persistent functional morbidity after critical illness.

Conclusions

For pediatric HCT patients, PICU survival with new functional morbidity is as prevalent an outcome as PICU mortality. Relative to previously healthy age-, sex-, and PRISM-matched control subjects and previously healthy patients with LRTIs, pediatric HCT patients continue to have elevated rates of PICU mortality. However, pediatric HCT patients who survive PICU admission have similar rates of new and *recoverable* functional impairment and thus should receive aggressive rehabilitation services aimed at maximizing recovery. Future

interventions focused on improving functional status in pediatric HCT survivors of critical illness are warranted.

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