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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