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Critical complications in pediatric oncology and hematopoietic cell transplant, volume II

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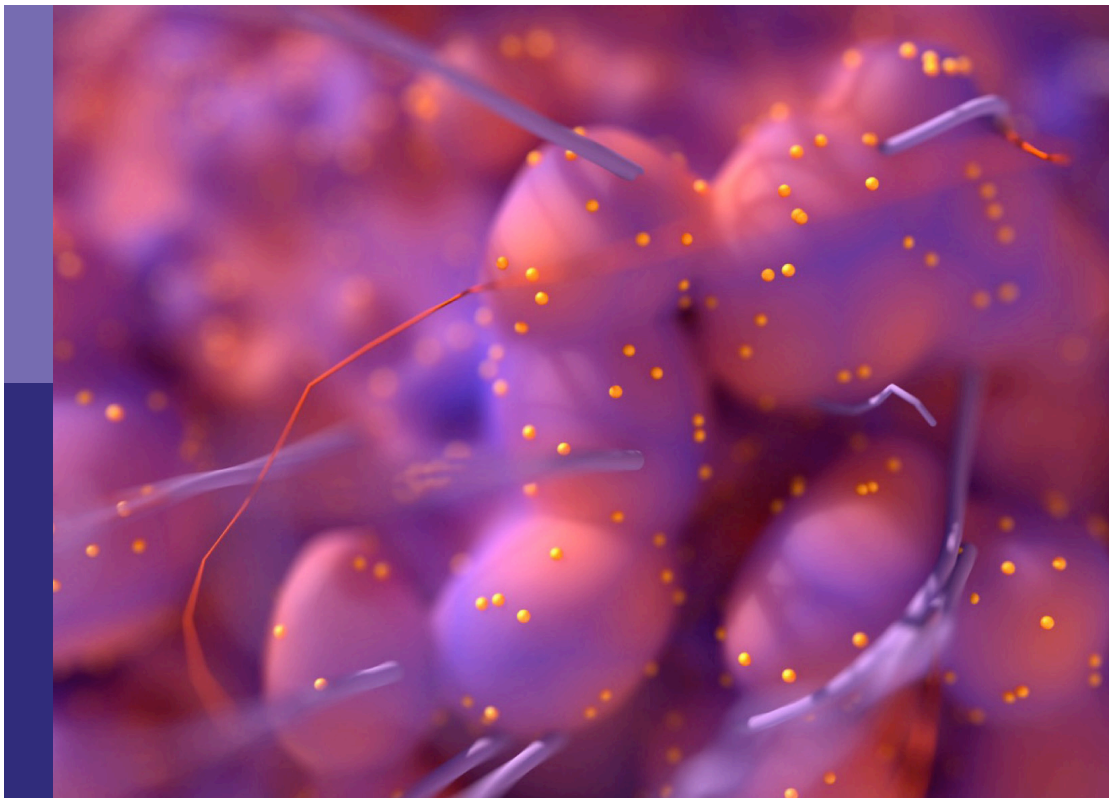

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Critical complications in pediatric oncology and hematopoietic cell transplant, volume II

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Editorial: Critical complications in pediatric oncology and hematopoietic cell transplant, volume II

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Editorial on the Research Topic
Critical complications in pediatric oncology and hematopoietic cell transplant, volume II

Summary of volume 1

In the early years, mortality rates for pediatric hematopoietic cell transplant (HCT) patients with critical illness were abysmal, exceeding 80%. This led to the general belief that providing critical care resources to this population was futile (1). Volume I of this Research Topic published 30 articles from 211 authors in 9 different countries (2). In this first volume, Pechlaner et al. reported a PICU mortality of 11% for pediatric hematology/oncology patients (3) – a significant improvement from the early years. This volume extensively discussed management of complications from HCT, cancer, and chimeric antigen receptor therapy (CAR-T) (4–6). Management of these complications involved utilization of critical care resources such as continuous renal replacement therapy (CRRT) (7), extracorporeal membrane oxygenation (ECMO) (8), and mechanical ventilation (9) – resources that would not have been considered for this population in the early years.

Improvement in outcomes may be partially explained by topics discussed in this first volume. These include 1) utilization of strategies to promote early recognition of clinical deterioration leading to earlier interventions and involvement of critical care teams (5, 9–13); 2) use of invasive diagnostic procedures such as bronchial alveolar lavage and lung biopsy which may lead to more accurate diagnoses and targeted therapies (14, 15); and 3) careful attention to detail such as prevention of the detrimental effects of fluid overload (16).

In the current Research Topic, Critical Complications in Pediatric Oncology and Hematopoietic Cell Transplant, Volume II, there is a continuation of the themes of improving outcomes and strengthening collaboration. This Research Topic contains 21 publications from 195 authors representing 22 different countries on 5 continents

(Figure 1). Volume II provides ongoing evidence that the field of pediatric onco-critical care is not going back to the era of the self-fulfilling prophecy that critically ill children with cancer have abysmal outcomes rendering use of critical care resources futile.

Predictive factors for critical care needs

Knowing which HCT patients are at highest risk for requiring ICU care would be very valuable for clinicians. Using data from pediatric oncology patients in the Colorado Sepsis and Treatment Registry, serum lactate within 2 hours of presentation was found to be predictive of clinical deterioration events (OR 1.82, p<0.001), need for ICU admission (OR 1.68, p<0.001) and bacteremia (OR 1.49, p<0.001) (Slatnick et al.). Johnson et al. performed a single center retrospective review of pediatric patients who received HCT at their institution between January 2015-December 2020. Risk factors for PICU admission were: 1) younger age; 2) lower weight; 3) inborn error of metabolism as a reason for HCT and 4) use of busulfan conditioning. There was overlap in these results with those found by Zinter et al. in a multi-center study merging the Center for International Bone Marrow Transplantation (CIBMTR) and Virtual PICU Performance System (VPS) databases. They also found younger age and inborn errors of metabolism as risk factors for requiring ICU care (17). However, there was disagreement where Zinter found pre-HCT organ dysfunction was associated with increased requirement for ICU admission, whereas Johnson did not. This may represent an improvement over time in managing complex patients during HCT versus differences in study design. A better understand organ dysfunction in these unique patients is imperative for continued improvements in outcomes.

PICU resource utilizations and outcomes

Accurate data surrounding the risks and benefits of ICU therapies will lead to better informed decisions regarding PICU interventions. In a retrospective single center study, Schober et al. found that admissions for respiratory support (OR 1.04, p=0.04) and dialysis (OR 1.21, p=0.03) increased 6-month mortality compared to other reasons for PICU admission. In a multi-variate analysis of pediatric oncology patients, hemato-oncology diagnosis, number of failing organs at baseline and unplanned admissions were associated with development of new or progressive multi-organ failure (Soeteman et al.). Data from the Health Facts (Cerner Corporation, Kansas City, MO) database containing 473 pediatric HCT patients found 11% required positive pressure ventilation, 25% received vasopressor medications and 3% received dialysis. Decreased survival was seen in allogeneic transplant (p<0.01), graft versus host disease (p=0.02), infection (p<0.01) and need for ICU therapies (p<0.01) (Olson et al.). Interestingly, survival improved over time for patients who received allogeneic transplants. The improved survival in the later era of the study was associated with decreased infections and increased use of vasopressor agents. The improvement in survival could represent a change in practice due to recent publications addressing the detrimental effects of fluid overload in HCT patients (16, 18) with a shift towards earlier use of vasopressors rather than fluid resuscitation.

Chimeric antigen receptor therapy, CAR-T, is being used in a growing number of cancers. However, it carries an increased risk for life threatening complications and critical illness. In a multi-center study, Ragoonanan et al. compared PICU courses for pediatric ALL patients who were receiving conventional therapy vs those who received tisagenlecleucel. They found PICU resource utilization between the 2 groups to be similar. The authors concluded that improved management of complications and need for ICU care should decline over time making CAR-T an important therapy to pursue, potentially beyond high resource settings.

Cardenas-Aguirre et al. show us that critically ill pediatric oncology patients in resource limited-settings can have PICU outcomes similar to those seen in high income countries. In their dedicated pediatric oncology hospital in Mexico, they describe overall PICU mortality of 6.9% with mortality for unplanned PICU admissions of 9.1%. This is similar to that described in high income countries (19, 20) The authors felt their center's low mortality was likely the result of implementing a number of quality improvement practices aimed at earlier recognition of deterioration allowing for earlier interventions.

Complications of HCT and oncology therapy

Endotheliopathy has been considered an underlying cause of multiple complications of HCT including sinusoidal obstructive disorder (SOS), transplant associated – thrombotic microangiopathy (TA-TMA), diffuse alveolar hemorrhage (DAH), pulmonary hypertension and graft-versus-host disease (GVHD). In a review article, Pace et al. explore the interaction between host and donor endothelial cells in hematopoietic cell transplantation as well as solid organ transplant. Kafa et al. described their single center experience with TA-TMA. Factors associated with developing TA-TMA were allogeneic transplant and use of total body irradiation as part of the conditioning regimen. Despite a good response to therapy, their patients experienced several complications with the most frequent being renal impairment and chronic kidney disease in 80%.

This Research Topic also addresses strategies for improving management of respiratory failure, a deadly complication. Pediatric HCT patients have been shown to have a high rate of peri-intubation cardiac arrest (9) which may represent a delay in intubation timing. Hume et al. undertook a survey of PICU and HCT providers to understand beliefs around timing of intubation. Clinicians agreed that a patient's poor prognosis may delayed their decision to intubate. However, their decision was not influenced by increased risk for lung injury from prolonged non-invasive intubation and/or oxygen, factors likely to be important (21–23).

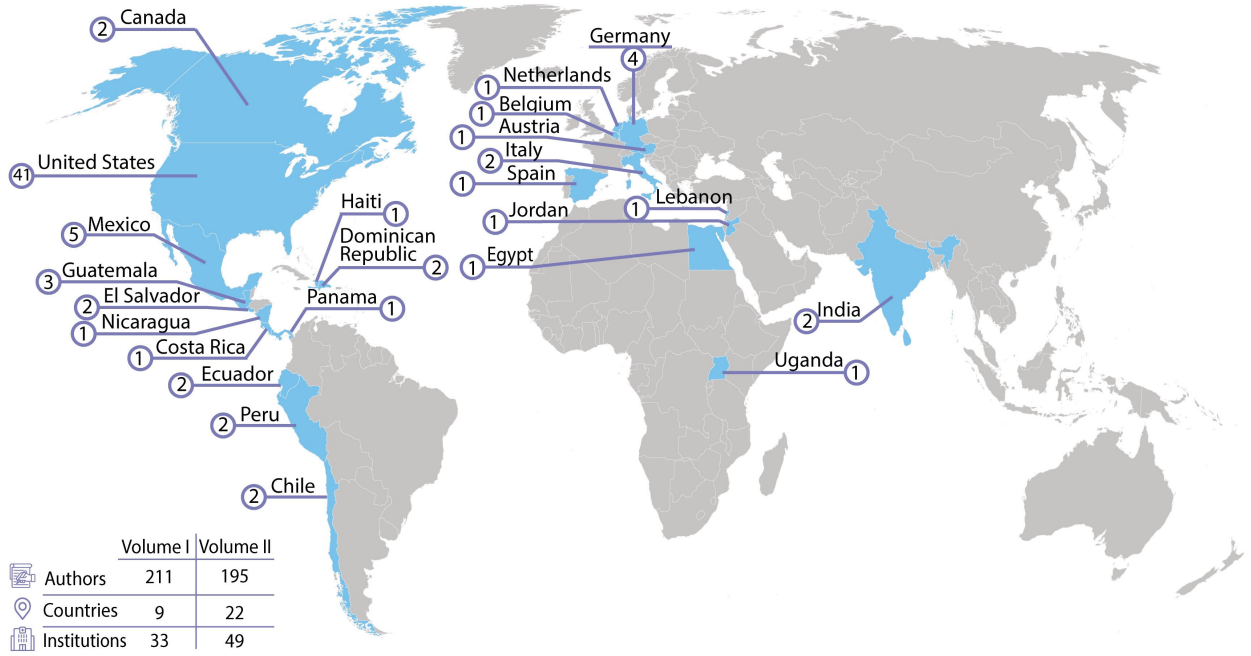

FIGURE 1
Evidence for growing international interest in the field of pediatric onco-critical care.

DAH after HCT has historically had high mortality rates (24–27). Our Research Topic has two retrospective chart review studies discussing novel therapies in DAH. In a multi-center study, there was an increased risk of non-relapse mortality with use of steroids (p=0.03), once considered standard therapy for DAH, and a survival advantage with use of inhalation of tranexamic acid (p=0.04) or recombinant activated factor VII (p=0.005) (Schoettler et al.). A single center study confirmed the safety of inhaled recombinant activated Factor VII for management of DAH in these patients (Hurley et al.).

Pulmonary hypertension (PH) is yet another complication of cancer treatment and HCT thought to be related to endothelial injury. An analysis of merged Center for International Blood and Marrow Transplant Research (CIBMTR) and the Virtual Pediatric System (VPS) databases showed a PH prevalence of 2.7% in pediatric HCT patients requiring ICU care. Of patients with PH admitted to the PICU, 72.4% required invasive mechanical ventilation and 27.6% renal replacement therapies. Survival 6 months after PH diagnosis was 51.7%, making this a very deadly disease lacking effective therapy (Smith et al.).

Renal failure as a complication of HCT is common and known to be a strong predictor of mortality (28, 29). Vuong et al. reviewed the available published data on acute kidney injury and chronic kidney disease in patients post-HCT. This review points out the importance of early identification of renal dysfunction enabling timely interventions to decrease risk of progression to end stage renal disease. Anderson et al. performed a single center retrospective chart review study of 222 pediatric oncology patients admitted for tumor lysis syndrome. They discovered 9% of patients with tumor lysis syndrome required renal replacement therapy (RRT), most commonly for metabolic abnormalities. All patients with tumor lysis syndrome survived to hospital discharge and none required chronic renal support. The experience for RRT in patients with tumor lysis differs significantly from the experience in patients post-HCT.

Cytomegalovirus (CMV) is one of the most concerning infections for patients post-transplant. Many patients go into their transplant course with latent infections which may reactivate during periods of immunosuppression. Hiskey et al. provide us with an excellent review of strategies for prevention, early detection, and intervention to mitigate the impact of CMV in these patients.

Multidisciplinary care and communication

In Volume I, Agulnik et al. demonstrated that implementation of a bedside pediatric early warning system (PEWS) led to earlier recognition of critical illness and prompt interventions (12). In Volume II, Abutineh et al. describe the implementation of PEWS at 23 pediatric cancer centers across Latin America. The authors found that resources were important in enabling the adaptation and implementation of PEWS in these settings. Prior experience of the hospital or its leaders with quality improvement (QI), however, was helpful for overcoming the inevitable challenges involved in implementing PEWS. In the absence of prior QI experience, QI training was also helpful. Mirochnik et al. analyzed 71 structured interviews with clinical staff in 5 resource limited pediatric oncology centers in Latin America. Interviewed clinicians described PEWS as making them feel more knowledgeable, confident, and empowered in their patient care duties leading to improved job satisfaction and patient outcomes.

Rivera et al. described the development of a first-in-kind tool to measure the quality of multi-disciplinary and interprofessional communication around clinical deterioration in children with cancer. Their tool, CritCom, was developed through literature review and use of a multidisciplinary panel of experts. A later publication from Counts et al. discussed the process involved in refining the CritCom reports given to centers to communicate CritCom findings and allow their use for local QI. This process can be utilized by other groups wanting to improve communication of research/QI findings to stakeholders.

Cuviello et al. discuss the importance of interdisciplinary communication during end-of-life care. They performed a retrospective chart review study involving 43 pediatric oncology patients receiving end-of-life care in the PICU. They found 18.6% of patients did not have palliative care involvement until the day of death and that almost half of patients were receiving cancer directed therapy in their last week of life. Their findings suggest room for improvement through earlier collaboration between the palliative care, oncology, and ICU teams.

Future of onco-critical care

Critical care resources for critically ill pediatric oncology, and HCT patients in high resource settings is clearly no longer futile. Patients are now routinely offered aggressive supportive care measures with improving survival and reduced morbidity. We are not going back to the days of the self-fulfilling prophecy that these patients have poor outcomes making PICU care futile. We look to the future as we progress towards improving outcomes globally, especially in limited resource settings where 90% of children with cancer reside.

Some of the most promising strategies to improve outcomes are aimed at early recognition of clinical deterioration enabling earlier interventions. These strategies can be implemented successfully in lower-resource settings as has been discussed in both volumes of this Research Topic. An additional advantage of implementing these systems is that they can improve multi-disciplinary and multiprofessional communication leading to improved job satisfaction and better patient care.

Improved understanding of the pathophysiologic mechanisms behind complications of HCT and cancer therapies will lead us toward more specific and effective novel therapies. We are just beginning to understand all the functions of the endothelium and what can go wrong when it is damaged. Next generation cancer therapies will include expansion of the scope of CAR-T and other targeted therapies. These therapies aim to harness the patient's immune system to attack the cancer but incur risk of life-threatening complications. In the future, we expect improved therapies specifically targeting side effects while maintaining anti-cancer activity. The future of the field of onco-critical care is bright as we collaborate globally to achieve better outcomes for critically ill children with cancer worldwide.

Author contributions

JM: Writing – original draft, Writing – review & editing. KM: Writing – original draft, Writing – review & editing. AA: Writing – original draft, Writing – review & editing. MS: Writing – original draft, Writing – review & editing.

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Conflict of interest

KM has served as a consultant for Vertex and Pierre Fabre. He has received investigator funding from Sobi, Jazz, Syndax, Adaptimmune. AA is supported by the NCI R37CA276215-01 and 1R01CA287374 MS holds an hemostasis education contract with Medtronic, receives NHLBI support as DSMB chair for the PumpKIN trial Infant Jarvik Phase 3 trial and has Department of Defense grant support for a cold stored platelet transfusion trial.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Serum lactate is associated with increased illness severity in immunocompromised pediatric hematology oncology patients presenting to the emergency department with fever

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Introduction: Determining which febrile pediatric hematology/oncology (PHO) patients will decompensate from severe infection is a significant challenge. Serum lactate is a well-established marker of illness severity in general adult and pediatric populations, however its utility in PHO patients is unclear given that chemotherapy, organ dysfunction, and cancer itself can alter lactate metabolism. In this retrospective analysis, we studied the association of initial serum lactate in febrile immunosuppressed PHO patients with illness severity, defined by the incidence of clinical deterioration events (CDE) and invasive bacterial infection (IBI) within 48 hours.

Methods: Receiver operating characteristic (ROC) curves were reported using initial lactate within two hours of arrival as the sole predictor for CDE and IBI within 48 hours. Using a generalized estimating equations (GEE) approach, the association of lactate with CDE and IBI within 48 hours was tested in univariate and multivariable analyses including covariates based on Quasi-likelihood under Independence Model Criterion (QIC). Additionally, the association of lactate with secondary outcomes (i.e., hospital length of stay (LOS), intensive care unit (PICU) admission, PICU LOS, non-invasive infection) was assessed.

Results: Among 897 encounters, 48 encounters had ≥1 CDE (5%), and 96 had ≥1 IBI (11%) within 48 hours. Elevated lactate was associated with increased CDE in univariate (OR 1.77, 95%CI: 1.48-2.12, p<0.001) and multivariable (OR 1.82, 95%CI: 1.43-2.32, p<0.001) analyses, longer hospitalization (OR 1.15, 95% CI: 1.07-1.24, p<0.001), increased PICU admission (OR 1.68, 95%CI: 1.41-2.0,

p<0.001), and longer PICU LOS (OR 1.21, 95%CI: 1.04-1.4, p=0.01). Elevated lactate was associated with increased IBI in univariate (OR 1.40, 95%CI: 1.16-1.69, p<0.001) and multivariable (OR 1.49, 95%CI: 1.23-1.79, p<0.001) analyses. Lactate level was not significantly associated with increased odds of non-invasive infection (p=0.09). The QIC of the model was superior with lactate included for both CDE (305 vs. 325) and IBI (563 vs. 579).

Conclusions: These data demonstrated an independent association of elevated initial lactate level and increased illness severity in febrile PHO patients, suggesting that serum lactate could be incorporated into future risk stratification strategies for this population.

KEYWORDS

lactate, pediatric oncology, sepsis, serious bacterial infection, immunocompromised, chemotherapy-related immunosuppression, clinical deterioration

Introduction

Infectious complications in the setting of therapy-related immunosuppression are a significant cause of morbidity and mortality in pediatric hematology/oncology (PHO) patients. Due to the risk of rapid clinical deterioration from bacterial infection in this population (1–3), patients with fever who are categorized as high risk due to neutropenia (absolute neutrophil count <500 cells/mm^3, or <0.5 x10^3/μL) are often started on empiric broad spectrum intravenous (IV) antibiotics. Although the majority of these patients remain clinically well without an identifiable source of fever (4, 5), a subset of febrile PHO patients will decompensate despite empiric antimicrobial administration, with an associated mortality of 12-30% in those who progress to sepsis or septic shock (1, 6, 7). Timely recognition and treatment of septic shock is associated with reduced mortality and organ dysfunction. Thus, tools that enhance early detection of patients at greatest risk for progression to septic shock has potential to improve patient outcomes (8, 9). The ability to distinguish which patients will clinically deteriorate due to sepsis is challenging given the lack of effective reliable tools to risk stratify febrile PHO patients.

There remains a critical need in this population to optimize strategies that improve the ability to recognize which febrile patients require immediate intervention and identify patients whose antimicrobial therapy can be safely withheld or de-escalated. The PHO patient population presents unique challenges when it comes to the development of risk stratification tools as patients often lack the clinical signs and symptoms of severe infection at initial fever presentation due to an insufficient immune response (10–12). Furthermore, laboratory markers that are useful in distinguishing septic from non-septic patients in general pediatric and adult populations have questionable reliability in PHO patients who have altered baseline metabolism, immune capabilities, and organ function (13–17). For instance, previous studies evaluating the utility of c-reactive protein (CRP), procalcitonin (PCT), and inflammatory cytokines in this population have yielded conflicting results, thus no reliable biomarker has been established (11, 18–23).

The absolute neutrophil count (ANC) at the time of febrile presentation is a widely incorporated prognostic laboratory value used in PHO patients, typically characterized by the presence or absence of neutropenia, which is often incorporated into institutional clinical management guidelines in terms of antimicrobial administration and need for inpatient hospital admission. Although the risk of invasive infection is higher in this group compared to the general pediatric population (24–26), it is difficult to identify exactly which febrile patients with neutropenia have an active infection and which patients will go on to clinically deteriorate. Furthermore, severe infection can still develop in patients with adequate neutrophil counts, and the widespread incorporation of immune stimulating drugs into cancer therapy regimens may cloud the reliability of ANC as a prognostic indicator of poor infectious outcomes.

Lactate, a byproduct of tissue hypoperfusion, is one of the most extensively studied biomarkers for sepsis in adult and pediatric patients (27–32), and elevated serum lactate levels are associated with poor outcomes even in the setting of maintained oxygenation and arterial blood pressure (33, 34). It is well-established that patients with malignancy have altered lactate metabolism, as evidenced by presence of lactic acidosis in patients with malignancy in the absence of infection (35–37), and

chemotherapy-related fluctuations in levels of serum lactate and lactate dehydrogenase (LDH), an enzyme which catalyzes the interconversion of pyruvate and lactate (38–40). Furthermore, many chemotherapeutic agents and immunosuppressive therapies can affect liver and kidney function, which play an essential role in lactate clearance (41, 42). Although studies in broad pediatric populations which include patients with chronic comorbidities have demonstrated an association of increased lactate with organ dysfunction, pediatric intensive care unit (PICU) admission, bacterial infection, and mortality (34, 43–45), there is a paucity of data regarding the discriminatory value of serum lactate in PHO patients explicitly.

A systematic review of 37 studies evaluating 24 different biomarkers in pediatric patients with fever and neutropenia by Haeusler et al. reported extensive evaluation of CRP (n=17 studies), PCT (n=9 studies), and several cytokines, most commonly IL-6 and IL-8 (46). Conversely, the literature regarding serum lactate in PHO patients is limited to a study performed by Pacheco-Rosas et al. at the Hospital de Pediatría del CMN Siglo XXI, which demonstrated an association (81% sensitivity, 83% specificity) between serum lactate level ≥2 mmol/L obtained within 48 hours of admission and severe sepsis in 100 pediatric oncology patients with fever and neutropenia (47), and a study performed in Thailand by Suwanpakdee et al. which reported an association between initial serum lactate >2.5 mmol/L with septic shock in 100 hemodynamically stable pediatric oncology patients with fever and neutropenia (ROC area 0.90, 95% CI: 0.81, 0.98) (48). Both studies suggest that there is a role for measuring serum lactate in this patient population, however generalizability is limited by small sample size, exclusion of non-neutropenic patients, and variable time allotted for initial serum lactate collection.

Identification of patients at high risk of sepsis or septic shock prior to progression of their symptoms is essential for early diagnosis and prompt resuscitation, the most efficacious strategy for preventing clinical decompensation, organ failure, and/or death (8, 9, 49–53). The objective of this study is to better understand the implications of lactate levels in febrile PHO patients by determining the association between initial venous lactate level and poor clinical outcomes, including clinical deterioration events (CDE) and invasive bacterial infection (IBI).

Methods

Data source

This single-center, observational study utilized the Colorado Sepsis Treatment and Recognition Registry, a database approved by the Children's Hospital Colorado (CHCO) Organization Research Risk and Quality Improvement Review Panel and the Colorado Multiple Institution Review Board, which contains retrospectively collected data extracted from the electronic medical record (EMR) from pediatric Emergency Department (ED) encounters with ED clinician concern for possible sepsis as described by Scott et al (43). The registry includes ED encounter data for pediatric patients who are identified as high risk for sepsis, including patients with underlying oncologic or hematologic disorders who presented with fever or concern for infection. Relevant data that was not included in the registry was extracted from the EMR.

Encounters among immunocompromised PHO patients 0-25 years of age who underwent evaluation for fever in the CHCO ED between May 2012 and February 2019 were eligible for inclusion. This institution defines fever as a single temperature ≥101°F or two temperatures ≥100°F within a 24-hour period separated by at least two hours. PHO patients were considered immunocompromised if they were being treated with chemotherapy or were within six months of therapy completion, had a hematologic disorder requiring immunosuppressive therapy, or underwent hematopoietic stem cell transplantation (HSCT) within the previous six months. Encounters during which the patient was diagnosed with a new oncologic process were also included. Encounters were excluded if the patient had a known metabolic disorder, was transferred from an outside medical facility, arrived *via* emergency medical services (EMS) transport, or if a venous lactate level was not assessed within two hours of ED arrival. Multiple encounters per patient could be included, however encounters were excluded if the patient had been evaluated for fever/infection within the previous 72 hours.

Encounters among patients who were critically ill appearing upon ED presentation were considered separately, characterized by one or more of the following criteria: systolic hypotension <5th percentile for age (54) on intake vital sign assessment, occurrence of at least one (≥1) CDE qualifying event (defined below) or PICU transfer within two hours of ED arrival, or provider documentation of critical appearance on initial assessment. Clinical data and outcomes for these encounters are briefly described in the results section, but were otherwise not incorporated into the analysis, as the goal of this study was to evaluate the association of lactate level with poor outcomes in patients whose illness severity was not immediately apparent upon initial presentation.

Variables and outcomes

We tested the association of initial venous lactate level (mmol/L) obtained within two hours of ED arrival (primary variable) and covariates with the occurrence of CDE, IBI, and secondary outcomes pertaining to illness severity. Per institutional standard practice, a serum lactate level is obtained in conjunction with a complete blood count and blood cultures from all PHO patients who present to the ED with fever. Covariates were selected *a priori* based on clinical relevance for PHO patients and other established sepsis risk factors, including patient characteristics (i.e., age, underlying diagnosis, chemotherapy regimen intensity, phase of therapy, central

venous access), encounter-specific variables assessed within two hours of ED arrival (i.e., WBC counts, presence of vital sign abnormalities), and patient- or provider-reported symptoms noted in the EMR (i.e., upper respiratory infection (URI) symptoms, chills and/or rigors). Vital sign cutoffs were determined using age-specific ranges defined by Goldstein, et al (54), and chemotherapy regimen intensity was categorized as least (level 1), moderate (level 2), very (level 3), or most (level 4) intensive based on the Intensity of Treatment Rating Scale (ITR-3.0) as previously defined (55). Maximum temperature (Tmax) was determined by the Tmax reported by the patient caregiver prior to arrival, or the Tmax documented within the first two hours of ED arrival, whichever value was higher.

The CDE outcome was met if the patient experienced ≥1 CDE within 48 hours of ED arrival. A CDE was characterized as a significant change in clinical status, as previously defined (56) by the following qualifying events: transfer from a pediatric ward to PICU, respiratory failure (initiation of non-invasive positive pressure ventilation (NIPPV) or endotracheal intubation), administration of ≥60 ml/kg (or ≥3 L if weight ≥50 kg) of crystalloid bolus intravenous fluids (IVF) in a 24-hour period, vasopressor or inotrope initiation, altered mental status, or death (56). Bolus IVF administration was based on provider discretion. In patients with chronic mechanical ventilatory needs, respiratory failure was defined as a need for increased ventilator settings above baseline.

A separate analysis was performed evaluating the occurrence of at least one (≥1) IBI within 48 hours of ED arrival. IBI was defined as the isolation of a bacterial organism from a normally sterile body fluid (i.e., blood, urine, cerebrospinal fluid, pleural fluid) (57), lobar pneumonia identified by chest radiograph (CXR) or computed tomography (CT) scan, intraabdominal infection, or skin/soft tissue infection (SSTI) necessitating IV antibiotics. Bacterial identification *via* blood culture was only included as an IBI if the result was not considered to be a contaminant (58) and resulted in a full antimicrobial treatment course for bacteremia.

Secondary outcomes included: hospital length of stay (LOS), PICU admission, PICU LOS, non-invasive infection within 48 hours, and 30-day mortality. Given that the clinical implications of an IBI exceed those of a non-invasive infection, analysis of non-invasive infection as a secondary outcome did not include encounters among patients who were diagnosed with an IBI within 48 hours. Thirty-day mortality was included as a descriptive outcome only due to the low incidence in the cohort.

Statistical analysis

Analysis was performed using R version 4.0.2 and the significance level was set to 0.05. Variables were summarized using median (interquartile range, IQR) or frequency (percentage) for each encounter. Receiver operating characteristic (ROC) curves were reported for each outcome (CDE and IBI) with with lactate level as the sole predictor as the sole predictor. PHO patients with multiple fever encounters have the possibility of introducing correlation with their specific patient characteristics, therefore generalized estimating equations (GEE) with a logit link were used to model risk factors for CDE and IBI within 48 hours using an exchangeable correlation structure to account for correlation among patients with multiple encounters. Univariate models were fit for each risk factor of interest with lactate level included both as a continuous and categorical variable, utilizing the frequently reported cut offs in the literature of 0-2 mmol/L, 2-4 mmol/L, and ≥4 mmol/L (29, 34, 43, 59–64). Variables in the univariate model were considered for selection in a multivariable model for each outcome based on significance and clinical relevance. Lactate level (continuous) was forced in, and the final set of predictors was selected based on the lowest Quasi-likelihood under Independence Model Criterion (QIC), a metric that assesses the degree to which data fits the GEE model and can be used for covariate selection (65). The QIC for the final multivariable models with and without lactate were established. Lower QIC values indicate better model fit, and a difference of 2-4 units is considered meaningfully different.

Lactate was tested for association with secondary outcomes. GEE was used to model PICU admission and non-invasive infection (binomial) and hospital LOS, PICU LOS, and vasopressor duration (gaussian). Continuous outcomes were log transformed before modeling due to non-normality, and results were back-transformed for reporting. The R package gee was used for modeling and reproducible code can be found here: https://github.com/campbkri/lactate_paper.

Results

Patient characteristics

As outlined in the study flowchart in Figure 1, there were 1290 total eligible encounters, among which 372 were excluded. In an additional 21 encounters, the patient appeared critically ill at presentation; clinical data and outcomes for these 21 encounters are described separately below, but were otherwise excluded from the remainder of these analyses. Encounter data and relevant initial lab values for the remaining 897 encounters included in the analysis are listed in Table 1, including those with occurrence of one or more (≥1) CDE within 48 hours (n=48 encounters among 45 patients), and one or more (≥1) IBI within 48 hours (n=96 encounters among 85 patients).

The median age for the overall cohort was 6.5 years (IQR: 3.8-11.7). Leukemia/lymphoma accounted for over half of underlying patient diagnoses (55%), followed by solid tumors (31%), CNS tumors (13%), and non-malignant hematologic disorders (0.6%). Similar proportions of each underlying patient diagnosis were noted among encounters that met the CDE and IBI outcomes. Almost every encounter (n=885, 99%)

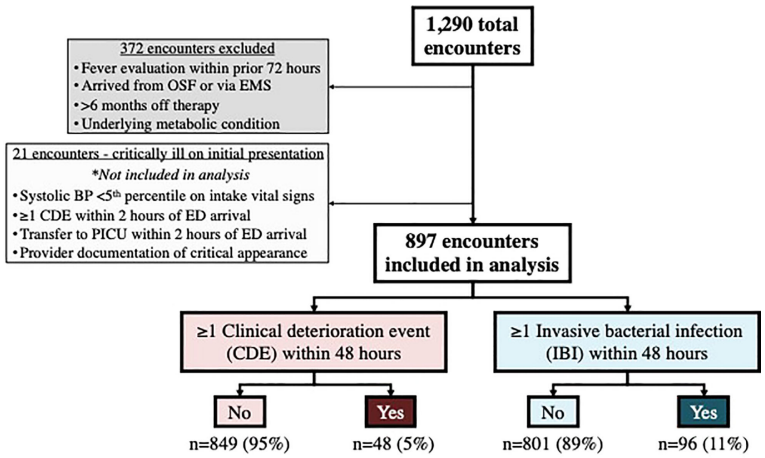

FIGURE 1
Study flowchart. OSF, Outside facility; EMS, Emergency medical services; BP, Blood pressure; CDE, Clinical deterioration event; ED, Emergency department; PICU, Pediatric intensive care unit; IBI, Invasive bacterial infection.

occurred among patients who were actively undergoing therapy, including those who had undergone HSCT (n=52) within the past six months. A small subset of patients had recently completed therapy (n=7), or were newly diagnosed with a malignancy while admitted to the ED (n=5). Chemotherapy regimen intensity varied among the cohort and regimens received characterized as very (level 3) intensive were seen most frequently (n=529, 59%). Implanted ports were the most common type of central venous access, whereas external tunneled catheters, peripherally inserted central catheter (PICC) lines, and peripheral IV's were less common. The median initial lactate level was 1.4 mmol/L (IQR 1.0-2.0) among the overall cohort, 2.0 mmol/L (IQR 1.4-3.0) among those who had ≥1 CDE, and 1.7 mol/L (IQR 1.2-2.3) among those diagnosed with ≥1 IBI. White blood cell (WBC) counts were assessed within two hours for nearly all encounters (the absolute monocyte count was not reported for one encounter) and nearly half of the febrile encounters occurred in neutropenic patients (n=414, 46%). Unlike WBC counts and venous lactate, c-reactive protein (CRP) and procalcitonin (PCT) were infrequently obtained within two hours (CRP: 3%, PCT: 1%).

Association of lactate level with clinical deterioration events within 48 hours

At least one (≥1) CDE occurred within 48 hours in 48 of the 897 included encounters (5%). In 22 of these, one isolated CDE qualifying event occurred, whereas multiple CDE qualifying events occurred in the remaining 26, together accounting for 83 total individual CDE qualifying events among the entire cohort, shown in Figure 2. The most common categories of CDE qualifying events were bolus IVF administration (n=39, 47% of all CDEs) and initiation of vasopressors (n=20, 24% of all CDEs), whereas ward to PICU transfer (n=9, 11% of all CDEs), respiratory failure (n=8, 10% of all CDEs), altered mental status (n=6, 7% of all CDEs), and death (n=1, 1% of all CDEs) occurred less frequently.

Comparing the distribution of initial lactate levels and CDE occurrence revealed an increased proportion of patient encounters with ≥1 CDE with incremental increases in initial lactate level (Figure 3A). At least one CDE was seen in four of 204 encounters (2%) with lactate <1.0 mmol/L, 16 of 459 encounters (4%) with lactate 1-1.99 mmol/L, 15 of 153 encounters (10%) with lactate 2-2.99 mmol/L, 6 of 49 encounters (12%) with lactate 3-3.99 mmol/L, 4 of 20 encounters (20%) with lactate 4-4.99 mmol/L, and 3 of 12 encounters (25%) with lactate ≥5 mmol/L. The ROC curve (AUC 0.704) shown in Figure 3B demonstrates the sensitivity and specificity of individual lactate level cutoffs for predicting the occurrence of ≥1 CDE within 48 hours.

Univariate analysis results, occurrence of ≥1 CDE by risk factor

Results of the univariate analysis testing the association of lactate level and covariates with the occurrence of ≥1 CDE within 48 hours are shown in Supplemental Table 1. The odds of clinical deterioration increased by 77% with each unit increase in lactate level ($p<0.001$). Evaluation of lactate level using previously reported

TABLE 1 Patient encounter characteristics and initial laboratory values.

Characteristic	All encounters (n=897) n (%)	CDE within 48 hours (n=48) n (%)	IBI within 48 hours (n=96) n (%)
Number of unique patients	456	45	85
Age in years, *median (IQR)*	6.5 (3.8, 11.7)	12.4 (7.0, 15.7)	6.9 (3.1, 12.9)
Sex			
Female	366 (41%)	19 (40%)	45 (47%)
Male	531 (59%)	29 (60%)	51 (53%)
Underlying Diagnosis			
Acute lymphoblastic leukemia	421 (47%)	22 (46%)	43 (45%)
Acute myeloid leukemia	13 (1%)	1 (2%)	2 (2%)
Lymphoma	65 (7%)	4 (8%)	7 (7%)
Solid Tumor	277 (31%)	17 (35%)	30 (31%)
CNS Tumor	116 (13%)	4 (8%)	13 (14%)
*Other	5 (0.6%)	0 (0%)	1 (1%)
Phase of therapy			
†On therapy	885 (99%)	48 (100%)	98 (96%)
New diagnosis during ED encounter	5 (0.6%)	0 (0%)	0 (0%)
Off therapy within <6 months	7 (0.8%)	0 (0%)	4 (4%)
HSCT within past 6 months, *yes*	52 (6%)	3 (6%)	12 (12%)
Allogeneic	18 (2%)	0 (0%)	8 (8%)
Autologous	34 (4%)	3 (6%)	4 (4%)
††Chemotherapy intensity			
Most (level 4)	94 (11%)	9 (18%)	17 (18%)
Very (level 3)	529 (59%)	25 (52%)	56 (58%)
Least/moderate (levels 1&2)	267 (30%)	14 (29%)	22 (23%)
Unknown/other	7 (0.8%)	0 (0%)	1 (1%)
Venous catheter type			
Implanted port	769 (86%)	38 (79%)	67 (70%)
External tunneled catheter	102 (11%)	8 (17%)	24 (25%)
PICC line	10 (1%)	1 (2%)	4 (4%)
Peripheral IV	15 (2%)	1 (2%)	1 (1%)
¶Initial ED laboratory values			
Lactate in mmol/L, *median (IQR)*	1.4 (1.0, 2.0)	2.0 (1.4, 3.0)	1.7 (1.2, 2.3)
Lactate <2 mmol/L, *categorical* (n, %)	665 (74%)	21 (44%)	61 (64%)
Lactate 2-4 mmol/L, *categorical* (n, %)	200 (22%)	20 (42%)	35 (36%)
Lactate ≥4 mmol/L, *categorical* (n, %)	32 (4%)	7 (15%)	10 (10%)
Absolute monocyte count ($x10^3/\mu L$)	0.22 (0.03, 0.54)	0.06 (0.01, 0.30)	0.04 (0.01, 0.27)
Absolute lymphocyte count ($x10^3/\mu L$)	0.38 (0.16, 0.88)	0.27 (0.09, 0.75)	0.21 (0.08, 0.65)
Absolute neutrophil count ($x10^3/\mu L$)	0.76 (0.04, 3.57)	0.13 (0.01, 1.46)	0.06 (0.01, 2.48)
§Neutropenic, yes (n, %)	414 (46%)	29 (60%)	63 (66%)

CDE, Clinical deterioration event IBI, Invasive bacterial infection; IQR, Interquartile range; CNS, Central nervous system; PICC, Peripherally inserted central catheter; HSCT, Hematopoietic stem cell transplantation; ED, Emergency department.
*Other: Aplastic anemia (n=3), antiphospholipid syndrome (n=1), β-thalassemia (n=1).
†Includes patients receiving chemotherapy or within 6 months of HSCT.
††Based on Intensity of Treatment Rating criteria (Kazak, et al. Pediatric Blood & Cancer, 2012).
¶Initial values within two hours of ED arrival (lactate in mmol/L and white blood cell counts) are reported as median (IQR). Categorical lactate levels and presence of neutropenia are reported as n (%).
§Neutropenia defined as absolute neutrophil count <0.5 $x10^3/\mu L$.

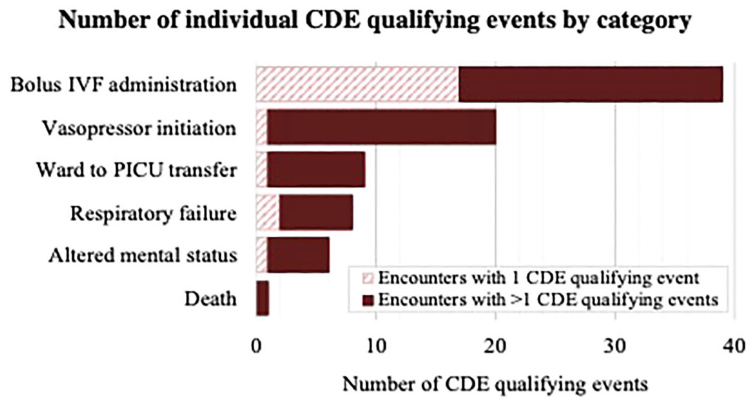

FIGURE 2
Diagram demonstrating number of CDE qualifying events per category (bolus IVF administration, vasopressor initiation, ward to PICU transfer, respiratory failure, altered mental status, death) among encounters with one CDE qualifying event and encounters with multiple CDE qualifying events. IVF, Intravenous fluid; PICU, Pediatric intensive care unit.

cutoffs revealed increased odds of ≥1 CDE with moderate lactate elevation 2-4 mmol/L (OR 3.74, 95%CI: 2.00-7.01, p<0.001), and even higher odds with lactate levels ≥4 mmol/L (OR 8.82, 95% CI: 3.51-22.20, p<0.001), when compared to those with lactate < 2 mmol/L. Older age (p<0.001), vital sign abnormalities including hypotension (p<0.001) and tachycardia (p<0.001) within the first two hours of ED arrival, chills or rigors (p<0.05), and neutropenia (p<0.05) were also associated with the occurrence of ≥1 CDE in the unadjusted analysis, whereas underlying diagnosis, chemotherapy regimen intensity, recent HSCT, type of venous access, Tmax, presence of tachypnea within two hours, and WBC counts were not.

Multivariable analysis results, occurrence of ≥1 CDE by risk factor

The optimal set of predictors for inclusion in the multivariable model based on QIC were lactate level (continuous), age,

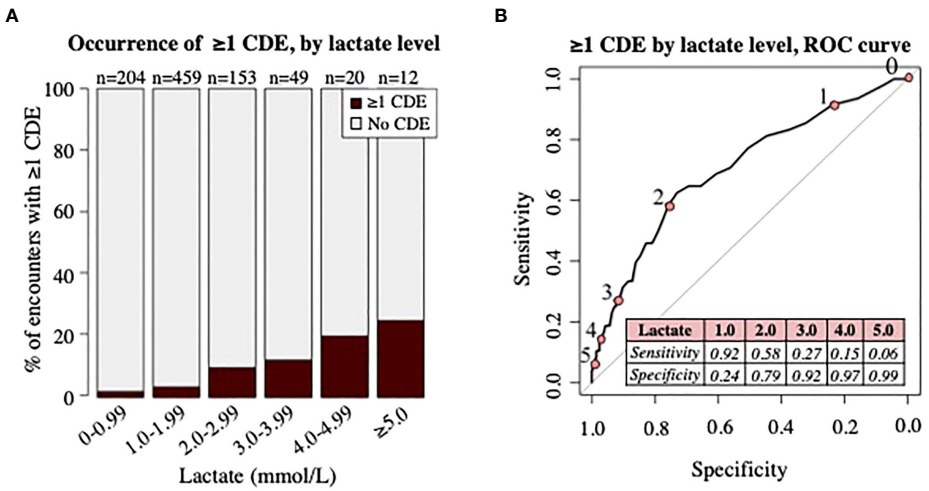

FIGURE 3
Analysis of clinical deterioration events (CDE) by lactate level. **(A)** Proportion of patient encounters with occurrence of ≥1 CDE by lactate level in increments of 1mmol/L. Numbers (n) on top of bars signify the total number of patient encounters with initial lactate level in specified range. **(B)** ROC curve demonstrating association of lactate level with occurrence of ≥1 CDE. Numbers 0-5 along ROC curve represent ROC curve points for lactate level cutoffs (pink circles) in mmol/L, shown in the table. Area under the curve = 0.704.

chemotherapy regimen intensity, and presence of hypotension and tachycardia within two hours. Given the clinical relevance of neutropenia at the time of fever in PHO patients, a sensitivity analysis was performed with neutropenia added into the same model, which showed a non-significant association of neutropenia with having ≥1 CDE (p=0.17) and a higher QIC, thus neutropenia was not forced into the model. The results of the multivariable analysis are shown in Table 2. After adjusting for age, chemotherapy regimen intensity, and the presence of hypotension and tachycardia within two hours of ED arrival, increased lactate level was significantly associated with occurrence of ≥1 CDE (OR 1.82, 95% CI: 1.43-2.32, p<0.001). After controlling for covariates, odds of ≥1 CDE were increased with older age (OR: 1.13, 95% CI: 1.07-1.19, p<0.001). Outcomes also differed significantly among chemotherapy regimen intensity groups (p<0.05). Presence of hypotension (OR: 3.78, 95% CI: 2.64-15.99, p<0.001) and tachycardia (OR: 3.78, 95% CI: 1.61-8.84, p<0.01) within two hours of ED arrival were also significant after adjusting for confounding variables. The QIC of the multivariable model without lactate level was 325, whereas the QIC of the model with lactate level included was 305. This difference in 20 points of QIC indicates a significantly better fit of the model when lactate was included.

Association of lactate level with incidence of invasive bacterial infection (IBI) within 48 hours

Within 48 hours of ED arrival, at least one (≥1) IBI was diagnosed in 96 of 897 encounters (11%), including 16 encounters in which the patient was diagnosed with a non-invasive infection in addition to IBI within 48 hours. Frequency of IBI by source of infection and corresponding median lactate levels are outlined in Supplemental Table 2. Bacterial bloodstream infection (BSI) was the most common source of IBI, seen in 58 encounters (6%). Other sources of IBI were less common, including pneumonia (n=18, 2%), genitourinary (GU, n=10, 1%), SSTI (n=10, 1%), and intraabdominal (n=6, 0.7%). Median initial lactate levels were similar across encounters with ≥1 IBI regardless of infection source with exception of a relatively higher median initial lactate (2.7 mmol/L, IQR 1.3-4.2) in those with intraabdominal infection, although this discrepancy may be due the infrequency of each IBI type rather than true variation.

The distribution of initial lactate levels with occurrence of ≥1 IBI demonstrated in Figure 4A revealed an increased proportion of patients diagnosed with ≥1 IBI within 48 hours as lactate level incrementally increased, although the most notable difference occurred once lactate levels reached 4 mmol/L and above. An ROC curve (AUC: 0.608) including the sensitivity and specificity of individual lactate level cutoffs for predicting the occurrence of ≥1 IBI within 48 hours is shown in Figure 4B.

Univariate analysis results, occurrence of ≥1 IBI by risk factor

Results of the univariate analysis demonstrating the association of lactate level and covariates with the occurrence of ≥1 IBI within 48 hours are shown in Supplemental Table 3. For each unit increase in lactate level, the odds of being diagnosed with ≥1 IBI within 48 hours increased by 40% (p<0.001). When compared to patients with lactate levels <2 mmol/l, categorical evaluation of lactate level demonstrated increased odds of ≥1 IBI with lactate level ≥4 mmol/L (OR: 4.34, 95% CI: 1.91-9.86, p<0.001), but no significant difference in patients with moderately elevated lactate 2-4 mmol/L (p=0.20). Compared to patients with implanted ports, those with external tunneled catheters (OR: 3.21, 95% CI: 1.83-5.65, p<0.001) and peripherally inserted central catheter (PICC) lines (OR: 7.00, 95% CI: 1.82-26.94, p<0.01) were associated with increased IBI.

TABLE 2 Occurrence of ≥1 clinical deterioration event (CDE) within 48 hours, adjusted odds by risk factor (results of multivariable analysis).

Risk Factor	Reference	Odds Ratio	95% CI	p value
Lactate (mmol/L), *continuous*	–	1.82	1.43, 2.32	<0.001
Age in years	–	1.13	1.07, 1.19	<0.001
†Chemotherapy intensity	Most (level 4)			0.03
Very (level 3)		0.30	0.11, 0.78	0.01
Least/moderate (levels 1&2)		0.56	0.21, 1.51	0.25
***ED clinical status**				
Hypotension	No	6.49	2.64, 15.99	<0.001
Tachycardia	No	3.78	1.61, 8.84	<0.01

QIC of model *without* lactate: 325, QIC *with* lactate: 305

QIC, Quasilikelihood under the Independence model Criterion; ED, Emergency department.
*Based on Intensity of Treatment Rating criteria (Kazak, et al. Pediatric Blood & Cancer, 2012).
†Hypotension and tachycardia refer to presence of age-based vital sign abnormalities within two hours of ED arrival.

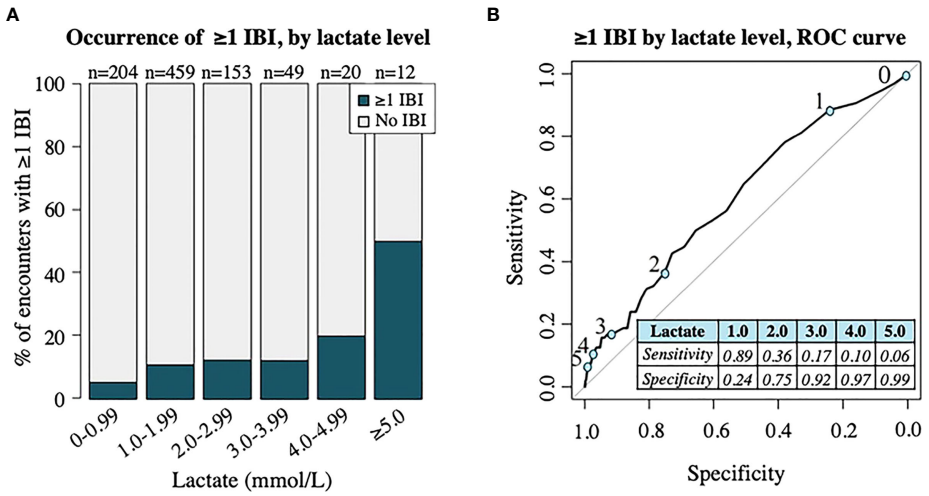

FIGURE 4
Analysis of invasive bacterial infection (IBI) by lactate level. **(A)** Proportion of patient encounters with occurrence of ≥1 IBI by lactate level in increments of 1 mmol/L. Numbers (n) on top of bars signify the total number of patient encounters with initial lactate level in specified range. **(B)** ROC curve demonstrating association of lactate level with occurrence of one ≥1 IBI. Numbers 0-5 along ROC curve represent ROC curve points (blue circles) for lactate level cutoffs in mmol/L, shown in table. Area under the curve = 0.608.

The presence of chills or rigors was associated with increased odds of ≥1 IBI (OR: 2.35, 95% CI: 1.15-4.81, p<0.05).

There was no association between occurrence of ≥1 IBI and initial WBC counts when analyzed continuously, including ANC, absolute monocyte count (AMC), and absolute lymphocyte count (ALC); however, neutropenic patients had 2.5-times higher odds of ≥1 IBI when compared to non-neutropenic patients (p<0.001). No association was observed between age or underlying diagnosis and the occurrence of ≥1 IBI. Outcomes did not significantly differ among chemotherapy regimens (p=0.06), however compared to those in the most (level 4) intensive category, the diagnosis of IBI was less common as chemotherapy regimen intensity decreased. Despite the increased incidence of IBI seen in patients with tachycardia and hypotension, the lack of a significant association between these vital sign abnormalities and IBI was an unexpected finding.

Multivariable analysis results, occurrence of ≥1 IBI by risk factor

Covariates included in the multivariable analysis based on QIC were lactate level (continuous), type of venous access, presence of chills or rigors, and presence of neutropenia as shown in Table 3. The QIC of the model with and without lactate included was 563 and 579, respectively. A difference of 16 points of QIC indicates the model with lactate fits the data significantly better than the model without lactate.

TABLE 3 Occurrence of ≥1 invasive bacterial infection (IBI) within 48 hours, adjusted odds by risk factor (results of multivariable analysis).

Risk Factor	Reference	Odds Ratio	95% CI	p value
Lactate (mmol/L), *continuous*	–	1.49	1.23, 1.79	< 0.001
Type of venous access	Implanted port			< 0.001
External tunneled catheter		4.28	2.32, 7.87	< 0.001
PICC line		5.56	1.29, 23.90	0.02
Peripheral IV		0.77	0.10, 6.19	0.81
Chills or rigors	No	2.23	1.04, 4.80	< 0.001
***Neutropenic, yes**	No	2.54	1.60, 4.03	< 0.001
QIC of model *without* lactate: 579, QIC *with* lactate: 563				

PICC, Peripherally inserted central catheter; QIC, Quasilikelihood under the Independence model Criterion.
*Neutropenia defined as absolute neutrophil count <0.5 x10^3/μL.

Elevated lactate level (OR: 1.49, 95% CI: 1.23-1.79, p<0.001), neutropenia (OR: 2.54, 95% CI: 1.60-4.03, p<0.001), and presence of chills or rigors (OR: 2.23, 95% CI: 1.04-4.80, p<0.001) were all associated with increased odds of ≥1 IBI after adjusting for covariates. Additionally, patients with external tunneled catheters (OR 4.28, 95% CI: 2.23-7.87, p<0.001) and PICC lines (OR 5.56, 95% CI: 1.29-23.90, p<0.05) had increased odds of ≥1 IBI compared to those with implanted ports in the adjusted analysis, whereas those with peripheral IVs did not (p=0.81).

Association of initial lactate level with secondary outcomes

In addition to CDE and IBI, increased lactate level was associated with secondary outcomes pertaining to illness severity as shown in Supplemental Table 4. Among all encounters, the median hospital LOS was 3.8 days (IQR 2.5-6.8) for patients admitted from the ED. PICU admission was required in 55 encounters (6%), and the median PICU LOS was 1.4 days (IQR 0.9-2.7). With each 1 mmol/L increase in lactate level, there was an associated 15% increase in hospital LOS, 68% higher odds of being admitted to the PICU during hospitalization, and 21% increase in PICU LOS (all p values <0.05).

One or more non-invasive infection(s) were diagnosed within 48 hours in 168 encounters (19%), excluding the 16 in which patients who were diagnosed with both IBI and non-invasive infection(s). Sources of non-invasive infection and median lactate levels are shown in Supplemental Table 2. Viral URI was the most common source of non-invasive infection (n=125, 14%) in this group. Lactate level did not significantly differ among patients who were diagnosed with non-invasive infection(s) only and those who were not diagnosed with any infection within 48 hours (p=0.09). Thirty-day mortality was low for the cohort. Six patients died within 30 days of ED presentation (<1%), two from infection-related causes, and four from underlying disease progression. In those six patients, the median time to death was 16.5 days (range 2-26 days) from ED arrival. The two infection-related deaths included one patient with T-cell acute lymphoblastic leukemia (ALL) undergoing delayed intensification therapy who died 10 days after ED presentation due to septic shock with multi-organ failure from disseminated fungal infection and a patient with progressive metastatic atypical rhabdoid tumor (ATRT) found to have to have widely disseminated fungal infection during hospitalization. Due to poor prognosis, all antifungals were discontinued, and he was discharged on hospice care, and ultimately died 19 days after ED presentation.

Patients who appeared critically ill upon ED arrival

Here we describe the 21 encounters among 20 patients (median age 13.3 years, IQR 3.7-16.0) who were critically ill appearing upon initial ED presentation, summarized in Supplemental Table 5. These patients were not included in the remainder of the analysis and expectedly had worse outcomes than the remainder of the cohort. Underlying diagnoses varied, including acute lymphoblastic leukemia (ALL, n=6), acute myeloid leukemia (AML, n=2 encounters for one patient), lymphoma (n=12), solid tumors (n=5), CNS tumors (n=2), and non-malignant hematologic disorders (n=2). Three patients had undergone HSCT within six months prior to presentation. The median initial lactate level in this ill-appearing cohort was 3.2 mmol/L (IQR 1.7-5.1), the median ANC was 0.54 x 10^3/μL (IQR 0.01-3.62), and almost half of the patients were neutropenic at presentation (10 of 21 encounters, 48%). In all but one encounter (95%) the patient experienced ≥1 CDE within 48 hours, and the majority (n=14) experienced multiple CDE qualifying events rather than a single CDE qualifying event (n=6). At least one IBI was diagnosed within 48 hours in two-thirds of the encounters (n=14). The most common type of IBI was BSI (n=14) whereas focal infections (pneumonia: n=3, intraabdominal: n=1, GU: n=1) were less common. Five patients (25%) died within 30 days of ED presentation (median duration from ED arrival to death: 8 days, range 0-26 days). Four deaths were infection-related, and one patient died from underlying disease progression.

Discussion

PHO patients are at high risk for life-threatening infectious complications and progression to sepsis/septic shock. Prompt detection and resuscitation is critical for improving outcomes, which can be challenging as PHO patients often lack typical signs of illness and may present with fever as the sole sign of occult infection and impending deterioration (66). Thus, understanding the implications of objective laboratory markers in PHO patients specifically is essential for the development of superior risk stratification strategies in this group.

Serum lactate is well-established prognostic indicator for general adult and pediatric populations (27–32), and the importance of lactate as a reliable laboratory marker is emphasized by its incorporation in the most recent adult sepsis-3 criteria (67). Results of general pediatric studies indicate an association between elevated lactate and serious bacterial infection (SBI), organ dysfunction, prolonged hospitalization, and mortality (28, 34, 43, 68). Notably, the benefit of lactate measurement has been shown to be independent of hemodynamic variables and organ dysfunction (29, 33, 34).

Although serum lactate has been evaluated as a prognostic indicatior to some extent in adult oncology patients, data is limited and contradictory (30, 69, 70). There is minimal data regarding interpretability of lactate levels in PHO patients who have substantial differences compared to their adult counterparts in terms of underlying malignancies, comorbidities, metabolism/

developmental stages, infectious considerations, and increased treatment regimen intensities (10, 71). We report the association of initial lactate level with poor outcomes in the largest study assessing this laboratory marker in PHO patients to date. Although two existing studies in PHO patients similarly describe an association with lactate levels and illness severity (47, 48), these studies are considerably limited due to small sample size.

Importantly, we demonstrate a similarly reported association between serum lactate levels and increased illness severity in other patient populations, suggesting these values are not routinely elevated or uninterpretable in PHO patients despite the known impact that malignancy, chemotherapy, and organ dysfunction have on lactate metabolism. Given the strength of these data, they provide the basis for further investigation of serum lactate as a tool that can be incorporated into risk stratification models to optimize detection of patients at high risk for deterioration.

Our results demonstrate an association between lactate level and clinical deterioration in PHO patients when analyzed both as a continuous variable and a categorical variable using cutoffs that have been most frequently reported in the literature. While interpretation of this type of laboratory marker using distinct cut points such as ≥2 mmol/L or ≥4 mmol/L rather than as a continuous value may be more practical in the clinical setting, studies in other populations have yielded similar results to our findings: severe outcomes increase linearly with increases in lactate without a clear clinical inflection point (72). Prospective studies validating the utility of this marker as a stratification tool may require different cut points based on the goal of ruling in or ruling out patients at risk for deterioration.

In efforts to capture patients with undifferentiated illness severity at initial evaluation, patients who were critically ill-appearing at presentation were not included in the analysis, and this group predictably had worse outcomes. It is important to note that provider determination of illness severity should remain the primary basis for escalation of care, regardless of what is dictated by any risk prediction model or laboratory result. While the median lactate level was notably higher in this group, this result adds minimal clinical benefit in the context of an ill-appearing patient but does support the concept of elevated lactate as a physiologic response to critical illness in PHO patients.

Among all patients with CDEs, the frequency of IV fluid resuscitation and vasopressor initiation we report are concordant with sepsis as a well-established cause of clinical deterioration in PHO patients (6, 73–75). Moreover, the exclusion of patients who were critically ill at the time of febrile presentation supports the notion that PHO patients may not initially demonstrate classic signs of severe illness with fever but remain at risk for rapid deterioration from sepsis in the subsequent hours. Compared to prior studies which cite respiratory failure as an equal or more frequent contributor to clinical deterioration in this population (7, 73, 76, 77), it only represented 10% of all CDE qualifying events in this study. This may be attributed to multiple factors including the ED setting of this study resulting in exclusion of patients at risk for different complications (e.g., AML and immediate post-HSCT patients), exclusion of patients who were immediately ill-appearing from the overall analysis, and variable definitions of respiratory failure utilized in the literature.

In addition to increased lactate level, older age, highly intensive chemotherapy regimens, and the presence of tachycardia and/or hypotension within two hours of ED arrival were all associated with increased CDE within 48 hours in an adjusted model. The substantial improvement of the multivariable model based on the QIC seen when lactate was included with the remaining risk factors suggests that lactate level can provide additional benefit to other established predictors of illness severity. Hypotension as a predictive variable is difficult to interpret given its intricate link to two potential CDEs (IVF resuscitation and vasopressor initiation), thus the strong association with the primary outcome (≥1 CDE) was expected. Importantly, increased lactate level maintained a significant association with CDE after controlling for the presence of hypotension, supporting the notion that hypotension may be a late finding in pediatric sepsis (78), and lactate elevation can denote inadequate perfusion despite normal blood pressure values (33, 34).

Unlike many studies evaluating risk factors for deterioration in the PHO patient population, we elected to include non-neutropenic patients. In addition to identifying which patients need urgent intervention, there is also significant interest in risk models that enable decreased intervention for patients at lower risk, which largely includes the non-neutropenic population. The incidence of CDE was significantly higher in neutropenic patients compared to non-neutropenic patients. Despite this, neutropenia was not determined to be a necessary variable in the multivariable model of risk factors for CDE. Not only did the best-fit of the model decrease when neutropenia was incorporated, but the presence of neutropenia was no longer significant when evaluated in the context of other relevant covariates. This suggests that although the presence and duration of neutropenia is associated with risk of severe infection, there is likely a role for incorporation of additional clinical and laboratory factors to improve risk prediction for clinical decompensation specifically.

While often linked with clinical deterioration in PHO patients, IBI was included in this study as a separate outcome to test the association of lactate level with serious infection, regardless of clinical illness severity. This has implications for potential incorporation of serum lactate into future prediction models targeted towards decision-making about antimicrobial administration. Our overall incidence of IBI was lower than reported in other studies of PHO patients (79–83), however this was expected given our inclusion of non-neutropenic patients. The majority of studies reporting infectious outcomes in PHO are limited to neutropenic patients as neutropenia is an established risk factor for bacterial infection, which is in accordance with our study results.

As an isolated risk factor, increased lactate level was significantly associated with increased odds of IBI, although

distinct differences in IBI rates were not appreciated unless lactate was substantially elevated to levels ≥4 mmol/L. A possible explanation for this is that lactate may not be as tightly associated with IBI, compared to CDE, due to lactate being a marker of tissue hypoperfusion and organ dysfunction regardless of etiology. In other words, lactate is more suitable for detecting the negative downstream effects of severe infection, rather than infection itself.

Despite the trend toward increased incidence of IBI seen in patients with tachycardia and hypotension, the lack of a significant association between these vital sign abnormalities and IBI was an unexpected finding. This result may represent an insufficient immune response in the setting of bacterial infection due to immunosuppressive therapies, which further emphasizes the need for improved strategies to determine infection risk in this group. It is also possible that a difference was not appreciated as more discrete measures of the degree of tachycardia and hypotension such as z-scores were not utilized (84). In accordance with prior studies, external central catheters were associated with increased IBI (85, 86), although this may have been influenced in part by the underlying diagnoses and treatment regimens that mandate external catheters versus implanted ports. Additionally, chills or rigors reported by patients or documented by ED providers was an important risk factor for IBI, suggesting that this should be part of the routine evaluation of PHO patients presenting with fever. As described above, substantial improvement in the multivariable model of risk factor association with IBI seen with the incorporation of lactate level demonstrates that it can provide additional benefit in distinguishing which patients are at highest risk for IBI. Moreover, elevated lactate level was associated with IBI but not non-invasive infection types. This suggests a role in specifically distinguishing patients with the most clinically significant infection types. This has important implications for risk stratification strategies as there is significant interest in improving our ability to distinguish which patients require aggressive intervention with broad-spectrum antimicrobials from those who would benefit from less intensive therapy.

In accordance with other pediatric studies, we chose clinical deterioration events as a primary marker of illness severity in addition to other secondary outcomes that signify more severe illness including PICU admission and LOS, duration of hospitalization, and mortality. While mortality is the most extreme predictor of illness severity, mortality rates are relatively low in our pediatric population as seen in this study, and clinical deterioration events still hold significant implications for both short and long-term healthcare outcomes and quality of life. We demonstrated longer length of hospitalization, increased rates of PICU admission, and longer PICU LOS as lactate level increased, suggesting this cohort represents a sicker group of patients. The longer hospital LOS seen with elevated lactate level may represent a subacute difference in illness severity. Although the increase in hospital LOS may seem inconsequential, it approximates to an additional day of hospitalization above the median LOS for every 1 mmol/L increase in initial lactate level. Thirty-day infection-related mortality was exceptionally low for the overall cohort, which is in line with improvements seen in supportive care practices for critically ill patients over the last several decades. We suspect that in a larger cohort, there would be a significant difference in mortality, especially in a shorter time-period following a septic event.

The use of lactate in monitoring hemodynamic resuscitation in general populations of children with septic shock is recommended in the evidence-based consensus guidelines of the Surviving Sepsis Campaign and is already common practice in many pediatric EDs in the care of sepsis (78, 87). While this study cannot establish exactly which clinical actions should be taken based on a specific lactate level in a PHO patient, it gives support to this practice in PHO patients with suspected sepsis in the ED, in alignment with current standard of care for all children with sepsis. Further research may establish specific considerations needed to interpret lactate in PHO patients, but it is a low-cost, readily available laboratory test already strongly supported in pediatric sepsis generally, and it is likely to aid in early detection and monitoring of PHO patients, as it already does non-PHO children with sepsis.

There are limitations to this study, including the retrospective nature and unblinded analysis. While our results indicate an association between initial lactate level and increased severity of illness in febrile PHO patients, the most effective way to incorporate serum lactate levels in the clinical setting cannot be derived from these study results alone. The utility of any predictive laboratory marker cannot be established without understanding its meaning in the context of other relevant risk factors. We attempted to account for this by demonstrating that models including known risk factors for CDE and IBI were superior when lactate level was included.

This study is subject to selection bias as it was limited to a single-center tertiary care center that included only ED encounters, which may limit generalizability. Utilizing this available ED database allowed for substantial patient numbers but resulted in omission of patients who are already admitted to the inpatient unit at the time of fever. While this study included a larger number of febrile episodes compared to other studies of serum lactate in PHO patients due to inclusion of non-neutropenic patients, the number of neutropenic patients in this study (n=414) still far exceeded the number evaluated in previous studies (i.e. Suwanpakdee et al. n=99, and Pacheco-Rosas et al. n=100). Although our results indicated that serum lactate remained a significant prognostic indicator after controlling for the presence of neutropenia as a covariate in the statistical analysis, there may be more nuanced implications for this laboratory marker if analyzed specifically in neutropenic versus non-neutropenic patients. Additionally, patients who were transferred from an outside institution or *via* EMS were excluded to ensure that patients had not undergone interventions prior to arrival that may impact lactate level. This limits the potential study population to patients who live

within one-hour driving distance, hereby creating a demographically restricted subject group.

Outcomes may have been influenced by performance bias because clinicians were not blinded to the lactate levels, and they may have specifically carried out interventions such as fluid administration directly in response to elevated lactate levels, which would bias towards supporting the study hypothesis. Conversely, performance bias may have led clinicians to deliver more timely, high quality care to patients with elevated lactate levels, because they were aware and concerned about this lab value. If this were the case, this would potentially disproportionately improve outcomes in the high-lactate patients. Notably, we expect that this effect would have resulted in diminished variance between groups based on lactate levels, and bias towards the null hypothesis. As described above, the link between vital sign abnormalities such as hypotension and the CDE outcome were unavoidable. We elected to include this to ensure that we considered the utility of serum lactate after accounting for typical signs and symptoms of illness severity.

In conclusion, this is the largest study to date that demonstrates the association of initial serum lactate levels with adverse clinical outcomes in PHO patients specifically, who have unique metabolic considerations in the setting of malignancy and treatment regimens. While clinical decision making cannot be made based on an isolated laboratory value, this study suggests that there may be a role for serum lactate as a tool that can be incorporated into other clinical prediction tools in this unique population. The association between serum lactate and poor outcomes in PHO patients demonstrated in this study provides a foundation for future prospective investigations into the most efficacious use of this marker for this group in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Approved by the University of Colorado Cancer Center Protocol Review and Monitoring System and the Colorado Multiple Institutional Review Board (#21-2600). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Contribution: LS, AE, HS, ML, KM, AF, and AL-S designed analyses and analyzed data. LS and KM performed analyses. LS, AE, HS, ML, KM, AF, and AL-S wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.990279/full#supplementary-material

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Multilevel impacts of a pediatric early warning system in resource-limited pediatric oncology hospitals

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Background: Pediatric Early Warning Systems (PEWS) reduce clinical deterioration, improve interdisciplinary communication, and provide cost savings; however, little is known about how these impacts are achieved or related. This study evaluates the multi-level impacts of PEWS in resource-limited pediatric oncology centers.

Methods: We conducted 71 semi-structured interviews including physicians (45%), nurses (45%), and administrators (10%) from 5 resource-limited pediatric oncology centers in 4 Latin American countries. Interviews were conducted in Spanish, transcribed, and translated into English. A code book was developed using *a priori* and inductively derived codes. Transcripts were independently coded by 2 coders, achieving a kappa of 0.8-0.9. Thematic content analysis explored perceived impacts of PEWS at the level of the *patient*, *clinician*, healthcare *team*, and *institution*.

Results: PEWS improved the quality of attention for *patients*, reducing morbidity and mortality. *Clinicians* felt more knowledgeable, confident, and empowered providing patient care, resulting in greater job satisfaction. PEWS affected *team* dynamics by improving interdisciplinary (ward and intensive care

unit) and interprofessional (physicians and nurses) relationships and communication. This ultimately led to *institutional* culture change with emphasis on patient safety, collaboration with other centers, and receipt of institutional awards. Together, these impacts led to hospital-wide support of ongoing PEWS use.

Conclusions: In resource-limited hospitals, PEWS use results in multi-level positive impacts on *patients*, *clinicians*, *teams*, and *institutions*, creating a feedback loop that further supports ongoing PEWS use. These findings can guide advocacy for PEWS to various stakeholders, improve PEWS effectiveness, and inform assessment of other interventions to improve childhood cancer outcomes.

KEYWORDS

Pediatric Early Warning System (PEWS), pediatric oncology, global health, quality improvement, resource-limited, Latin America, pediatric critical care

Introduction

Hospitalized pediatric oncology patients are at high risk for clinical deterioration, particularly in resource-limited settings (1, 2). Pediatric Early Warning Systems (PEWS) are bedside assessment tools associated with an action algorithm used for early identification of patients at risk for deterioration (3), and have been validated to predict clinical deterioration in hospitals of all resource levels (4–7).

The impacts of PEWS have been demonstrated across multiple levels of hospital care. PEWS decrease clinical deterioration events and pediatric intensive care unit (PICU) utilization (8), and improve the perceived quality of care (9). PEWS have also been shown to foster nursing empowerment and increase confidence in recognizing and managing clinical deterioration (10), improve interdisciplinary communication and relationships (11, 12), and lead to cost savings (13).

While many positive impacts of PEWS have been identified in resource-limited settings, little is known about how these effects are achieved or interrelated. This study explores hospital staff perceptions of the multilevel impacts of PEWS, how they are achieved, and the process by which they facilitate and augment one another.

Methods

This is a secondary analysis of a study designed to identify barriers and enablers to PEWS implementation, and study methods have been previously described in detail (14). The study was approved by the St. Jude institutional review board as a minimal risk and thereby exempt study. Additional approvals were obtained by participating facilities as required. Written participant consent was waived on account of the study's exempt status; each participant provided verbal consent prior to the start of their interview. The Consolidated Criteria for Reporting of Qualitative Research (COREQ) guidelines were used to maintain rigor of qualitative reporting (15).

Hospital and participant selection

Escala de Valoración de Alerta Temprana (EVAT) is a Spanish-language PEWS validated in pediatric oncology patients (4). Proyecto EVAT is an international collaborative led by St. Jude Children's Research Hospital (St. Jude) to support PEWS implementation in resource-limited hospitals providing pediatric oncology care in Latin America (16, 17).

Five Proyecto EVAT centers which completed PEWS implementation prior to March 2020 were selected to participate in the study with representation from Mexico, Central America, and South America. Center characteristics are described in Supplemental Table 1. Each center selected a study lead who identified 10-15 participants involved in PEWS implementation, including PEWS implementation leaders, hospital administrators, and staff indirectly involved in utilizing PEWS.

Data collection

An interview guide (Supplemental Figure 1) was designed to identify barriers and enablers to PEWS implementation at

participating centers (14). The guide was translated to Spanish, iteratively revised for relevance and clarity, pilot tested with three individuals from hospitals not participating in this study but demonstrative of the target population, and modified based on feedback. Interviews were conducted in participants' native language (Spanish) by bilingual members of the research team (PE, SG) *via* a video conferencing platform (WebEx) from June to August of 2020. The interviewers were previously unknown to participants, not affiliated with their hospital, and not involved in PEWS implementation. Audio recordings of the interviews were professionally transcribed, translated to English, and de-identified (removing all names and other identifiers) prior to analysis.

Analysis

A codebook was established using *a priori (*18) along with inductively-derived codes defined by two authors (AA, GF) through iterative review of nine transcripts. Two authors (AA, GF) independently coded each transcript using MAXQDA software (VERBI GMBH, Berlin, Germany), achieving a kappa of 0.8-0.9. Incongruities in coding were resolved by a third author (DG) serving as an arbitrator.

Three "outcomes" codes were identified to describe perceived impacts of PEWS at the level of the *patient*, *individual*, and *institution* (Supplemental Table 2). *Individual* outcomes were subsequently split into impacts on the *clinician* and healthcare *team*. Thematic content analysis explored participant perceptions of these multilevel impacts of PEWS at their centers. Codes were examined independently and concurrently with constant comparative analysis of transcripts by site, participant role (e.g., clinician vs. non-clinician and nurse vs. physician), and center characteristics (e.g., presence or absence of a dedicated PICU).

Results

Seventy-one interviews were conducted at 5 pediatric oncology centers in Latin America (see Table 1 for participant characteristics). Content analysis revealed perceived benefits of PEWS for *patients*, *clinicians*, *team* dynamics, and *institutions*. Figure 1 summarizes these multilevel effects and their interplay, which is further described below.

Patient

Participants at all centers described similar benefits of PEWS for patients including higher-quality patient attention, earlier detection of deterioration, and a reduction in morbidity and mortality (Table 2).

Using PEWS required frequent and focused patient assessments leading to increased situational staff awareness and more individualized attention: "*we're not only applying a routine on that patient, there was more specific care depending on their current situation,"* (Nurse, Xalapa). Staff explained that, prior to PEWS, deteriorating patients would go undetected for hours as their bed was the last discussed on rounds or because vital signs were checked only once or twice a shift: *"before when a child got critical in the [ward] no one was aware of him"* (Ward Physician, San Luis Potosi). With the PEWS algorithm, patients were monitored at appropriate intervals based on their clinical status (Supplemental Figure 2). Thus, staff were better able to track the condition of each patient and focus their attention and resources where they were most needed: *"they enter the service and the first thing they do is check the sheet and see if someone has a red or yellow [PEWS] so they can start to work on that patient"* (Nurse, Lima); *"now, the detection of the child is done on time"* (Ward Physician, San Luis Potosi).

Greater situational awareness facilitated early detection of clinical deterioration and increased opportunities for prevention of critical illness: *"if you see a patient who doesn't look that bad but he has a yellow [PEWS], it makes you act before; you prevent a bigger complication and it doesn't depend on what you see but it's something more objective"* (Ward Physician, Lima). As a result, deteriorating patients were identified and treated earlier, leading to fewer unplanned PICU transfers. Patients who did need PICU care were transferred earlier and required fewer interventions: *"The patient doesn't need to go to intensive therapy to get better. In case the patient goes to intensive therapy … he won't stay too long or need a tube,"* (Nurse, San Luis Potosi).

These improvements led to a perceived reduction in the morbidity and mortality of hospitalized patients: "*the mortality was highly reduced*," (Ward Physician, San Luis Potosi). Additionally, with early detection, a patient transfer to the PICU was no longer synonymous with death: *"Before [PEWS], children with cancer would go to the ICU and it was considered a child with no opportunity, that child should die. Once [PEWS] came, our children began to get out and we started saying a child with cancer doesn't die, we just transfer him too late"* (Nurse, Lima).

Clinician

In addition to improving patient care, PEWS use led to multiple benefits for *clinicians*, including reduced nursing workload, improved job satisfaction, increased knowledge, and empowerment (Table 3).

While nurses initially perceived PEWS use as increasing their workload, with continued use, it became part of their workflow, and ultimately, the reduction in deterioration events and earlier PICU transfers due to PEWS was felt to decrease nursing workload as they were caring for fewer critical patients:

TABLE 1 Characteristics of interview participants.

Characteristic		n	%
Center			
	Lima, Peru	18	25.4%
	San Luis Potosi, Mexico	11	15.5%
	San Salvador, El Salvador	15	21.1%
	Cuenca, Ecuador	15	21.1%
	Xalapa, Mexico	12	16.9%
Profession			
	Ward Physician	26	36.6%
	ICU Physician	6	8.5%
	Nurse	32	45.1%
	Other	7	9.9%
Gender			
	Male	21	29.6%
	Female	50	70.4%
Years working in center			
	0-10	27	38.0%
	11-20	25	35.2%
	21+	19	26.8%
Role in hospital			
	Administrator	8	11.3%
	Clinician	30	42.3%
	Clinician-Director	33	46.5%
Role in PEWS Implementation			
	Implementation Leader	39	54.9%
	Director	21	29.6%
	Other	11	15.5%
Total		**71**	**100.0%**

Adapted from Agulnik et al. (14).

"with the implementation of [PEWS] we have patients that stay only a few days at the hospital, less patients at ICU, etc. So they see results, they see less work for them" (Administrator, Xalapa). Additionally, some centers leveraged the initial increase in nursing workload to advocate for a reduction in the nurse-to-patient ratio: *"Without [PEWS] we couldn't justify the need of a nurse to take care of 6 children, they used to take care of 10 or 12 before,"* (Nurse, INEN).

As a result of using PEWS to positively impact the care of their patients, clinicians experienced greater job satisfaction: "*you can intervene your patients early and avoid ICU or even death; that gives you great satisfaction,"* (Nurse, San Luis Potosi). Staff members across all disciplines found this to be motivating: *"they see that their work is represented in a patient who is discharged in very good conditions, that makes their effort worthy,"* (Ward Physician, Lima).

Additionally, many staff members, especially nurses, found that PEWS and the accompanied trainings expanded their knowledge-base: "*we used to take signs without knowing what was normal … now with [PEWS], we know how different it is to have a bradycardia or an asymptomatic bradycardia, it changes a lot,*" (Nurse, Cuenca). As a result, they were better able to monitor their patients and felt more confident speaking up when necessary to raise an alarm.

As staff gained knowledge and confidence, they reported increasing feelings of empowerment: "*little by little the nurses found out they could go beyond with their work in the service, more than just give medicine, prepare chemotherapies, the fact that they could evaluate a patient … makes them feel more educated, with more power for decision*," (Ward Physician, Xalapa). PEWS empowered nurses to take a more active role in patient assessment and management, and physicians felt empowered to contribute to ongoing improvements in patient care: "*there is motivation from the resident part knowing the supervision is higher in the entire service*" (Ward Physician, San Luis Potosi).

Team

In addition to benefits for patients and clinicians, PEWS led to benefits for the interprofessional *team* including better

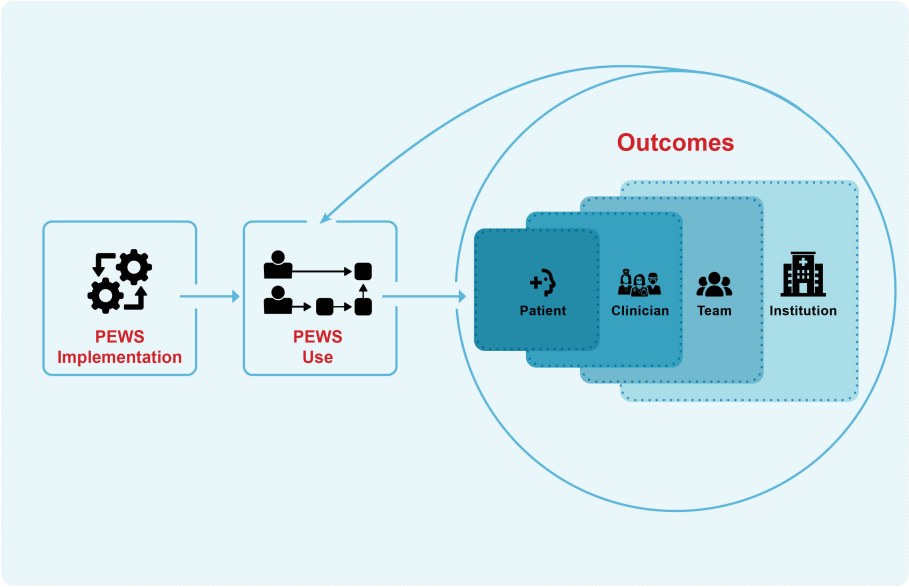

FIGURE 1
PEWS Cycle of Reinforcement. This figure describes staff perception of the impact of PEWS use on patients, clinicians, teams, and institutions. The benefits at each of these levels facilitate, augment, and reinforce the positive outcomes at the other levels and support ongoing PEWS use.

communication between healthcare providers and improved interprofessional (e.g., nurses and doctors) and interdisciplinary (e.g., ward and ICU) team dynamics (Table 4).

Participants explained that prior to the introduction of PEWS, nurses and physicians did not have common terminology to discuss patient status, resulting in ineffective communication: *"Before [PEWS] … we would come to the doctor and say I can see the patient is getting worse, the patient is not well, but it was subjective; the doctor would say maybe you're just seeing him that way and maybe you're wrong,"* (Nurse, Cuenca). PEWS use provided teams a common language, improving interprofessional and interdisciplinary communication: *"with the [PEWS] score, it was so easy with everyone talking about the same thing to detect a patient when he needed to be transferred to the ICU or when they could treat him in the [ward] … now we all speak the same language"* (Ward Physician, San Luis Potosi).

Improvements in team dynamics not only enhanced communication but also improved interprofessional and interdisciplinary relationships. Prior to implementation of PEWS, collaboration between professions was minimal; after implementation, nurses and doctors interacted more frequently and the *"relationship between them improved a lot"* (Ward Physician, Cuenca), *"not only professionally, but friendly"* (Ward Physician, Lima). PEWS diminished hierarchies between physicians and nurses, and as a result, nurses felt

TABLE 2 Patient outcomes.

Higher Quality Patient Attention	Attention for the patient according to their disease, the kind of risks they have (Nurse, Xalapa)
	Improving the quality of attention for the hospitalized oncology patient has been the main thing (Ward Physician, San Salvador)
	The attention is faster and more precise (Nurse, Cuenca)
Early Detection & Prevention of Deterioration	[PEWS] allows us to control and monitor the patient before deterioration … before the vital functions are too late to act (Ward Physician, Lima)
	Children's health conditions were deteriorating and we didn't know until they were in critical condition, but with [PEWS] everything changed … we don't wait until it's too late (Nurse, Cuenca)
	We're able to capture the probability for this patient to get critical in the next few hours and everything we must do to prevent this (Ward Physician, San Salvador)
Reduced Morbidity & Mortality	The most important thing was the reduction of the morbimortality of the patient, that has been very visible. (Ward Physician, Xalapa)
	Mortality has decreased by 2/3. (ICU Physician, San Salvador)
	We saw a decrease of adverse events and complications (Nurse, San Luis Potosi)

TABLE 3 Clinician outcomes.

Reduced Nursing Workload	They realized it wasn't more work, on the contrary, at some point, it would decrease their amount of work (Administrator, Xalapa)
	Thanks to the result of this project, nurses can treat fewer patients (Nurse, Lima)
Job Satisfaction	It's personally very satisfying to be able to bring that kind of attention to the patients (Nurse, Xalapa)
	The effort that [PEWS] requires is not that big and the satisfaction that we have to prevent a cardiac arrest or death on a patient is much higher (ICU Physician, Cuenca)
	The satisfaction of contributing to my patient's health, preventing deterioration because my vital signs were taken on time, because my interventions were correct (Nurse, San Salvador)
Knowledge	[Nurses] would take the vital signs … without knowing if the patient was okay or bad until this program was implemented (Ward Physician, San Luis Potosi)
	It helped my knowledge; it expanded my ideas about attention (Nurse, Xalapa)
Empowerment	This situation has helped for the empowerment of the nursing staff, to say hey my job is valuable (Ward Physician, Lima)
	That empowerment, not just from the nursing staff but from the entire multidisciplinary team that participated in the improvement of the patient, has helped with the success of the project (Nurse, San Salvador)

their input was welcome and valued in ways that it was not previously: *"that we would all talk the same language and that the nurse would have voice and vote in the evaluation of the patient, it's been one of the biggest and most successful projects,"* (Nurse, San Salvador). Similarly, the use of PEWS facilitated better relationships between the ward and PICU teams: *"before it was like we must transfer him to the ICU, I'm scared they won't accept him, but not anymore … they are more sensitized, more accessible,"* (Ward Physician, Lima). Following PEWS implementation, PICU transfers were less chaotic as PICU clinicians were more willing to evaluate and admit patients earlier in the course of illness.

Institution

Perceived *institutional* impacts of PEWS included cost reduction, a change in hospital culture emphasizing high-quality patient care, receipt of institutional awards, and opportunities for collaboration with other hospitals (Table 5).

PEWS use reduced hospital costs by decreasing inpatient days and resource utilization: *"we are spending less; patients arrive in ICU on time and they don't need a ventilator, vasopressors, they stay in ICU only one or two days … compared to the times when it was too late for them, they would stay a lot of days in ICU, they needed ventilator, expensive medicine … the before and after is remarkable,"* (Nurse, Cuenca).

Additionally, participants at all sites noted that PEWS implementation altered hospital culture to increase emphasis on patient-centered care: *"the culture changed, the culture for the whole medical staff to see the patient in a comprehensive way,"* (ICU Physician, San Salvador). Staff experience using PEWS demonstrated that clinical deterioration was largely preventable, leading to a hospital-wide focus on patient safety: *"[Clinicians] see that his life is in danger or that he could get critical … they visualize that it is very important to be on alert with that patient so he won't have risks, and applying [PEWS] on all our patients has influenced a lot as part of their safety"* (Ward Physician, Xalapa). Quality improvement projects became more common as staff were inspired to explore other strategies to improve patient care: *"A lot of us have started to get involved in other quality improvement projects that maybe didn't exist before [PEWS], but it has helped us and pushed us to work … to motivate ourselves as professionals to keep looking for alternatives for our patients,"* (Ward Physician, Lima).

Centers were further motivated by receiving awards honoring their PEWS program from entities such as the Ministry of Health: *"all we wanted was to implement [PEWS] and try to give quality to our patients, but it has been recognized by the Ministry, so that's an achievement bigger than we expected,"* (Nurse, San Salvador). Additionally, participation in

TABLE 4 Team outcomes.

Better Communication	Now we're talking the same language in relation to the patient (Nurse, San Salvador)
	Communication, at the beginning this was a weakness, but then it became a strength (Ward Physician, Lima)
	A lot of benefits regarding the communication between doctors and nurses … even communication with the department of nutrition … the department of physiotherapy (ICU Physician, Cuenca)
Improved Team Dynamics	We saw teamwork which very often is not seen in other units. The involvement of the medical part with the nursing staff and the service staff, with the administrative staff (Nurse, San Salvador)
	The chance to work as a team both with the nurses … the pediatric oncology staff and also the staff at the ICU (Ward Physician, Lima)
	[The doctors] now let us give them suggestions, and before they never heard the observations we told them. (Nurse, San Salvador)

TABLE 5 Institutional outcomes.

Cost Reduction	We need less resources … we are spending less (Nurse, Cuenca)
	It has resulted in reduction of spending, in hospitalization, in used treatments, the situation of the hospital has been highly improved in that part (Ward Physician, Xalapa)
Emphasis on High-Quality Patient Care	[PEWS] is a strength … moving forward to quality and safety of the patient as well as the institution (Nurse, San Luis Potosi)
	[PEWS] has given us a change in the culture of attention (Nurse, Xalapa)
	This was the example to have bigger or better projects in quality improvement in order to help us with the rest of the processes at the hospital (Ward Physician, Lima)
Awards & Accolades	They gave an award for continued quality improvement from the Ministry (Nurse, San Salvador)
	We were nominated a center of excellence in [PEWS] for Latin America. I think this is one of the biggest achievements, reference for Latin America. (Ward Physician, Lima)
Opportunities for Collaboration	We go outside to train other institutions both in the country and abroad … so [PEWS] grew beyond the hospital and we are very proud as an institution (Ward Physician, Lima)
	They have to come here and we have to go there so we can exchange knowledge and improve every day (Ward Physician, Cuenca)

Proyecto EVAT provided new opportunities to collaborate with other hospitals: *"We're able to visit other countries, know the realities of other people, share experiences, share situations,"* (Nurse, Lima).

Cycle of reinforcement

PEWS implementation led to benefits for patients, clinicians, teams, and institutions initiating a feedback loop that reinforced ongoing PEWS use (Figure 1). Recognition of the patient-level benefits of PEWS led to increased buy-in as clinicians were motivated by opportunities to directly improve patient outcomes: *"It was the motivation of seeing the children who could have had a fatal ending return to the [ward] in a better condition"* (Nurse, Cuenca). Greater job satisfaction and empowerment among staff led to improved interdisciplinary and interprofessional relationships and communication. Hierarchical barriers were reduced and the interprofessional team functioned more cohesively: *"we gained friendship and fellowship, which reinforced our work"* (Ward Physician, Cuenca). As relations improved, so did the work environment, facilitating a change in hospital culture with implications for staff's wellbeing and patient safety. Additionally, observed reduction in resource utilization and mortality galvanized support for PEWS among hospital leadership: "*Even in the administration field, we can see that if there's a better response to the patient's need before he gets critical, this reduces spending and reduces the probability to go to the ICU or get critical or even die"* (Ward Physician, San Salvador). This encouraged leadership support for ongoing staff training and expansion of PEWS within the hospital. Over time, PEWS became embedded in the hospital's culture and workflow, further reinforcing its continued use: *"The hospital has accepted [PEWS] as part of the staff's work, so they give us the sheets, they open the doors for the training"* (Nurse, Lima).

Discussion

Our study demonstrates multiple benefits of PEWS implementation for patients, clinicians, healthcare teams, and institutions and the ways in which these benefits modulate and reinforce one another. Similar to prior studies, we found that staff perceived PEWS to reduce adverse events (8), improve quality-of-care (9), increase staff knowledge, confidence, and empowerment (10), improve interprofessional and interdisciplinary communication (11), and reduce hospital costs (13). Our study, however, additionally demonstrates that improvements in patient outcomes increase staff motivation and job satisfaction, and better interpersonal relationships foster an improved work environment leading to changes in hospital culture including increased emphasis on patient-centered care, patient safety, and quality improvement. The use of qualitative methods allowed for this in-depth exploration of the interplay between the multi-level impacts of PEWS and development of an explanatory model for these impacts as understood by staff directly engaged in PEWS use. Our findings can be used to advocate for PEWS implementation to stakeholders at various levels within an institution by focusing on the outcomes most relevant to them.

Implementation and improvement research is important in resource-limited settings where contextual and infrastructural challenges make implementing evidence-based practices more difficult (14). Correct use of any evidence-based practice is integral to assuring impact, and quality of use must be measured and iteratively improved over time. Process evaluation is a strategy to identify and address gaps at each level of an intervention to maximize implementation success and address barriers to successful use (19, 20). Understanding how PEWS impacts are interrelated helps explain how they are achieved. Our study revealed a cycle of reinforcement which outlines the mechanism by which multilevel outcomes contribute to PEWS success. This process evaluation helps

identify critical components of effective quality improvement interventions in settings of all resource-levels, creating a framework for implementation and continuous monitoring (19). Furthermore, understanding impacts relevant to different stakeholders can help address specific barriers and inform targeted and contextually-appropriate strategies to improve intervention adoption and use. This approach can help inform the assessment of PEWS and other clinical interventions.

The cycle of reinforcement identified in our study provides a model to promote the sustainability and expansion (scale) of effective quality improvement interventions. Prior work suggests that an institution's capacity to sustain an evidence-based practice such as PEWS increases with time (21), and the cycle of reinforcement described in this work identifies a potential mechanism to explain this finding. Furthermore, participants identified components of the clinical capacity for sustainability framework (22), which describes an organization's capacity to sustain evidence-based interventions across seven domains, including engaged stakeholders, outcomes and effectiveness, implementation and training, and workflow integration (23), as important outcomes of PEWS implementation. More work is needed to prospectively evaluate whether these factors contribute to the maintenance of high-quality PEWS use over time and explore possible strategies to promote sustainability of the multi-level benefits of PEWS use.

Our study has several limitations. Key stakeholder interviews have a risk of social desirability bias (24); however, we attempted to mitigate this by using interviewers previously unknown to participants and not involved in PEWS implementation and by explaining the process of interview de-identification to participants. In addition, interview questions were designed to explore barriers and enablers to PEWS implementation rather than its impacts; identified themes regarding PEWS outcomes were largely spontaneously reported by participants, minimizing bias. All data were collected in Spanish with analysis conducted in English, potentially influencing the interpretation of original statements. To minimize inaccuracies, a professional service was used for translation and 20% of transcripts were audited by a bilingual team member (SG) to confirm accuracy. Finally, this study was conducted in one region (Latin America) among pediatric oncology centers, potentially limiting generalizability of study findings to other regions and patient populations. However, diversity of participating hospitals and similarities between our findings and prior literature on PEWS supports the applicability of these findings to other settings.

This study uniquely describes the interplay between the multilevel impacts of PEWS implementation in resource-limited settings. Benefits at the level of the patient, clinician, team, and institution create a cycle of reinforcement that amplifies impact and supports ongoing PEWS use. These findings can guide advocacy for PEWS to different stakeholders, improve PEWS implementation and efficacy, and inform the implementation and evaluation of other quality improvement initiatives to reduce disparities in childhood cancer outcomes globally.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by St. Jude Children's Research Hospital Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AA and DG developed the idea. MP-T, SG, PE, HM-T, AGR, MA, CB, RDC, CH, SJ, JJL, AM, EMo, EPe, and EPi collected the data. AA and DG provided supervision. EMi, GF, and AA conducted the data analyses. EMi, AA, and DG drafted manuscript and prepared the tables and figures. EMi, GF, and AA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. All authors contributed to the interpretation of the findings, the editing of the article, and the approval of the final submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Compassionate de-escalation of life-sustaining treatments in pediatric oncology: An opportunity for palliative care and intensive care collaboration

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Context: Approximately 40%-60% of deaths in the pediatric intensive care unit (PICU) are in the context of de-escalation of life-sustaining treatments (LSTs), including compassionate extubation, withdrawal of vasopressors, or other LSTs. Suffering at the end of life (EOL) is often undertreated and underrecognized. Pain and poor quality of life are common concerns amongst parents and providers at a child's EOL. Integration of palliative care (PC) may decrease suffering and improve symptom management in many clinical situations; however, few studies have described medical management and symptom burden in children with cancer in the pediatric intensive care unit (PICU) undergoing de-escalation of LSTs.

Methods: A retrospective chart review was completed for deceased pediatric oncology patients who experienced compassionate extubation and/or withdrawal of vasopressor support at EOL in the PICU. Demographics, EOL characteristics, and medication use for symptom management were abstracted. Descriptive analyses were applied.

Results: Charts of 43 patients treated over a 10-year period were reviewed. Most patients (69.8%) were white males who had undergone hematopoietic stem cell transplantation and experienced compassionate extubation (67.4%) and/or withdrawal of vasopressor support (44.2%). The majority (88.3%) had a physician order for scope of treatment (POST – DNaR) in place an average of 13.9 days before death. PC was consulted for all but one patient; however, in 18.6% of cases, consultations occurred on the day of death. During EOL, many patients received medications to treat or prevent respiratory distress, pain, and agitation/anxiety. Sedative medications were utilized, specifically propofol

(14%), dexmedetomidine (12%), or both (44%), often with opioids and benzodiazepines.

Conclusions: Pediatric oncology patients undergoing de-escalation of LSTs experience symptoms of pain, anxiety, and respiratory distress during EOL. Dexmedetomidine and propofol may help prevent and/or relieve suffering during compassionate de-escalation of LSTs. Further efforts to optimize institutional policies, education, and collaborations between pediatric intensivists and PC teams are needed.

KEYWORDS

palliative care, palliative sedation therapy, dexmedetomidine, propofol, pediatric oncology, symptom management, end of life

Introduction

Each year in the United States, approximately 20,000 children die, and beyond the first year of life, the majority of those deaths are due to accidental trauma, congenital anomalies, malignancy, or intentional injury (1, 2). Although the distribution of the causes of pediatric deaths has not changed significantly over several decades (2), the events leading up to death have. The advancement of medical treatments and evolution of pediatric critical care has altered the progression of several pediatric disorders and increased invasive interventions during the end-of-life (EOL) period (1, 3).

Life-sustaining treatments (LSTs), such as mechanical ventilation and vasoactive support, play a substantial role in supporting patients during EOL; nevertheless, they may contribute to symptom burden and suffering (4, 5). Palliative care (PC) as a medical subspecialty focuses on improving quality of life (QOL) and decreasing suffering through symptom management, psychosocial support, and advanced-care planning (5–7). Integration of PC throughout the disease trajectory and within the pediatric intensive care unit (PICU) may improve outcomes and has become increasingly accepted, yet such services remain underutilized (8, 9).

In pediatric oncology, advancements in hematopoietic cell transplantation (HCT) and immunotherapy have increased overall survival and critical care needs in this population have risen accordingly (10). In fact, nearly 40% of pediatric oncology patients are admitted to the PICU at some point during therapy, and more than half of these patients require multiple PICU admissions (3, 11). Additionally, mortality rates for pediatric oncology patients admitted to the PICU are notably 4-fold greater than those for the general pediatric population who require intensive care (12, 13). Patients undergoing HCT can have further increases in mortality risk that are associated with respiratory failure requiring mechanical ventilation and prolonged PICU stays (>15 days) (10, 14).

However, regardless of diagnosis, prognosticating in the PICU is difficult and comes with substantial uncertainty (15). When faced with a terminal prognosis, families can find themselves having to make difficult decisions regarding LSTs (16). In this context, involvement of PC specialists during PICU admissions can improve shared medical decision making, decrease parental regret, and assist with bereavement (8, 17). Nearly 40%-60% of pediatric deaths in the PICU occur after a decision is made to withdraw LSTs (1, 18–20); however, little is known about how parents and families arrive at that decision. One study suggests that, in most cases, medical professionals initiate conversations about compassionate de-escalation of LSTs, and consensus is reached between medical teams and families after 1-2 meetings (21). The role of PC during this time remains poorly defined, with the potential for missed opportunities to provide improved QOL, support decision making, and give psychosocial support to these families.

In general, literature on compassionate de-escalation of LSTs is limited and it is rarely specific to pediatric oncology. To address this gap in the literature, we conducted a retrospective review of deceased pediatric hematology/oncology patients treated at an academic hospital over a 10-year period, with the goal of describing this patient population and their EOL experiences.

Abbreviations: DOD, day of death; EOL, end of life; HCT, hematopoietic cell transplantation; LST, life-sustaining treatment; PC, palliative care; PICU, pediatric intensive care unit; POST, physician order for scope of treatment; PST, palliative sedation therapy; QOL, quality of life; TOD, time of death.

Methods

An Institutional Review Board–exempt, retrospective review was performed of pediatric hematology/oncology patients treated at St. Jude Children's Research Hospital between April 1, 2011, and January 1, 2021. This date range defines a period when patients would have all pertinent data for this study placed into the electronic medical record system.

For the purposes of this study, the term LSTs was defined as patients who required mechanical ventilation and/or vasoactive support. Patients requiring non-invasive respiratory support eventually progressed to intubation and mechanical ventilation and thus are also represented in this definition. Inclusion criteria consisted of age <25 years, a confirmed hematologic or oncologic diagnosis, death occurring in the PICU, and patients who had de-escalation of LSTs, specifically compassionate extubation, withdrawal of vasopressor support, or both. Other LST withdrawal was not assessed due to the complexity of recognizing the rationale for withdrawal in our electronic medical record.

Two study members (AC and MP) performed data extraction in a systematic fashion using a data dictionary to ensure consistency. Data collected included demographics [age at diagnosis, sex, race/ethnicity, religious affiliation, date of diagnosis, date of death, age at time of death (TOD)], disease characteristics (primary oncology or hematology diagnosis, stage of disease, presence of relapse or recurrence, history of hematopoietic cell transplantation, type of transplant, cancer-directed treatment within the last month and week of life, infectious complications during last admission), EOL care characteristics (date of PC first contact, goal of care at the time of PC consultation, number of PC visits, hospice enrollment and date if applicable, date of first pain service consultation, number of pain service visits, intubation status at TOD, withdrawal of LSTs, cardiopulmonary resuscitation on day of death (DOD), Do Not Resuscitate status) and medications used for symptom control within 24 hours of death. Of note, the presence of symptoms (i.e., pain, anxiety, nausea, etc.) was ascertained through daily progress note documentation. Discrepancies were reviewed by both study members until a consensus was reached.

Descriptive statistics of the data included frequency (percent), mean ± standard deviation (SD), and median [Max, Min]. SAS (version 9.4, SAS Inc.) was used for all analyses.

Results

Patient demographics

A total of 721 patients died during the study period: 244 deaths occurred in the inpatient setting, and 107 occurred in the PICU. Of those patients who died in the PICU, 43 (40.2%) had withdrawal of LSTs and thus met the study's criteria. The majority (58.1%) were male, primarily white (69.8%), and their mean age at diagnosis was 5.54 years (median [Min, Max] = 3 [0.02, 18]) (Table 1).

Disease characteristics

Sixteen (37.2%) patients had acute lymphoblastic leukemia, and 11 (25.6%) had acute myelogenous leukemia. Evidence of relapsed disease was found in 24 (55.8%) patients, and 23 (53.5%) had undergone allogeneic HCT (Table 2).

End-of-life care

Of the 43 patients included in the study, 25 (58.1%) received cancer-directed therapy during their last month of life, and 20 (46.5%) received it during their last week (Table 3). Among the patients requiring compassionate de-escalation of LSTs, 24 (55.8%) underwent compassionate extubation, 14 (32.6%) had withdrawal of vasoactive support, and 5 (11.6%) experienced both (Table 4).

TABLE 1 Demographics of 43 pediatric hematology/oncology patients who received compassionate de-escalation of life-sustaining treatments.

Demographic characteristic	Frequency (%)[a]
Sex	
Female	18 (41.2)
Male	25 (58.1)
Age at diagnosis (years)	
Mean (SD)	5.54 (5.67)
Median [Min, Max]	3 [0.02, 18.0]
Age at TOD (years)	
Mean (SD)	7.56 (6.52)
Median [Min, Max]	7 [0.17, 23]
Race/Ethnicity	
White/Non-Hispanic	30 (69.8)
Black	6 (14.0)
White/Hispanic	3 (7.0)
White, South/Central American	1 (2.3)
Multiple races	1 (2.3)
Hispanic	1 (2.3)
Declined	1 (2.3)
Status Post Hematopoietic cell transplantation (allogeneic)	
Yes	24 (55.8)
No	19 (44.2)

[a]Data represents the number of patients (%), unless otherwise indicated.
Max, maximum value; Min, minimum value; No., number of; SD, standard deviation; TOD, time of death.

TABLE 2 Disease characteristics of 43 pediatric hematology/oncology patients who received compassionate de-escalation of life-sustaining treatments.

Disease characteristic	No. patients (%)
Primary Oncology Service	
Bone Marrow Transplantation	23 (53.5)
Hematology	3 (7.0)
Leukemia	7 (16.3)
Neuro-Oncology	8 (18.6)
Solid Tumor	2 (4.7)
Primary Diagnosis	
Acute lymphoblastic leukemia	16 (37.2)
Acute myelogenous leukemia	12 (27.9)
Atypical teratoid rhabdoid tumor	5 (11.6)
Rhabdoid tumor	1 (2.3)
Severe aplastic anemia	1 (2.3)
Dyskeratosis Congenita	1 (2.3)
Ependymoma	1 (2.3)
Evans syndrome	1 (2.3)
Fanconi anemia	1 (2.3)
Wilms tumor	1 (2.3)
Glioblastoma	1 (2.3)
Retinoblastoma	1 (2.3)
Medulloblastoma	1 (2.3)
Disease relapse	
Yes	24 (55.8)
No	19 (44.2)

Regarding EOL characteristics, 38 (88.3%) patients had a physician order for scope of treatment (POST - DNaR) in place before death, and only 1 (2.3%) patient received cardiopulmonary resuscitation on the DOD (Table 3). POSTs were completed an average of 13.9 days (median [Min, Max] = 1 [0, 373]) before DOD (Table 3).

Palliative care consultation

PC was consulted for 42 (97.6%) patients, and the average number of PC visits was 14.2 (median [Min, Max] = 9 [0, 61]) (Table 3). Of note, 8 (18.6%) patients received PC consultation on the DOD; however, for the remainder, PC was involved approximately 2 weeks before the DOD. For many patients and families, the goal of care remained cure, despite PC involvement, and only 5 (11.6%) patients enrolled in hospice.

TABLE 3 End-of-life characteristics of 43 pediatric patients undergoing compassionate de-escalation of life-sustaining treatments.

End-of-life characteristic	Frequency (%)[a]
Cancer-directed treatment during the last month of life	
Yes	25 (58.1)
No	18 (41.9)
Cancer-directed treatment during the last week of life	
Yes	20 (46.5)
No	23 (53.5)
No. Palliative Care visits	
Mean (SD)	14.2 (14.7)
Median [Min, Max]	9 [0, 61]
No. patients who met Palliative Care on DOD	8 (18.6)
No. Pain Service visits	
Mean (SD)	6.98 (25.2)
Median [Min, Max]	0 [0, 118]
No. patients who did not interact with the Pain Service	36 (83.7)
Goal of Care	
Cure	24 (55.8)
Comfort	10 (23.2)
Life prolongation	4 (9.3)
Poor prognosis[b]	2 (4.7)
Life prolongation and comfort	1 (2.3)
Not documented	2 (4.7)
Enrolled in Hospice	
Yes	5 (11.6)
No	38 (88.3)
POST in place	
Yes	38 (88.3)
No	5 (11.6)
CPR administered on DOD	
Yes	1 (2.3)
No	42 (97.6)
Time between POST and DOD (days)	
Mean (SD)	13.9 (61)
Median [Min, Max]	1 [0, 373]
Time between intubation and DOD (days)	
Mean (SD)	1 (2.78)
Median [Min, Max]	0 [0, 14]
Examination for brain death[c]	
Yes	5 (11.6)
No	38 (88.4)

[a]Frequency indicates the number of patients (%), unless otherwise indicated.
[b]Poor prognosis, while not a true "goal of care" was part of the documentation template for the goals of care section.
[c]One patient with no formal examination for brain death was noted as having brainstem disruption.
DOD, day of death; CPR, cardiopulmonary resuscitation; EOL, end of life; Max, maximum value; Min, minimum value; No., number of; PICU, pediatric intensive care unit; POST, physician order for scope of treatment; SD, standard deviation; TOD, time of death.

TABLE 4 Frequency of life-sustaining treatments withdrawn at the end of life and symptoms experienced.

Life-sustaining treatment	Frequency (%)
Intubated at the TOD	
Yes	15 (34.9%)
No	28 (49.1%)
Vasopressors withdrawn before DOD	
Yes	19 (44.2%)
No	24 (55.8)
Symptoms at EOL in the PICU	
Respiratory distress	
Yes	42 (97.7%)
No	1 (2.3%)
Anxiety/agitation	
Yes	34 (79.0%)
No	9 (21.0%)
Pain	
Yes	40 (93.0%)
No	3 (7.0%)

DOD, day of death; EOL, end of life; PICU, pediatric intensive care unit; TOD, time of death.

Pain management consultation

Only 6 (14.2%) patients received pain service consultation, and the average number of pain service visits was 6.9 (median [Min, Max] = 0 [0, 118]) (Table 3). Those who received pain service consultation did so on average 4.3 months before the DOD and the consult was for pharmacological pain management. None of the patients received interventional pain modalities for pain management at the end of life.

Medication management

Complex medication regimens addresses the symptom burden at the EOL. Respiratory distress (97.6%, n=42), pain (93.0%, n=40), and anxiety/agitation (79.1%, n=34) were the most commonly reported symptoms experienced at the EOL (Table 4).

All patients received one or more opioid medication to manage their symptoms. Midazolam (79.1%, n=34) and lorazepam (62.8%, n=27) were the two benzodiazepines most often prescribed (Figure 1A). For vasopressor and inotropic support, norepinephrine and dopamine were most commonly prescribed (46.5%, n=20), followed by epinephrine (44.2%, n=19) and vasopressin (32.6%, n=14) (Figure 1B). Sedative agents, such as propofol (14.0%, n=6), dexmedetomidine (11.6%, n=5), or both (44.2%, n=19), were administered (Figure 1C).

Discussion

Our study examined de-escalation of LSTs for pediatric hematology/oncology patients at the EOL in the PICU setting, a topic that has not been summarized in more than a decade and is often generalized for all pediatric patients (13). The need for intensive care, and by default implementation of LSTs, such as mechanical ventilation and vasopressor or inotropic support, for pediatric hematology/oncology patients is associated with increased mortality risk (13, 22–25), especially for patients undergoing HCT (10, 14). Additional factors associated with poor overall survival of patients admitted to the PICU include multisystem organ dysfunction (24, 26–28) and sepsis (13). Despite advances in the treatment of childhood cancers, the risk for therapeutic toxicities, including death, and the prevalence of suffering at the EOL remain prominent (29).

We found that across all deaths that occurred in the PICU during the study period, 40.2% of patients experienced compassionate de-escalation of LSTs, specifically either removal of vasopressor/inotropic support, or compassionate extubation, or both. This is consistent with the literature, which suggests that approximately 40%-60% of all PICU deaths occur after removal of LSTs (18–20). The majority of patients had leukemia, which was not surprising, as leukemia is the most common oncologic diagnosis in children (30). Additionally, HCT is performed primarily for hematologic malignancies at the study institution, as noticed in over half of the study cohort, and is associated with significant risk for treatment-related toxicity, including death (31–34). Despite medical advances in the treatment of childhood cancer, 1 in 5 patients will still succumb to their disease (35), and it is well documented that the EOL period can be complicated by physical, psychosocial, emotional, and spiritual suffering (5, 31, 35–37).

From the onset of diagnosis, oncologists facilitate important conversations surrounding disease status and therapeutic options and partner with pediatric intensivists to care for patients when intensive care is required and potentially during the EOL period (38). One way to help minimize the suffering experienced by patients during the EOL in the PICU setting and improve QOL may be through early engagement and collaboration with PC teams. Our study showed that early collaboration between intensivists and PC teams is feasible and it is supported by the literature. Evidence throughout the literature suggests several opportunities for interfacing and collaboration between intensivists and PC team, to improve the EOL experience of patients, their families, and even medical teams, through assistance with advanced-care planning, shared medical decision making, particularly when faced with decisions about de-escalation of care and symptom management, which may include palliative sedation therapy (PST) (3, 7, 32, 39). PST is defined as, "the use of sedative medications to relieve intolerable and refractory distress by the reduction in patient consciousness" (40–44). Over the last several years, acceptance of early integration of PC in the realm of pediatric oncology and PICU care has grown with institutions using the PICU admission as a trigger for PC consultation (38, 45–49).

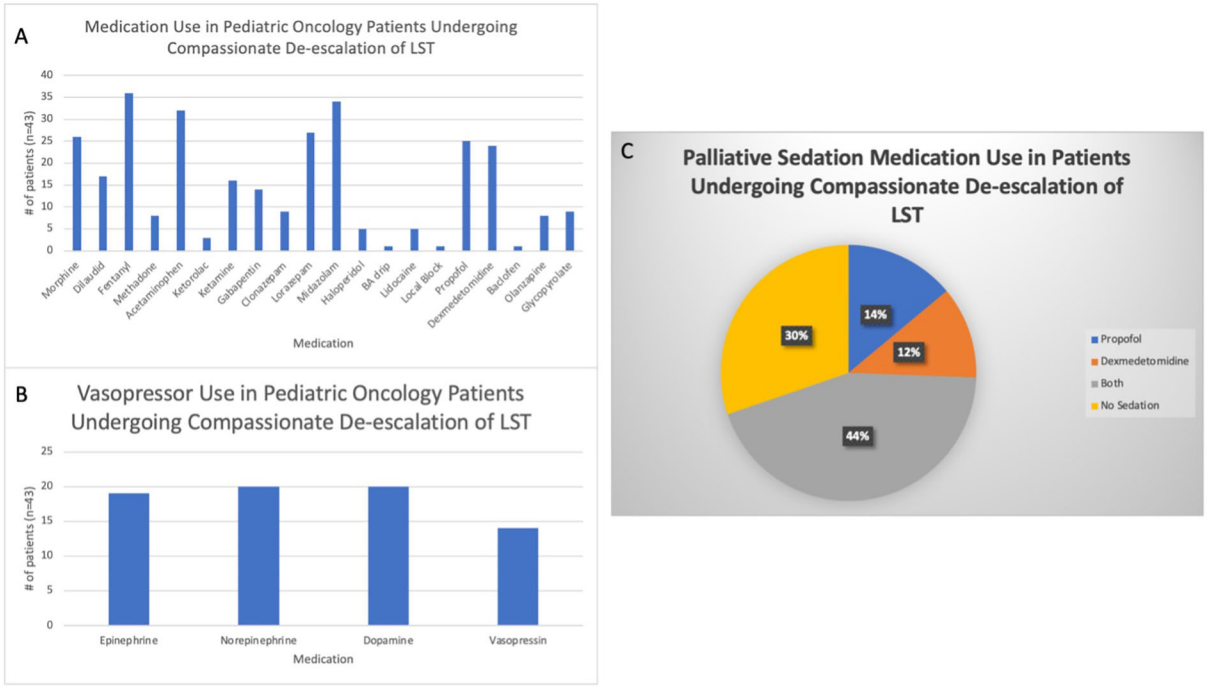

FIGURE 1
Medications used to treat pediatric oncology patients during compassionate de-escalation of life-sustaining treatments (LSTs). **(A)** All medications prescribed to the study population to treat symptoms at the end of life. BA= Benadryl/Ativan. **(B)** Vasopressor medications used to treat hypotension in the study cohort. **(C)** Use of palliative sedation therapy, specifically dexmedetomidine and propofol, during the end of life.

All but one patient in our study engaged with the PC team. The PC team was involved an average of 2 weeks before the DOD, allowing for time to build rapport and trust with families. This is important for the patient and family, as well as all medical teams, as this time enables providers to gain a better understanding of what is important to a patient and family and what their goals may be. For example, most of the families reported a goal of cure for their child, which may explain the finding that approximately half of our study population received cancer-directed treatment during the last month and/or week of life. By extension, this information helps the medical team provide support and guidance to patients and families through shared medical decision making. Although the literature is rich on the topic of shared medical decision making, little is known about how families come to the decision to forgo LSTs (50–53). One prospective study found that parents initiate a conversation about compassionate de-escalation of care in about 25% of cases, and that consensus can be reached between medical teams and families after one meeting in about 50% of cases (21). Future exploration of the timing of decision making, withdrawal of LSTs, use of PST, and barriers to family consensus are recommended.

In addition to augmenting discussions on de-escalation of LSTs, the PC team can work with the medical teams to facilitate conversations of advanced-care planning, specifically in providing an extra layer of support for families and medical staff. In some instances, these conversation may include facilitating death in the home setting and coordinating hospice services, and for many patients in an acute ICU setting these conversations simply revolve around creating a calm, loving EOL period with family members at the bedside and forgoing cardiopulmonary resuscitation that may incur suffering (1, 54, 55). More than 80% of our cohort had a Do Not Resuscitate order in place before death, and only 1 patient received cardiopulmonary resuscitation. Additionally, the average time between Do Not Resuscitate decisions and death was approximately 14 days, which we hypothesized allowed families time to discuss all options and make a well-informed, goal-centric decision for their child and family. In contrast, approximately 20% of the patients in our cohort met the PC team on the DOD. We believe that unexpected acute changes to signify a high likelihood of death and consultation occurring as the team was preparing to remove LSTs most likely contributed to this delay and poses a potential opportunity for practice improvement. As PC encompasses a holistic approach to caring for patients and families, this concept becomes increasingly important during points of high patient acuity in one's care journey, especially when PICU care is required.

Previous research suggests the PICU admission as a time point for consideration in engaging PC teams (56, 57) and optimizing PC integration in the PICU setting. One way this may be accomplished is through an embedded model in which PICU staff members are identified and trained to be PC champions; a model that currently exists with success in some PICUs, as well as pediatric critical care fellowship programs across the nation (48). Training would include PC course work and subspecialty clinical rotation experience, with the goal of increasing awareness and education of ICU staff about PC services available to patients and families (48). Prospective studies and qualitative data would help determine the most effective way for PC teams to support patients and families during EOL in a PICU.

When death becomes inevitable, many families and caregivers begin to hope for a "good death" for their child (58, 59). The concept of a good death looks different to each family unit, and in some instances, compassionate de-escalation of LSTs has been requested to occur in the home, an option that may not be considered by healthcare professionals (4, 60–62). Many parents describe a high symptom burden at the EOL and state this as a major contributor to their child's suffering (29). Specifically, pain, dyspnea, fatigue, and anxiety are commonly reported by patients and noted as a source of suffering by parents (7, 29, 36). Our finding of pain, anxiety/agitation, and respiratory distress being present for nearly all patients in our study further supports this. Traditional symptom management, with medications and psychological coping behaviors, are often enough to alleviate suffering, but what happens when they are not? In some cases, advanced adjuvant medications for pain can be employed (lidocaine or ketamine infusions), or interventional strategies (e.g., nerve blocks or neuraxial blocks), and even implants, such as epidural catheters, can be employed (63–67).

In rare cases, suffering persists despite all interventions, and PST is an effective tool for refractory suffering at the EOL (40–44). PST practices are variable in pediatric oncology, and medication choices for implementation of PST are evolving (40, 68, 69). Propofol and dexmedetomidine are utilized more commonly for this intervention (68–71).

Dexmedetomidine and propofol are commonly used in the PICU setting (72). However, we took a closer look at what medications were used within 24 hours of the TOD to decipher how often patients received medication regimens like those used in PST practices. Many patients were actively receiving propofol, dexmedetomidine, or both at the TOD. We hypothesize that these medications are often used for sedation while the patient receives mechanical ventilation and/or for symptom control before de-escalation of care and were continued to avoid withdrawal and ensure adequate symptom management until the TOD. An observational study of death in the PICU completed more than 2 decades ago demonstrated similar findings of sedative and analgesic use after de-escalation of LSTs in the PICU (1). It also noted 13% of medical professionals were dissatisfied with the EOL care provided and felt that the level of medication administration was inadequate for symptom management (1). However, the patient population in that study encompassed all of pediatrics and was not focused on pediatric hematology/oncology. Propofol or dexmedetomidine administration in our study may not have been intended for PST, but it remains a fascinating finding and offers an opportunity for increased education, awareness, and implementation of PST practices in the PICU. Of the 13 patients who did not receive propofol or dexmedetomidine, four had one formal documented brain death exam and died prior to a second, confirmatory exam, and one patient had documented compression of the brainstem. It is also important to note that medications, such as opioids, benzodiazepines, antiemetics, muscle relaxants, and gabapentinoids, still have an important role in symptom management at the EOL and many patients in this study required these medications as part of their symptom management.

Pain medicine specialists and anesthesiologists are an additional resource for patients, families, and medical teams mediating EOL symptoms. Our study showed that after compassionate de-escalation of LSTs, most pediatric oncology patients who died in the PICU did not involve the pain service in their care. Collaboration between the PC team and pain specialists can help optimize traditional strategies, incorporate interventional tactics (e.g., nerve blocks), and initiate PST if warranted (40).

Overall, this study builds on the limited literature on pediatric oncology patients facing de-escalation of LSTs at the EOL. We highlight opportunities for further PC integration to help optimize shared decision making, advanced-care planning, and symptom management at the EOL in the PICU. Future studies characterizing how families decide to compassionately de-escalate LSTs and prospective studies analyzing symptom burden, relief, and interventions specifically surrounding PST practices and drugs like propofol and dexmedetomidine, would be most informative.

This study had several limitations. First, it represents the experience of a single institution that sees a focused patient population with a higher level of patient acuity and death. Second, retrospective data collection relies on precise documentation; therefore, information, such as timing of discontinuation of a medication or LST, and specifics around decision making are not always easily identified. As such, this study design limits our ability to draw conclusions on causality or intent of medication use (i.e., propofol for PST) and necessitates the need for future prospective investigations.

Conclusion

Pediatric hematology/oncology patients admitted to the PICU have increased risk of mortality, and especially when LSTs are necessary, early integration of PC may be beneficial.

It remains unclear how families decide to compassionately de-escalate LSTs, how this decision may affect suffering at the EOL, and how medication practices in the PICU may incorporate concepts of PST. Collaborations between oncologists, intensivists, and PC specialists may help optimize QOL and minimize suffering. Furthermore, prospective and qualitative studies in this realm and increased educational awareness of EOL interventions, including the use of PST, are needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A multicenter study of ICU resource utilization in pediatric, adolescent and young adult patients post CAR-T therapy

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Tisagenlecleucel is associated with remarkable outcomes in treating patients up to the age of 25 years with refractory B-cell acute lymphoblastic leukemia (ALL). Yet, due to unique and potentially life-threatening complications, access remains limited to higher-resource and certified centers. Reports of inequity and related disparities in care are emerging. In this multicenter study of ALL patients admitted for anti-leukemia therapy, who required pediatric intensive care (ICU) support (n = 205), patients receiving tisagenlecleucel (n = 39) were compared to those receiving conventional chemotherapy (n = 166). The median time to ICU transfer was 6 (0–43) versus 1 (0–116) days, respectively ($p < 0.0001$). There was no difference in the use of vasopressor, ionotropic, sedating, and/or paralytic agents between groups, but use of dexamethasone was higher among tisagenlecleucel patients. Patients receiving tisagenlecleucel were more likely to have cardiorespiratory toxicity ($p = 0.0002$), but there were no differences in diagnostic interventions between both groups and/or differences in ICU length of stay and/or overall hospital survival. Toxicities associated with tisagenlecleucel are generally reversible, and

our findings suggest that resource utilization once admitted to the ICU may be similar among patients with ALL receiving tisagenlecleucel versus conventional chemotherapy. As centers consider improved access to care and the feasibility of tisagenlecleucel certification, our study may inform strategic planning.

KEYWORDS

Immunotherapy, CAR (chimeric antigen receptor) T-cell therapy, pediatric cancer, AYA (adolescents and young adults), Resource utilisation

Introduction

Therapeutic strategies for patients with relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) may differ based on disease characteristics, cooperative group recommendations, and resource availability. (1) Chimeric antigen receptor T-cell (CAR-T) therapy is a promising strategy for patients with R/R ALL. Tisagenlecleucel has demonstrated impressive minimal residual disease negative remission rates of 81% at 3 months (2). Yet, CAR-T therapy is associated with unique and potentially life-threatening toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (3). Up to 40% of patients receiving tisagenlecleucel may require transfer to the intensive care unit (ICU) (2). While the availability of tisagenlecleucel has been limited to certified centers with adequate training and resources to deliver this therapy safely and effectively, emerging reports of disparities in therapy suggest that wider availability may be indicated (4, 5). We hypothesized that among patients admitted for anti-ALL therapy who require ICU support, ICU resource utilization and outcomes would not differ among patients receiving tisagenlecleucel versus those who did not.

Methods

This study was reviewed by the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, Hematopoietic Cellular Therapy-Cancer Immunotherapy Subgroup and approved by the institutional review board (IRB) at each participating PALISI Network sites (n = 5). We conducted a retrospective analysis of patients up to age 25 years who received tisagenlecleucel for ALL and required admission to the ICU between 1 November 2017 and 1 June 2020. Patients with ALL receiving conventional chemotherapy admitted to the ICU during this period were used as comparators. CRS and ICANS toxicities were graded as per the American Society for Transplantation and Cellular Therapy (ASTCT) (6). Patients with incomplete medical records and those receiving CAR-T therapy other than tisagenlecleucel for ALL were excluded.

Data extracted from the electronic medical record included demographics, reason for ICU admission, incidence and grading of CRS and ICANS, pediatric sequential organ failure assessment (pSOFA) score (7), resource utilization including imaging, procedures and medications, ICU and overall hospital length of stay (LOS), and mortality.

Patients' demographic and clinical characteristics were summarized as median and range for continuous variables and as frequency and percentage for categorical variables and compared between patient groups admitted to the ICU who did and did not receive tisagenlecleucel using t-test, Mann–Whitney test, negative binomial regression for continuous variables, or Fisher's exact test or chi-square test for discrete variables, as appropriate. ICU survival and hospital survival were summarized by Kaplan–Meier methods, with differences between patient groups assessed by the log-rank test. Statistical analyses were performed using R statistical software (8). Statistical significance was set at a p-value of <0.05.

Results

Of the patients with ALL admitted to the ICU (n = 205), 39 patients (19.0%) received tisagenlecleucel and 166 (81.0%) did not. Patient characteristics, resource utilization, and outcomes are summarized in Table 1. Patients undergoing CAR-T therapy were older as they underwent conventional chemotherapy prior. The most common indication for ICU admission in the non-CAR-T therapy group was respiratory failure requiring mechanical ventilation (n = 82; 49.4%), whereas hypotensive shock (associated with CRS) was the most common indication in the CAR-T therapy group (n = 22; 56.4%). Non-CAR-T therapy patients were more likely to be admitted to the ICU for hyperleukocytosis (p = 0.001). The median time to ICU admission from day of hospital admission was shorter in the conventional chemotherapy group at 1 day (0–116 days) versus

TABLE 1 Characteristics, resource utilization, and clinical outcomes of patients with acute lymphoblastic leukemia admitted to the intensive care unit.

		CAR-T therapy n = 39	Non-CAR-T therapy n = 166	P value
Age (years)		13 (1.5-25)	11 (0.3-25)	0.047
Gender	**Men**	16 (41.0%)	111 (66.9%)	0.003
	Women	23 (59.0%)	55 (33.1%)	
Prior hematopoietic cell transplantation	**Yes**	8 (20.5%)	41 (24.7%)	0.68
	No	31 (79.5%)	125 (75.3%)	
Days from CAR-T therapy to ICU admission		6 (0-43)	—	<0.0001
Days from hospital admission to ICU admission		—	1 (0-116)	
pSOFA score on admission to the ICU		6 (1-12)	6 (0-17)	0.67
Max pSOFA score during ICU admission		8 (1-18)	9 (1-23)	0.81
Reason for ICU admission	**Respiratory failure**	17 (43.6%)	82 (49.4%)	0.59
	Shock	22 (56.4%)	72 (43.4%)	0.16
	Altered mental status	9 (23.1%)	22 (13.3%)	0.14
	Renal failure	3 (7.7%)	18 (10.8%)	0.77
	Seizures	0 (0%)	9 (5.4%)	0.21
	Hyperleukocytosis	0 (0%)	31 (18.7%)	0.001
Medications	**Vasopressors**	23 (59.0%)	73 (44.0%)	0.11
	Inotropes	2 (5.1%)	17 (10.2%)	0.54
	Sedatives	14 (35.9%)	82 (49.4%)	0.15
	Paralytics	5 (12.8%)	27 (16.3%)	0.81
	Dexamethasone	19 (48.7%)	2 (1.2%)	<.0001
Max CRS score	**1**	3 (7.7%)		
	2	9 (23.1%)		
	3	14 (35.9%)		
	4	13 (33.3%)		
Max ICANS score	**0**	17 (43.6%)		
	1	3 (7.7%)		
	2	10 (25.6%)		
	3	6 (15.4%)		
	4	3 (7.7%)		
Evidence of liver dysfunction[1]		30 (76.9%)	123 (74.1%)	0.84
No. of patients requiring paracentesis **Median no. of paracentesis performed**		2 (5.1%) 0 (0-3)	6 (3.6%) 0 (0-10)	0.65
Evidence of cardiotoxicity[2]		31 (79.5%)	87 (52.4%)	0.002
No. of patients requiring ECHOs **Median no. of ECHOs performed**		26 (66.7%) 1 (0-4)	119 (71.7%) 1 (0-8)	0.56
Transesophageal echocardiogram		0 (0%)	4 (2.4%)	1.0
No. of patients requiring EKGs **Median no. of EKGs performed**		27 (69.2%) 1 (0-16)	135 (81.3%) 1 (0-19)	0.12
No. of patients requiring pericardiocentesis		0 (0%)	1 (0.6%)	1.0
No. of patients requiring cardiac catheterization		0 (0%)	2 (1.2%)	1.0
Evidence of respiratory toxicity[3]		28 (71.8%)	82 (49.4%)	0.013
Evidence of cardiac and/or respiratory toxicity		38 (97.4%)	119 (71.7%)	0.0002
No. of patients requiring invasive mechanical ventilation		6 (15.4%)	58 (34.9%)	0.02
No. of patients requiring CPAP **Median duration of CPAP (days)**		5 (12.8%) 0 (0-5)	13 (7.8%) 0 (0-27)	0.35
No. of patients requiring BiPAP **Median duration of BiPAP (days)**		10 (25.6%) 0 (0-8)	52 (31.3%) 0 (0-68)	0.56
No. of patients requiring HFNC **Median duration of HFNC (days)**		18 (46.2%) 0 (0-37)	53 (31.9%) 0 (0-31)	0.1

(Continued)

TABLE 1 Continued

	CAR-T therapy n = 39	Non-CAR-T therapy n = 166	P value
No. of patients requiring chest X-rays **Median no. of chest X-rays performed**	33 (84.6%) 4 (0-60)	155 (93.4%) 4 (0-83)	0.1
No. of patients requiring bronchoscopy **Median no. of bronchoscopies performed**	1 (2.6%) 0 (0-1)	24 (14.5%) 0 (0-2)	0.05
No. of patients requiring tracheostomy **Median no. of tracheostomies performed**	0 (0.0%) 0	2 (1.2%) 0 (0-1)	1.0
No. of patients requiring thoracentesis **Median no. of thoracentesis performed**	1 (2.6%) 0 (0-1)	11 (6.6%) 0 (0-2)	0.47
No. of patients requiring CRRT	6 (15.4%)	30 (18.1%)	0.82
No. of patients requiring CT brain **Median no. of CT brain performed**	13 (33.3%) 0 (0-2)	50 (30.1%) 0 (0-5)	0.7
No. of patients requiring MRI brain **Median no. of MRI brain performed**	7 (17.9%) 0 (0-3)	35 (21.1%) 0 (0-7)	0.83
No. of patients requiring EEG **Median no.of EEG performed**	12 (30.8%) 0 (0-17)	35(21.1%) 0 (0-17)	0.21
No. of patients requiring LP **Median no. of LPs performed**	5 (12.8%) 0 (0-7)	61 (36.7%) 0 (0-5)	0.004
ICU LOS (days)	6 (2-55)	7.5 (1-125)	0.22
Hospital LOS (days)	28 (5-150)	21 (1-183)	0.019
Death during ICU admission	6 (15.4%)	45 (27.1%)	0.03
Death during hospital admission	8 (20.5%)	48 (28.9%)	0.33

[1]Defined as new-onset CTCAE ≥Grade 3 transaminitis, coagulopathy, or hepatomegaly.
[2]Defined as new-onset cardiomyopathy, arrhythmia, tachycardia, hypotension, or hypotensive shock.
[3]Defined as hypoxia requiring any oxygen supplementation or respiratory failure.
CAR-T, chimeric antigen receptor T cell; ICU, intensive care unit; pSOFA, pediatric sequential organ failure assessment; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ECHO, echocardiogram; EKG, electrocardiogram; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; HFNC, high flow nasal cannula; CRRT, continuous renal replacement therapy; CT, computerized tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; LP, lumbar puncture; LOS, length of stay.

6 days (0–43 days) in the CAR-T therapy group, respectively ($p < 0.0001$).

All CAR-T therapy patients admitted to the ICU had CRS and/or ICANS. Seventeen patients (43.6%) developed CRS only, and 22 (56.4%) patients had concurrent CRS and ICANS. Twenty-seven (69.2%) patients developed a maximum CRS score of ≥Grade 3, eight of which had concurrent ICANS Grade ≥ 3. Given the high incidence of CRS, patients in the CAR-T therapy group were more likely to have evidence of cardiac toxicity (defined as new-onset cardiomyopathy, arrhythmia, tachycardia, or hypotension/shock) compared with the non-CAR-T therapy group (79.5% *vs.* 52.4%; $p = 0.002$). Likewise, respiratory toxicity (defined as hypoxia requiring oxygen supplementation or respiratory failure) was higher in the CAR-T versus the non-CAR-T therapy group, respectively (71.8% *vs.* 49.4%; $p = 0.013$). Despite the higher incidence of respiratory toxicity in the CAR-T therapy group, invasive mechanical ventilation (15.4% *vs.* 34.9%; p value = 0.02) and bronchoscopies (2.6% *vs.* 14.5%; $p = 0.05$) were lower in the CAR- therapy *vs.* the non-CAR-T therapy groups, respectively.

There were no significant differences between groups in the use of procedures including paracentesis, pericardiocentesis, cardiac catheterization, thoracentesis, tracheostomy, or continuous renal replacement therapy. A higher proportion of patients in the non-CAR-T therapy group underwent lumbar puncture ($p = 0.004$) to facilitate the administration of intrathecal chemotherapy. There was no significant difference in the use of vasopressors, inotropes, sedatives, or paralytics between both groups. The use of dexamethasone was significantly higher in the CAR-T therapy group for the treatment of CRS/ICANS (48.7% *vs.* 1.2%; $p < 0.0001$).

There was no significant difference in the number of imaging investigations between groups, including transesophageal echocardiogram, echocardiogram (ECHO), electrocardiogram (EKG), chest X-ray, magnetic resonance imaging (MRI), and computer tomography (CT) of the brain and electroencephalogram (EEG).

Median ICU length of stay (LOS) was similar in the CAR-T and non-CAR-T therapy groups, respectively (6 (2–55) versus 7.5 (1–125) days; $p = 0.22$). Overall hospital LOS was longer in the CAR-T *vs.* the non-CAR-T therapy group (28 (5–150) *vs.* 21 (1–183) days; $p = 0.019$), which may be associated with a longer preceding time to ICU admission in the CAR-T therapy group. The pSOFA score, which is a measure of organ dysfunction with higher scores on ICU admission being associated with higher in-hospital mortality (7), was comparable between the CAR-T therapy *vs.* non-CAR-T therapy groups (6 (1–12) *vs.* 6 (0–17), respectively; $p = 0.67$). ICU mortality was higher in the non-

CAR-T therapy than the CAR-T therapy group (27.1% *vs.* 15.4%; p = 0.03), although the difference in overall hospital mortality was not significant (28.9% *vs.* 20.5%; p = 0.33). Neither ICU nor hospital mortality differed significantly between CAR-T groups per log-rank test (Figure 1).

Discussion

CAR-T therapy has revolutionized the therapeutic landscape for patients with R/R ALL who previously had limited treatment options. While its short-term benefits are well established, given its lack of durable response in 50% of patients at 12 months and with an estimated lifetime cost of $667,000, tisagenlecleucel is currently the most expensive oncological therapy whose long-term benefit remains to be established (2, 9). In 2018, however, the institute for clinical and economic review estimated that the cost-effectiveness of tisagenlecleucel fell within commonly cited thresholds for cost-effective oncology drugs of $50,000 to $150,000/QALY over a lifetime with 10.34 life years and 9.28 QALYs gained with tisagenlecleucel compared with 2.43 life years and 2.10 QALYs gained with a conventional chemotherapy-based regimen (9).

To our knowledge, this is the first multicenter study to explore resource utilization in pediatric patients admitted to the ICU for CAR-T therapy-related complications. Previous reports suggest that up to 40% of patients receiving tisagenlecleucel may require ICU support (2). Our study was limited to outcomes of patients admitted to the ICU. As expertise grows, however, ICU admission rates for patients receiving CAR-T therapy may decline as many toxicities may be managed without ICU intervention.

In this study, overall hospital LOS and time to ICU admission were longer in patients undergoing CAR-T therapy as they were all admitted for lymphodepletion at least 6 days pre-infusion as per standard of care. Furthermore, patients in the non-CAR-T group were more likely to be admitted due to the acute nature of complications secondary to their disease course and/or treatment such as septic shock or leukocytosis at initial diagnosis. During their admission, overall resource utilization appears comparable in patients with ALL receiving CAR-T therapy and conventional chemotherapy. Additionally, CAR-T therapy and non-CAR-T therapy patients appear to have similar organ dysfunction and expected risk of hospital mortality upon ICU admission (p-SOFA), although our study did not analyze the effect of poor prognostic factors or cause of mortality. CAR-T therapy patients, however, appear to require less invasive mechanical ventilatory support and may demonstrate superior outcomes, which is likely reflective of the potentially reversible toxicities of CRS and ICANS when recognized and treated promptly (10, 11).

Overall, while the administration of CAR-T therapy is associated with increased upfront costs, resource utilization in these patients requiring critical care is comparable with ALL patients undergoing conventional chemotherapy. Given its remarkable remission rates, CAR-T therapy is, therefore, an excellent therapeutic strategy. As more centers introduce CAR-T therapy, rigorous protocols for clinical monitoring and prompt toxicity management available at certified centers may mitigate ICU admissions and support needs (11). Longer-term studies,

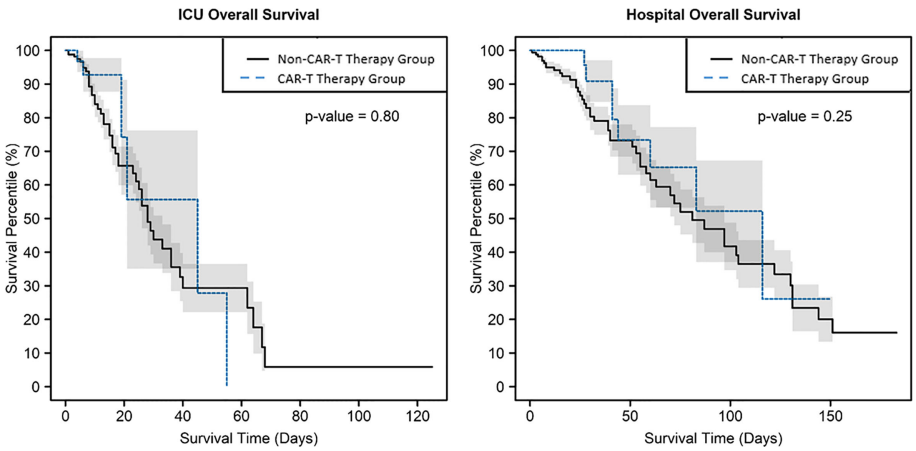

FIGURE 1
Kaplan–Meier survival curves, which account for mortality over time, with shaded +/- standard error, showed no evidence of difference by CAR-T therapy group in intensive care unit mortality or hospital mortality, with p = 0.80 and 0.25, respectively.

however, are needed to fully understand the critical care needs of patients undergoing CAR-T therapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study of human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients OR patients legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DR, CR, and KM designed the study and wrote the protocol and the manuscript. DR, SB, GM, FB, SK, CH, CA, BS, SM, SN, ES, CG, AT, PT, DM, CN, BC, FPT, DP, HA, and KM assisted with data collection and review. CA led the biostatistical analysis for this study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

KM is the site PI for Atara Biotherapeutics, Jazz Pharma, Allovir, and BMS. CG has served in the Advisory Board for Legend Biotech & Janssen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prevention and management of human cytomegalovirus in pediatric HSCT recipients: A review

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Cytomegalovirus (CMV), like other herpesviruses, has the unique ability to establish latent infection with subsequent reactivation during periods of stress and immunosuppression. Herpesviruses cause potentially devastating disease, particularly in hematopoietic stem cell transplant (HSCT) recipients. CMV is especially of concern in HSCT recipients given the high community seroprevalence, high risk of reactivation and high risk of transmission from HSCT donors to recipients causing primary infection after transplantation. The risk of CMV infection and severity of CMV disease varies depending on the underlying disease of the HSCT recipient, donor and recipient CMV status prior to HSCT, type of conditioning therapy in preparation for HSCT, allogeneic versus autologous HSCT, donor graft source, timing of infection in relation to HSCT, and other patient comorbidities. Different strategies exist for prevention (e.g., preemptive therapy vs. universal prophylaxis) as well as management of CMV disease (e.g., antiviral therapy, augmenting immune reconstitution, cytotoxic T-cell therapy). The purpose of this narrative review is to discuss diagnosis, prevention, and management of CMV infection and disease at different stages of HSCT, including key points illustrated through presentations of complex cases and difficult clinical scenarios. Traditional and novel strategies for CMV management will be discussed in the context of these unique clinical cases.

KEYWORDS

cytomegalovirus, pediatrics, hematopoietic (stem) cell transplantation (HSCT), immunosuppression, infection, herpesviruses

Introduction

Hematopoietic stem cell transplant (HSCT) is a curative therapy for several diseases in pediatric patients, including hematologic malignancies, primary immune deficiencies, myelodysplastic syndrome, congenital metabolic disorders, and hemoglobinopathies (1, 2). More than 12,000 HSCTs were performed in children <18 years of age in the United States between 2016 and 2020 (3). HSCT recipients have severely compromised immune systems (due to their underlying disease and secondary to HSCT conditioning),

increasing their risk for bacterial, fungal, viral, and parasitic infections. These infections can be derived from donors, environmental sources or *via* reactivation of endogenous latent infections (4, 5).

Among viral infections, herpesviruses, particularly cytomegalovirus (CMV), present significant concerns for infection in HSCT patients. CMV has a high community seroprevalence with approximately 50% of people in the United States seropositive, with variations depending on age, geography, and socioeconomic status (6, 7). Many patients will therefore enter HSCT with an established latent CMV infection (as indicated by a positive pre-transplant CMV IgG serology). In addition, CMV can also be transmitted to HSCT recipients from the donor. This may result in devastating and possibly fatal disease with the potential to precipitate several indirect outcomes such as graft-vs.-host-disease (GVHD), autoimmunity, malignancy, and increased risk of other opportunistic infections (4, 8, 9).

Pre-transplant evaluation

Among many other predisposing factors, the risk of CMV infection and disease is highly dependent on the combination of recipient and donor CMV serostatus. HSCT recipients are at highest risk of CMV infection when the recipient is CMV seropositive and the donor is CMV seronegative pre-transplant (9). In this case, the recipient will be at high risk for endogenous CMV reactivation during immune suppression following HSCT, at a time when the cell-mediated immune system is suppressed from the conditioning regimen for HSCT. Eventually, there will be a gradual development or reconstitution of CMV-specific T-cell immunity, but this may take time (10). Fifty percent of patients develop detectable CMV cytotoxic T-cell (CTL) response by 3 months after allogeneic HSCT, and reconstitution of CMV-specific CD4+ and CD8+ T-cells has been shown to be a good indicator of absolute CD4+ and CD8+ T-cell numbers (11, 12). Failure to produce CMV-specific immunity by 3 months post-HSCT has been shown to be significantly associated with late CMV reactivation and increased mortality (13). Among CMV seropositive patients, approximately 80% will experience CMV reactivation after allogeneic HSCT in the absence of CMV prophylaxis (14).

When interpreting serologies, it is important to consider pre-transplant receipt of intravenous immunoglobulin (IVIG) or blood products within the preceding 8–11 months, as these treatments are common among pre-HSCT recipients and can lead to false-positive serologies (15, 16). Care should also be taken when interpreting CMV serologies in infants ≤12 months of age, given influence of transplacental maternal antibody (17, 18).

Providers should also consider the graft source. Matched unrelated, mismatched and HLA-haploidentical transplants have an increased risk of CMV infection compared to matched related transplants, possibly secondary to greater immune suppression (9, 19–21). Receipt of T-cell depleted or umbilical cord allografts (which are deficient in CMV-specific T-cells) are particularly associated with a very high risk of CMV infection.

It is also important to consider if the patient is currently breastfeeding, as CMV can be transmitted *via* breast milk. Up to 96% of CMV seropositive breastfeeding mothers develop CMV reactivation at some time during lactation (22). Amongst patients with severe combined immune deficiency breastfed by CMV seropositive mothers, there is a 5%–6% CMV transmission rate (23). For mothers of infants undergoing evaluation for HSCT, consideration can be given to testing for CMV antibodies. Some advocate for CMV seropositive mothers to refrain from breastfeeding due to the risk of CMV transmission and the potential for devastating outcomes (24).

CMV prevention strategies

There are two main strategies for CMV disease prevention following HSCT: preemptive therapy and universal prophylaxis. The overall risk of CMV disease is considered in determining the appropriate preventive approach.

Preemptive therapy involves instituting serial CMV monitoring and beginning CMV antiviral therapy at a pre-defined threshold of viral load (25). This approach is more likely to be considered in patients deemed to be at a lower risk of CMV reactivation. Preemptive therapy involves once weekly CMV quantitative polymerase chain reaction (PCR) monitoring until day +100 with initiation of CMV-active antivirals if CMV PCR becomes positive or rises above a certain level. Though some thresholds have been suggested, there is no widely-accepted universal viral load threshold at which to initiate therapy; the decision to initiate therapy should be determined by each treatment center based on the assay used, patient risk factors (e.g., donor/recipient CMV serostatus, overall state of immune suppression), and the rate of rise of viral load (7, 26).

Universal prophylaxis is the strategy of administering anti-CMV drug prophylaxis (**Table 1**) to at-risk recipients prior to the development of CMV viremia at a pre-defined time point after transplant. Universal prophylaxis is often pursued in patients at higher risk such as recent primary CMV infection immediately prior to transplant, CMV-seropositive patients receiving a graft from seronegative donors, those who receive T-cell depleting therapies (e.g., alemtuzumab or antithymocyte globulin) and recipients of T-cell depleted, HLA-mismatched, haploidentical or umbilical cord blood allografts (36). Potential adverse effects of antiviral medications are an important consideration with use of universal prophylaxis. Ganciclovir

TABLE 1 Antiviral prophylaxis and treatment in pediatric HSCT recipients (27–35).

Medication	Prophylaxis	Prophylaxis dose[a]	Treatment	Treatment dose[a]
Ganciclovir	Y	5 mg/kg/dose IV q24 h	Y	5 mg/kg/dose IV q12 h
Valganciclovir	Y	7 × BSA[b] × CrCl[c] PO q24 h (max 900 mg/day)	Y	7 × BSA[b] × CrCl[c] PO q12 h (max: 900 mg/dose)
Foscarnet[d]	Y	60 mg/kg/dose IV q12 h for 7 days then 90–120 mg/kg/dose qDay	Y	60 mg/kg/dose IV q8 h; Maintenance: 90 mg/kg qDay
Cidofovir[e]	Y[f]	5 mg/kg/dose qWeek × 2 weeks then 5 mg/kg/dose every other week	Y	5 mg/kg/dose qWeek × 2 weeks then 5 mg/kg/dose every other week
Letermovir (≥18 years)	Y	480 mg PO IV q24 h	N	NA
Maribavir (≥12 years and ≥35 kg)	N	NA	Y	400 mg PO BID

[a]Dosing given is for patients with normal renal function.
[b]BSA, body surface area.
[c]CrCl, creatinine clearance, using modified Schwartz formula which bases k constant on age.
[d]IV hydration should be given as 10–20 ml/kg (max 1,000 ml) prior to initial infusion and then 10–20 ml/kg (max 1,000 ml) given concurrently with subsequent doses.
[e]Should be given with probenecid (25–40 mg/kg/dose (max 2,000mg) PO 3 h prior to cidofovir and 10–20 mg/kg/dose (max 1,000 mg) 2–3 h and 8–9 h after cidofovir) as well as IV hydration (10–20 ml/kg pre- and post-cidofovir OR increase maintenance IVF by 1.5–2x).
[f]Less commonly used due to availability of other agents with more favorable side effect profiles.

and valganciclovir have the undesirable side effect of myelosuppression, which can delay or reverse neutrophil engraftment. The resulting prolonged lymphopenia and/or neutropenia places the patient at risk for other opportunistic bacterial and fungal infections (37, 38). Foscarnet and cidofovir could also be considered and may be preferred due to less bone marrow toxicity. However, these medications can lead to renal toxicity and/or electrolyte abnormalities. Letermovir has been Food and Drug Administration (FDA) approved for CMV prophylaxis in adult HSCT recipients aged 18 years or older, though has not yet received approval for use in children (27). Despite this, several centers have begun using letermovir in pediatric HSCT patients and have reported promising outcomes (39–42). Maribavir is the newest antiviral to have received FDA approval. This medication is only approved for the treatment of refractory/resistant CMV infection or disease in patients 12 years of age and older and weighing ≥35 kg, and has not been approved for prophylaxis (28).

Another proposed prevention strategy is pre-transplant ganciclovir or valganciclovir. With this strategy, CMV seropositive patients receive ganciclovir or valganciclovir at the start of conditioning and through day −2. Patients are subsequently followed by preemptive therapy as noted above. Research has shown lower rates of CMV reactivation amongst patients receiving pre-transplant ganciclovir, with incidence of reactivation comparable to patients receiving letermovir (43). One study showed earlier time to reactivation amongst patients who did not receive pre-transplant valganciclovir, though noted no overall impact on rate of CMV reactivation or survival at 100 days (44).

Blood transfusions carry an additional risk of CMV transmission. Transfusion-associated CMV infection occurs due to reactivation of latent CMV infection in transfused monocytes (45), although the risk is exceedingly small with the use of leukoreduced blood products (46). Therefore, only CMV-negative or leukocyte-reduced blood products should be administered to patients in whom HSCT is anticipated or planned (47).

CMV hyperimmune globulin (CMVIG) is not recommended for routine use for prophylaxis in pediatric HSCT recipients. While some research has indicated that receipt of IVIG may decrease risk of CMV infection or disease, particularly in the first year after transplant, other studies have indicated no benefit beyond what is provided by antiviral drugs (48–50).

Despite a decades-long effort to develop a CMV vaccine, there is no vaccine available for clinical use. Research is ongoing regarding vaccinations to boost CMV immunity in high-risk patients. There are several vaccines under investigation, including clinical trials in pediatric patients (51, 52).

Diagnosis of CMV infection and disease

In this section, we will discuss general diagnostic principles. Further details on diagnosis of specific disease manifestations are discussed in the relevant case presentations.

When CMV is detected in a clinical sample, it should then be determined if the patient is experiencing CMV infection or CMV disease. CMV infection is defined as the presence of CMV replication in tissue, blood, or other bodily fluids regardless of symptoms. CMV disease is the presence of CMV infection in the setting of attributable symptoms (e.g., fever, hypoxia, or diarrhea). CMV disease is generally divided into CMV syndrome (a term used only in solid organ transplantation) or CMV end-organ disease. CMV syndrome often manifests with constitutional symptoms of fever and malaise as well as laboratory findings of atypical lymphocytosis, leukopenia,

neutropenia, thrombocytopenia and/or elevated hepatic transaminases; this terminology is generally not used in HSCT because of the common occurrence of the signs and symptoms (e.g., leukopenia, thrombocytopenia) even in the absence of active CMV replication. CMV end-organ disease presents with symptoms in the affected organ, such as abdominal pain or diarrhea in gastrointestinal disease or hypoxia, dyspnea, and new pulmonary infiltrates in pneumonia (7, 14).

Nucleic acid amplification testing (NAT) is the preferred method of diagnosis of CMV infection. This testing most commonly uses PCR to detect viral DNA (or, less commonly, RNA). Detection of RNA is a more specific marker for viral replication (but it is a less sensitive target), while presence of DNA does not necessarily reflect active viral replication (7, 53–55). There is currently no commercial assay available for CMV RNA. When NAT testing is performed, quantitative methods should be used. Quantitative methods allow differentiation between detection of latent virus (e.g., low-level DNA-emia) vs. active replication (such as with high or rising viral load) and allow for monitoring of change in viral load over time. The change in viral load is important to measure treatment response, progression of viremia and risk of CMV disease (7). Research has indicated that a higher initial viral load as well as a higher logarithmic rate of rise in viral load are both risk factors for development of CMV disease (56).

Histopathology is the gold standard for definitive diagnosis of end-organ CMV disease (7, 57). Samples can be collected from the source tissue of interest, such as the intestine or lung. Hematoxylin and eosin preparations as well as immunohistochemical stains are performed and the samples are evaluated for CMV viral inclusions (58). The exception to this is CMV retinitis, which is diagnosed primarily through classic ophthalmologic examination findings, with PCR of vitreous fluid used only at times to confirm the diagnosis, particularly in atypical cases (9, 59, 60). It should be noted that obtaining samples for confirmative histopathology review may not always be feasible given the inherent invasive nature of this testing. Often, HSCT patients have thrombocytopenia that limits the performance of invasive procedures.

Other methods of testing, including pp65 antigen testing (detection of CMV antigen on peripheral blood leukocytes) and conventional or shell vial viral culture, have largely fallen out of favor in the era of molecular assays. Viral culture, though highly specific for diagnosis of CMV infection, has poor sensitivity and takes longer to result (61, 62). CMV pp65 antigenemia on the other hand is labor intensive and lacks standardization (7).

General management strategies

Management of CMV infection and disease in HSCT patients requires a multidisciplinary approach involving the infectious diseases specialist, stem cell transplant physician, pharmacist, and other providers. Immunosuppression should be reduced as a first step, as rapidly as possible (7). In allogeneic HSCT recipients, this may mean a rapid wean and discontinuation of tacrolimus, sirolimus, mycophenolic acid or other prophylactic drugs against GVHD. In cases of asymptomatic, low-grade CMV viremia, this may be the only intervention necessary to control infection.

However, in some HSCT patients, particularly those with active GVHD, reduction of immune suppression may not always be feasible. Antiviral therapy is often necessary for management of CMV infection and disease in these patients.

First-line antiviral agents are intravenous (IV) ganciclovir and oral (PO) valganciclovir. As noted previously, these agents are myelosuppressive. IV ganciclovir is recommended for initial management in those with severe disease, very high viral load, and those with concerns regarding absorption. PO valganciclovir is a reasonable option in mild-moderate disease when the patient can reliably take oral medication. Valganciclovir is also used as oral step-down therapy in patients with CMV disease who have demonstrated good clinical and virologic response to initial IV ganciclovir treatment (7, 36). Doses of ganciclovir and valganciclovir are noted in **Table 1**.

Other antiviral medications include foscarnet and cidofovir. Both medications are only available in IV form, and both are nephrotoxic. In some centers, foscarnet is the preferred drug for CMV treatment in the pre-engraftment period given concerns of bone marrow toxicity with ganciclovir and valganciclovir (**Table 1**). Additionally, both medications can be used for treatment of refractory or resistant CMV infection or disease (**Figure 1**) (7).

Maribavir is a CMV antiviral agent that was approved in November 2021 for treatment of refractory and/or resistant CMV infection and disease in adults and children aged 12 years or older and weighing at least 35 kg (28). As noted previously, letermovir is approved for CMV prophylaxis, though is not approved for treatment of CMV infection or disease (**Table 1**) (27). There are case reports of letermovir use as salvage therapy in refractory/resistant CMV infection, however, there is concern for low threshold for resistance following exposure to letermovir (65, 66).

CMV antiviral therapy should be continued until symptomatic resolution and viral clearance, and all patients should receive at least 2 weeks of therapy. Depending on the sensitivity of the assay used, viral clearance may be defined as undetectable viral load for 1–2 weeks (7). The role of secondary antiviral prophylaxis is debated but may be considered for HSCT patients with ongoing risk factors for recurrence of CMV infection. If secondary antiviral prophylaxis is not provided, HSCT patients should undergo weekly CMV surveillance to monitor for recurrence or relapse (47).

A more recent investigational therapy is the utilization of CMV-specific cytotoxic T lymphocytes (CTLs). CTLs are produced by using CMV antigen peptides to induce CMV-

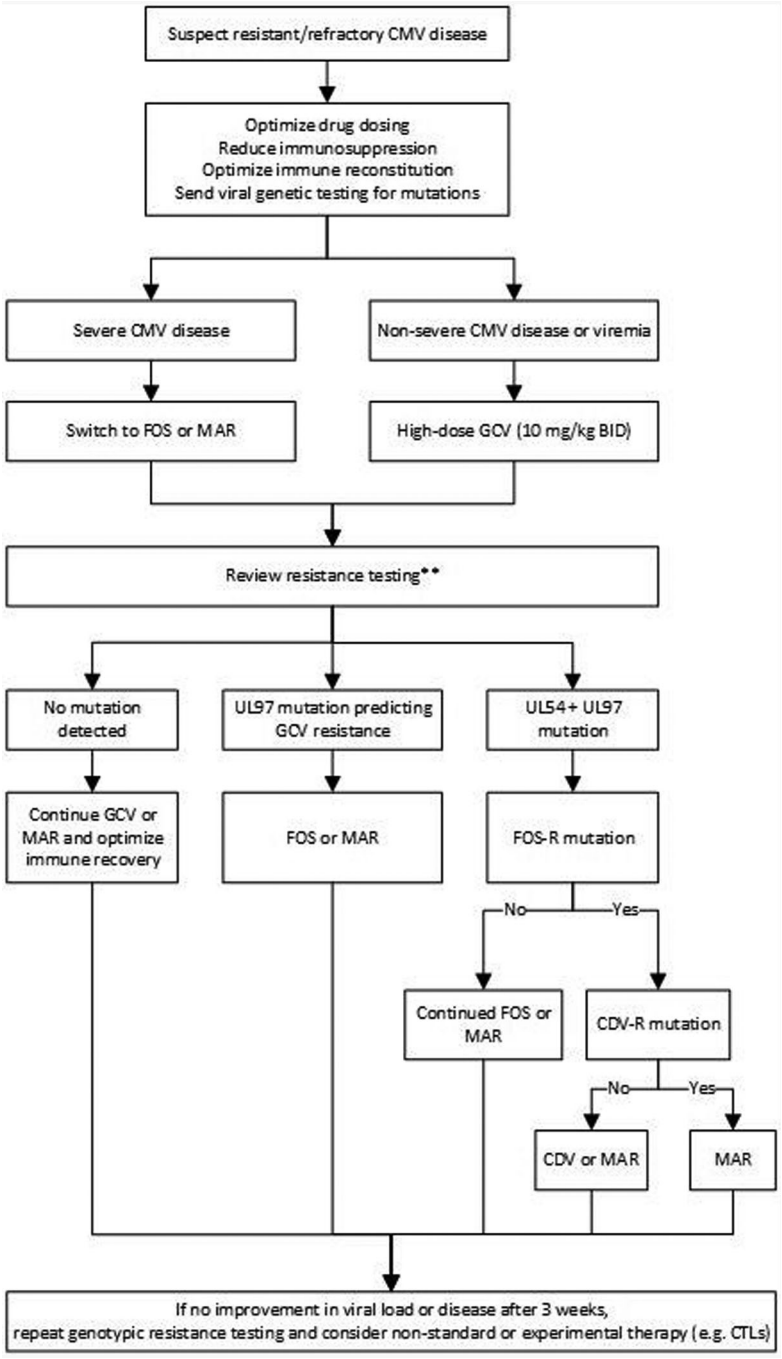

FIGURE 1
Proposed treatment algorithm for refractory/resistant CMV infection or disease (7, 9, 63, 64). GCV, ganciclovir; FOS, foscarnet; MAR, maribavir; CDV, cidofovir. **In the rare instance of UL54 mutation that predicts FOS-R alone (GCV-S) and without UL97 mutation, resume GCV.

specific T-cells in donor blood (67). There are limited studies on the use of CTLs for treatment of CMV infection in children, though available data suggest this could be a safe and effective therapy for treatment in pediatric HSCT recipients (68, 69). Availability of this therapy is currently limited to clinical trials.

CMVIG is another available therapeutic option in addition to an antiviral drug. CMVIG is a pooled plasma product containing a high titer of anti-CMV antibody (70). CMVIG has been investigated as salvage therapy in adults with CMV infection post allogeneic HSCT (71, 72). While this therapy has been well-tolerated, the benefit has not been proven.

CMVIG has also been used as salvage therapy in pediatric populations, though pediatric-centered research is lacking. Additionally, intrathecal CMVIG has been suggested as a potential adjunctive treatment for CMV encephalitis. With few anecdotal cases in adults showing mixed results, this is not regarded as a preferred strategy (73, 74).

Non-CMV-specific high-dose IVIG has historically been used in management of CMV disease, particularly in treatment of CMV pneumonia (75). However, recent research has failed to clearly support the role of IVIG these patients (75–77). Current pediatric HSCT guidelines recommend IVIG therapy only in cases of hypogammaglobulinemia (78, 79).

Clinical case examples

Case presentation 1: CMV DNAemia pre-transplant

A 6-month-old boy with Wiskott-Aldrich Syndrome was admitted for conditioning in preparation for a matched unrelated donor bone marrow transplant (MUD HSCT) (CMV D−/R+). Pre-transplant antimicrobial prophylaxis included daily trimethoprim-sulfamethoxazole, amoxicillin, and monthly IVIG. Pre-transplant infectious diseases work-up demonstrated positive CMV, Epstein-Barr (EBV) and herpes simplex virus (HSV) IgG though interpretation of these results was complicated by recent receipt of IVIG as well as possible maternal antibodies. A CMV viral load was obtained one day prior to transplant and was noted to be 5,000 IU/ml. The patient had no evidence of CMV disease, including retinitis. He received busulfan and cyclophosphamide for conditioning and underwent BMT as planned. He subsequently received GVHD prophylaxis with daily tacrolimus 0.6 mg BID, a single dose of alemtuzumab 3 mg and mini methotrexate 1.75 mg on days +1, +3, +6 and +11.

Due to CMV viremia, he was started on foscarnet 90 mg/kg/dose IV q12 h on day +1 for treatment, in order to avoid bone marrow toxicity associated with ganciclovir pre-engraftment. On day +11, CMVIG was initiated in addition to antiviral therapy. At the end of 2 weeks of therapy, the CMV viral load demonstrated a nearly 1-log increase. Though resistance testing through next-generation sequencing did not demonstrate any drug resistance-conferring mutations, there was concern for foscarnet resistance and the patient was switched to induction dosing ganciclovir of 5 mg/kg IV q12 h which was subsequently increased to 10 mg/kg IV q12 h due to a further rising viral load. The viral load then demonstrated a slow improvement and ganciclovir dosing was decreased to 7.5 mg/kg q12 h and then back to 5 mg/kg q12 h.

On day +31, approximately 1 month into antiviral therapy and shortly after the decrease in ganciclovir dosing to 5 mg/kg q12, the patient started to require supplemental oxygen. A computed tomography (CT) scan of the chest revealed diffuse ground-glass opacities in the setting of a rising viral load up to 110,000 IU/ml (5.04 log). The patient was transitioned back to foscarnet 60 mg/kg q8 h. A bronchoalveolar lavage (BAL) was concerning for diffuse alveolar hemorrhage (DAH). The CMV PCR on BAL fluid was positive, as would be expected with DAH in a patient with significant viremia. Cytology from the BAL fluid showed abnormal epithelial cells favored to be of a reactive/degenerative etiology with rare degenerative cells demonstrating staining suspicious for CMV. The patient required oxygen therapy for several days during this evaluation, though was quickly weaned to room air. It was felt that DAH was the primary contributor to the patient's respiratory symptoms, though CMV likely played a role, as well.

During this time, the patient's absolute lymphocyte count (ALC) remained profoundly low at $<0.1 \times 10^9$/L (normal 1.56–7.83×10^9/L). This was potentially a combined consequence of recent HSCT with myeloablative conditioning, alemtuzumab, CMV infection, and the bone marrow suppressive effects of intermittent ganciclovir. Due to persistent lymphopenia likely contributing to the difficulty in controlling infection, CTL therapy was considered. However, given the recent receipt of alemtuzumab, a T-cell antibody, CTL therapy was initially deferred. The patient underwent plasmapheresis to remove alemtuzumab, with close monitoring of alemtuzumab levels. Once the alemtuzumab level was <0.15 μg/ml, the patient was referred to a nearby study center for CTL therapy and received 2 doses, given 3 weeks apart. The CMV viral load subsequently decreased and repeat resistance testing was again negative. The ALC demonstrated improvement to 1.71×10^9/L. With an improved viral load and lymphocyte recovery, the patient was transitioned to valganciclovir 180 mg PO BID for home-going therapy.

Case discussion

This case highlights the unique challenges of managing CMV viremia before and during bone marrow transplant while awaiting immune reconstitution. Patients with CMV DNAemia at the time of transplant are among the highest risk patients for CMV infection and disease (9). This patient's course was complicated by delayed lymphocyte recovery, likely a result of the combination of his myeloablative conditioning regimen, GVHD prophylaxis with alemtuzumab, CMV-induced lymphopenia, and possible contribution of bone marrow suppression secondary to intermittent therapy with ganciclovir.

Also highlighted in this case is the patient's diagnosis of probable CMV pneumonia. He had bronchoscopy findings concerning for DAH with cytology suspicious for CMV. DAH is an uncommon complication of HSCT, typically occurring in the early post-transplant period. Additionally, DAH in HSCT patients is, by definition, non-infectious (80). However, CMV viremia with cytology suspicious for CMV was

concerning for possible contribution of CMV to the patient's respiratory symptomatology.

While not the clear sole cause of this patient's symptoms, CMV pneumonia is a significant concern in immunocompromised patients. CMV pneumonia is one of the most severe manifestations of CMV infection in HSCT recipients and has a mortality rate of up to 50% even with treatment (81, 82). This diagnosis is made by a combination of new infiltrates on imaging and respiratory symptoms (e.g., tachypnea, dyspnea, hypoxia) in the setting of CMV detected in lung tissue or BAL fluid. The diagnosis is considered proven if CMV is documented in lung tissue by viral isolation, culture, histopathology, immunohistochemistry, or DNA hybridization techniques and probable if CMV is detected in BAL fluid by viral isolation, culture, or PCR (7).

Case presentation 2: Resistant CMV

In continuation of case #1, the patient was noted to have a rising CMV viral load once again after 4 months of antiviral therapy [from 653 (2.81 log) to 3,310 IU/ml (3.52 log)]. He also had chronic diarrhea, which raised concern for CMV intestinal disease or gastrointestinal GVHD. A duodenal biopsy was obtained and demonstrated sparse inflammatory cells in the lamina propria with crypt apoptosis and negative CMV immunostain. While crypt apoptosis can be associated with GVHD, the patient was also noted to have *Clostridioides difficile* infection, which can also cause these findings (83, 84). The patient had no other symptoms suggestive of CMV disease, including respiratory compromise. Given prolonged exposure to ganciclovir, valganciclovir and foscarnet, resistance testing was performed, and showed a L595W mutation in the UL97 gene, predicting resistance to ganciclovir. Notably, although the patient's ALC had improved to around 1.0×10^9/L, quantitative lymphocyte subsets revealed primarily (70%) CD19 cells with a CD4 count of 12 cells/mcl, CD8 count of 2 cells/mcl and CD3 count of 28 cells/mcl. T-cell receptor excision circles (TREC) analysis demonstrated pan-T-cell lymphopenia, consistent with poor T-cell reconstitution following HSCT. It was felt that lymphopenia was contributing significantly to the patient's ongoing CMV viremia. For therapy optimization, the patient was transitioned to foscarnet 60 mg/kg q8 h and received a third dose of CMV-specific CTLs.

After 2 months on foscarnet (and approx. 6 months post-transplant), the patient continued to have detectable viral load, rising again to a height of 7,900 IU/ml. He was re-admitted due to hematemesis. Ophthalmologic exam showed CMV retinitis with small intraretinal hemorrhages and small subretinal lesions amenable to monitoring. Repeat resistance testing revealed a A834P mutation of UL54 (with no UL97 mutation), predicting resistance to ganciclovir, foscarnet and cidofovir. His ALC had improved to 2.01×10^9/L, though still with predominance (59%) of CD19 cells, and improved but persistently low CD4 count of 141 cells/mcl, CD8 count of 157 cells/mcl and CD3 count of 377 cells/mcl. Ganciclovir was restarted, in addition to foscarnet.

After approximately 1 week on dual antiviral therapy, the patient developed respiratory distress with hypoxia and increased work of breathing. A CT chest revealed bilateral opacities. The CMV viral load was 1,100 IU/ml. Due to concern for CMV pneumonia in the setting of multi-drug resistant CMV, ganciclovir was discontinued, and the patient was started on maribavir 400 mg/dose BID. CMVIG was continued weekly. Within 24 h of transition to maribavir, however, the patient developed worsening respiratory distress and required transfer to the pediatric intensive care unit. Bronchoscopy with BAL demonstrated normal lower airways. The BAL fluid analysis showed a total nucleated cell count of 1.8 and predominance of alveolar macrophages. Infectious diseases work-up on the BAL fluid showed negative bacterial, fungal and mycobacterial cultures, as well as negative aspergillus antigen and negative PCRs for *Pneumocystis jirovecii*, adenovirus, CMV, influenza and respiratory syncytial virus. An esophagogastroduodenoscopy showed esophageal ulcers; biopsy of the esophagus revealed reactive squamous esophageal mucosa with rare inflammatory infiltrate, no apoptotic bodies, no definitive GVHD, negative periodic acid-Schiff (PAS) stain and negative CMV immunostain.

CMV viral load remained elevated at 1,620 IU/ml 3 days after initiation of dual therapy with maribavir and foscarnet. The patient received a fourth dose of CTLs. The ophthalmologic exam remained stable. The patient unfortunately progressed to severe acute respiratory distress syndrome (ARDS) with refractory hypoxia, necessitating transition to extracorporeal membrane oxygenation (ECMO). Suspicion rose for an alternative etiology of ARDS, including DAH, idiopathic pneumonia syndrome (IPS) or cryptogenic organizing pneumonia. The patient was started on methylprednisolone. After approximately 2 weeks on maribavir, the CMV viral load showed improvement, decreasing to 550 IU/ml. However, given the patient's critical status, he was also started on letermovir 240 mg IV BID, leflunomide 5 mg PO q24 h and artesunate 3 mg/kg IV q24 h for additional CMV-active antiviral therapy. A lung biopsy revealed acute lung injury with predominant features of organizing diffuse alveolar damage and a component of necrotizing bronchiolitis. Immunohistochemical stains were initially negative for CMV, varicella zoster virus (VZV), adenovirus and HSV 1 and 2. With initial negative infectious work-up of lung biopsy, artesunate, leflunomide and letermovir were discontinued and the patient was started on etanercept and tocilizumab for management of a post-HSCT inflammatory disorder. Later re-evaluation of the lung biopsy showed rare CMV positive cells of unclear significance in the setting of ongoing CMV viremia.

The CMV viral load continued to improve on combination therapy with maribavir and foscarnet (to 94 IU/ml). Unfortunately, the patient continued to have complications of ARDS, prompting redirection of cares to comfort measures and the patient passed away.

Case discussion

Refractory or resistant CMV infection or disease occurs in cases where the CMV viral load continues to rise and/or symptoms of CMV disease fail to improve despite appropriate antiviral therapy for 2 weeks or more (7).

Refractory CMV infection is defined as a CMV viral load increasing by 1 log or more, or fails to decline by 1 log, after 2 weeks of appropriately dosed antiviral therapy. Probable refractory infection is considered if the viral load increases by <1 log after at least 2 weeks of appropriately dosed antiviral therapy. Refractory CMV disease occurs when symptoms are persistent despite at least 2 weeks of appropriate treatment. In cases of refractory infection, one must reassess status of immune suppression, confirm appropriate antiviral drug dosing and consider genotypic resistance testing. If resistance is present, drug therapy should be tailored to susceptible medications (**Figure 1**). Individual mutations can confer low- or high-level resistance, and multiple mutations can be additive, leading to high-levels of resistance (85).

As reported previously, maribavir is approved for treatment of refractory/resistant CMV infection or disease in patients 12 years of age and older. There is no dosing information available for children under 12 years of age. As this patient had multi-drug resistant CMV with few remaining therapy options and was clinically worsening on dual therapy with ganciclovir and foscarnet, we proceeded with full-dose therapy with maribavir in combination with continued foscarnet. This therapy did appear to have some effect, with decreasing viral load within 2 weeks of starting maribavir.

In this case, the patient also briefly received letermovir in the setting of ARDS and concern for CMV pneumonia. As noted previously, letermovir is not FDA approved for CMV prophylaxis or treatment in children, though is used off-label at some pediatric centers for prophylaxis and in select cases reported as salvage therapy (39–42, 86–88). With the lack of treatment options in resistant CMV infection, the favorable side effect profile of letermovir (including less bone marrow toxicity) and lack of cross-resistance with other antivirals (due to different therapeutic target sites), interest in the use of letermovir as salvage therapy has grown. As noted above, while some studies have shown a potential benefit with letermovir monotherapy or combination antiviral therapy in refractory or resistant CMV infection, resistance can develop quickly (66, 86).

Antiviral therapy is the mainstay of therapy for CMV infection and disease post-HSCT, though several adjunctive therapies are available. Adjunctive treatments are largely of questionable benefit, particularly in pediatrics. This patient received adjunctive treatment with leflunomide, artesunate and CMVIG. Leflunomide is an immunosuppressive drug typically used to treat autoimmune conditions or solid-organ transplant rejection (89). Leflunomide has also been found to have novel anti-CMV activity (either by inhibition of pyrimidine synthesis or inhibition of tyrosine kinase activity) and potential use in treatment of refractory/resistant CMV infection and disease (89–91). Artesunate, an anti-malarial medication, is thought to have antiviral activity *via* inhibition of CMV replication by interference with host cell kinase signaling systems (92). Studies on use of artesunate in resistant CMV infections have shown mixed results, with most success noted in mild CMV infection without organ involvement, though failure to prevent development of disease in some patients (93–95). The benefit of CMVIG as salvage or adjunctive therapy is also questionable, though is generally well tolerated.

Case presentation 3: CMV pre-engraftment

A 3-year-old girl with acute lymphoblastic leukemia (ALL) and stage 4 neuroblastoma was admitted for allogeneic HSCT from a MUD (CMV D+/R+, EBV D−/R−). She received myeloablative conditioning with total body irradiation, cyclophosphamide 60 mg/kg, and etoposide 1,500 mg/m^2. Within 1 week following HSCT, she developed CMV reactivation with low-level viremia (<100 IU/ml). Viremia was initially monitored without treatment, though with rapid rise of nearly one-log within 4 days (up to 424 IU/ml), she was started on foscarnet 60 mg/kg/dose q12 h. Foscarnet was continued for nearly 2 weeks, though the patient was transitioned to ganciclovir 5 mg/kg q12 h when the viral load continued to rise, due to concerns for resistance. She was noted to have diarrhea and rising ALT, concerning for CMV enteritis. An endoscopy was performed, and pathology demonstrated a single inclusion of a normal-sized nucleus with no CMV-type cytomegalic changes; this finding was felt to be of questionable clinical significance. In the setting of concern for probable CMV gastrointestinal disease, she was started on adjunctive CMVIG once weekly. The patient continued to have fevers, diarrhea, and elevated liver enzymes, prompting extensive work-up including unrevealing CT chest/abdomen and stool testing positive for *C. difficile*. The patient was started on PO vancomycin for *C. difficile*. Additional evaluation revealed adenovirus viremia (45,720 copies/ml of plasma) providing an alternate explanation for colitis and hepatitis. Cidofovir 5 mg/kg weekly was subsequently added (in addition to ganciclovir) to the antiviral regimen to provide treatment for adenovirus.

The patient responded to ganciclovir and was transitioned to valganciclovir. However, after a little over a month of ganciclovir/

valganciclovir therapy, the CMV viral load rose substantially (up to 19,500 IU/ml). Throughout her treatment course, the patient had continued to have profound lymphopenia ($<0.2 \times 10^9$/L), which likely hindered her ability to mount an appropriate response to concurrent viral infections. Therefore, she was transferred to a study center for treatment with CMV- and adenovirus-specific CTLs. Letermovir 240 mg daily was also added for salvage therapy for approximately 1 week, later discontinued due to lack of evidence of benefit and to preserve letermovir for future prophylactic use.

CMV resistance testing was performed and demonstrated resistance to ganciclovir and cidofovir *via* A594V and T503I mutations, respectively. Ganciclovir was stopped and foscarnet 60 mg/kg q8 h was restarted. Cidofovir was continued for management of adenovirus viremia.

The patient underwent ophthalmologic exam shortly after diagnosis of CMV viremia that demonstrated no evidence of retinitis. However, approximately 1 month later, she was noted to have findings concerning for bilateral CMV retinitis, including white fibrotic lesions and white-centered intraretinal hemorrhages as well as a possible juxtafoveal lesion that was felt to be potentially vision-threatening. Despite this, the patient did not have any vision changes. A CMV PCR from the intravitreal fluid was negative. With concern for threatened vision and findings consistent with CMV retinitis, intravitreal foscarnet dose of 2,400 mcg was administered once at the time of intravitreal aspiration. Eye examinations were continued once weekly and demonstrated steady improvement. It was ultimately determined that ophthalmologic exam abnormalities might have been secondary to CMV retinitis or changes secondary to blood dyscrasia.

In the setting of ongoing lymphopenia and concern for graft failure, the patient ultimately received a second CTL infusion. She also received a peripheral blood stem cell boost with 4.86×10^6 CD34 cells/kg from her original HSCT donor. Foscarnet was discontinued when the CMV quantitative PCR was undetected twice, measured 1 week apart, and she was transitioned to letermovir 240 mg PO daily for secondary CMV prophylaxis.

Case discussion

This case illustrates several principles in management of CMV infection and disease, including the diagnosis of CMV gastrointestinal (GI) disease, CMV retinitis monitoring and treatment, and adjunctive therapies.

Though not ultimately found to be the cause of this patient's diarrhea and transaminitis, CMV gastrointestinal disease is a well-known manifestation of CMV disease (81). CMV can affect the entire gastrointestinal tract (e.g., esophagitis, colitis). Clinical manifestations include abdominal pain, nausea, vomiting, diarrhea, GI bleeding and fever (96). Diagnosis is made based on the presence of upper and/or lower GI symptoms and CMV documented in tissue by histopathology, virus isolation, culture, immunohistochemistry, or DNA hybridization. Probable diagnosis is considered if the above are present, with proven or definite disease defined as presence of the above plus macroscopic mucosal lesions (7). It is important to note that CMV GI disease can present similarly to or occur concurrently with other conditions that can cause diarrhea, including intestinal GVHD, parenteral tube feedings, or other viral infections such as adenovirus. Therefore, one must have a high level of suspicion and pursue endoscopic evaluation with biopsies in patients with recent HSCT (especially within the first 100 days post-transplant) and abdominal symptoms.

Our patient was also evaluated for CMV retinitis, a potentially vision-threatening involvement of the eye. Early stage CMV retinitis is often asymptomatic, particularly in young children who may be unable to report or describe their symptoms (97). Even in the absence of symptoms, all HSCT patients with CMV viremia who are unable to clearly articulate visual symptoms should undergo thorough evaluation by an experienced ophthalmologist; this may require sedation in some children. Diagnosis of CMV retinitis is based on ophthalmologic examination alone in the majority of cases, with positive intravitreal CMV PCR considered as supportive of the diagnosis, especially in the presence of atypical ophthalmologic exam findings (7). Ophthalmologic findings consistent with CMV retinitis include areas of white/pale necrotic retina and focal areas of hemorrhage spreading centrifugally along vascular arcades (98). Treatment includes systemic antiviral therapy and/or intravitreal injections of antivirals (99–101).

As noted in case 2, adjunctive therapies including letermovir and CMVIG are of questionable benefit, particularly in the pediatric population.

Case presentation 4: CMV during treatment for GVHD

A 12-year-old boy with chronic myeloid leukemia (CML) was admitted for allogeneic HSCT from a matched sibling donor (CMV D−/R+, EBV D+/R+). He received conditioning with busulfan, cyclophosphamide. He received daily tacrolimus and methotrexate on days +1, +3, +6 and +11 for GVHD prophylaxis. He tolerated HSCT well and engrafted on day +21. Due to his high-risk CMV status, he received letermovir 480 mg PO daily until day +100 with undetected weekly CMV blood PCR.

Approximately 3 months post-engraftment, the patient presented to the transplant clinic with a generalized rash, conjunctivitis, photophobia, and mouth sores. A skin biopsy was obtained which showed interface vacuolar dermatitis, focal subepidermal blisters and mixed dermal inflammation with few eosinophils, consistent with grade III GVHD. CMV stain of the skin biopsy was negative. He was treated with

light therapy as well as prednisone 30 mg PO BID with improvement and subsequent slow steroid wean.

Five months post-engraftment, the patient was readmitted with chronic cough, progressively increasing shortness of breath and exercise intolerance. He was found to have low oxygen saturations in the mid-80s on room-air. A CT chest demonstrated multifocal ground-glass opacities bilaterally, predominantly in a peribronchial vascular distribution, scattered subpleural ground-glass opacities and mild cystic bronchiectasis. A bronchoscopy with BAL showed thick cloudy secretions in multiple segments with no mucosal edema and negative infectious evaluation, including negative bacterial, fungal, and mycobacterial cultures, negative *P. jirovecii* PCR and negative CMV PCR. With negative infectious work-up, the patient was diagnosed with pulmonary GVHD and started on 5 mg ruxolitinib PO daily.

Due to the risk of reactivation of CMV and EBV on ruxolitinib, CMV and EBV quantitative PCRs were monitored once weekly. Approximately 3 weeks after starting ruxolitinib, the patient developed CMV viremia up to 5,000 IU/ml. He was started on ganciclovir 5 mg/kg/dose q12 h with a rapid decline in CMV viral load. After 4 weeks of induction therapy with ganciclovir, the patient had 2 consecutive undetected CMV PCRs and he was transitioned to ganciclovir 5 mg/kg/dose q24 h followed by valganciclovir for maintenance while receiving treatment for GVHD.

Case discussion

This case demonstrates the importance of CMV monitoring, prophylaxis, and treatment during treatment for GVHD. Immune suppression given for treatment of GVHD increases the risk of several infections, including reactivation of herpesviruses, other viral illnesses, fungal infections and bacterial infections (5). Some GVHD management strategies may increase risk of CMV reactivation compared to others. Specifically, post-transplant cyclophosphamide has been associated with increased incidence of CMV infection in both haploidentical and matched HSCT (102, 103).

During treatment for GVHD, patients should have serial monitoring for reactivation of herpesviruses, including both CMV and EBV. Antiviral induction therapy should be initiated with detection of CMV viremia and continued until CMV viremia has resolved. Following resolution of viremia, regular CMV monitoring with pre-emptive antiviral therapy vs. secondary prophylaxis should be continued until the patient has completed therapy for GVHD and risk factors for CMV reactivation are no longer present (104).

Case presentation 5: Late-phase CMV

A 16-year-old boy with refractory acute myelogenous leukemia (AML) underwent a haploidentical allogeneic HSCT (CMV D+/R+, EBV D+/R+). He had previously received two cycles of FLAG-IDA chemotherapy. He received conditioning with fludarabine 25 mg/m^2 for 3 days and total body irradiation 150 cGy BID for 4 days. Though he initially appropriately engrafted, he subsequently developed lymphopenia as low as 0.44×10^9/L (normal $1.0–3.2 \times 10^9$/L). His post-transplant course was complicated by peripheral demyelinating and axonal sensorimotor neuropathy (requiring plasma exchange and rituximab), aspiration pneumonia, ventilator-associated pneumonia, central line-associated bloodstream infection, and pulmonary aspergillosis. He continued to receive prophylactic antivirals, letermovir and acyclovir, which were begun in the immediate peri-transplant period, until he demonstrated appropriate lymphocyte recovery.

At that time, immune competence studies were performed to determine if ongoing antiviral prophylaxis was required. These studies were relatively reassuring with a CMV immune competence assay consistent with effective immunologic response, normal lymphocyte proliferation to mitogens and moderately decreased lymphocyte proliferation to antigens. With this reassuring evaluation, consistent improvement of ALC to $>1.0 \times 10^9$/L and normal CD4 count at 600 cells/mcl (normal 497–2,267 cells/mcl), both antivirals were stopped approximately 6 months after engraftment. CMV PCRs were monitored once weekly for 4 weeks after stopping letermovir. One month after stopping CMV prophylaxis, the patient was noted to have a CMV viral load of 454 IU/ml, which increased to 826 IU/ml 2 days later with concurrent ALC of 2.0×10^9/L. He remained an outpatient and clinically stable. Valganciclovir was started with rapid improvement in viral load to 43 IU/ml.

Given the history of long-term antiviral therapy, resistance testing was sent and revealed a L501F mutation in UL54, conferring predicted resistance to ganciclovir and cidofovir. However, given his rapid response to valganciclovir, this therapy was continued. The patient completed a total of 4 weeks of therapy with valganciclovir, having two undetected quantitative CMV PCRs documented prior to completing therapy. The patient returned to his home country during this time and recommendations were provided to administer secondary CMV antiviral prophylaxis and repeat immunologic testing.

Case discussion

This case demonstrates the ongoing risk of CMV reactivation in the late-phase (>100 days) following HSCT. Risk factors for late-phase reactivation include allogeneic HSCT (most notably MUD or T-cell depleted HSCT), chronic GVHD, steroid use, low lymphocyte counts (particularly low CD4), and delay in development of high-avidity anti-CMV antibody (105).

CMV immune competence assays, which quantitatively and qualitatively measure T-cells against CMV antigens, are used as

a means of evaluating immune reconstitution following HSCT or solid-organ transplant. Research indicates that recovery of CMV-specific CD4+ and CD8+ T-cells is important in controlling CMV disease after HSCT (106).

This patient experienced CMV reactivation following T-cell reconstitution and demonstration of CD8 immune competence. It should be noted that this patient did not develop CMV disease and, despite predicted resistance to ganciclovir, this patient responded to a rather short course of therapy with valganciclovir. Both findings are likely secondary to immune reconstitution, improving the patient's ability to manage CMV reactivation without multiple or prolonged interventions.

Discussion

Pediatric patients receiving HSCTs are at high risk of infectious complications from bacterial, fungal, parasitic, and viral pathogens. Among viruses, CMV is an important cause of illness in these patients, including life or vision-threatening disease. CMV must be considered at pre-transplant evaluations, at the time of transplant and in the early and late-phases post-transplant.

Prior to transplant, providers should ascertain donor and recipient CMV serostatus and consider the planned conditioning regimen and HSCT source to determine the ultimate risk of CMV infection and disease in each individual patient. CMV prophylaxis should be administered in patients at high risk for CMV infection and disease, or pre-emptive monitoring enacted to ensure early identification of viremia. As illustrated by the cases in this review, treatment of CMV infection can be complicated, particularly in HSCT patients, in whom T-cell recovery may be delayed, and considering the high incidence of myelosuppression with antiviral agents. Adjunctive therapies are available, though often have limited data support, particularly in the pediatric population.

Preventing and managing CMV in pediatric HSCT patients is a team effort with experts in stem cell transplant, infectious diseases, and pharmacy involvement. This review serves as a reference to manage these patients, including some of the most complex and difficult scenarios as illustrated by the cases presented in this report.

Author contributions

All authors listed have contributed to conception and design; critically revised the manuscript; gave final approval; agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interest

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Publisher's note

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Outcomes for critical illness in children with cancer: Analysis of risk factors for adverse outcome and resource utilization from a specialized center in Mexico

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Introduction: Children with cancer have a higher risk of adverse outcomes during critical illness than general pediatric populations. In Low- and middle-income countries, lack of resources can further negatively impact outcomes in critically ill children with cancer.

Methods: In this study, we describe the outcomes of a large cohort of children with cancer including mortality and resource utilization. We performed a retrospective review of all patients admitted to our PICU between December 12th, 2013 and December 31st, 2019. Outcomes were defined as recovery or death and resource utilization was described via use of critical care interventions, Length of stay as well as PICU- and Mechanical Ventilation-free days.

Results: Overall mortality was 6.9% while mortality in the unplanned admissions was 9.1%. This remained lower than expected mortality based on PIM2 scoring. Type of PICU admission, Neurological Deterioration as a cause of PICU admission, and PIM2 were significant as risk factors in univariate analysis, but only PIM2 remained significant in the multivariate analysis.

Discussion: Our Study shows that high survival rates are achievable for children with cancer with critical illness in resource-limited settings with provision of high-quality critical care. Organizational and clinical practice facilitating quality improvement and early identification and management of critical illness may attenuate the impact of known risk factors for mortality in this population.

KEYWORDS

pediatric intensive care unit (PICU), onco-critical care, pediatric cancer, low- and middle-income countries (LMIC), outcomes, resource utilization

Introduction

An estimated 400,000 children and adolescents are diagnosed with cancer every year worldwide (1). The burden of pediatric cancer is very high, with an estimated 11.1 million years-of-life-lost (YLL) in 2017, and this burden is disproportionately shifted towards low- and middle-income countries (LMICs) where unfortunately 90% of the cases occur (2). Up to 40% of these children experience critical illness and will require care in a pediatric intensive care unit (PICU) during the course of their cancer treatment (3, 4).

While the true burden of acute critical illness is unknown, previous point prevalence studies focusing on specific diseases suggest that at least 80% of the 64 million annual deaths in children take place in LMICs, where lack of resources can negatively impact the outcomes for acute critical illness (5, 6) and oncological disease (7). In High-income countries (HICs), children with cancer have a higher risk for adverse outcomes than general pediatric patients during critical illness, with mortality ranging from 6.8-27% (4), representing mortality almost three times higher than that of previously healthy children with critical illness (8). Furthermore, a recent meta-analysis found a 27.8% mortality rate for this population in HIC, with little change over the past 20 years (9).

Although there is limited data on outcomes of critical illness for children with cancer in LMICs, available studies report higher mortality (17-50%) for selected cohorts (10–12). For instance, a recent multi-site analysis describing characteristics of deterioration events in hospitalized children with cancer in Latin America found a mortality of 27% (13). However, more data is needed to better understand the outcomes of critical illness and prognostic factors for these patients in LMICs. Moreover, critical care resource utilization in this population has not been previously described in resource-limited settings, which is particularly relevant to adequately and effectively allocate available but limited resources in LMICs.

In this study, we describe the outcomes of a large cohort of children with cancer admitted to the PICU of a single specialized pediatric cancer center in Mexico and identified potential risk factors associated with adverse outcomes. We also aim to provide a description of resource utilization in this setting.

Material and methods

Setting

Hospital Infantil Teleton de Oncologia (HITO) is a dedicated pediatric cancer hospital located in central Mexico. It is the only dedicated pediatric cancer center in the country caring for children aged 0 to 18 years old (at the time of diagnosis) and is a national referral center. HITO is a comprehensive facility with a mixed private and public funding management scheme. It includes a 27-bed inpatient ward, a 4-bed dedicated PICU and a 4-bed Hematopoietic Stem Cell transplant (HSCT) unit, as well as a patient housing facility located at walking distance from the hospital.

Data collection

We conducted a retrospective review of all patients admitted to our PICU between December 12th, 2013 and December 31st, 2019. Patients older than 18 years of age and those without a diagnosis of malignancy were excluded. In addition, patients transferred out of our PICU to another institution before resolution of their acute illness were excluded since critical illness outcomes could not be adequately followed. This study was approved by the Institutional Review Boards at HITO and St. Jude Children's Research Hospital (SJCRH).

Patients were identified using the electronic PICU admissions and discharge log and clinical information was extracted from a retrospective review of electronic medical records using a case report form. Each patient was assigned a personal study ID number and likewise each admission event was assigned an admission ID number. The de-identified data was saved in MS Excel and used for data analysis.

Definitions

Outcomes were defined as recovery or death (including death in the PICU or within 48 hrs. of PICU discharge). Patient characteristics

included gender, age, type of malignancy, type of oncological treatment received prior to PICU admission, tumor activity (relapsed or refractory disease – defined as new or persistent tumoral activity after oncological treatment vs. all others), use of steroids prior to PICU admission (yes/no), mucosal barrier injury (defined by the Center of Diseases Control in the United States of America) (14), type of PICU admission (planned - defined as an elective admission that could potentially be delayed or cancelled without increasing the immediate risk of patient death or injury, e.g., scheduled surgical admissions, vs. unplanned – medical or other emergencies where the admission cannot be delayed), main cause for PICU admission, Pediatric index of mortality 2 (PIM2) score (15) on admission, use of mechanical ventilation (yes/no), use of renal replacement therapies (RRT), PICU length of stay, duration of mechanical ventilation, PICU free days within the first 30 days and mechanical ventilation free days within the first 30 days (defined as days where the patient was alive and free of the intervention during the first 30 days following the onset of their critical illness).

Statistical analysis

Descriptive statistics were used to summarize characteristics, outcomes, and resource utilization for all PICU admissions identified. Chi-square test, Fisher Exact test, t-test or ANOVA were used to identify univariate risk factors for ICU mortality, as appropriate. Multivariable analysis of risk factors for mortality used a generalized estimating equation (GEE) model, controlling for multiple sampling (multiple ICU admissions for individual patients).

Results

A total of 469 PICU admissions in 238 individual patients were identified during the 6 years of the study period. Of these, 1 was excluded because of age >18 years and an additional 8 were excluded because they did not have a cancer diagnosis. An additional patient was eliminated because he was transferred per guardians' request to a different facility from our PICU before resolution of critical Illness, and no follow up data was available. This resulted in a final sample size of 459 admissions among 228 patients (mean 2.1 admissions/patient) used for analysis.

Admission characteristics

Patient characteristics are summarized in Table 1. The most frequent causes of PICU admission were: Post-surgical admission (167, 36.4%), Sepsis (121, 26.4%), Respiratory distress (88, 19.2%), and Neurological deterioration (69, 15%). Other less common causes for PICU admission include Oncologic emergencies (24, 5.2%), Non-septic cardiovascular dysfunction (19, 4.1%), Coagulopathy, hemorrhage and/or anemia (14, 3.1%) and primary toxicity from drugs including chemotherapy (12, 2.6%). Some patients presented multiple causes for the same PICU Admission. Unplanned admissions represented 66.7% of all admissions (n=306).

Outcomes and risk factors for mortality

Thirty-two patients died during their PICU stay or within the first 48 hours after discharge, for a mortality of 6.9%. This was higher for unplanned admissions (28/306, 9.1%.) than for planned admissions (4/153, 2.3%, p=0.0104). Of the 32 deaths, 1 (3%) patient death occurred within 24 hours, 6 (18.7%) within the first 48 hours and 9 (29.1%) within the first 72 hours of PICU admission. Most PICU deaths occurred before 21 days of admission, accounting for 28 of the 32 deaths (87.5%).

The observed mortality was similar to the expected mean mortality for all admissions as predicted by the PIM2 (6.9% vs 7.2% respectively) and for the unplanned admissions group (9.1% vs 9.7%). When analyzing mortality by quartiles for 'all admissions' and 'unplanned admissions only', the observed mortality was higher in the lower risk groups (Q1 and Q2), similar in the Q3, and lower in the sickest patients (Q4) (Supplementary Table 1).

In the univariate analysis, type of PICU admission, Neurological Deterioration as a cause of PICU admission, and PIM2 were the only risk factors at admission associated to mortality (Table 2). Notably, of the 202 PICU admissions requiring mechanical ventilation, 14.9% (30/202) resulted in mortality, and for the 20 admissions requiring RRT, 55% (11/20) resulted mortality. In our multivariate analysis, only PIM2 was an independent risk factor for mortality (See Table 3); when this was removed from the model, no other factors reached significance, though Neurological deterioration as an admission diagnosis had a trend towards higher mortality (See Table 4). This was similar in our analysis focused only on unplanned admissions (Supplementary Table 2).

Resource utilization

Overall, 202 admissions (44%) required mechanical ventilation and of these 132 were unplanned admissions (n= 306, 43%). Mean and median duration of mechanical ventilation was 9.35 and 5 days respectively (range of 1-79 days). Twenty patients (4.4%) required renal replacement therapy alone or in combination with other extracorporeal depuration techniques (3 of these patients received plasmapheresis and RRT simultaneously), and 5 patients (1.1%) received other extracorporeal depuration therapies without RRT (4 patients received plasmapheresis and 1 leukapheresis). The mean and median PICU Length of stay were 9.04 and 5 days respectively (range 1-89 days).

Neither duration of mechanical ventilation (among those who received it) or length of stay (among all patients) were significantly different among survivors and non-survivors (p=0.96 and 0.60, respectively; See Supplementary Table 3). When analyzing all admissions, hematological malignancies were associated with both

TABLE 1 Summary of Patient Characteristics.

	Total (N=459)
Age (years)	
Mean (sd)	7.62 (5.24)
Median (Min, Q1, Q3, Max)	7 (0.04, 3.00, 12.00, 18.00)
Gender, n(%)	
Female	203 (44.2)
Male	256 (55.8)
Type of PICU admission (Planned vs Unplanned, n(%)	
Elective (planned)	153 (33.3)
Non-Elective (unplanned)	306 (66.7)
PICU Diagnosis on admission, n=521(%)	
Neurological Deterioration	69 (15.0)
Other	76 (16.6)
Respiratory distress	88 (19.2)
Sepsis	121 (26.4)
Major Surgery Post-operative admission	167 (36.4)
Oncological disease group, n(%)	
Central Nervous System Tumor	112 (24.4)
Hematological Malignancy	204 (44.4)
Solid tumor (outside CNS)	143 (31.2)
Outcome, n(%)	
Death	32 (7.0)
Survival	427 (93.0)
PIM2 (%)	
Mean (SD)	7.24 (13.15)
Median (Min, Q1, Q3, Max)	2.6 (0.05, 1.10, 7.90, 94.10)
Total ICU stay (days)	
Mean (SD)	9.04 (11.35)
Median	5
Min, Q1, Q3, Max	1.00, 3.00, 9.00, 89.00
Mechanical Ventilation (Yes or No), n(%)	
No	257 (56.0)
Yes	202 (44.0)
Total days with mechanical ventilation (Among Yes)	
Mean (SD)	9.35 (11.12)
Median (Min, Q1, Q3, Max)	5 (1.00, 2.00, 12.00, 79.00)

an increased PIM2 score and less mechanical ventilation-free and PICU-free days (Supplementary Table 4). However, when focusing only on unplanned admissions, hematological malignancies were only associated with higher disease severity (PIM2 score) and not with increased resource utilization (mechanical ventilation-free or PICU-free days.) (Supplementary Table 5).

Seventy-six (16.5%) patients had a prolonged PICU length of stay (defined as LOS > 14 days) with 27 patients having a PICU LOS greater than 30 days (5.8%). Of note, survival for these admissions was 89.5% (68/76 patients) for the group with LOS > 14 days and 92.6% (25/27 patients) for the group with LOS > 30 days (Figure 1).

Out of 202 admissions, 40 patients (19.8%) who required mechanical ventilation (MV) needed prolonged mechanical ventilatory support (longer than 14 days), and 13 (6.4%) required mechanical ventilation for more than 30 days. Survival for the > 14 days MV group was 82% (33/40) and 92% (12/13) for the more than 30 days MV group.

Discussion

Our study of PICU admissions at a dedicated pediatric oncology hospital in Mexico over a period of 6 years found a lower mortality rate (9.1%) for unplanned admissions than previously described in LMIC (between 27% and 77% (13, 16, 17). Despite being a resource-limited hospital in an upper-middle income country, this is comparable to reported mortality rates in HIC between 6.8% to 17.5% (4, 18). These findings highlight the fact that it is possible to attain high survival rates for critically ill children with cancer in resource-limited settings.

The main causes for PICU admission in this cohort were consistent with published literature, including planned post-surgical admissions and unplanned admissions for neurological deterioration, respiratory distress, and sepsis (3, 19). In our study, the only characteristics at admission identified as significant risk factors were severity of illness (PIM2) score and unplanned admission, similar to prior studies (9, 13). The distinction between planned and unplanned PICU admissions is important, since planned/post-surgical admissions make up the majority of oncology PICU admissions and have a significantly lower risk of mortality. Thus, further studies seeking to improve outcomes for critically ill children with cancer should focus on unplanned or emergency admissions and hospitalized patients with deterioration events, which represent the majority of adverse outcomes and mortality.

In previous studies, the need for mechanical ventilation (20) and renal replacement therapy (4, 9, 21) during the PICU stay have been associated with poor survival. This finding was confirmed in our study population, where outcomes for children requiring mechanical ventilation and RRT were similar to those reported on HIC, (MV mortality rate of 14.8% in our population vs 15-40% in reported literature (4, 9) and a mortality of 55% for those requiring RRT vs 54.5% in published literature (22).

Most deaths in this cohort occurred before 21 days of PICU stay, with longer PICU admissions having relatively high survival rates. These prolonged-stay admissions included patients with central nervous tumors or hematological malignancies and multiple PICU reasons for PICU admission including a combination of sepsis, respiratory distress, coagulopathy and/or neurological deterioration. Patients in this subgroup required prolonged stays for rehabilitation and weaning or subsequent myelotoxic chemotherapy after resolution of the primary event with potential for additional toxicity-related complications. Encouragingly, the survival rates for these long-stay patients are similar in our study to those described in the literature for all unplanned PICU admissions (4, 9) and higher than that described for prolonged-stay in general PICU admissions(95.2% vs 80%) (23). This exemplifies the fact that despite risk factors, many children with cancer who experience critical illness can recover with

TABLE 2 Univariate analysis of risk factors for mortality (GEE MODEL) among all admissions.

Factor	Category	All Admissions (n=459)		Univariate Analysis	
		Survivors N (%)	Non-Survivors N(%)	P-value	Odds Ratio
Type of PICU admit	Non-Elective (Unplanned)	278 (90.8)	28 (9.2)	0.0022	3.75 (1.29 - 10.88)
	Elective (Planned)	149 (97.4)	4 (2.6)		1.00 (ref)
Neurological Deterioration as cause of PICU admission	Yes	59 (85.5)	10 (14.5)	0.0446	2.84 (1.32 - 6.12)
	No	368 (94.4)	22 (5.6)		1.00 (ref)
Respiratory distress as cause of PICU admission	Yes	79 (89.8)	9 (10.2)	0.2392	1.74 (0.78 - 3.88)
	No	348 (93.8)	23 (6.2)		1.00 (ref)
Sepsis as cause of PICU Admission	Yes	108 (89.3)	13 (10.7)	0.0933	2.02 (0.97 - 4.19)
	No	319 (94.4)	19 (5.6)		1.00 (ref)
Type of Malignancy	CNS tumor	103 (92.0)	9 (8.0)	0.0743	2.43 (0.82 - 7.19)
	Hematological Malignancy	186 (91.2)	18 (8.8)		2.69 (1.00 - 7.29)
	Solid tumor (outside CNS)	138 (96.5)	5 (3.5)		1.00 (ref)
Oncologic treatment prior to PICU admission	HSCT	11 (100.0)	0		
	Low toxicity treatment	54 (93)	4 (7)	0.3696	1.48 (0.37 - 5.98)
	Myelotoxic chemotherapy	181 (93.3)	13 (6.7)		1.47 (0.51 - 4.24)
	None (New Diagnosis)	77 (88.5)	10 (11.5)		2.73 (0.91 - 8.21)
	Surgery	104 (95.4)	5 (4.6)		1.00 (ref)
Tumor activity	Relapsed or refractory disease	61 (91.0)	6 (9.0)	0.5277	1.39 (0.55 - 3.52)
	All others	366 (93.3%)	26 (6.7%)		1.00 (ref)
Steroids prior to PICU admission	No	252 (92.3)	21 (7.7)	0.4340	1.34 (0.63 - 2.84)
	Yes	175 (94.1)	11 (5.9)		1.00 (ref)
PIM2	Mean (median)	6% (2.4%)	23.9% (8.55%)	0.0040*	1.05 (1.03 - 1.07)
Mucosal barrier injury	No	318 (93.8)	21 (6.2)	0.3148	0.65 (0.30 - 1.42)
	Yes	109 (90.8)	11 (9.2)		1.00 (ref)

adequate supportive care. This finding is an important divergence from the common belief that many of these patients will not survive critical illness in resource-limited settings, leading to inadequate resource and ultimately poor outcomes (8).

Our center's relatively low mortality in critically ill children with cancer compared to other resource-limited settings is likely due to a combination of factors and practices that may improve outcomes in these patients. As a dedicated pediatric cancer center, we have systematically implemented a number of quality practices intended to improve care for this patient population, including: a) training and education of the clinical staff managing critical illness in the child with cancer b) early identification of deterioration events facilitated by a Pediatric Early Warning System (PEWS) (12) validated in oncology patients (12, 24), c) timely PICU transfer of deteriorating patients due to a proactive critical care outreach team and our favorable ratio of critical care beds to regular floor beds leading to few PICU-level interventions performed on the ward; d) Rapid access to clinical care for outpatients in the nearby housing facility, e) Implementation of a Golden Hour initiative for antibiotic administration in febrile neutropenia, among others. Consequently, our center's lower

TABLE 3 Multivariate analysis of Risk Factors for Mortality (GEE Model) among all admissions (including PIM2).

Factor	Category	Multivariable Analysis	
		P-value	Odds Ratio
Type of PICU admit	Non-Elective (Unplanned)	0.0433	2.75 (0.91 - 8.30)
	Elective (Planned)		1.00 (ref)
Neurological Deterioration as cause of PICU admission	Yes	0.1914	2.21 (0.77 - 6.35)
	No		1.00 (ref)
PIM2		0.0068	1.05 (1.03 - 1.07)

TABLE 4 Multivariate analysis of Risk Factors for Mortality (GEE Model) among all admissions (NOT including PIM2).

Factor	Category	Multivariable Analysis	
		P-value	Odds Ratio
Type of PICU admit	Non-Elective (Unplanned)	0.4235	1.82 (0.42 - 7.93)
	Elective (Planned)		1.00 (ref)
Neurological Deterioration as cause of PICU admission	Yes	0.0966	2.94 (0.94 - 9.21)
	No		1.00 (ref)
Sepsis	Yes	0.1207	2.05 (0.83 - 5.07)
	No		1.00 (ref)
Type of Malignancy	CNS tumor	0.4512	1.74 (0.54 - 5.60)
	Hematological		1.84 (0.62 - 5.48)
	Solid tumor (outside CNS)		1.00 (ref)

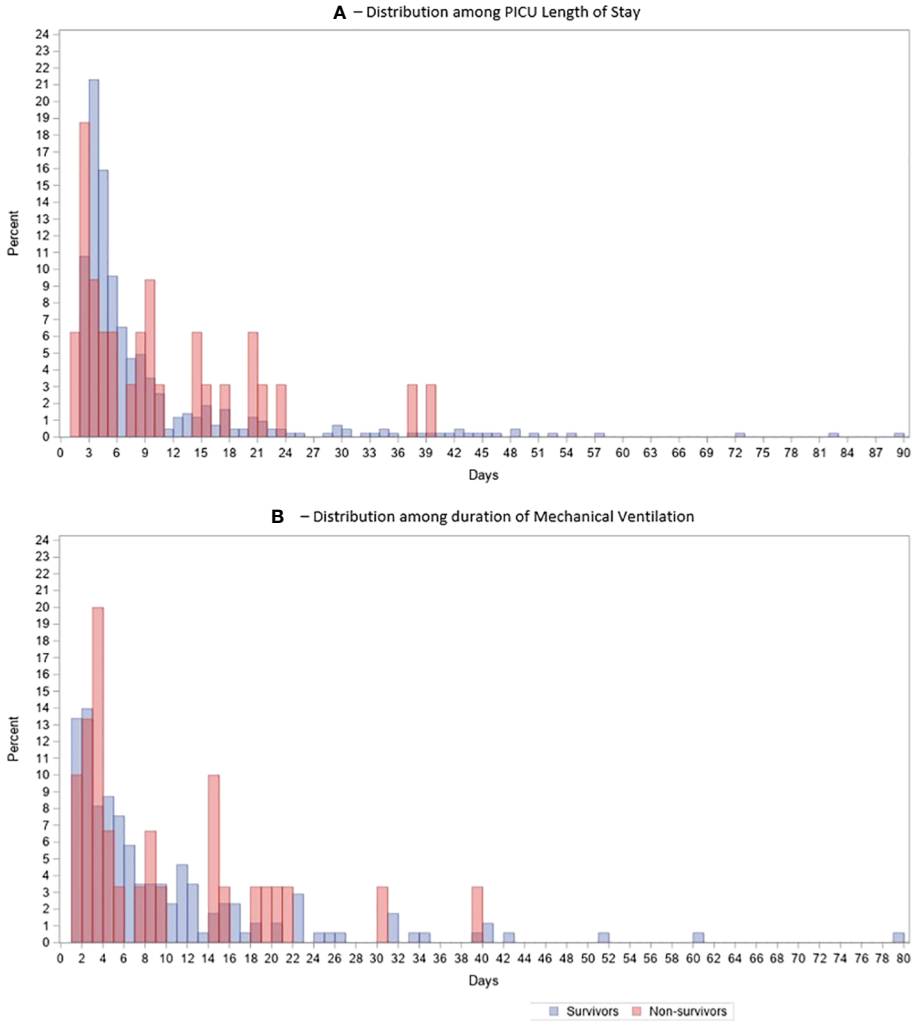

FIGURE 1
Histogram Distribution of Survivors vs Non-survivors over time, **(A)** Distribution over days of PICU stay, **(B)** Same distribution over duration of Mechanical Ventilation.

mortality rates support prior work demonstrating that simple organizational and clinical interventions can lead to significant improvement in outcomes for these patients in centers of all resource-levels (13)

Notably, more than half our PICU patients did not require mechanical ventilation, even in the unplanned admission group (43%), which is similar to that reported in previous studies, including a large multicenter cohort in Latin America (48-53%%) (13, 20) We interpret this as a marker of proactive identification of deterioration events and timely PICU transfer of patients with critical illness. While it may be argued that some of these admissions do not actually experience critical illness, our expected mortality is similar to that of a large Argentinian cohort (25). Similarly, our observed mortality and performance (observed/expected mortality) in the unplanned admissions, mechanical ventilation and RRT subgroups is comparable to that of high-resource settings. Early intervention before the need for invasive mechanical ventilation may lead to resolution of critical illness through early institution of non-invasive respiratory support, vasoactive infusions, or extracorporeal purifying therapies such as plasmapheresis, leukapheresis or conventional renal replacement therapies. Early institution of continuous multisystem monitoring only available in an PICU setting may also improve our ability to detect deterioration, allowing for earlier intervention and resolution of critical illness in these high-risk patients.

There are some limitations to our study. First, this is a single center cohort from a hospital specializing in the care of children with cancer and our results may not be generalizable to all resource-limited hospitals. Also, the retrospective nature of our study limited our data analysis to that available in the patients' charts; data on the use of vasoactive infusions and organ dysfunction scores were unavailable. The relatively low mortality in our study may also have prevented identification of significant risk factors for mortality due to power limitations. Despite these limitations, we included all eligible admissions and had no exclusions due to incomplete data, and this study represents one of the largest cohorts of pediatric oncology patients with critical illness in a hospital in Latin America. Our study's demonstrated low mortality represents an important addition to the literature and highlights the impact of dedicated expertise and prioritization of this high-risk patient population despite resource limitations.

Conclusion

High survival rates for children with cancer with critical illness are achievable in resource-limited settings with provision of high-quality critical care. As exemplified in our study, organizational and clinical practice facilitating quality improvement and early identification and management of critical illness may attenuate the impact of known risk factors for mortality in this population. Future collaborative studies in different regions and hospital resource levels should be aimed at evaluating the impact of these interventions to improve outcomes for children with cancer globally.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: De-identified datasets are available upon requests to the authors. Original data (codebreaker) is derived from patient charts and contains patient information (PHI), thus it is not available for sharing, only available to collaborators at the study site. Requests to access these datasets should be directed to AC-A - adolfo.cardenas-aguirre@stjude.org.

Author contributions

AC-A, conceptualization, methodology, data entry and cleaning, and writing original draft. MH-G, conceptualization, methodology – variable design and definitions, writing review, and editing. BL-D-L, data entry, data cleaning, writing review, and editing. YM-B, methodology, data entry, writing review, and editing. HW, methodology – statistical analysis, and data cleaning. IV-D, ER-P, JM-T, and AG-G, data entry, writing review, and editing. JM, conceptualization, writing review, and editing. GE-A, supervision, writing review, and editing. AAr, writing review, and editing. MD, conceptualization, methodology – statistical analysis, writing review, and editing. AAg, conceptualization, methodology, supervision, writing review, and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1038879/full#supplementary-material

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Endothelial cell provenance: an unclear role in transplant medicine

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An understanding of the interplay between both donor endothelial progenitors and the recipient endothelium (in the case of hematopoietic cell transplant) and recipient endothelial provenance upon the established donor endothelium (in the case of solid organ transplant) is unknown. It is postulated that this interplay and consequences of purported dual endothelial populations may be a component of the post-transplant disease process and contribute to complications of engraftment or rejection. To address this potential confounding and often overlooked arena of vascular biology, a directed brief overview primarily focused on literature presented over the last decade is presented herein.

KEYWORDS
endothelial cell provenance, endothelial chimerism, cellular transplantation, organ transplantation, hematopoietic stem cell transplantation

1. Introduction

Endothelial cells comprise a physical and functional interface between blood and tissues, and in the context of transplant medicine, between self and non-self. Beyond their role in metabolic hemostasis, endothelia provide biological linkages in the dynamic regulation of vascular tone, permeability, coagulation, and inflammation (1). Endothelial cells express Class 1 and Class II MHC antigens, ABO antigens and a variety of surface molecules in response to ischemia/reperfusion physiology, cytokine exposure and cell injury pathways. Human endothelial cell can act as antigen presenting cells to T cells *via* LFA3/CD2, CD45 and allo antibody responses leading to organ rejection. Pre-formed endothelial antibodies in recipients can further fuel this process. The endothelium is exposed to inflammatory cytokines, alloreactive lymphocytes, activated neutrophils, donor-specific antibodies, procoagulant proteases and complement fragments. This leads to further endothelial cell activation and potentially organ rejection or graft vs. host disease (2–4). Recipient endothelial cells that repave the vasculature with HLA and ABO compatible surfaces may be a homeostatic attempt to attenuate this inflammatory process. Hence, an understanding of the provenance of the endothelial cell may yield clinical implication in terms of graft function and survival.

The transplant population has grown in recent years with 22,013 hematopoietic stem cell transplants performed in the United States in 2020 including both pediatric and adult cases (5). Similarly, 33,309 solid organ transplants were completed in 2020 according to the Organ Procurement and Transplantation Network data (6). Both cellular and solid organ transplants

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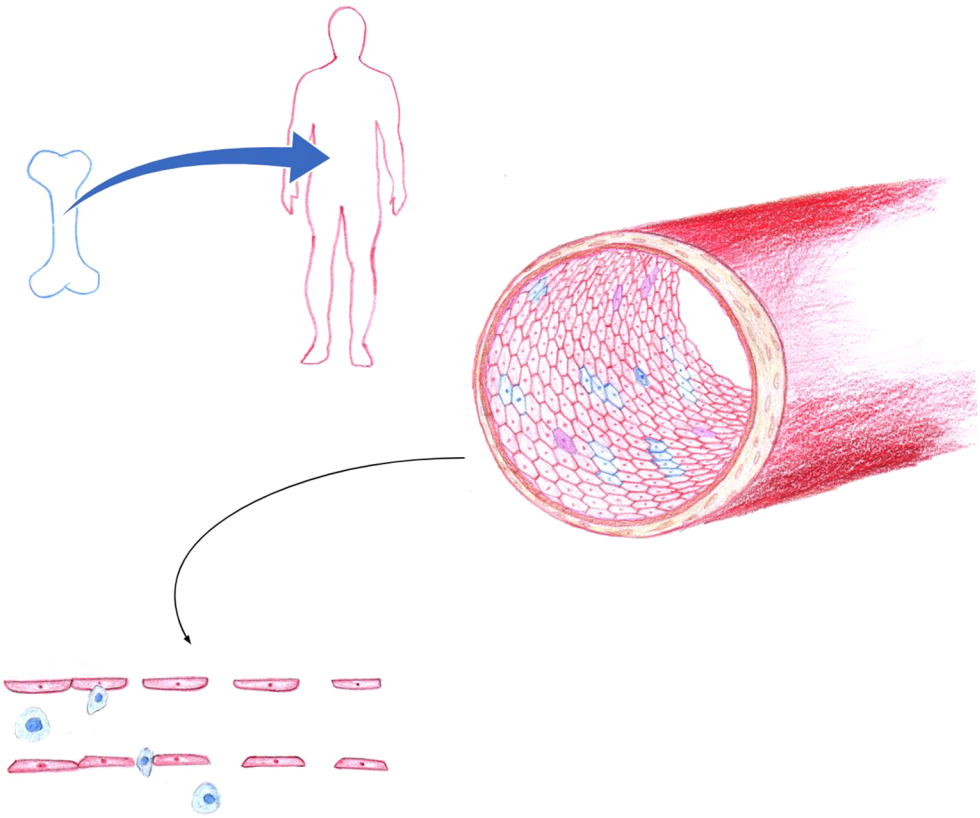

FIGURE 1
In hematopoietic stem cell transplantation, endothelial chimerism is a result of the process by which recipient endothelium is gradually repopulated by endothelial progenitor cells of donor bone marrow origin. Blue, indicates of donor origin. Red, indicates of recipient origin. Purple represents monocyte to endothelial transformation or fusion cell phenomena. Endothelial dysfunction is exacerbated by HLA and ABO disparity, along with loss of tight junction integrity, overexpression of adhesion molecules that promote leukocyte recruitment and transmigration across the endothelium. The resultant endotheliopathy contributes to the pathogenesis of graft versus host disease, sinusoidal obstruction syndrome, capillary leak, transplant associated thrombotic microangiopathy, and idiopathic pneumonia syndrome. (Figure by S. Somani).

face potential compromised graft and host viability from required immunosuppressive medications, resultant infections and both acute and chronic rejection (6). While this is clearly documented in the literature, an understanding of the interplay between both donor endothelial progenitors and the recipient endothelium (in the case of cellular transplant) and recipient endothelial ontology upon the established donor endothelium (in the case of solid organ transplant) is unknown. It is postulated that this interplay and consequences of purported dual endothelial populations (i.e., of donor and recipient origin) may be a component of the post-transplant disease process. To address this potential confounding and often overlooked arena of vascular biology, a directed brief overview primarily focused on literature presented over the last decade is presented herein. Moreover, given that both cellular and solid organ transplant present complementary yet inverse donor and host endothelial interactions, both processes are subsequently alluded to.

Given that transplant rejection is a common occurrence, there have been many studies aimed at improving the understanding of this pathophysiological process. One of these hypothesized mechanisms may be related to the concept of endothelial chimerism at the organ level, whereby donor and host endothelial cell populations both line the vasculature. Endothelial chimerism varies depending on the type of transplant which is being discussed. In HSCT patients, endothelial chimerism is a result of the process by which recipient endothelium is gradually repopulated by immature donor-derived cells of ontological donor bone marrow providence (7) (**Figure 1**). In solid organ transplantation, organ derived mature senescent donor endothelial cells are transplanted with the organ graft. For this reason, it is commonly referred to as reverse endothelial chimerism, which is defined as recipient-derived cells replacing the donor-derived endothelial cells within the vasculature of the grafted organ (8) (**Figure 2**). Endothelial or reverse endothelial chimerism may be assessed in a variety of ways, using fluorescence *in situ* hybridization (FISH), immunohistochemistry (IHC), or flow cytometry to evaluate sex-mismatched transplants, ABO-incompatible transplants, and/or unique genetic markers (7, 9–11). Age-associated vascular changes may further affect the endothelial chimerism occurring after transplantation. With aging, vessel density and pericyte numbers decline significantly in tissues displaying lower remodeling capacity (such as the kidney, muscle, and spleen) vs. tissues with a greater regenerative potential (such as the gut, skin, uterus, and the human liver). Secondly, at the cellular level accumulation of

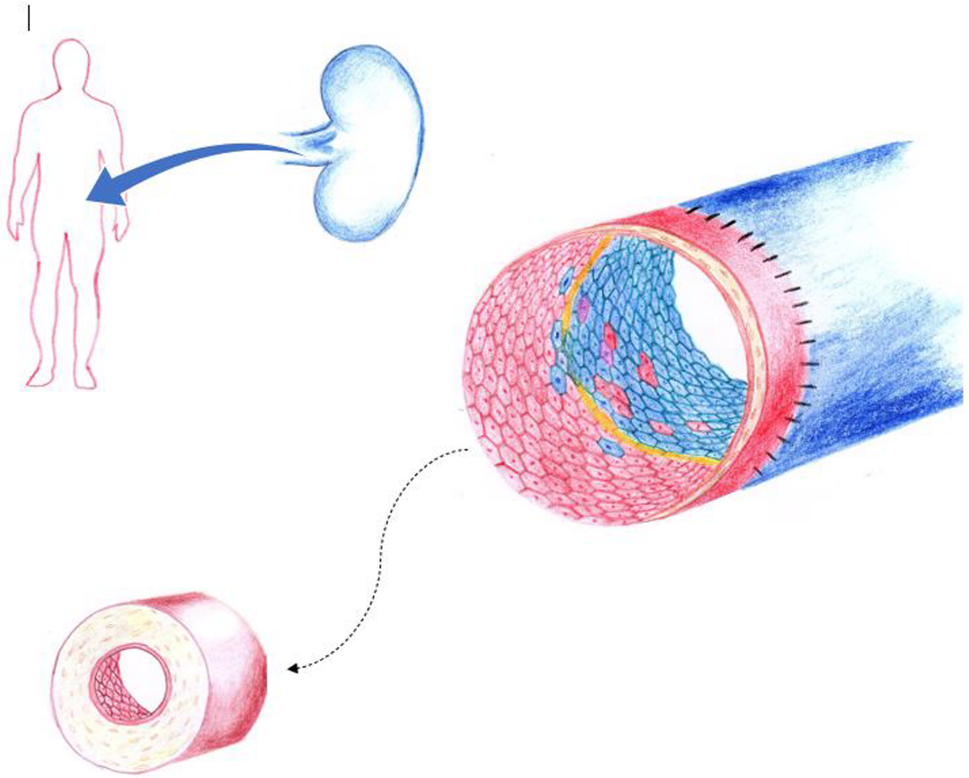

FIGURE 2
In solid organ transplantation, organ derived mature senescent donor endothelial cells are transplanted with the organ graft. Here, reverse endothelial chimerism occurs as recipient-derived cells replace the donor-derived endothelial cells within the vasculature of the grafted organ. At the zone of vascular anastomosis, exposed basement membrane (yellow) may also be reendothelized by donor graft endothelial cells (facilitated by cell-to-cell contact expansion). Blue, indicates of donor origin. Red, indicates of recipient origin. Purple represents monocyte to endothelial transformation or fusion cell phenomena. Chronic alloimmune injury leads to intimal thickening, accumulation of extracellular matrix, smooth muscle cell proliferation with resultant luminal narrowing. Here an indolent host versus graft reaction results in transplant vasculopathy that is associated with long-term organ loss. (Figure by S. Somani).

reactive oxygen species, low grade inflammation, mitochondrial dysfunction, and even pericyte to fibroblast differentiation that occur with aging may be compounded and triggered by vascular injury and could be expected to develop from chemotherapy, radiation, infection, or surgical manipulation occurring in transplant settings (12). Likewise, the aged bone marrow has limited lymphatic endothelial cell expansion ability, diminished cellular cross-talk capacity, and attenuated hematopoietic stem cell (including EPCs) regeneration (13). The age-associated tissue-specific molecular changes could thus variably repopulate the endothelium following transplant with unknown consequences but has not been specifically studied.

In 1965, Medawar hypothesized that replacement of donor vascular endothelium by host endothelium may lead to increased survival of the graft (presumably by allowing for preservation of microvascular architecture and function that would otherwise be obliterated by immune mediated acute or indolent rejection) (14). At that time, studies had predicted the site of graft rejection was against the donor endothelium (15–18). Complementary to this concept, Calne suggested that early reverse endothelial chimerism would protect the donor endothelium from graft rejection and improve viability of graft acceptance (18). These controversial topics are still widely debated and continue to be an active area of investigation in transplant medicine.

2. Methods

A literature search using the keywords "endothelial" "chimerism" and "transplant" was conducted within the PubMed database. The results were filtered to only include publications which were published between 2010 and 2020 to summarize current knowledge. This resulted in 43 abstracts, which were reviewed to determine possible pertinent papers.

Abstracts were excluded at this point if the entire paper was not available or printed in English, if it was a duplicate article, or if there was duplicate data published which had been included in a previous paper. Of these 43 abstracts, 19 papers were selected for further screening for relevance to this review. Of the 19 papers that were included, 13 of these proved to be pertinent and included specific information related to this review. Manuscripts were excluded if they mentioned chimerism of various types of cells after transplant but did not specifically address or discuss endothelial chimerism. References of the final 13 manuscripts were cross-referenced and an additional 4 papers were added for further references (Figure 3).

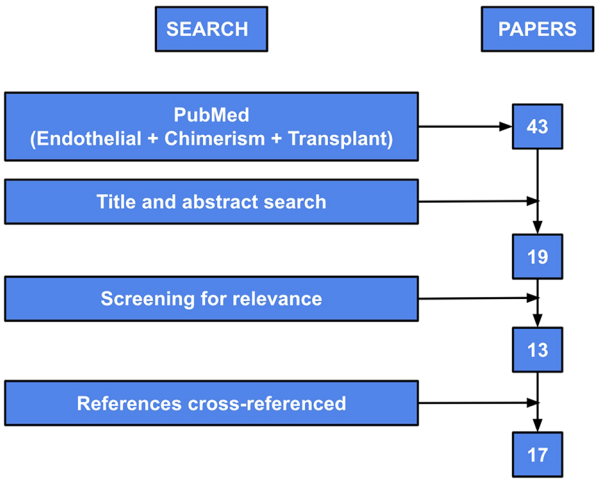

FIGURE 3
Diagram of search methods used to perform systematic review. "PubMed" refers to the initial keyword search within the PubMed database. "Title and abstract search" refers to review of titles and abstracts and exclusion per exclusion criteria noted above. "Full article search" refers to full paper review and exclusion at that point per exclusion criteria noted above. "Screening for relevance" refers to assessment of the publications' relevance to this review. "References cross-referenced" refers to review of the references from the original included papers and the addition of papers if they satisfied inclusion and exclusion criteria. Figure adapted from Bolado and Landin (19).

3. Results

3.1. Endothelial chimerism after bone marrow transplant in animal models

Multiple studies have readily established that bone marrow-derived cells are the primary ontologic progenitors of mature endothelial cells, however the terminology, surface marker definition, quantity and doubling potential of donor derived endothelial cells is debated and varies between different studies (20). Within the past 10 years, two animal studies have been published that investigated endothelial chimerism after bone marrow transplant (10, 21). However, neither of these studies investigated any association with graft vs. host disease or transplant rejection.

Bonfim-Silva et al. demonstrated in a mouse model that endothelial chimerism happens frequently within the bone marrow as early as 30 days after bone marrow transplant (10). Green fluorescent protein (GFP) positive donor cells in GFP negative mice showed significantly more endothelial cells derived from the transplanted GFP + bone marrow than native cells from the GFP- recipients ($39.58 \pm 10.66\%$ vs. $2.75 \pm 0.9\%$, $p = 0.04$). Bone marrow derived cells (BMDC) are also recruited into the melanoma tumor microenvironment and contribute to vascular development. The GFP + bone marrow transplanted GFP- mice were found to have $11.5 \pm 6.85\%$ of GFP + cells present as CD31 + endothelial cells by flow cytometry. Additionally, these CD31+ GFP + endothelial cells were localized to blood vessels supplying the melanoma tumor microenvironment (10). While this study confirms that bone marrow derived cells can contribute to the bone marrow environment and tumor environment, the study does not evaluate or correlate its findings with clinical significance. Further, the tumor microenvironment is metabolically active with likely novel angiogenesis that may limit inferences into the more quiescent or senescent vascular beds.

A second animal study published within the past 10 years demonstrated that endothelial chimerism happens diffusely throughout multiple different organ systems. BXSB mice were transplanted with GFP + unfractionated bone marrow cells or *ex vivo* expanded mesenchymal stem cells delivered by intravenous injection (21). Organs that demonstrated endothelial chimerism at 62 weeks after injection included the liver sinusoids, brain choroid plexus and the endothelium of adipose, lung, and kidney tissue. GFP + chimeric endothelial cells were also found in the capillaries of the gut, skin, and striated muscle, but not within capillaries of the pancreas or brain parenchyma. While endothelial cells derived from transplanted unfractionated bone marrow was demonstrated in various organs in this study, the frequency at which these transplanted cells were found was not addressed. The authors speculated that the multisystem engraftment of endothelial cells following intravenous progenitor cell infusion coupled with immune modulation of the host and organ-specific factors might contribute to disease control through endothelial cell chimerism (21).

3.2. Bone marrow transplant in humans

Following human hematopoietic stem cell transplantation (HSCT), donor stem cells migrate into numerous tissues where they proliferate and differentiate, creating varying degrees of chimerism between recipient and donor cells. Pulmonary chimerism involving bronchial and alveolar epithelium and endothelium, including Type II pneumocytes, has been described in association with various lung injuries (22). In a recent study, Hijiya et al. studied pulmonary endothelial chimerism in patients who had previously received an ABO-incompatible hematopoietic stem cell transplant. Immunohistochemical staining to ABO antigens was used to determine the percentage of vessels expressing donor antigens on the pulmonary endothelium. Of the 16 samples which were analyzed, 7 of the samples came from explanted lungs in patients who had required pulmonary transplants for severe chronic pulmonary graft-vs. host disease (GVHD). The other 9 samples were obtained from autopsy samples with 6 of these 9 autopsy samples posthumously diagnosed with chronic pulmonary GVHD. Of the overall 13 samples which were diagnosed with pulmonary GVHD, all of them showed pulmonary endothelial chimerism. The frequency of donor group antigens on vessel endothelium ranged widely from 0.1 to 17.5% in these patients with pulmonary GVHD but no endothelial ABO chimerism was observed in the 3 samples from patients unaffected by GVHD ($9.28\% \pm 6.59$ vs. 0 ± 0, $p < 0.001$). There was also a positive correlation between percentage of chimeric vessels and recipient age at transplant ($r = 0.85$, $p = 0.02$), which may co-correlate with development of GVHD. A literature review included in this study tabulated 20 of 28

patients reported with endothelial chimerism and 5 of 11 with epithelial chimerism with different pathologies, including diffuse alveolar hemorrhage, bronchiolitis obliterans and "chronic inflammation" (22). Of note, transplant toxicities such as thrombotic microangiopathy are likely due to multi-factorial insults, but endothelial chimerism has not been clearly implicated as a pathogenic mechanism (23).

Skin GVHD has been associated with endothelial chimerism as well (22). Two cases reported by Kaffenberger et al. also demonstrated endothelial cell chimerism but within GVHD-associated angiomatosis (GVHD-AA) diagnosed at 46- and 30-months post-transplant respectively (24). The frequency or percentage of chimeric endothelial cells was not documented in either of these cases.

Tran et al. described endothelial chimerism in salivary glands after stem cell transplantation. Five females who transplanted from male donors who underwent salivary gland biopsy had scattered Y-positive cells in acini, ducts, stroma, and endothelial cells of their salivary glands (mean 1.01%) from 13 to 201 months following transplant. Four had GVHD (liver, skin, oral and/or cryptogenic organizing pneumonia) (25).

Mueller's series of endothelial chimerism included 52 HSCT patients who underwent a combination of 22 normal skin biopsies, 12 GVHD skin biopsies, 4 tumor biopsies, and 5 autopsies variably sampling heart, liver, skin, and marrow following HSCT (7). Analysis *via* ABO immunohistochemistry, XY fluorescence or short tandem repeat analysis of laser captured endothelial cells failed to show physiologic endothelial turnover resulting in donor endothelial chimerism. Endothelial cell chimerism was detected at low levels (0.9% and 3.3%) in skin biopsies from only two patients with chronic GVHD. Tumor tissues showed 1.2% and 2.5% of donor derived endothelial cells in two patients. The authors concluded that "endothelial cell replacement by bone marrow derived donor cells… is a rare event" and "does not represent a major repair mechanism". However, they did not sample lung tissue in their patients (7).

Thus, the mechanisms by which circulating donor stem cells may populate vascular endothelial surfaces remain unclear. Prior injury or inflammation appears to be a precipitating factor and the circulating stem cells may contribute to a healing effect of regional or tissue-specific chimerism. Whether this chimerism is beneficial and can/should be facilitated in early stages of injury to mitigate severe adverse transplant-related toxicities, particularly in the lung, remains to be studied.

3.3. Solid organ transplant in animals

Three studies were conducted recently which investigated endothelial chimerism within solid organ transplants in animal models. In this situation, (reverse) endothelial chimerism is defined as having recipient-derived endothelial cells replace the donor-derived endothelial cells or co-populate within the vasculature of the grafted organ (8).

While Chen et al. primarily focused their study on pancreatic islet transplants, they made some comparisons to mouse models of heart transplants to evaluate how donor specific antibodies can lead to solid organ transplant failure (26). Syngeneic and allogeneic heart transplants were evaluated in a mouse model, which was injected with either donor specific antibodies or placebo (HB13 monoclonal antibody vs. phosphate buffered saline). At 30 days after cardiac transplantation, the transplant was harvested for histological evaluation. Cardiac transplants which were exposed to donor specific antibodies showed evidence of humoral rejection (as documented by complement activation, leukocyte infiltration, and destructive ultrastructural endothelial changes noted on staining and electron microscopy) while the hearts that were exposed to phosphate buffered saline did not. Additionally, the transplanted hearts were assessed using flow cytometry at 4 weeks post-transplantation and the endothelial cells were deemed to be of donor origin (although not quantified). In contrast, a progressive replacement of donor endothelial cells by recipient endothelial cells was observed over a six-week period in their pancreatic islet cell aggregate transplanted into the renal subcapsular area. Acknowledging that in solid organ transplant, immediate viability depends on establishing perfusion by surgical connection of prominent vessels (as in their cardiac model) vs. angiogenesis and diffusion capacity in cellular aggregate transplant (as in the their subcapsular islet cell model), they postulate that reverse endothelial chimerism and the diffusion restriction of large proteins (complement activators and donor specific antibodies) is protective against humoral mediated rejection in the latter situation, which is clearly not afforded in their cardiac transplant model (26).

Interestingly and in contrast, Onuta et al. found a positive association between the frequency of host-endothelial chimerism and the frequency of transplant vasculopathy (27). In their experiments, MHC-incompatible transplants were performed between various strains of rats, specifically Lewis and Brown Norway. After one and two weeks of MHC-incompatible aortic transplantation, the host-endothelial chimerism was assessed histologically. In the BN-to-Lew transplants, 2%–3% of endothelial cells were host derived; while in the Lew-to-BN transplants, 37% and 27% of endothelial cells were host derived at the respective one- and two-week time point post-transplant. This increased host-derived endothelial cell chimerism may be reflective of an injured intimal layer on the transplanted aortic graft and was correlated with a more pronounced profibrotic state and transplant vasculopathy noted over 4 to 8 weeks. Lew-to-BN grafts also had earlier, and more aggressive acute vascular rejection compared to BN-to-Lew allografts, which may be influenced by underlying non-MHC-immunologic determinants, intrinsic neointimal smooth muscle cell proliferative capacity and availability of host-derived fibrocytes. However, this is correlation, not causation, and the timeline and details regarding level of vascular rejection were not discussed within the study (27).

Schirutschke et al. attempted to quantify incorporation of nonrenal host endothelial cells (defined by double staining for RECA-1 and *hPAP*) in R26-*hPAP* transgenic Fischer F-344 rats

(with confirmed hPAP positivity of all bone marrow cells) who received Fischer F-344 wild type rat kidney grafts (28). They used both an acute and reversible endothelial cell-specific nephritis model (GEN model with loss of 85% of the glomerular endothelial cells and a loss of 69% of the peritubular endothelium at day three post renal injury) and a complex, chronic progressive model of kidney endothelial injury (5/6 nephrectomy model with noted endothelial rarefaction of 23% in the glomeruli and 49% in the peritubular capillaries after 14-week post injury). Both models demonstrated infiltration of *hPAP* + cells (thought to be macrophages or inflammatory cells); however, limited incorporation of host endothelium was noted at both the glomerular (0.25% at GEN week 4 and 0.05% at 5/6 Nx week 14) and the peritubular level (0.1% at GEN week 4 and 0.86% at 5/6 Nx week 14).They conclude that independent of acute vs. chronic or healing vs. progressive disease outcome, actual recipient derived incorporated endothelium is a rare event and that endothelial regeneration likely originated primarily from intrinsic kidney cells in their syngeneic transplant model (28).

The syngeneic animal model does necessarily limit our inferences for most human transplantation situations.

3.4. Solid organ transplant in humans

An additional three articles have been published within our search time frame (2010–2020), further supplemented by a 2010 paper (29) and 2013 synopsis article (19) that investigated reverse endothelial chimerism of solid organ transplants within human patients and its association with transplanted organ rejection.

Tanabe et al. 2011 evaluated the rate of endothelial chimerism expression of blood type A or B antigens in the transplanted kidneys of 6 patients who had received ABO-*in*compatible kidney transplants over the 10 years post-transplant (10). In general, the expression of blood-type A or B antigen (on identified CD34 positive capillaries) decreased as the duration from transplant increased. Expression of blood-type A or B antigen decreased to 91.8%, 85.8%, 64.1%, and 57.6% in the respective first three months, five years, ten years, and greater than ten years post-ABO-incompatible kidney transplantation. In comparison to a control group of ABO-*compatible* transplant recipients, no change in blood-type A or B antigen expression was seen after transplant with 99.8% of vessel endothelium expressing the expected blood-type antigen more than 10 years after an ABO-compatible renal transplant. While (antigenic, not necessarily cellular) endothelial chimerism in the long-term period post-ABO-incompatible renal transplant was demonstrated here, it could not be associated with either graft accommodation *(i.e., resistance to humoral rejection despite the presence of antibodies against the donor endothelium)* or antibody-mediated rejection. Only one of the 6 patients was diagnosed with chronic antibody mediated rejection, which occurred about 7 years after ABO-incompatible transplant, however the rate of this patient's endothelial chimerism was similar compared to the remainder of the 5 patients. Moreover, similar graft and patient survival rates between ABO-incompatible and compatible kidney transplants are likely due to the efficacy of post-transplant immunosuppression regimens clouding inferences at the endothelial level. However, Tanabe et al. 2012 suggested that patients with acute or chronic antibody mediated rejection had a higher incidence of chimerism (7/9 patients), leading to poor graft survival (8). Hence, it is still unclear whether replacement chimerism may allow for graft adaption (whereby donor endothelial cells repopulate the donor's organ vessel walls) or are involved in graft compromise.

Varga et al. also evaluated the frequency of endothelial chimerism in sex-mismatched kidney allograft recipients (identifying XX or XY chromosomes *via* FISH or CISH) and its relationship to signs of rejection (9). 16 patients were evaluated 1–12 years duration after a sex-mismatched renal transplant. Endothelial chimerism was not noted in any of the 4 female recipients, however endothelial chimerism was noted in lymphatic vessels in 25% (3/12) of male recipients and in capillary vessels in 17% (2/12) of male recipients. In all the grafts which showed endothelial chimerism, tubular cell chimerism was also noted, so there were no grafts with isolated endothelial chimerism. In the 5 patients with demonstrated endothelial and tubular cell chimerism, 3 of these patients also had acute T-cell rejection, however this association was not statistically evaluated nor associated with antibody mediated rejection (9).

Ferlicot et al. evaluated the frequency of chimerism in sex-mismatched renal transplants using FISH (for the Y chromosome) and IHC (for endothelial marker CD31) in 33 renal biopsies from 22 male recipients who had received female kidney transplants (29). Endothelial cell chimerism was present in 67% of patients with a mean percentage of 61.8% chimeric glomeruli or a mean number of 3.53 chimeric cells per glomerular section. They did find endothelial chimerism was associated with a prior (but not necessarily acute current) episode of acute T-cell mediated rejection ($p = 0.02$). Moreover, having had higher grade II/III acute-T-cell mediated rejection appeared correlated to a greater number of chimeric cells per glomerular section compared to prior grade I rejection in these patients (29). This may support the contention that donor graft endothelium is replaced after rejection associated vascular injury.

Bolado and Landin published a review article evaluating a total of 33 articles published between 1972 and 2012 on the frequency of reverse endothelial chimerism in solid graft recipients of cardiac, kidney, liver, and lung transplants (19). The incidence of reverse chimerism was respectively 50%, 58.95%, 79.12%, and 33.34% in cardiac, kidney, liver, and lung allografts. The estimated percentage of host derived endothelial cells within the donor allografts was 14.04% (cardiac), 9.96% (kidney), 49.33% (liver), and 0.56% (lung). Across all patient transplant types, reverse endothelial chimerism and transplant rejection co-existed in 31.86% of patients; however, there was no significant association that could be determined between these variables (19). Hence, inferences on whether host endothelial cell integration into donor tissue is an adaptive and presumably protective

phenomena or a reflection of vascular injury and rejection is unclear and yet to be determined.

4. Discussion

The endothelial layer serves as an interface between blood borne elements and underlying tissue, and in transplant medicine, between the self and non-self. As such it is both the site of, and an effector in immune homeostasis, and in defining the balance between rejection and tolerance (30, 31).

In HSCT, the recipient endothelium in the bone marrow niche and in the systemic vasculature may be affected by pre-existing host vulnerabilities (atherosclerosis, testosterone deficiency, heart failure) and especially by pretransplant conditioning (chemotherapy, radiotherapy, lymphodepleting regimens) that may compromise graft viability and end organ function (32, 33). Further, endothelial dysfunction is exacerbated by HLA and ABO disparity, increased synthesis of angiopoietin-2 (furthering permeability) along with loss of tight junction integrity, overexpression of adhesion molecules (ICAM, VCAM, E-selectin, P-selectin) that promote leukocyte recruitment and transmigration across the endothelium, diminished eNOS and prostacyclin that dysregulates vascular tone, and altered VEGF and FGF2. Oxidative stress, the cytokine milieu, monocyte/macrophage involvement and complement activation pathways are also implicated (34, 35). Moreover, endothelial cells act as non-professional antigen presenting cells with increased MHC class II, CD40, and ICOSL expression promoting T cell activation and chemotaxis (36).

This resultant endotheliopathy contributes to the pathogenesis of sinusoidal obstruction syndrome, engraftment syndrome, capillary leak, transplant associated thrombotic microangiopathy, graft vs. host disease and idiopathic pneumonia syndrome (34). Administration of VEGF, pigment derived endothelial factor, defibrotide, and N-acetyl-L-cysteine may ameliorate clinical outcomes (33). Animal studies published within the past decade suggest that HSCT derived donor cells contribute to the endothelial microenvironment, however the abundance of donor-derived cells varies between studies and does not address any association with GVHD or transplant rejection (10, 21). In patients that have received an ABO-incompatible HSCT, there was a statistically significant association between severe chronic pulmonary graft-vs. host disease and pulmonary endothelial chimerism ($p < 0.001$) (22), suggesting post injury seeding. Promisingly, in a mouse BMT model of acute GVHD, co-infusion of bone marrow derived EPCs mobilized to and stabilized the affected endothelium, downregulated MHC class II expression and attenuated CD3+ T cells infiltration improving pathological scores and survival outcomes in test animals (36).

In solid organ transplantation, recipient endothelial susceptibility may be exacerbated by end stage organ disease, comorbidities (hypertension, diabetes etc.), pre-existing HLA sensitization from previous blood transfusions, pregnancies, or allografts (which have been partially managed with exchange transfusions, IVIG, and depleting antibodies to attenuated B cell lineage (rituximab) or both B and T cells (thymoglobulin, alemtuzumab), as well as complicating infections. Donor derived inflammation from brain death induced cytokine storm or ischemia/reperfusion insult in the donated organ also compounds endothelial injury and activation resulting in microvascular inflammation and thrombosis. Both recipient immune cell activation as well as donor immune cells and extracellular vesicles from the transplanted organ heighten the inflammatory state that compromise graft endothelial integrity and function. Ultimately, chronic alloimmune injury leads to intimal thickening, accumulation of extracellular matrix, smooth muscle cell proliferation with resultant luminal narrowing. Here an indolent host vs. graft reaction results in transplant vasculopathy that is associated with long-term organ loss (30, 31, 37).

Some studies have investigated reverse endothelial chimerism in solid organ transplantation, both in animal models and in human studies over the last decade. Cardiac allografts demonstrated reverse endothelial chimerism at 4 weeks post-transplant in a mouse model, however quantification or association with rejection was not delineated (26). A positive association between the frequency of host-endothelial chimerism and the acute vascular rejection was seen in a rat aortic allograft model; this may be reflective of an accelerated underlying intimal injury (with associated inflammation and fibrosis) overwhelming putative stabilizing effects of a more gradual neo-endothelial seeding (27). Independent of acute vs. chronic or healing vs. progressive disease states in a rat renal transplant model, actual recipient bone marrow derived incorporated endothelium was deemed to be a rare event and endothelial regeneration from intrinsic kidney cells should also be considered at least in the syngeneic transplant model (28). A review of cardiac, kidney, liver, and lung transplants in human recipients demonstrated varying levels of reverse endothelial chimerism but no significant association with transplant rejection (19). ABO-incompatible renal transplants had decreased levels of expected blood-type antigens on graft capillaries over time suggestive endothelial chimerism but association with either graft accommodation or rejection could not be determined (10). Whereas having both a prior episode and a higher grade (II/III) of acute-T-cell mediated rejection appeared to correlate with greater number of chimeric cells per glomerular section (29). This tends to support the contention that donor graft endothelium is replaced after rejection associated vascular injury.

Whether reverse chimerism occurs primarily post graft endothelial injury or as a gradual process to "repave" the donor vasculature or a likely a combination of both is yet to be fully defined. Chimerism at the endothelial level, monocyte to endothelial transformation (particularly of VEGFR1 monocytes that express M2 phenotype to promote barrier integrity and angiogenesis) (35), cell fusion phenomena (9), and/or alloantigen incorporation by recipient antigen presenting cells may promote long term tolerance and graft survival (30); perhaps, by upregulation of protective anti-oxidant and anti-inflammatory genes (Bcl-2, Bcl-xL, HO-1) and downregulation of adhesion molecules and pro-inflammatory cytokines (35, 37, 38).

Harvesting the potential of accelerating endothelial chimerism, human placental endothelial progenitor cells are

able adhere with expected alignment and morphology to decellularized vascular surfaces on rat aorta (*in vitro*) and rat kidney, lung and hindlimb (ex vivo model). Beyond the conceptual approach of promoting graft immune tolerance, placental EPCs may be harvested readily (with ABO and HLA matching), expanded, and stored for future use. Further, they retain phenotypic plasticity to adapt to the specifically seeded organ microenvironment and/or may serve as temporary vascular lining until replacement by recruited recipient endothelial cells (39). Of interest, human umbilical vein endothelial cells were co-cultured to create vessel-like structure in an *in vitro* kidney organoid model (40). Enhancing host endothelial "repaving" of the donor organ or co-infusion of donor EPCs in HSCT may prove to be promising modalities to attenuate morbidity in transplant medicine (36).

4.1. Limitations

There is a paucity of studies which investigated endothelial chimerism after hematopoietic stem cell or solid organ transplant and any association with graft tolerance or rejection. Given the wide variety in study designs, patient population, and outcomes analyzed, in addition to the minimal number of studies to begin with, a meta-analysis is not feasible. Many of the studies which assess sex-mismatched transplantation are lacking data on whether the donors or recipients had ever received blood transfusions, or if any of the females had miscarriages, abortions or given birth to a son—examples of a potential source of Y chromosomes and false positive signal. Additionally, cell fusion phenomena may obfuscate identification of endothelial cell ontology. Varga et al. noted endothelial chimerism within a control patient, most likely due to endothelial cell fusion in a male patient noted to have cells with double × chromosomes within tubular epithelium and double Y chromosomes within the interlobular artery (9). Further, tissue specific or circulating mesenchymal precursor cells may confound clear identification of endothelial chimerism and preclude inferences on clinical significance. Heterogeneity of techniques to assess chimerism and dependence on a single endothelial cell surface marker pose challenges to study design and conclusions. Moreover, functional assessment of presumed chimeric endothelial cells is challenging (and lacking at the cellular level) also obscuring clinical implications.

4.2. Future directions

Given the level of controversial data regarding the frequency of which endothelial chimerism occurs after a bone marrow or solid organ transplant, a broad multimodal study covering thousands of patients *via* coordination between multiple sites (including harvesting data from already existing biopsy samples correlated to clinical outcomes) may be necessary to determine baseline endothelial chimerism levels and to validate or refute current data and associated clinical implications.

One aspect of this chimerism suggests that immune-mediated endothelial cell injury either in a transplanted organ due to ABO incompatibility or GVHD after a HSCT activates a repair response leading to bone marrow or organ derived endothelial cells to migrate to this point of possible de-endothelialization. Monitoring the number and activation state of circulating endothelial cell populations in the transplant setting would allow an assessment of their genotypic ontology and phenotypic expression. Human endothelial progenitor cells (EPCs) express a variety of cell surface markers similar to those expressed by vascular endothelial cells, adhere to endothelium at sites of injury, have expansive potential and are purported to assist in vascular intimal healing. Circulating endothelial cells (CEC) represent peripheral blood cell subpopulation detached from an established vascular network characterized by mature endothelial features with limited proliferative potential. Flow cytometry can identify and quantify these cell subtypes allowing for inferences over time in cheremic incidence and associated disease state (41). Further an assessment of angiogenic factors such as VEGF, FGF, angiopoietin -1 and -2, Tie-2, thrombospondin-1, heparan sulfate proteoglycans, etc especially in hypoxic microenvironments such as organ rejection may serve as modulating factors for this chimerism. The injury to the vessel may signal procoagulant factors such as von Willebrand's factor, tissue factor, EPCR, D-dimer and thrombin-antithrombin complexes and complement activation. This analysis may be complementing by assessing shed endothelium microparticles (which have transmembrane proteins and surface markers present on their phospholipid bilayer and contain cytosolic components such as enzymes, transcription factors and mRNA from their parent cells) (42). Pairing blood sampling with pathology from needle biopsy or even whole explanted donated organs (the latter in the event of graft failure or at autopsy) may yield further mechanistic insights.

To answer these questions, use of spatial transcriptomics whereby quantification of mRNA (as a proxy for gene expression) in relation to the spatial context of cells within tissue architecture may be sought. Especially relevant here would be the zone of the anastomosis between the donor organ vessels and the recipient's arterial and venous vasculature. The goal being broad transcriptome profiling and high gene detection efficiency at the single cell resolution level to infer cell ontology and functional state (even at the proteome level). Single-molecule fluorescent *in situ* hybridization in series and sequentially to create combinatorial barcoding to reconstruct gene expression in 3D and cross referenced to tissue atlases (currently primarily focused on brain, lung and breast tissue in humans) would likely yield such information. Optimizing signal to noise ratio, limiting optical crowding, balancing spatial resolution with tissue field of view, leveraging automation for high throughput analysis, sharing open-source code, integrating data bases, moving beyond institute of origin specific protocols to commercial systems with decreasing cost would all yield beneficial insights (43). As an example, single cell transcriptome methods have been

successfully applied to define the heterogeneity and chimerism of endothelial cells in a mouse liver cancer model (44).

Incorporation of above cited detection techniques (45) would be required to identify previously undiagnosed chimeric states and aid in the understanding of pathophysiology and clinical management.

Author contributions

The authors confirm contribution to the paper as follows: study conception and design: AS, MS, and GV. Data collection: AP, MS, and AS. Analysis and interpretation of results: AP, MS, and AS. Draft manuscript preparation: AP, MS, GV and AS. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Impact of hospital characteristics on implementation of a Pediatric Early Warning System in resource-limited cancer hospitals

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Background: Pediatric Early Warning Systems (PEWS) aid in identification of deterioration in hospitalized children with cancer but are underutilized in resource-limited settings. Proyecto EVAT is a multicenter quality improvement (QI) collaborative in Latin America to implement PEWS. This study investigates the relationship between hospital characteristics and time required for PEWS implementation.

Methods: This convergent mixed-methods study included 23 Proyecto EVAT childhood cancer centers; 5 hospitals representing quick and slow implementers were selected for qualitative analysis. Semi-structured interviews were conducted with 71 stakeholders involved in PEWS implementation. Interviews were recorded, transcribed and translated to English, then coded using *a priori* and novel codes. Thematic content analysis explored the impact of *hospital characteristics* and *QI experience* on time required for PEWS implementation and was supplemented by quantitative analysis exploring the relationship between hospital characteristics and implementation time.

Results: In both quantitative and qualitative analysis, material and human resources to support PEWS significantly impacted time to implementation. Lack of resources produced various obstacles that extended time necessary for centers to achieve successful implementation. Hospital characteristics, such as funding structure and type, influenced PEWS implementation time by determining their resource-availability. Prior hospital or implementation leader experience with QI, however, helped facilitate implementation by assisting implementers predict and overcome resource-related challenges.

Conclusions: Hospital characteristics impact time required to implement PEWS in resource-limited childhood cancer centers; however, prior QI experience helps anticipate and adapt to resource challenges and more quickly implement PEWS. QI training should be a component of strategies to scale-up use of evidence-based interventions like PEWS in resource-limited settings.

KEYWORDS

Pediatric Early Warning Systems (PEWS), quality improvement collaborative (QIC), implementation science, pediatric oncology, resource-limited settings, global health

Introduction

With modern advancements in treatments and supportive care, survival of children with cancer in high-income countries has risen to over 80% (1, 2). However, survival in low-middle-income countries (LMICs), where roughly 90% of children with cancer reside (1), remains low, between 10% and 50% (1, 3). Treatment-related toxicity (3) and infections (4) contribute to cancer mortality in resource-limited settings, where hospitals face limitations in staff and equipment needed for supportive care (5–10). There is an urgent need for evidence-based practices that reduce preventable mortality and improve global childhood cancer survival.

Pediatric Early Warning Systems (PEWS) are evidence-based interventions that allow for early detection of clinical deterioration in hospitalized children with cancer (11–13). PEWS produce multi-level advantages beyond the patient (14), such as improving interdisciplinary (15) and family communication (16), reducing hospital costs (17), and empowering providers (18). Resource-limited hospitals, however, face additional challenges implementing PEWS (19). More work is needed to understand how to address implementation challenges and support PEWS adoption in these settings.

The Consolidated Framework for Implementation Research (CFIR) describes factors influencing implementation of evidence-based interventions across five domains: *inner setting, characteristics of individuals, outer setting, intervention characteristics, and implementation process* (20–22), with modifications suggested for LMICs (22). CFIR constructs like *culture* (23), *individual need* (23), and *teaming* (23) characterize different aspects of the implementation process and their impact on its outcomes, e.g. time (24). The inner setting domain, including characteristics like resource availability and infrastructure, has been identified as particularly relevant to implementation of evidence-based interventions in resource-limited

hospitals (22, 25, 26). Our prior work similarly suggested the importance of hospital characteristics on PEWS implementation (5); however, it remains unclear *how* these characteristics influence time required to implement PEWS, or what strategies can mitigate these effects. In this study, we evaluate the impact of hospital characteristics on PEWS implementation time in resource-limited pediatric oncology centers.

Methods

Setting

Proyecto Escala de Valoración de Alerta Temprana (EVAT) is a multicenter quality improvement (QI) collaborative in Latin America to implement PEWS (12). At participating centers, local implementation teams work with regional PEWS experts to plan, pilot, implement, and assess impact of PEWS (5, 27).

Data collection

This mixed-methods study included 23 Proyecto EVAT centers across 11 Latin American countries completing PEWS implementation prior to March 2020. Time required for PEWS implementation was calculated from the start of the PEWS pilot to implementation completion.

Qualitative data collection has been described previously (5). Briefly, we selected 5 centers representing extremes of implementation time for in-depth analysis, including 3 high-performing centers (3-4 months for PEWS implementation) and 2 low-performing centers (10-11 months). At each center, two researchers conducted semi-structured interviews with 10 to 15 stakeholders involved in PEWS implementation, including hospital directors, PEWS implementation leaders, or other staff (see Supplementary Table 1 for participant demographics). Interviews were conducted virtually using WebEx, recorded, transcribed, and translated to English for analysis.

Quantitative data included measures of various center features. Initially collected on enrollment in Proyecto EVAT, site leads confirmed hospital data at the start of this study.

Definitions

Consistent with Proyecto EVAT criteria, "implementation completion" was defined as having at least 2 months with high-quality PEWS use (5, 27). Centers are considered to have high-quality PEWS use when they have less than 15% in the three types of PEWS use errors: errors in PEWS scoring, PEWS algorithm non-adherence, and PEWS omissions (documented vital signs without using PEWS) (27). Implementation time was defined as time from the PEWS pilot start to implementation completion.

For analysis, research team members *a priori* identified hospital attributes hypothesized to be related to PEWS implementation time; these were supplemented with data from quantitative findings during analysis. Their definitions can also be found in Supplementary Table 2.

Hospital *material resources* included pediatric intensive care unit (PICU) capacity, physical pediatric hematology-oncology (PHO) ward space, and available finances. PICU capacity described available space in the ICU where pediatric patients were treated or the total number of PICU beds. Physical space was described by the number of beds per shared room on the PHO ward. Available finances describe available hospital economic resources for equipment and supplies needed for PEWS.

Human resources included the PHO ward nurse-to-patient ratio, number of PICU physicians, and staff turnover (how often hospital staff are replaced by new staff). In quantitative analysis, the nurse-to-patient ratio was interpreted according to the International Society of Paediatric Oncology (SIOP) nursing standards for LMICs, which recommend a ratio of one nurse to five or fewer pediatric oncology patients (28, 29). The number of PICU physicians included pediatric intensivists, fellows, and other critical care providers with expertise treating critically ill children with cancer.

Hospital characteristics encompassed funding structure (public or private), type (academic or not, specialized or general), relative PHO patient prioritization, and PHO service complexity. Specialized hospitals consisted of oncology or pediatric multidisciplinary centers while general hospitals included both general and women children's hospitals. PHO patient prioritization conveyed the relative importance placed on PHO patient care and was quantitatively described by number of PHO beds and PHO ward structure (separate PHO ward or general pediatric ward). Service complexity was measured by the number of wards requiring PEWS implementation and number of staff requiring PEWS training.

Finally, we characterized hospitals by the participants' self-reported prior individual or institutional *experience with QI* initiatives.

Data analysis

This study used a convergent mixed method design to investigate hospital characteristics that impact PEWS implementation time. For qualitative data, the study team developed a codebook *a priori* from the CFIR (20, 21) and supplemented by novel codes from iterative transcript review. Two researchers coded transcripts using the 2020 edition of MAXQDA software (VERBI Software GmbH), achieving a kappa of 0.8 to 0.9.

We used thematic content analysis focusing on the impact of *hospital characteristics* and *QI experience* on time required for PEWS implementation (Supplementary Table 3 for code definitions) Constant comparative analysis was used to explore perceived characteristics related to PEWS implementation across different hospitals and participant roles.

Quantitative analyses evaluated the relationship between hospital characteristics and PEWS implementation time. Association of PEWS implementation time with categorical and continuous covariates were analyzed using Wilcoxon rank sum test and univariate non-parametric regression analysis (Theil-Sen median estimators), respectively. P-values < 0.05 were considered statistically significant. Analyses were conducted using R 4.2.0 (https://www.r-project.org/).

We iteratively compared quantitative and qualitative results to synthesize common themes and statistical trends of how hospital characteristics related to PEWS implementation time.

Results

Mixed methods analysis identified multiple factors associated with time required to implement PEWS, including material and human resources, hospital characteristics, and QI experience (Figure 1).

Material resources

In qualitative analysis, participants described various material resource limitations that impacted time for PEWS implementation, including PICU capacity, physical space, and available finances (Table 1).

Participants at hospitals with limited PICU capacity had challenges implementing PEWS due to limited ability to transfer a patient with deterioration to a higher level-of-care: *"There are few beds in the [P] ICU, so when the patient needed to be transferred because he was getting worse, there was no free space"* (physician director, San Louis Potosi [SLP]). In hospitals without a dedicated PICU, pediatric patients were admitted to adult ICUs, further stretching limited resources: "*it's a multi-use ICU … we had to manage bed limitation to admit both adult patients and pediatric patients … we don't have the necessary number of beds to treat all patients*" (physician director, Lima).

Similarly, hospitals' physical space limitation obstructed implementation of PEWS: "*reduced space where we cannot monitor the child 24/7…made it difficult to find the way to the patient and move him to a space for higher supervision*" (implementation leader, SLP). Additionally, financial limitations increased time required for PEWS implementation as hospitals struggled to obtain necessary medical equipment: "*I wanted to do things well, but I didn't have the equipment, and I ended up doing nothing*" (implementation leader, Xalapa).

Quantitative data supported these findings (Table 2); hospitals with more PICU beds required less time for PEWS implementation ($p = 0.045$) and those with fewer beds per shared room implemented faster ($p = < 0.0001$).

Human resources

In qualitative analysis, participants also identified human resource limitations that impacted PEWS implementation time,

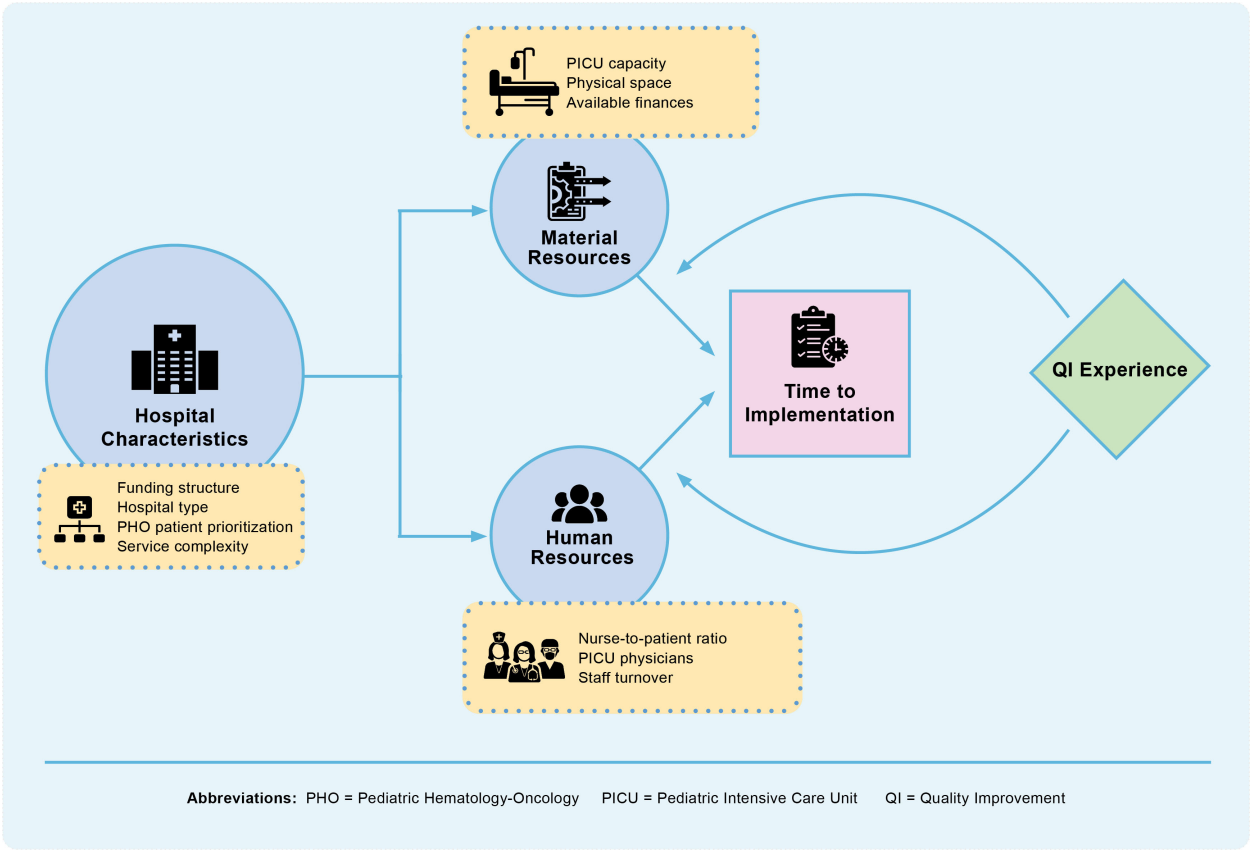

FIGURE 1
During implementation of Pediatric Early Warning Systems (PEWS), hospital characteristics such as funding structure and type impact resource availability, which in turn influences time required to implement PEWS. A hospital's experience with Quality Improvement (QI) can alter this relationship between its resource availability and time to implementation, supporting faster PEWS implementation by enabling implementers to proactively identify and address PEWS barriers.

TABLE 1 Participant perspectives on material and human resources.

Theme	Sub-theme	Example Quote
Material Resources	PICU capacity	"because my hospital doesn't have intensive care for children, we have limitations, so, finally we end up treating children who should be in ICU on the service floor until we can get a bed in ICU" (nurse director, Lima)
		"One of the biggest limitations has been the number of patients and beds, and the deficit in beds is more notable" (physician director, Lima)
	Physical space	"So our demand from oncology patients is very high. For example, we used to have 8 beds and we would reach up to 372 oncology admission, just to our service" (nurse director, SLP)
		"a little girl had just died of a common situation, a patient who was not assisted in the general room, died and she could have been saved" (implementation leader, Xalapa)
	Available finances	"we didn't have bracelets of every size to measure the blood pressure, we didn't have oximeters, the stethoscopes we used were bad quality, some old, damaged, they even hurt the ears" (implementation leader, Xalapa)
		"We committed, in the training, to the acquisition of equipment so the staff could do it. Because if they had the training but not the equipment or the supplies it wouldn't work" (nurse director, El Salvador)
Human Resources	Nurse-to-patient ratio	"our department has 22 beds, we are a very small team of nurses and I think that was the main obstacle and we thought that was not going allow us to implement in our department" (implementation leader, Cuenca)
		"Among the barriers we found, there was the human resources, we didn't have … we used to be 1 nurse for 8 patients" (implementation leader, Lima)
	PICU physicians	"The other limitation we already talked about is that we don't have an intensivist for every shift … the ideal thing would be to have an intensivist who can evaluate the patient because I think they have more experience and can better manage the deterioration" (physician director, SLP)
		"the limitations we have are staff … we had to be careful to select what patients receive the intervention because if we did the intervention to all patients then probably our team would have been insufficient" (physician director, Lima)
	Staff turnover	"We have a high level of absenteeism in the hospital, the ones that stayed are ready to a leave, so every time we're less people working "(implementation leader, Xalapa)
		"we have people taking leaves, human resource is very limited … the absenteeism, the load of work, is a huge barrier for us" (implementation leader, El Salvador)

including nurse-to-patient ratios, availability of PICU physicians, and staff turnover (Table 1).

A low ratio of clinical staff to patient volume increased workload and threatened the quality of patient care, including ability to use PEWS. Nurses especially voiced this concern: "*we've tried to have one nurse per child … taking care of one child implies a bigger effort and that couldn't be shared if there was an extra adult or child*" (nurse director, Lima). Nurses across all hospitals considered high nurse-to-patient ratios a significant barrier to PEWS use: "*we have a big workload, one nurse for 8 or 9 patients, sometimes 11…the human factor is a big barrier for us … we cannot manage that*" (implementation leader, El Salvador).

Similarly, hospitals lacking physicians specialized in PICU management struggled with timely evaluation and transfer of deteriorating patients, negatively affecting both patient outcomes and PEWS implementation: "*We only work with one on-call intensivist … when they call saying this patient is having a cardiac arrest, even though I'd do everything in my power, I won't be able to get there in time*" (implementation leader, Cuenca). Even in settings with adequate physician staffing, a lack of specialists trained in management of critically ill children with cancer was felt to increase implementation time: "*pediatrics is not our chosen specialty … Even though we have all the knowledge and experience from the courses, the health care staff don't have the vocation or the affinity to work with children*" (physician director, Lima).

In some hospitals, staff turnover, through both absenteeism and rotations, prolonged implementation as it was necessary to retrain staff in PEWS, and new staff without prior training struggled to consistently use PEWS correctly: "*the new [resident] comes in …*

TABLE 2 Association of continuous data with implementation time.

Characteristic	Min	Median	Max	p*
Number of PICU beds	0	8	27	0.045
Number of beds per shared room	1	4	15	<0.0001
Number of PICU physicians	0	3	28	0.18
Number of PHO beds	0	22	65	0.039
Number of staff (physicians + nurses) requiring PEWS training	16	49	901	0.0014

PICU, pediatric intensive care unit; PHO, pediatric hematology-oncology; PEWS, pediatric early warning systems.
p*: p-values using univariate nonparametric regression analyses (Theil-Sen single median estimator).

without good training, so some things may happen regarding the management that are incorrect" (physician director, SLP).

This perceived relationship between human resources and time to PEWS implementation was not observed in the quantitative analysis; neither the number of PICU physicians, nor the nurse-to-patient ratio significantly impacted implementation time (p = 0.18, Table 2 and p = 0.85, Table 3, respectively). The relationship between nurse-to-patient ratio and implementation time can be visualized with Supplementary Figure 1.

Hospital characteristics

Across all hospitals, hospital characteristics such as funding structure, type, and PHO patient prioritization were seen by participants to impact PEWS implementation time by determining the relative availability of material and human resources for PEWS (Table 4).

Public hospitals rely on government resources, and participants from these settings described their centers as frequently underfunded, reducing available material and human resources necessary to quickly implement PEWS: "*Our country is a poor country, our hospital is a public hospital, we lack many resources and it's difficult to request them*" (implementation leader, Lima). Conversely, participants viewed private hospitals as having greater access to human and material resources and fewer administrative barriers when requesting resources for new projects: "*our hospital is a hospital that has its own resources. We were able to quickly approve it and prove that this was a sustainable project which helped the implementation go faster*" (research director, Cuenca).

Similarly, academic teaching hospitals were perceived as having less resources and thus required more time for PEWS adoption. Academic hospitals faced more implementation barriers due to the prioritization of training healthcare staff, thus reducing time for initiatives like PEWS: *"[Non-academic hospitals] can dedicate all the time to assisting patients. In academic hospitals, you have the excuse of preparing human resources, so it's not feasible to develop certain types of initiatives*" (quality director, SLP). In some teaching facilities, trainees with limited experience managing pediatric emergencies increased implementation time: *"We don't prepare residents in pediatric emergencies … so the hospitals that prepare residents in pediatric intensive care would have an earlier adoption than us"* (quality director, SLP). Additionally, academic hospitals experienced more rotations among trainees, contributing to issues with PEWS use: *"[in an academic hospital] they complete their training period, and they leave … So, it's very variable to capture the critical state of a patient"* (physician director, SLP).

TABLE 3 Association of categorical data with implementation time.

Characteristic		n	%	t (median months)	p**
Nurse-to-patient ratio (1 nurse to how many patients)					**0.85**
	Five or less	9	39	6.0	
	Greater than five	14	61	6.0	
Funding structure					**0.94**
	Public	18	78	6.0	
	Private + Mix (public/private)	5	22	5.5	
Hospital type					**NA***
	Academic	22	96	6.0	
	Non-academic	1	4	8.4	
	General (general + women children's hospital)	9	39	7.0	**0.025**
	Specialized (pediatric multidisciplinary + oncology)	14	61	5.2	
PHO ward structure					**0.071**
	Separate PHO ward	21	91	6.0	
	No PHO ward (general pediatric only)	2	9	9.7	
Number of PHO wards requiring PEWS implementation					**0.013**
	One ward	19	83	5.5	
	More than one ward	4	17	9.6	
QI Experience					**0.13**
	Yes	6	26	4.5	
	No	17	74	6.5	

PHO, pediatric hematology-oncology; PEWS, pediatric early warning systems; QI, quality improvement.
p**: p-value using Wilcoxon rank sum test.
NA*: Analysis unavailable for academic hospital type due to low sample size (1 non-academic hospital).

TABLE 4 Participant perspectives on hospital characteristics and QI experience.

Theme	Sub-theme	Example Quote
Hospital Characteristics	Funding structure	"we're a public hospital and we have limited economic resources" (implementation leader, Xalapa)
		"one thing that I see as important is this hospital is not a public hospital that depends on state resources, because probably things are slower" (research director, Cuenca)
	Academic centers	"the non-academic would be the fastest, the academic hospitals would the slowest because they prepare human resources" (quality director, SLP)
		We're an academic hospital … they come to our hospital to become pediatricians, surgeon" (QI coordinator, El Salvador).
	Hospital type	"general hospitals don't offer pediatric oncology services because they don't have enough specialists and they don't have enough technology" (physician director, Lima)
		"it's a general hospital. In that service we treat from onco-hematology patients to surgery patients, so we don't only treat oncology patients, maybe 60%" (nurse director, SLP)
QI Experience	Impact on implementation	"like I was telling you we have 10 years working on continuous quality improvement programs, in the oncology service, the nurses already had their equipment and they gave orientation seminars to all the staff and training" (QI coordinator, El Salvador)
		"because we had traveled some part of the road already … we had to follow certain standards for attention, so, when PEWS came we had all this background and it was easier to make it run" (data manager, Xalapa)
	Plans for future initiatives	"This was the example to have better or bigger projects in quality improvement in order to help us with the rest of the processes at the hospital" (implementation leader, Lima).
		"we proposed that PEWS could be implemented to other departments, general pediatrics, pulmonology, etc. not only oncology" (physician director, El Salvador).

PICU, pediatric intensive care unit; QI, quality improvement.

Finally, participants across all centers reported that specialized hospitals, such as pediatric multidisciplinary or oncology hospitals, encountered fewer implementation barriers due to staff experience with and institutional prioritization of pediatric and/or oncology patients: "*Since we are an oncology hospital … we try to be updated and have good reception for those programs that strengthen our patient's safety*" (nurse director, Xalapa). General hospitals were felt to have other competing priorities and less experience with pediatric oncology, resulting in fewer resources for projects like PEWS: "*This generated some rejection because our [general] hospital has limited resources and we would need oximeters for children*" (implementation leader, Lima).

Of the 23 participating hospitals, only 2 were private and 3 were mixed private/public; in quantitative analysis, we did not find an association between funding structure and implementation time (p = 0.94, Table 3). Similarly, only 1 hospital was non-academic, preventing analysis of the relationship between academic status and implementation time. Aligned with qualitative findings, however, quantitative analysis demonstrated that specialized hospitals implemented faster than general hospitals (p = 0.025, Table 3). Hospital prioritization of PHO patients was also significantly related to PEWS implementation time; hospitals with more PHO inpatient beds implemented faster (p = 0.039, Table 2), and those with a dedicated PHO ward trended towards shorter implementation times (p = 0.071, Table 3).

In quantitative analysis, service complexity emerged as an additional barrier to PEWS implementation. Hospitals with more than one PHO ward requiring PEWS implementation and those with more nurses and physicians requiring PEWS training required more time for PEWS implementation (p = 0.013, Table 3 and p = 0.0014, Table 2, respectively). Further conceptualization of various hospital characteristics impact on implementation time are available in Supplementary Figures 2A–D respectively.

QI experience

Prior QI experience, both at the hospital and among implementation team members, was seen by participants to facilitate PEWS implementation by allowing centers to more easily overcome existing resource limitations (Table 4). Examples of these experiences included involvement with initiatives related to central venous catheters, decreasing hospitalization times, and shortening time to antibiotic administration in febrile neutropenia.

Past experience with QI was seen to facilitate PEWS implementation by allowing centers to anticipate and proactively address potential implementation barriers: "*I think the knowledge exchange allows you to identify the difficulties you have in your center and learn from the experience of other centers*" (physician director, Lima). Nurses also felt empowered by QI experience to participate in PEWS implementation as members of the multidisciplinary team: "*since I'm a nurse I know how to take care of a patient, that [and to learn about quality] facilitated my support to conducting that project [PEWS] and to my colleagues*" (nurse director, El Salvador).

Conversely, hospitals without QI experience struggled with implementation and were initially intimidated by the PEWS project: "*it was something big … maybe we wouldn't be able to accomplish it … maybe most of us felt the same way about not being able to accomplish it*" (implementation leader, Cuenca). Despite most hospitals lacking prior QI experience, all eventually achieved successful PEWS implementation, often applying QI methodology

learned in Proyecto EVAT: "*At the beginning, it was kind of a barrier because we were afraid of the unknown, but then we were very successful*" (implementation leader, Cuenca). Successfully implementing PEWS also empowered hospitals to apply their experience to future improvement initiatives: "*A lot of us have started to get involved in other quality improvement projects that maybe didn't exist before PEWS, it has helped us and pushed us to work*" (implementation leader, Lima).

Most hospitals lacked QI experience prior to PEWS implementation (n = 17, 74%, Table 3). Supporting qualitative findings, quantitative analysis demonstrated hospitals without QI experience trended towards longer PEWS implementation times (6.5 months vs. 4.5 months, p = 0.13, Table 3). This relationship is also displayed in Supplementary Figure 3.

Discussion

This study analyzed the relationship between hospital characteristics and PEWS implementation time in resource-limited settings. Fixed hospital characteristics, like funding structure and type, determined the relative availability of resources for PEWS and impacted time needed for implementation. Previous QI experience, however, either at the center or among members of the implementation team, mitigated these barriers by empowering centers to proactively anticipate and overcome implementation challenges. In centers without prior QI experience, implementation leaders leveraged training obtained through Proyecto EVAT to successfully implement PEWS.

Our findings are consistent with prior work in LMICs demonstrating the impact of resource availability on QI and intervention implementation (7, 8), including the barriers of staff turnover (26, 30), large organization size (31), and poor infrastructure (25). Similarly, the importance of hospital and staff specialization have been identified as important to the quality and capacity of pediatric onco-critical care (10, 32). Additionally, a systematic review evaluating the use of the CFIR in LMICs proposed a new domain, "Characteristics of Systems," that affects organizational policies to produce changes to the inner setting (hospital) domain (22). This relationship reflects the impact of hospital characteristics (e.g., funding structure) on resource-availability we observed in this study.

Although data on the impact of QI collaboratives in LMICs is conflicting (33), our work supports findings that including QI training, as is done in Proyecto EVAT, can improve collaborative effectiveness (33, 34). In this study, few centers or implementation team members reported previous experience with QI, highlighting the importance of incorporating QI training into programs to scale-up interventions in resource-limited hospitals. Our findings suggest that QI training also provides additional benefits, including team empowerment and motivation to introduce other improvement projects, potentially resulting in more broad impact on patient outcomes.

Centers in our study more quickly completed implementation when they adapted the PEWS implementation process to the specific characteristics of their institution and resource-level. These findings provide actionable recommendations for clinicians, hospital leadership, and researchers wishing to implement PEWS or other QI interventions in resource-limited clinical settings. For clinicians, we recommend an iterative implementation strategy that includes aspects of successful methodologies from other resource-constrained sites and tailoring them to the needs of their center. This can include formal QI methods such as plan-do-study-act (PDSA) cycles, stakeholder analyses, and process mapping, among others. Hospital leadership looking to foster a culture of QI in their hospital should support local QI efforts and promote QI training options within the center to grow institutional and clinician capacity for QI. For researchers and public health experts leading collaborative efforts to scale-up evidence-based interventions, we recommend including training in QI methodology to better enable clinicians to leverage their knowledge to support improvement initiatives.

This study has several limitations. The relatively small sample size (23 centers) and low frequency of some variables (e.g., private funding structure) limited the power of our quantitative analysis to identify true relationships between some variables and PEWS implementation time. Our mixed methods design, however, supplemented this quantitative data with in-depth qualitative analysis from a diverse group of stakeholders. The synthesis between quantitative and qualitative findings strengthened our study and enriched the analysis of the relationship between hospital characteristics and PEWS implementation. At the time of this study, all Proyecto EVAT centers had successfully implemented PEWS (27). As a result, we used time needed for implementation, rather than implementation success or failure, as the implementation outcome. Implementation time is a relatively newly described implementation outcome (24), and this study further contributes to this emerging literature. Finally, this study focused on implementation of one intervention in pediatric oncology centers, potentially limiting generalizability of our findings to other interventions and settings. Future work should more broadly evaluate the impact of hospital characteristics on implementation of other interventions to improve childhood cancer care and explore the impact of external factors (e.g., the COVID pandemic) on intervention implementation and sustainability in resource-limited settings (35). This includes evaluation of the impact of changes in resources to promote intervention use over time and study of associated intervention costs and cost-benefits and their impact on sustainability.

Conclusions

This study describes how hospital characteristics impact time required for successful PEWS implementation in resource-limited pediatric oncology centers, with past hospital or individual QI experience mitigating implementation challenges by empowering implementation teams to proactively overcome identified barriers. Importantly, lack of prior QI experience can be addressed through teaching QI methods as part of the implementation process. These findings can be used by clinicians and researchers to conduct pre-implementation assessments to anticipate implementation challenges and guide future collaborative initiatives to scale up

interventions that improve outcomes of children with cancer in hospitals of all resource-levels.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the institutional review board of St. Jude Children's Research Hospital as an exempt, minimal-risk study. Additional approvals were obtained by participating centers as needed. As an exempt study, written participant consent was waived; verbal consent was provided at the start of each interview.

Author contributions

AA, DG developed the idea. MP-T, SG, PE, HM-T, AG-R, MA, CB, ZC, CH, MJ, JJL, AM, EM, EPe, EPi collected the data. AA provided supervision. FA and AA conducted the data analyses. FA, AA, DG drafted manuscript and prepared the tables and figures. All authors contributed to the interpretation of the findings, the editing of the article, and the approval of the final submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1122355/full#supplementary-material

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Review of acute kidney injury and progression to chronic kidney disease in pediatric patients undergoing hematopoietic cell transplant

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While acute kidney injury (AKI) after hematopoietic cell transplant (HCT) has been well-described in pediatric patients, literature regarding the long term renal consequences of HCT-related AKI, the development of chronic kidney disease (CKD), and CKD care in pediatric patients post-HCT is limited. CKD affects almost 50% of patients after HCT with multifactorial etiology including infection, nephrotoxic medications, transplant-associated thrombotic microangiopathy, graft-versus-host disease, and sinusoidal obstruction syndrome. As renal function declines in CKD, eventually progressing to end stage kidney disease (ESKD), mortality increases and is more than 80% among patients requiring dialysis. Using society guidelines and current literature, this review summarizes definitions and etiologies of and management strategies among patients with AKI and CKD post-HCT with an emphasis on albuminuria, hypertension, nutrition, metabolic acidosis, anemia, and mineral bone disease. The goal of this review is to aid early identification and intervention in patients with renal dysfunction prior to development of ESKD, and to discuss ESKD and renal transplant in these patients post-HCT.

KEYWORDS

hematopoietic cell transplant, chronic kidney disease, kidney injury, kidney transplant, nephrology

1 Introduction

Hematopoietic cell transplant (HCT) is an established treatment for various malignant and non-malignant disorders among both adults and children. According to the Center for International Blood and Marrow Transplant Research, between 2008 and 2014, there were over 4400 pediatric allo-HCTs across 119 centers in the United States (1). Prevalence of acute kidney injury (AKI) after HCT has been reported as high as 70% in adult literature with variable incidence of 21% to 84% in pediatric literature (2, 3). In a previous review by Hingorani et al. in 2016, AKI within the first 30 days of transplantation and increase in AKI

severity are associated with an increased risk of mortality, and mortality rates among those patients who require renal replacement therapy (RRT) ranges from 55-100%. A recent pediatric retrospective cohort study by Bauer et al. found that nephrology was consulted in less than 50% of patients with severe AKI, and risk of death was significantly higher in patients with severe AKI (RR 4.6, 95% CI 2.6-8.1) (4). Very little literature has been published about pediatric patients with chronic kidney disease (CKD) or who require RRT after HCT. The aim of this review is to describe the etiologies of kidney injury, strategies for AKI detection, and management of CKD in children following HCT. Given the broad scope of this review, we selected to focus on high yield topics and performed an unstructured search using PubMed to identify and summarize relevant literature.

2 Etiologies of kidney injury

Patients who undergo HCT have unique risk factors for AKI in addition to those of the general population. These can include nephrotoxic medication exposures such as antimicrobials, preconditioning chemotherapy, use of biologics or immunotherapies, radiation therapy possibly leading to radiation nephropathy, and use of calcineurin inhibitors (CNIs) as prophylaxis for graft-versus-host-disease (GVHD) (5). Mechanism of nephrotoxicity varies but has been categorized previously as vasoconstriction or altering intraglomerular hemodynamics, tubular cell toxicity, acute interstitial nephritis, tubular obstruction, hypersensitivity angiitis, and thrombotic microangiopathy (5). While CNIs can cause vasoconstriction of the renal artery, the exact mechanism between CNIs and AKI is unclear, as multiple studies have shown that neither the dose nor the drug level of CNIs in the blood, mostly cyclosporine, are significantly associated with AKI (2, 6). A recent review on CNI nephrotoxicity among renal transplant patients by Naesens et al. shows that local renal factors play a larger role than systemic overexposure to CNI, defined by CNI drug levels in the blood (7). These factors include patient variability in P-glycoprotein and CYP3A4/5 activity, older kidney transplant age, salt depletion and diuretic use, Non-Steroidal Anti-Inflammatory Drug (NSAID) use, and genetic polymorphisms in other genes such as ACE and TGF-β (7). Here, we discuss some unique clinical conditions that increase a patient's risk of AKI after undergoing a HCT by focusing on the most prevalent etiologies and summarize our recommendations in Figure 1.

2.1 Transplant-associated thrombotic microangiopathy

Transplant-Associated Thrombotic Microangiopathy (TA-TMA) is characterized by endothelial dysfunction leading to microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and multiorgan dysfunction typically within the kidneys, lungs, gastrointestinal (GI) tract, and central nervous system (8). Clinical diagnosis is made by the presence of MAHA, elevated lactate dehydrogenase level (LDH), renal dysfunction, and negative direct and indirect Coombs' test. While some TMA diagnostic criteria, such as the Clinical Trials Network TMA criteria, include concurrent renal and/or neurologic involvement without another identified etiology, this criterion has been questioned for its validity and applicability to those patients with TMA at the highest risk of death (9, 10). Incidence is variable from 0.5-64% and likely impacted by variations in diagnostic criteria used across centers as well as differing pre-transplant conditioning regimens (11). In children and adolescents, those with TA-TMA had significantly

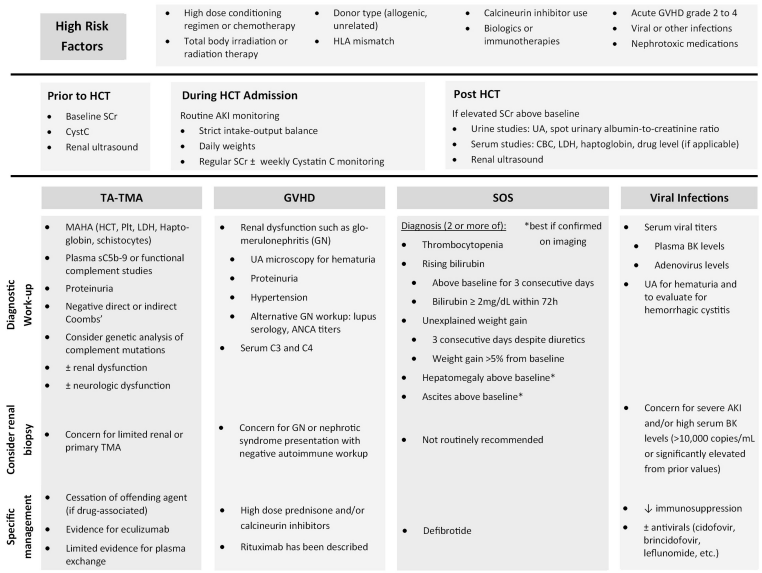

FIGURE 1
Summary of recommendations to identify high risk patients, etiology-based workup, and specific management.

greater non-relapse mortality at 1 year post-HCT compared to those without TA-TMA (43.6% vs 7.8%, P <0.0001) (12).

TA-TMA can be renally limited, but this does not always correlate with a rise in serum creatinine level. Kidney biopsy may be required to confirm the underlying diagnosis, especially in cases that exclusively involve the kidneys (13). A majority of TMA is caused by secondary TMA (80%-90%), and one of the most common forms is drug-induced TMA which makes up 10-13% of all TMAs and 20-30% of secondary TMAs (14, 15). Mazzierli et al. reviewed drug-induced TMA, which can present renally limited, and found complement deposition in half of the renal biopsies (57%, 37/66) of patients with complement deposition patterns associated with drug type, but also rare associations with pathological genetic mutations (1.6%, 2/122) (16). Similarly, abnormal complement activation without genetically identified complement disorders has been reported in a review of TMA caused by immune checkpoint inhibitors (17) and in an broad review of TMA among patients with C3 deposition on kidney biopsy (18).

Risk factors for TA-TMA include high dose conditioning regimen, high dose chemotherapy, total body irradiation, donor type (allogenic, unrelated), HLA mismatch, CNI use, acute GVHD grade 2 to 4, and viral or other infections (especially BK viremia) (2). High dose conditioning chemotherapy may cause direct endothelial injury while CNIs cause direct endothelial injury, increase thromboxane A2 and endothelin levels, and decrease nitric oxide and prostacyclin levels (19). Infections can cause endothelial injury directly or indirectly through inflammatory mediators such as TNF-alpha and IL-1 (11). GVHD is a risk factor for TA-TMA and is associated with a four-fold higher risk, independent of CNI levels or dosing regimen, and, conversely, an increased grade of GVHD leads to a higher risk of TA-TMA (13). While GVHD and TA-TMA can occur independently from one another, they can overlap clinically and both present with endothelial injury (20).

2.2 Graft-versus-host disease

GVHD is classically known to affect major organs including the skin, liver, and GI tract, but the kidney can also be involved. GVHD can present in the kidney as AKI, nephrotic syndrome, glomerulonephritis, or TA-TMA (8). Typical presentation is glomerulonephritis between 6 to 12 months after HCT, often as preventive immunosuppression in being weaned (21). While current GVHD grading does not include the kidneys, the presence of GVHD in other organs is a risk factor for kidney GVHD and is believed to be due to not only systemic inflammation but also local changes within the kidney, sharing similar GVHD-associated pathways as the other more common target organs (22). GVHD is independently associated with TA-TMA, likely due to targeting by donor graft cells to recipient's vascular endothelium (13). The presence of GVHD is also an independent risk factor for AKI and CKD (23).

2.3 Sinusoidal obstruction syndrome

Sinusoidal Obstruction Syndrome (SOS), previously known as hepatic veno-occlusive disease, occurs after endothelial injury within hepatic sinusoids and hepatocytes in zone 3 of the hepatic acinus causes hepatocellular necrosis, fibrosis, and vascular occlusion. Left untreated, this can result in liver failure, hepatorenal syndrome, multiorgan failure, and eventually death (21). This recent meta-analysis by Raina et al. estimates a pediatric incidence of 18.2% (95% CI: 9.6-28.8%) compared to an older meta-analysis by Coppell et al. with almost 25,000 patients which found an overall mean incidence of 13.7% (95% CI: 13.3%-14.1%) and mortality rate from severe VOD of 84.3% (95% CI: 79.6-88.9%) (24). Risk factors for SOS include high dose conditioning regimens that lead to acute portal hypertension from direct injury to endothelial cells in the hepatic sinusoids and activation of stellate cells (2, 24). This leads to portal hypertension which can impact renal perfusion and cause renal tubular injury (2). SOS is an independent predictor of all stages of AKI, including severe AKI requiring RRT, and the presence of both SOS and AKI are associated with worse clinical outcomes (2, 3).

Diagnostic criteria for SOS in children by the European Society of Blood and Marrow Transplantation (EBMT) was first proposed in 2017 and includes 2 or more of the following: thrombocytopenia (unexplained, consumptive, transfusion-refractory), unexplained weight gain for 3 consecutive days despite diuretics or weight gain >5% from baseline, hepatomegaly above baseline (best if confirmed on imaging), ascites above baseline (best if confirmed on imaging), and rising bilirubin above baseline on 3 consecutive days or bilirubin ≥ 2mg/dL within 72h (25). EBMT pediatric severity grading for SOS had previously defined renal function scoring by glomerular filtration rate (GFR), but in 2019 the internationally accepted criteria for acute kidney injury (AKI) staging defined by Kidney Disease: Improving Global Outcomes (KDIGO) was used instead (26).

2.4 Viral infections

Viral infections can cause a variety of renal conditions. BK virus or adenovirus are common causes of hemorrhagic cystitis (HC). HC presents with hematuria, dysuria, flank pain, and potentially AKI. Risk factors for BK virus HC (BKV-HC) include treatment with rabbit thymocyte globulin, high BK virus levels, cord-blood or peripheral blood stem cell transplant, presence of GVHD (grade 2 to 4), age greater than 7 years old, and concurrent infection with other viruses. BKV-HC among pediatric patients is reported between 9.9% to 21.3% of patients after HCT (27, 28). Ruderfer et al. found that BKV-HC is associated with increased all-cause mortality (HR 2.22; 95% CI: 1.35-3.65), more severe AKI (stages 2 and 3) when occurring in the first 60 days post-HCT, and development of acute renal failure requiring dialysis and CKD stage 2-3 when occurring in the first year post-HCT.

Plasma BK virus levels are more indicative of renal involvement than urine BK virus levels. A prospective pediatric study by Cesaro et al. found plasma BK is predictive with a viral load of 10,000 copies/mL significantly associated with BK-HC in multivariate analysis (HR 6.1, P = 0.0006), and BKV-HC associated with significantly higher risk of mortality (HR 2.6, p = 0.018) (29). A retrospective study comparing outcomes between children based on degree of viremia found that those with plasma BK virus levels of at least 10,000 copies/mL during their first year post-transplantation had lower rates of survival at 1 year, worse renal disease (with 7/10 = 70% requiring dialysis), and more severe BKV-HC (including urologic complications requiring surgery) than children with levels less than 10,000 copies/mL (27). Patients with BK viremia and AKI should be considered for renal biopsy, if it can be safely obtained, to confirm diagnosis of BK virus nephropathy before treatment with antivirals such as cidofovir. Treatment includes reduction of immunosuppression, if possible, prior to initiating antivirals including leflunomide, cidofovir, and brincidofovir. Cidofovir has had mixed success for treatment of HC. Similarly, adenovirus has been identified as a cause of AKI post-HCT and is sensitive to both cidofovir and brincidofovir treatment (30).

3 Identification and monitoring for kidney injury in a patient with HCT

Kidney injury associated with HCT has a prevalence of 10-70% in adult literature with median time to onset of AKI 33 to 38 days after transplantation (2). In pediatric literature, AKI incidence varies widely from 21 to 84%, likely due to variability in AKI definitions and patient heterogeneity (3). Consensus statement by the pediatric continuous renal replacement therapy (PCRRT) working group meta-analysis showed statistically significant higher AKI rate among allogenic (39.3%, 95% CI: 25.7–53%) than autologous transplant recipients (5%, 95% CI: 0–11.9%) as well as higher AKI incidence in patients with HCT due to malignancy (33.6%) than those undergoing HCT without malignancy (6.1%) (21). Those patients who have significant risk factors for AKI benefit from close monitoring to allow for early detection of AKI which can be challenging in pediatric patients.

3.1 Diagnosing AKI

There are several criteria published in the literature to diagnose AKI. These include the risk, injury, failure, loss of kidney function, and end stage kidney disease (RIFLE) system, the acute kidney injury network (AKIN) criteria for kidney injury, and KDIGO criteria (2, 31). As it is currently the most widely used and internationally accepted system for staging AKI, we recommend the KDIGO system (shown below in Table 1) for pediatric patients.

While current KDIGO criteria relies on SCr and increasing duration of oliguria to detect AKI, SCr can be a suboptimal AKI biomarker. SCr indicates actual loss of kidney function from an injury that occurred 48-72 hours prior and overestimates GFR due to tubular secretion. SCr is also impacted by sex, age, height, protein intake, and muscle mass (31–33). The most studied alternative AKI biomarker for pediatric patients is Cystatin C (CysC), a 13 kDa cysteine protease inhibitor that is freely filtered by the glomerulus and without any known tubular secretion (32). As a functional biomarker, serum CysC reflects a change in kidney function, rather than a loss of function, and can detect AKI earlier than SCr. However, some studies show that serum CysC can be influenced by inflammation, steroids, and age (32, 34–39). A systematic review and meta-analysis by Zhang et al. of primarily adult studies showed serum CysC was able to predict AKI with a diagnostic odds ratio (OR) of 23.5 (95% CI: 14.2-38.9), sensitivity of 0.84, specificity of 0.82, and area under the receiver operating characteristics curve of 0.96 (95% CI: 0.95-0.97). GFR estimating equations based solely on CysC or incorporating CysC and SCr exist for children. The three most common equations for estimating GFR include the bedside Schwartz equation based on Creatinine (40), Cystatin-C based equation (41), Creatinine-Cystatin C-based Chronic Kidney Disease in Children (CKiD) equation (42), and U25 modification for CKiD equation for patients under 25 years old (43).

Alternative biomarkers have been studied for more accurate diagnosis, but many are not currently available for widespread use. These include tubular injury biomarkers like urinary Neutrophil gelatinase-associated lipocalin (NGAL), urinary N-acetyl-beta-D-glycosaminidase (NAG), kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7). Data also exists for urine CXCL10 and CXCL9 in identifying AKI after HCT (44). Biomarkers of glomerular function and tubular injury can be combined with traditional markers (serum creatinine) for early AKI identification, especially within 28 days post-HCT. Benoit et al. monitored for AKI with weekly creatinine, cystatin C, and urinary NGAL to help identify highest risk patients for adverse outcomes (45).

3.2 Screening and evaluation for AKI

Prior to HCT, renal function should be evaluated with baseline SCr and CysC as well as imaging to evaluate for structural renal

TABLE 1 KDIGO staging of AKI based on serum creatinine and urine output (31).

Stage	Serum Creatinine (SCr)	Urine output
1	1.5-1.9x baseline Scr ≥ 0.3mg/dL above baseline	< 0.5ml/kg/hr for 6-12h
2	2-2.9x	< 0.5ml/kg/hr for ≥ 12h
3	3x baseline SCr SCr ≥ 4mg/dL Initiation of renal replacement therapy	< 0.3ml/kg/hr for ≥ 24h, or Anuria for ≥ 12h

abnormalities with ultrasound. Having a pre-HCT baseline SCr and CysC allow for more accurate staging and recognition of AKI post-HCT. During initial HCT admission, we recommend routine application of KDIGO AKI criteria to identify patients during earlier stages of AKI when intervention may prevent requirement prolonged AKI, severe AKI, or requiring renal replacement.

Those patients who are found to have an elevated creatinine post-HCT compared to their pre-HCT baseline should undergo further investigation to determine the cause, typically with a combination of urine studies (complete urinalysis, spot urinary albumin-to-creatinine ratio, urine sodium, urine urea, and urine creatinine), serum studies (complete blood count, serum lactate dehydrogenase (LDH), haptoglobin, and drug levels of calcineurin inhibitors, if applicable), serum viral studies for BK virus and adenovirus DNA, renal ultrasound (to assess for kidney size and look for signs of obstructive uropathy), and, if diagnosis is still unclear, possibly kidney biopsy (2, 19). If there is concern for TA-TMA, recommended evaluation includes hematocrit, platelet, LDH, haptoglobin, peripheral smear for schistocytes, urine studies for proteinuria, and plasma sC5b-9 level. If glomerulonephritis from GVHD is suspected, evaluation should include urinalysis with microscopy, serum complement C3 and C4, lupus serology, ANCA titers, and possible kidney biopsy (21).

4 Management of AKI in a patient with HCT

KDIGO practice guidelines recommend management of AKI based on stage of AKI. For those patients at risk of AKI, nephrotoxic agents should be discontinued where clinically possible, effective circulating volume should be optimized to ensure adequate perfusion pressure, functional hemodynamic monitoring should be considered, serum creatinine and urine output should be monitored closely, hyperglycemia should be avoided due to risk of osmotic diuresis, and radiocontrast should be avoided when clinically possible. Diagnostic workup should be considered starting at stage 1 AKI with possible changes in drug dosing by stage 2-3 and consideration for ICU admission and/or renal replacement therapy (RRT) (31).

4.1 Fluid balance

Among children with AKI after HCT, increased fluid overload is independently associated with worse clinical outcomes and increased mortality (46). Based on a review by Raina et al, fluid overload more than 10-20% is also associated with increased mortality, ICU length of stay, and mechanical ventilation (47). Due to this, these patients should be monitored closely for fluid overload including strict fluid intake and output, surveillance of percent fluid overload as part of their daily assessment, and targeted net fluid balance goals per day (21). To achieve these fluid balance goals, a study by Raina et al. recommended an algorithm to monitor daily fluid status after HCT and consider initiation of furosemide infusion for fluid overload of at least 5% (48). In the setting of increasing weight and decreased urine output, consultation with nephrology and restriction of fluid volume is recommended due to the possible need for RRT.

4.2 Renal replacement therapy

Several adult, and combined adult and pediatric studies, have shown that the degree of renal failure is associated with mortality, and mortality can be as high as 84% (49, 50). A meta-analysis by Raina et al. of pediatric patients post-HCT found that 31.1% (95% CI: 17.1-47.2%, P<0.0001) of patients with AKI required RRT, most often due obligatory fluid requirements significantly exceeding urine output (21). These investigators also found that indicators of successful termination of continuous RRT (CRRT) include improvement in fluid overload state and urine output irrespective of the use of diuretics at the time of discontinuation of CRRT (51). To help identify high risk characteristics of those patients who required RRT, a retrospective study by Lane et al. compared 30 pediatric patients who required dialysis early after HCT to general pediatric HCT patients. Compared to general HCT pediatric patients, those requiring dialysis had a greater proportion of neuroblastoma as well as fewer autologous and more unrelated HCT donors, potentially related to differences in conditioning regimen, GVHD prophylaxis, and infection prophylaxis or complications. While 77% (23/30) died without renal recovery mostly from sepsis, 23% (7/30) had renal recovery and survived. Clinical factors associated with persistent renal failure included requiring at least 3 medications for blood pressure support, hyperbilirubinemia, and fluid overload by weight >10% at RRT start (52). Reduced renal reserve among these patients was believed to be due to prior chemotherapy, tumor debulking surgery sometimes requiring nephrectomy, or prior abdominal radiation (53).

4.3 Etiology-based management

Targeted interventions focused on suspected etiology of AKI should also be performed. Nephrotoxic agents should be minimized or avoided as clinically able. For clinically necessary but potentially nephrotoxic medications, drug levels should be monitored closely with dosing adjusted based on estimated renal function. Glomerulonephritis due to GVHD can be treated with high dose prednisone and/or calcineurin inhibitors. Rituximab use has been described as well (54). For SOS, rapid and definitive diagnosis as well as timely initiation of defibrotide is critical. Defibrotide is a polydeoxyribonucleotide with aptameric activity on the endothelium and anti-inflammatory, anti-thrombotic, and anti-ischemic effects to counter the endothelial cell damage. Defibrotide is the only drug approved for prevention and treatment of SOS in the United States since it has been shown in a randomized controlled trial to reduce incidence of SOS-associated kidney failure (55).

For TA-TMA, especially secondary or drug-induced, management should focus on withdrawal of the inciting agents

such as calcineurin inhibitors, antimicrobial treatment for any active infection, and maintenance of metabolic balance by correcting fluid overload. There is limited evidence for the use of plasma exchange which has unclear benefit (lacks randomized controlled trial but anecdotal studies show <50% response and mortality >80%) while Eculizumab has been shown to improve outcomes in severe TA-TMA with 1 year survival and case reports supporting its use (56). However, it should be noted that several reviews report conflicting efficacy with therapeutic complement inhibition such as Eculizumab and low rates of pathogenic variants in complement genes in patients with TMA, especially drug-induced TMA. These authors caution that improvement after Eculizumab may be impacted by natural disease course after withdrawal of the offending agent in drug-induced TMA (16, 18).

4.4 AKI leading to CKD

Early nephrology involvement is recommended given even mild AKI can be associated with residual kidney damage. If etiology is unknown, biopsy should be considered if there is significant or persistent AKI after HCT. Biopsy could provide evidence of kidney involvement by GVHD, TA-TMA, or viral infections, allowing for more targeted treatment. Given most processes in the kidney leading to AKI are inflammatory, early identification and targeted treatment can help reduce duration of inflammation, reducing the progression to fibrosis and eventual irreversible kidney damage with loss of renal tubules and glomerular function (8). Recurrent renal GVHD can lead to tubular atrophy, peritubular capillary loss, and interstitial fibrosis. Recurrent episodes of AKI also increase the risk of progression to CKD. AKI is indicated by elevated serum Cr up to 100 days after HCT, chronic injury at or after 100 days, and CKD if AKI persists for 3 months or longer (2). After HCT, recommended evaluation for persistent kidney injury should occur at the 6- and 12-month post-transplant evaluation followed by at least yearly evaluations of serum blood urea nitrogen (BUN), serum creatinine, urinalysis, and blood pressure (21).

5 Management of CKD in a patient with HCT

It is important to identify those patients who have progressed from AKI to CKD due to the long term health implications and complications of CKD that require closer monitoring. Krist-van Holthe et al. found that high SCr within 3 months of HCT correlated with CKD at 1 year after HCT, so it is important to follow high risk patients long-term who have had prior AKI (57).

5.1 Definition

The National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) consensus guidelines from 2012 define CKD as at least 3 months of either decreased GFR (GFR < 60ml/min/1.73m^2) or one or more markers of kidney damage (albuminuria of at least 30mg/g, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation) (58). It should be noted that while these guidelines do not include patients with stage 2 CKD (defined by GFR 60-89 ml/min/1.73m^2), we recommend a similar monitoring and management strategies for these patients as they are still at risk of progressive renal dysfunction.

5.2 Etiology and risk factors

CKD is common among pediatric patients post-HCT with an incidence of 48% between 6mo and 10yr following HCT and with typical etiologies being idiopathic, TA-TMA, nephrotic syndrome, AKI, and drug toxicity usually attributed to calcineurin inhibitors (54). CKD caused by total body irradiation (TBI) or TA-TMA typically present 6-12mo following HCT (59). Risk factors include baseline GFR below 90ml/min/1.73m2, TBI exposure, nephrotoxic medications especially calcineurin inhibitors, infections including sepsis, recurrent AKI episodes, hypertension, and GVHD especially chronic GVHD due to prolonged immune-mediated renal damage (19).

5.3 CKD staging

As shown in Table 2, KDOQI and KDIGO recommend staging CKD by a combination of GFR as well as degree of albuminuria due to adult evidence that both are independently related to increased mortality, rates of end stage kidney disease (ESKD) progression, and cardiovascular events (58). Based on rate of CKD progression, acute medical events, or AKI episode, labs for CKD progression should be monitored closely. During acute complications or AKI, we recommend weekly CysC and at least weekly SCr. Outside of an acute episode, minimum frequency of monitoring for proteinuria/albuminuria, CysC, and SCr should occur with frequency based on CKD stage and degree of albuminuria (frequency of lab monitoring based on CKD stage is summarized in Table 3).

5.4 General management

Similar to AKI management, it is important to slow progression of CKD by minimizing nephrotoxic exposures and AKI episodes, dosing medications based on estimated GFR, measuring drug levels when available, ensuring adequate hydration, optimizing blood pressure, and minimizing proteinuria. If hypertension and proteinuria are identified, initiation of an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) is recommended as this has been shown to be renoprotective long term at slowing progression of CKD, especially among those patients with significant proteinuria (19). All patients who meet criteria for CKD should be referred for nephrology consultation. Close follow-up with a nephrologist is critical to monitor regular

TABLE 2 Staging of CKD by GFR and degree of albuminuria from KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD (58).

CKD staging by GFR and degree of albuminuria			Persistent Albuminuria		
			A1	A2	A3
			<30mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR (ml/min/1.73m²)	G1	≥ 90			
	G2	60-89			
	G3a	45-59			
	G3b	30-44			
	G4	15-39			
	G5	<15			

Low risk (if no other markers of kidney disease)
Moderately increased risk
High risk
Very high risk

labs for CKD complications including, but not limited to, abnormal blood pressure, nutrition issues, acidosis, anemia, and mineral bone disease. Multidisciplinary collaboration should include a dietitian who ideally has expertise in pediatric and renal nutrition, especially as patients without a gastrostomy tube may face challenges with oral tolerance during episodes of mucositis or esophagitis. Children with CKD benefit from multidisciplinary care given their risk of not only post-HCT complications but also CKD complications.

5.5 Complications of CKD: albuminuria

Albuminuria is associated with progression of CKD as well as decreased post-transplant survival (60). Development of any albuminuria in the first 100 days after HCT has been associated with increased risk of death at 1 year post-transplant (61). The most accurate method for assessing urinary albumin is a 24 hour urine collection. However, this can be difficult to accurately obtain particularly in younger patients. In a review by Hingorani et al, urinary albumin-to-creatinine ratios measured at days 80 to 100 days after transplantation has been shown to be predictive of subsequent kidney function and death, so any albuminuria during this time frame is associated with an increased risk of progression to CKD (2).

Albuminuria after HCT can occur as early as 2mo post-transplant, but typically occurs 6-12mo post-transplant which is temporally associated with discontinuation of immunosuppressive GVHD prophylaxis. Typical presentations include glomerulonephritis or nephrotic syndrome (NS). NS presents as proteinuria, hypoalbuminemia, edema, and hypercholesterolemia. NS in a patient who has undergone HCT should be evaluated with a renal biopsy as 60-80% of cases are due to membranous nephropathy, followed by 22% with minimal change disease (62). NS usually resolves after high dose prednisone treatment, restarting calcineurin inhibitors, or both. Rituximab has also been used successfully, typically among patients with membranous nephropathy after HCT.

If macroalbuminuria (>300mg albumin/g Cr) is detected, then the patient should be started on an ACE-I or ARB, and albuminuria should be monitored every 3-6 months. Macroalbuminuria can be a marker of renal GVHD, so it may be useful to continue immunosuppression after 100 days after transplantation even if there is no other evidence of GVHD in other organ systems (2). Macroalbuminuria as well as hypertension may also be early markers of TA-TMA in patients who have undergone HCT (12). If microalbuminuria (30-299 mg albumin/g Cr) is detected, then this should be repeated at least twice in the following 3-6 months to ensure albuminuria is stable before spacing monitoring to every 3-6 months. If the patient has microalbuminuria and hypertension then they should also be started on an ACE-I or ARB (63).

5.6 Complications of CKD: hypertension and blood pressure

Presence of HTN after HCT has been associated with poor long-term outcomes including increased risk of death, increased risk of CKD (in adult patients OR 4.03; 95% CI: 1.04-13.06 (64)), and increased risk of TA-TMA (19). HTN is defined as blood pressure greater than the 95th percentile for sex, age, and height as

TABLE 3 Frequency of monitoring based on CKD stage.

CKD Stage	Frequency of Lab Monitoring based on CKD stage											
	CKD Progression		Blood Pressure	Growth Monitoring		Anemia		CKD-MBD				
	CysC, SCr	Albuminuria	No HTN	HTN	Infants	Children	No anemia	Anemia	Ca, Phos	PTH	Vitamin 25(OH)D	AlkPhos
1	12mo	6*-12mo	In-office (12mo)	In-office (every visit) ABPM (12mo) Home BPs	Weight, Linear, HC (12mo)	Weight, Linear, +/- HC (12mo)	12mo	6mo	12mo	12mo	12mo	–
2	12mo	6*-12mo	In-office (3-6mo) ABPM (12mo)		Linear (3mo) Weight (6mo) HC (6mo) Dietitian	Linear (12mo) Weight (6mo) Dietitian	12mo	6mo	12mo	12mo	Baseline and 3-6mo based on level and supplements	–
3a	12mo	4*-12mo					12mo	3mo	6-12mo	Baseline and based on CKD progression		–
3b	6mo	4*-6mo					12mo	3mo	6-12mo			–
4	4mo	1*-4mo					6mo	3mo	3-6mo	6-12mo		–
5	1-3mo	1*-3m					3mo	1mo	1-3mo	3-6mo		12mo dependent on PTH

Asterix (*) indicates more frequent monitoring if the patient has significant albuminuria (A2 or A3).

measured on at least 3 occasions. HTN incidence has been reported as high as 80% in the first 2 years post-HCT in pediatric patients, typically occurring 1 month after HCT (65). A long term retrospective study by Hoffmeister et al. analyzing long term survivors of pediatric HCT found a 30-year cumulative incidence of 36% with median follow-up 16 years (range 5-36 years) and prevalence of 15% overall, which is 2-3 times that of the general population. Risk factors associated with HTN included AKI defined as doubling of baseline creatinine by day 100 after HCT, total body irradiation in preparative regimen, autologous donor type more so than unrelated donor type, obesity, diabetes, and history of growth hormone therapy. Longitudinal observation studies have shown that younger age, higher body mass index, and higher proteinuria, especially nephrotic range proteinuria, is more strongly associated with increasing BP over time (66).

BP should be checked using validated pediatric equipment with correct cuff size and position on upper extremity, as able. Ideally, patients should be seated with their feet on the floor and with arms and back supported. Patients should be relaxed and not talking or moving for at least 5 minutes prior to BP being measured (67). For young patients manual BP may be necessary due to intolerance. Standardized in-office blood pressure should be taken at least every 3-6 months. Where available, 24 hour mean arterial pressure by ambulatory blood pressure monitor (ABPM) should be performed at 80 days after transplantation and then annually, as this can provide a more accurate assessment of blood pressure variability and can help evaluate for white coat and masked HTN.

Treatment of HTN can help decrease not only progression of CKD but also cardiovascular disease risk. Lifestyle modifications should be implemented followed by antihypertensive treatment when BP is consistently >90th percentile for age, sex, and height. First line chronic antihypertensives in CKD are typically renin-angiotensin-aldosterone system antagonists (e.g. ACE-I and ARBs), and calcium channel blockers are also commonly used. Patients should be provided medical grade BP monitor for home and instructed to track daily BP log with notification parameters for high or low BP values. After BP monitor is obtained, it should be brought to clinic to confirm correlation with in-office BP monitor. If patient does not have electrolyte derangements requiring sodium supplementation, sodium restriction to <2g/day or adjusted for body size based on dietitian evaluation is also recommended (67, 68).

Among patients with CKD, target BP goals should be less than or equal to 50th percentile for age, sex, and height unless achieving this is limited by symptoms or signs of hypotension (67). This recommendation is based on the largest randomized control trial in pediatric CKD patients studying BP targets: the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CKD in Pediatric Patients (ESCAPE) trial. The ESCAPE trial included 385 children with baseline CKD with eGFR 20–80 ml/min/1.73m2 and 24 hour average ambulatory MAP >95th percentile. Children were randomized to intensified BP control (24 hour MAP <50th percentile) or to standard BP control (24 hour MAP 50th-99th percentile) using ramipril. The primary composite endpoint of 50% GFR decline and ESKD favored the intensive BP arm (HR: 0.65; 95% CI: 0.44–0.94) (69).

Children with systemic HTN have a narrower range of autoregulation in cerebral blood flow and an increased risk of cerebrovascular dysfunction, making them more susceptible to posterior reversible encephalopathy syndrome (PRES) (70). PRES presents with an abrupt, acute rise in BP along with seizures, visual changes, encephalopathy, headache, and radiologic findings on brain magnetic resonance imaging (MRI) with focal reversible vasogenic edema (71). PRES has been associated with a significant increase in length of stay and, when severe or if there are delays in treatment, can lead to secondary complications including ischemic infarction, intracranial hemorrhage, and status epilepticus. PRES is a neurological emergency requiring early identification and management including gradual reduction in BP and removal of any identifiable offending agents (72). Shah et al. studied the difference between PRES in pediatric oncology and post-HCT patients and found that oncology patients developed PRES at a younger age and were more likely to present with encephalopathy (70). Systemic HTN preceded PRES in 43.5% of patients, and this was more likely in post-HCT patients. Post-HCT patients were more likely to have rare neurological clinical presentations and more likely to die due to PRES-related complications.

5.7 Complications of CKD: nutrition and acidosis

Patients with CKD are at increased risk of protein energy malnutrition which can significantly impact linear growth, neurocognitive development, and sexual development (73). For patients with CKD stage 2-5, we recommend patients are seen by a dietitian who ideally has expertise in pediatric and renal nutrition. This allows patients to receive targeted recommendations and education based on their severity of CKD and any necessary dietary modifications including fluid, sodium (especially if hypertensive), phosphate, potassium, and protein goals. We do not recommend restricting nutrition without specific guidance from a renal dietitian given the patient's increased risk of protein energy malnutrition.

Growth parameters should be evaluated at least twice per year with greater frequency among patients with acute medical issues, polyuria, concern for growth delay, declining or low BMI, or decreased nutritional intake (73). Infants with CKD stage 2-5 should have length measured at least every 3 months, and children with CKD stage 2-5 should have linear growth measured at least annually (74). According to the National Kidney Foundation's recommendations of 2009, anthropometric parameters should include percentiles and standard deviation score (SDS) for length-for-age or height-for-age, length or height velocity for age, weight-for-age, BMI-for-height-age, head circumference-for-age (if less than 3 years of age). Patients with CKD after HCT are at higher risk for long term growth issues given frequent mucositis or GI symptoms limiting consistent nutrition delivery. A long term pediatric study by Perkins et al. of patients who received HCT under 3 years of age for acute lymphoblastic leukemia or acute myelogenous leukemia found growth hormone deficiency in 59%, abnormal pubertal development in 12%, and dyslipidemias in 59% (75).

Persistent metabolic acidosis can contribute to short stature and decreased linear growth potential, so patients with CKD stage 2-5 should have serum bicarbonate corrected to at least 22 mm/L (the lower limit of normal), often times requiring bicarbonate supplementation to achieve these goals. Typically in conjunction with endocrinology, initiation of recombinant human growth hormone (rhGH) therapy can be considered in patients with short stature (height SDS < 1.88 or height for age <3%ile) or linear growth failure (height velocity for age SDS < -1.88 or height velocity for age <3%ile) persisting for at least 3 months despite correction of metabolic derangements and nutritional deficiency. Contraindications to rhGH include pre-existing intracranial hypertension that could be worsened by rhGH, closed epiphyses, severe secondary hyperparathyroidism (PTH > 500pg/mL), proliferative or non-proliferative diabetic retinopathy, active malignancy, acute critical illness, within 1 year after renal transplantation, or known hypersensitivity to any component of rhGH medication (76).

5.8 Complications of CKD: anemia

As renal function declines, the kidneys are unable to synthesize adequate levels of erythropoietin which can lead to a progressively more severe anemia. Anemia is associated with increased mortality and hospitalization frequency in both adults and children. Left untreated, anemia can lead to cardiovascular dysfunction, decreased quality of life, impaired cognition, and reduced exercise capacity (77). Hemoglobin (Hgb) decline is gradual over time among patients with CKD but becomes a linear relationship with GFR below 43 ml/min/1.73m2, according to the CKiD Prospective Cohort Study which analyzed 340 North American children with CKD (78).

The diagnosis of anemia in children with CKD varies depending on age. Regardless of age or CKD stage, the evaluation for anemia should include: complete blood count (including Hgb concentration, red cell indices, white blood cell count, differential, platelet count), absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), serum vitamin B12 and folate levels (78). After initial evaluation, anemia evaluation frequency with Hgb is based on CKD staging as shown in Table 3. All CKD patients with anemia should be started on enteral iron if their TSAT ≤ 20% and ferritin ≤ 100ng/mL. For patients with CKD 5, erythropoiesis stimulating agents (ESA) are considered but should target lower Hgb range of 10.0 to 12.0 g/dL among patients with cancer (79). During ESA therapy, iron status (TSAT and ferritin) should be evaluated at least every 3 months. Patients should be counseled about and receive routine monitoring for possible adverse effects such as thromboembolic events, hypertension, thrombocytopenia, seizure, or hemorrhage, skin issues such as rash, irritation, or pruritus (80).

Limited pediatric randomized control trials (RCTs) show improved hemoglobin level, decreased transfusion need, and a positive correlation between hemoglobin changes and health related quality of life changes among those who received ESAs, but these RCTs had short treatment and follow-up periods (8 weeks (81), 16 weeks (80), 12 weeks of treatment then follow-up for 7

years (82)). A Cochrane review including one pediatric RCT (80) found ESA use reduced the risk of red blood cell transfusion by an average of one unit of blood (RR 0.65, 95% CI 0.62-0.68, 70 trials, N=16,093) (83).

While patients with CKD after HCT are at a higher risk for anemia given factors associated with underlying etiology requiring HCT, frequent infections and blood draws, and medication side effects, the use of ESAs in patients with cancer is controversial due to concern that ESAs may directly stimulate tumor growth and lead to worse outcomes. There is strong evidence between ESA use and increased mortality during active study period (HR 1.17, 95% CI 1.06 to 1.29, 70 trials, N=15,935), increased risk of thromboembolic complications (RR 1.52, 95% CI 1.34 to 1.74; 57 trials, N=15,498), suggestive but not robust evidence of increased risk of hypertension (RR 1.24, 95% CI 1.09 to 1.58), but insufficient evidence about ESA effect on tumor response (fixed effect RR 1.02, 95% CI 0.98 to 1.06, 15 trials, N=5,012) (83). A large (n=13,933) meta-analysis of primarily adult clinical trials (<1% in ESA group were < 18 years of age) found similar results (84). Due to these potential risks, clinical practice guidelines recommend against systematic administration of ESAs in children with oncologic diseases and a case-by-case decision by renal and oncology teams for those patients with barriers to transfusions. Lower hemoglobin targets of 10 g/dl have been proposed to minimize risk of thrombosis and mortality (79, 85).

5.9 Mineral bone disease (CKD-MBD)

Based on the National Kidney Foundation KDIGO work group, patients with CKD, especially stage G3a-G5D, have significantly higher fracture rates than the general population, and infants and children with CKD suffer growth retardation and severe short stature (73, 74). Patients with CKD after HCT are at an increased risk for MBD given prolonged exposure to medications that affect bone metabolism such as systemic steroids. The pediatric study by Perkins et al. found patients who received HCT under 3 years of age had decreased bone mineral density in 24% and short stature in 47% (75).

Many studies have also shown an increased risk of all-cause mortality in patients with increased levels of serum phosphate. Due to this, regular and comprehensive evaluation for CKD-MBD should include serum calcium (Ca), serum phosphate (Phos), serum parathyroid hormone (PTH), serum alkaline phosphatase activity (AlkPhos), and serum 25-hydroxyvitamin D levels (25(OH) D). Patients with CKD stage 5 should also be evaluated for fracture risk, sometimes including bone mineral density testing assessing for osteoporosis. Routine evaluation for CKD-MBD should begin at CKD stage 2. For patients with CKD stage 3-5, frequency of evaluation should be based on rate of progression of CKD, magnitude of abnormality, and baseline levels. More frequent monitoring may be required to assess treatment efficacy and side effects. Serum 25(OH)D < 30 ng/mL should be supplemented with ergocalciferol (Vitamin D2) or cholecalciferol (Vitamin D3).

6 End stage kidney disease and renal transplant after HCT

The prevalence of ESKD in adult HCT patients is as high as 4% of patients with CKD (64). Pediatric HCT recipients are unique compared to other ESKD patients given their prior chemotherapy, irradiation, and immunosuppression, as well as their degree of medical complexity with possible pre-existing GVHD, cardiovascular disease, bone disease, diabetes mellitus, short stature, gonadal failure, and risk of opportunistic infections. These patients are also at an increased risk of recurrence of their primary malignancy as well as development of a secondary malignancy, so they will require vigilant surveillance of multiple organ systems. Prolonged immunosuppression not only increases infectious risk in an already immunosuppressed HCT patient, but also can increase the risk of leukemic relapse (53). Due to these challenges, thoughtful multidisciplinary discussion about the risks and benefits of renal transplantation should take place.

Prior to renal transplantation, evaluation for pre-existing immune system impairment should take place when deciding on immunosuppressive agents following renal transplantation. The source of HCT (autologous compared to allogenic) and renal transplant (same allogenic donor compared to a different allogenic donor) can be thought of as biologically distinct groups, especially considering the differences in conditioning regimen (53). Given the presence of "passenger lymphocytes" in solid organ transplants, these donor-derived white blood cells and antigen presenting cells are believed to result in microchimerism which could be both tolerogenic and immunogenic. This can potentially increase the risk of GVHD but also theoretically offer immunologic tolerance in the long term, thereby reducing required immunosuppression (53, 86). Kidney transplant from the same donor can be successful in a patient after HCT without immunosuppression and has been confirmed in multiple studies (53, 87).

Adult data suggests favorable outcomes after renal transplantation in patients who have undergone HCT (53, 88, 89). Hamawi et al. described 10 patients with HCT nephropathy who underwent renal transplant including 6 patients with the same donor who did not receive immunosuppression and 4 patients with different donors (2 living, 2 deceased donors) who did receive immunosuppression. The median estimated graft survival was 105 mo, and there were no episodes of renal transplant rejection. All graft losses (n=4) were due to patient deaths with 3 deaths from an infectious process (2 were not on immunosuppression) and 1 death from myocardial infarction and post-transplant lymphoproliferative disorder (88). Butcher et al. described 6 patients who underwent renal transplant including 3 patients with the same donor who did not receive immunosuppression. Patients were followed up to 31mo and had only 1 mortality from a patient receiving immunosuppression who died from metastatic squamous cell cancer of genital tract (90).

Pediatric literature is limited, but Thomas et al. discusses their single center experience with 3 pediatric patients and Bunin et al. describe 2 pediatric patients (Table 4) (53, 91).

TABLE 4 Summary of pediatric literature on renal transplantation post-HCT.

	Age at HCT	Time to renal transplant	Transplant type	Underlying oncologic and renal diagnosis	Current graft survival	Post-renal transplant complications
53	2y	10y	LRKT (pre-emptive)	-Stage III neuroblastoma -Interstitial fibrosis	6y	None
	7y	1y	LRKT (hemodialysis prior)	-Schimke's immune-osseous dysplasia -Mesangioproliferative glomerulonephritis	3y 8m	None
	4y	10y	LRKT (pre-emptive)	-Stage IV neuroblastoma -Interstitial fibrosis	7m	Tacrolimus toxicity
91	15y	32m	LRKT (pre-emptive)	-Erythropoietic porphyria -CKD following 2 HCTs and prolonged foscarnet for CMV reactivation	1.7y	None
	6y	28m	DDKT (hemodialysis prior)	-Neuroblastoma -TA-TMA requiring bilateral nephrectomies	1.5y	CKD

Living related kidney transplant (LRKT) and deceased donor kidney transplant (DDKT). Pre-emptive refers to patients who were transplanted before starting dialysis.

7 Conclusion

Patients undergoing hematopoietic stem cell transplant have unique risk factors for AKI including frequent nephrotoxic exposure, sinusoidal obstruction syndrome, graft-versus-host-disease, and transplant-associated thrombotic microangiopathy, and viral infections such as BK viremia. These patients are at risk for progression to CKD and ESKD. Renal transplantation after HCT has had favorable outcomes in adults with limited pediatric data.

8 Future perspectives

Pediatric patients post-HCT are a growing group of high-risk patients who may progress to CKD, ESKD, and potentially renal transplantation in their lifetime. Future studies should focus on better characterizing renoprotective strategies and timely interventions within this population that are distinct from patients with CKD who have not undergone HCT.

Author contributions

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed upon by all authors. The authors have contributed in multiple roles. KV is responsible for writing the original draft and literature search. JA and CJ are responsible for literature search and editing for the original draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic factors for multi-organ dysfunction in pediatric oncology patients admitted to the pediatric intensive care unit

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Background: Pediatric oncology patients who require admission to the pediatric intensive care unit (PICU) have worse outcomes compared to their non-cancer peers. Although multi-organ dysfunction (MOD) plays a pivotal role in PICU mortality and morbidity, risk factors for MOD have not yet been identified. We aimed to identify risk factors at PICU admission for new or progressive MOD (NPMOD) during the first week of PICU stay.

Methods: This retrospective cohort study included all pediatric oncology patients aged 0 to 18 years admitted to the PICU between June 2018 and June 2021. We used the recently published PODIUM criteria for defining multi-organ dysfunction and estimated the association between covariates at PICU baseline and the outcome NPMOD using a multivariable logistic regression model, with PICU admission as unit of study. To study the predictive performance, the model was internally validated by using bootstrap.

Results: A total of 761 PICU admissions of 571 patients were included. NPMOD was present in 154 PICU admissions (20%). Patients with NPMOD had a high mortality compared to patients without NPMOD, 14% and 1.0% respectively. Hemato-oncological diagnosis, number of failing organs and unplanned admission were independent risk factors for NPMOD. The prognostic model had an overall good discrimination and calibration.

Conclusion: The risk factors at PICU admission for NPMOD may help to identify patients who may benefit from closer monitoring and early interventions. When applying the PODIUM criteria, we found some opportunities for fine-tuning these criteria for pediatric oncology patients, that need to be validated in future studies.

KEYWORDS

pediatric oncology, intensive care unit, multi-organ dysfunction, critical care, prognosis

Introduction

The simultaneous dysfunction of multiple organ systems plays a pivotal role in the mortality of children admitted to the pediatric intensive care unit (PICU) (1). Multiple organ dysfunction (MOD) is defined as two or more concurrent organ dysfunctions (1–3). While the term multiple organ dysfunction syndrome (MODS) has traditionally been used, it was recently posited that this term should be selectively applied to patients with a shared underlying mechanism that affects multiple organ systems simultaneously (4). MOD can be categorized in new MOD, defined as MOD in patients who have single or no organ dysfunction on PICU admission, and progressive MOD, defined as additional dysfunctional organ systems in patients who already meet MOD criteria at admission (5).

In children, the risk factors for developing MOD include sepsis, major trauma, severe hypoxemia, and young age (e.g., infancy) (6, 7). The number of dysfunctional organ systems is associated with mortality, with each additional failing organ system increasing the risk of death (7–10). Pediatric oncology patients are particular at high risk for MOD due to the aggressive cancer pathophysiology and intensive treatment regimens, that may lead to organ infiltration, systemic toxicity, and immunosuppression (11). Similarly to general pediatric patients, MOD plays a significant role in the high morbidity and mortality of these patients (12). Early recognition and intervention in organ dysfunction may provide the potential to modify its course and prevent further deterioration (13–16). In adult oncology patients, it was shown that early interventions in deteriorating patients improved both short- and long-term outcomes (14, 15). Therefore, identifying risk factors for MOD at start of the PICU admission could provide opportunities for intensified monitoring and early interventions, which may ultimately reduce morbidity and mortality in critically ill pediatric oncology patients (12, 16, 17). Despite the important role of MOD in PICU morbidity and mortality, risk factors for MOD in pediatric oncology patients have not yet been identified.

In this study, we aimed to identify risk factors at PICU admission for MOD during the first week of PICU stay in pediatric oncology patients. Recently, the Pediatric Organ Dysfunction Information Update Mandate (PODIUM) evidence-based pediatric organ dysfunction criteria were published (12); this is the first study in pediatric oncology patients using these criteria. In addition, fine-tuning of these criteria for pediatric oncology patients may be needed, as they frequently experience organ dysfunction as a result of their oncological treatment. This dysfunction may not necessarily indicate MOD. Therefore, the second objective of this study was to assess whether adjusting the PODIUM criteria for pediatric oncology patients would reveal different risk factors for MOD.

Methods

We performed a retrospective cohort study between June 1, 2018 and June 1, 2021, at an 18-bed PICU of the Wilhelmina Children's Hospital, that is shared with the adjacent Princess Máxima Center, an 80-bed national referral center for pediatric oncology. All pediatric oncology patients with International Classification of Diseases in Oncology (ICD-O) diagnosis of pediatric malignancy (morphology code 1, 2 or 3) aged 0 to 18 years admitted to the PICU were eligible for inclusion. Patients without consent for the use of clinical data were excluded. The study was approved by the ethical review board of our hospital (IRB protocol number 16-572/C).

Assessment of organ dysfunction

We classified organ dysfunction based on the PODIUM criteria (18) (Table 1 and Supplementary Table 1). Clinical data were extracted from the electronic health records and comprised patient characteristics, organ dysfunction in the 24 hours preceding PICU admission, and clinical time series with a frequency of 1 measurement per minute (vital signs and mechanical ventilator data), laboratory results, observations (e.g. Glasgow Coma scores), vasoactive medication, and fluid balance data. Additional data for organ dysfunction, e.g., cardiopulmonary resuscitation, encephalopathy and gastro-intestinal perforation,

TABLE 1 Assessment of the PODIUM and PONC-PODIUM criteria.

Organ system*	PODIUM criteria	PONC-PODIUM criteria adjustments
Neurologic	Glasgow Coma Scale (GCS) ≤ 8 Cornell Assessment of Pediatric Delirium (CAPD) score ≥ 9	
Respiratory	In patients on respiratory support but not invasively ventilated, i.e. on either high flow nasal cannula (HFNC), non-rebreathing mask (NRM) or non-invasive ventilation): o PaO_2/FiO_2 ratio ≤ 300 o SpO_2/FiO_2 ratio ≤ 264 o Non-invasive ventilation for ventilatory failure In invasively ventilated patients: o Oxygenation index (OI) ≥ 4 to ≤ 16 o OI >= 16 o Oxygen saturation index (OSI) ≥ 5 to < 12.3 o OSI ≥ 12.3	Only **severe** respiratory dysfunction; - Invasive ventilation with OI ≥ 16 and/or OSI ≥ 12.3

(Continued)

TABLE 1 Continued

Organ system*	PODIUM criteria	PONC-PODIUM criteria adjustments
Cardiovascular	Cardiac arrest HR > 2 SD above normal for age o 0–7 d: HR > 180 beats/min o > 1 wk to 1 m: HR > 180 beats/min o > 1 m to < 1 y: HR > 180 beats/min o 6 y to < 13 y: HR > 150 beats/min o 13 y to < 18 y: HR > 130 beats/min SBP > 2 SD above normal for age o 0–7 d: SBP <50 mm Hg o > 1 wk to 1 m: SBP < 70 mm Hg o > 1 m to < 1 y: SBP < 75 mm Hg o 1 y to < 6 y: SBP < 75 mm Hg o 6 y to < 13 y: SBP < 80 mm Hg o 13 y to < 18 y: SBP < 80 mm Hg Vasoactive-inotropic score ≥ 5 Serum lactate ≥ 3 mmol/L Echo cardiographic estimation of left ventricular ejection fraction (LVEF) < 50%	Only **severe** cardiovascular dysfunction in case it was graded; - Resuscitation; or - At least 2 out of 5 of the following criteria present at the same time: HR > 2 SD above normal for age; SBP > 2 SD above normal for age, vasoactive-inotropic score ≥ 5, serum lactate ≥ 5 mmol/L, echo cardiographic estimation of LVEF < 30%;
Renal criteria	- Urine output < 0.5 mL/kg/h for ≥ 6 hours and < 12 hours with concomitant serum creatinine increase 1.5 – 1.9 times baseline or ≥ 26.5 µmol/L increase. - Urine output < 0.5 mL/kg/h for ≥ 12 hours - Serum creatinine increase ≥ 2 times baseline - eGFR < 35 mL/min/1.73 m2 (and not age < 30 days) - Fluid overload ≥ 20% – starting 48 hours after start PICU admission - Initiation of continuous renal replacement therapy (CRRT)	- Oliguria for < 0.5 mL/kg/h for ≥ 6 hours **or** concomitant serum creatinine increase 1.5 – 1.9 times baseline **or** ≥ 26.5 µmol/L increase; or - Serum creatinine increase ≥ 2 times baseline; or - Fluid overload of **10%** from PICU admission onwards; or - eGFR < 35 mL/min/1.73; or - Initiation of renal replacement therapy
Gastrointestinal	Bowel perforation or pneumatosis intestinalis on plain abdominal film, CT or MRI	
Hepatic	o Biochemical evidence of acute liver injury (defined as aspartate aminotransferase > 100 IU/L, alanine aminotransferase > 100 IU/L, gamma-glutamyl transferase > 100 IU/L, total bilirubin > 85.5 µmol/L, or direct bilirubin > 34.2 µmol/L) with prothrombin time (PT) ≥ 15 secs or international normalize ratio (INR) ≥ 1.5 and hepatic encephalopathy o Biochemical evidence of acute liver injury with PT ≥ 20 secs or INR ≥ 2.0	
Hematology	Platelet count < 30 10E9/L or 50% decrease from baseline Hemoglobin < 4.3 mmol/L Leucocytes < 3.0 10E9/L	Only **new dysfunction** throughout PICU stay was included, defined as: - Platelet count < 30 10E9/L (30 000 cells/µL) or 50% decrease from baseline; **or** - Hemoglobin < 4.3 mmol/L
Coagulation	In the absence of liver dysfunction, a combination of ≥ 2 of the following criteria: o Platelet count < 30 10E9/L o INR > 1.5 o Fibrinogen 1.5 g/L o D-dimer > 5 µg/mL (= upper limit of normal)	Platelet count **< 30** 10E9/L (<30 000 cells/µL), and other coagulation criteria were classified according to the original PODIUM criteria.
Endocrine	Blood glucose ≥ 8.3 mmol/L or < 2.8 mmol/L	
Immunology	Peripheral absolute neutrophil count < 0.5 10E9/L	Only **new dysfunction** throughout PICU stay was included, defined as: - Peripheral absolute neutrophil count < 0.5 10E9/L (< 500 cells/µL) or if missing: leucocyte count < 1.0 10E9/L (< 1000 cells/µL)

The main adjustments compared to the original PODIUM criteria are depicted in bold.
*In case an organ system is not displayed, it is classified according to the original PODIUM criteria, see Supplementary Table S2.
PONC-PODIUM, pediatric oncology Pediatric Organ Dysfunction Information Update Mandate; NPMOD, new or progressive organ dysfunction; OI, oxygenation index; OSI, oxygenation saturation index; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

were acquired from free text fields in clinical or imaging reports through text-mining. In applying the PODIUM criteria, we made assumptions based on clinical expertise to get from a high frequency dataset to the classification of (concurrent) organ dysfunction, including handling measurement errors and missing data. Detailed information on the assessment of the PODIUM criteria is provided in the Supplementary Material. Single organ dysfunction was classified based on the PODIUM criteria within 1-hour windows, and the number of concurrent organ dysfunctions was classified within each 24-hour window.

We assessed presence of organ dysfunction at PICU admission (baseline) by evaluating all relevant laboratory values and free text

data in the 24 hours prior to and the first three hours of PICU admission. Missing data were classified as no organ dysfunction at PICU baseline. For further details on assessment of the organ dysfunction criteria, see Supplementary Table 2.

Adjustments in PODIUM criteria for pediatric oncology patients

Although some specific criteria for oncology patients are included in the PODIUM criteria, we proposed additional considerations for these patients since some laboratory variables may reflect side-effects of the cancer treatment instead of organ dysfunction in the context of MOD. We therefore adjusted some criteria for this specific patient population: the pediatric oncology (PONC) PODIUM criteria (Table 1).

Invasive ventilation and the use of vasoactive medication are associated with increased PICU mortality in pediatric oncology patients (19). Therefore, we used the thresholds of severe respiratory dysfunction, i.e., invasive ventilation and an oxygenation index of ≥ 16 or an oxygenation saturation index of ≥ 12.3. For cardiovascular dysfunction, we used the severe threshold for lactate and left ventricular ejection fraction (LVEF).

Considering the renal criteria, it was shown that patients with a fluid overload greater than 10% were 6 times more likely to die during PICU admission than those with less than or equal to 10% fluid overload (20). Moreover, oliguria is often not present in pediatric oncology patients with acute kidney injury (AKI) (20). We therefore adjusted the criteria for renal dysfunction: oliguria was not required and a fluid overload > 10%, instead of 20%, was used directly from the start of PICU admission onwards (as opposed to starting 48 hours after admission).

Since hematological and immunological dysfunction at baseline are less relevant due to the idiopathic nature of these in oncology patients and likely does not represent dysfunction due to critical illness, we excluded the leukocyte criterion from hematological dysfunction and only included hematological or immunological dysfunction that was newly developed during PICU stay for the classification of NPMOD. In classifying coagulation dysfunction, we used the platelet count threshold for pediatric oncology patients (i.e., < 30 10E9/L or < 30 000 cells/μL).

Primary outcome: new or progressive multi-organ dysfunction

The primary outcome was new or progressive MOD (NPMOD). New MOD was defined as no MOD at baseline and the concurrent dysfunction of at least 2 organs. Progressive MOD was defined as MOD (i.e., concurrent dysfunction of at least 2 organ systems) at baseline, and the development of one or more additional concurrent organ dysfunction(s).

Statistical analysis

A multivariable logistic regression model was used to estimate the association between covariates and the outcome. Covariates at baseline of PICU admission were selected based on literature and expert opinion. The included covariates encompassed diagnosis category (i.e., hemato-oncological, solid tumor or neuro-oncological); hematopoietic stem cell transplantation; neutropenia at baseline; a composite covariate of sepsis and/or infection (bacterial or fungal (21)); high-flow oxygen therapy preceding PICU admission; the number of organ dysfunctions at baseline (categorized into 0, 1 or ≥ 2), unplanned PICU admission, and previous relevant PICU admission (i.e., a previous PICU admission that was either unplanned or had a protracted course). See Supplementary Material for a detailed description of the covariates.

We analyzed the first week of PICU admission, or up to discharge within seven days, whichever event first occurred. We assessed the outcome NPMOD based on both the original and our PONC-PODIUM criteria, to determine whether adjustments of the organ dysfunction criteria for pediatric oncology population yielded different significant risk factors. In addition, we performed a subgroup analysis of only unplanned PICU admissions to identify possible different significant risk factors for NPMOD. A multivariable logistic regression model was used to estimate the association between covariates and the outcome, including the same covariates as before except for unplanned PICU admission. The outcome NPMOD within one week based on both original PODIUM criteria and PONC-PODIUM criteria was assessed.

To study the predictive performance of the model, internal validation was performed by using Efron's bootstrap (i.e. resampling the dataset 500 times) (22). Statistical analyses were performed using R-statistical software (23), version 4.2.1 (2022–06–23)., see Supplementary Material for associated packages.

Results

A total of 761 PICU admissions of 571 patients were included. Table 2 reports the clinical characteristics of the PICU admissions. The median age [interquartile range] at PICU admission was 6.0 [2.7 – 12.8] years. The cohort included 25% hemato-oncological patients, 35% solid tumor patients, 40% neuro-oncology patients, and 2% had a hematopoietic stem cell transplantation (HSCT) in the year preceding PICU admission. Among the 761 PICU admissions, 288 (38%) were unplanned admissions. Neuro-oncology and solid tumor patients most often had planned postoperative PICU admissions (89% and 67% respectively), whereas hemato-oncology patients largely required unplanned PICU admissions (93%). Data of at least 2 organ systems were available at baseline in 744 of 761 PICU admissions (98%) for the classification of MOD at baseline.

NPMOD classified according to original PODIUM criteria

NPMOD was present in 154 PICU admissions (20%). The PICU mortality was 4% in all PICU admissions, 1% in the group without NPMOD, and 14% in the group with NPMOD. In the PICU admissions where patients developed NPMOD, the three most frequently failing organ systems at PICU baseline included hematological (41%), immunological (23%) and respiratory (20%) dysfunction (see Figure 1A).

The results of the univariate and multivariable model are displayed in Table 3. Hemato-oncological diagnosis, number of failing organs at baseline and unplanned PICU admissions were significantly associated with NPMOD in the multivariable model.

TABLE 2 Clinical and demographic characteristics of PICU admissions overall and by occurrence of NPMOD (defined according to PODIUM criteria).

Characteristic	Total PICU admissions (n = 761)	PICU admissions without NPMOD (n = 607)	PICU admissions with NPMOD (n = 154)
General characteristics per PICU admission			
Age at admission (years), median [IQR]	6.0 [2.7 – 12.8]	6.5 [3.0 – 13.1]	4.0 [1.5 – 11.0]
Female sex, n (%)	351 (46)	265 (44)	86 (56)
PICU admission reason, n (%)			
Planned post-operative care	473 (62.2)	444 (73.1)	29 (18.8)
Respiratory failure	106 (13.9)	49 (8.1)	57 (37.0)
Sepsis	40 (5.3)	25 (4.1)	15 (9.7)
Neurological deterioration	36 (4.7)	27 (4.4)	9 (5.8)
Cardiovascular failure	33 (4.3)	20 (3.3)	13 (8.4)
Renal failure	7 (0.9)	1 (0.2)	6 (3.9)
Liver failure	2 (0.3)	1 (0.2)	1 (0.6)
Unplanned post-operative care	24 (3.2)	16 (2.6)	8 (5.2)
Other	40 (5.3)	24 (4.0)	16 (10.4)
Covariates			
Oncological diagnosis groups			
Hemato-oncological	190 (25.0)	101 (16.6)	89 (57.8)
Solid tumor	268 (35.2)	225 (37.1)	43 (27.9)
Brain/CNS tumor	303 (39.8)	281 (46.3)	22 (14.3)
HSCT, n (%)	16 (2.1)	5 (0.8)	11 (7.1)
Infection or sepsis at baseline, n (%)	100 (13.1)	52 (8.6)	48 (31.2)
Neutropenia at baseline, n (%)	82 (10.8)	47 (7.7)	35 (22.7)
HFNC preceding admission, n (%)	86 (11.3)	46 (7.6)	40 (26.0)
Previous relevant PICU admission, n (%)	104 (13.7)	67 (11.0)	37 (24.0)
Unplanned PICU admission, n (%)	288 (37.8)	163 (26.9)	125 (81.2)
Number of failing organs at baseline, n (%)			
0	471 (61.9)	416 (68.5)	49 (31.8)
1	159 (20.9)	117 (19.3)	45 (29.2)
>= 2	131 (17.2)	74 (12.2)	60 (39.0)
Outcome			
Maximum number of concomitantly failing organs during first week of PICU stay			

(Continued)

TABLE 2 Continued

Characteristic	Total PICU admissions (n = 761)	PICU admissions without NPMOD (n = 607)	PICU admissions with NPMOD (n = 154)
0	346 (45.5)	346 (57.3)	0 (0)
1	209 (27.5)	209 (34.6)	0 (0)
2	78 (10.2)	28 (4.6)	50 (32.5)
3	56 (7.4)	16 (2.6)	40 (26.0)
4	34 (4.5)	5 (0.8)	29 (18.8)
>= 5	38 (4.9)	3 (0.5)	35 (22.3)
PICU length of stay (days), median [IQR]	0.9 [0.8 – 2.5]	0.9 [0.7 – 1.4]	5.0 [2.1 – 10.0]
PICU mortality, n (%)	28 (3.7)	6 (1.0)	22 (14.3)

IQR, interquartile range; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; HFNC, high flow nasal cannula oxygen therapy; NPMOD, new or progressive multi-organ dysfunction; PICU, paediatric intensive care unit.

Internal validation of the model yielded a c-index of 0.81, indicating a reasonable discriminative ability. The calibration plot showed an overall good calibration, with an index-corrected slope of 0.93.

NPMOD classified according to PONC-PODIUM criteria

Using the PONC-PODIUM criteria, NPMOD was present in 157 PICU admissions (21%), see Supplementary Table S3. Applying these adjusted criteria revealed a different top three of frequently failing organ systems at PICU baseline, namely endocrine (22%), renal (21%), and severe cardiovascular dysfunction (10%) (Figure 1B). In the multivariable model, we found the same significant risk factors for NPMOD including hemato-oncological diagnosis, number of failing organs at baseline and unplanned PICU admission (Supplementary Table S4).

Unplanned PICU admissions

We performed a subgroup analysis including only the unplanned admissions (Table 4). NPMOD according to the original PODIUM criteria was present in 125 unplanned PICU admissions (43%). Respiratory failure, sepsis and neurological deterioration were the three major PICU admission reasons for

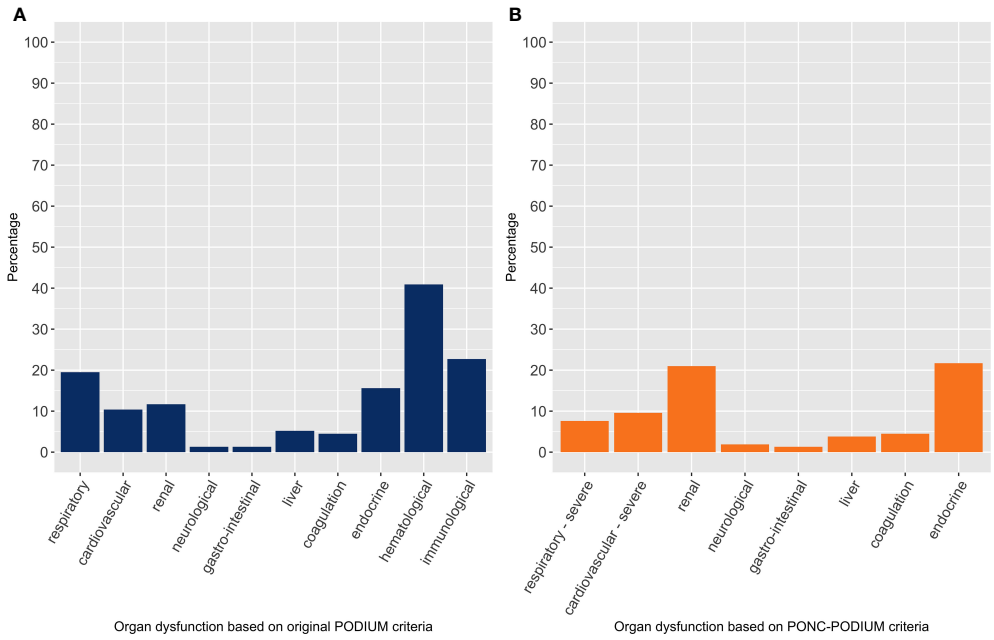

FIGURE 1
Organ dysfunction at PICU baseline in all PICU admissions with new or progressive multi-organ dysfunction, per organ system with percentage of failing organ system. The left panel **(A)** considers organ dysfunction based on the original PODIUM criteria, whereas the right panel **(B)** considers organ dysfunction based on the PONC-PODIUM criteria, thus adjusted for pediatric oncology patients.

TABLE 3 Results of the univariate and multivariable logistic regression model, with estimated odds ratio (OR) along with the 95% confidence interval (CI), for outcome of new or progressive multi organ dysfunction (NPMOD) - defined according to the PODIUM criteria.

Covariate	Univariate OR (95% CI)	Multivariable OR (95% CI)
Oncological diagnosis groups		
Hemato-oncological	11.19 [6.71 – 18.67]	**2.23 [1.14 – 4.36]**
Solid tumor	2.33 [1.36 – 3.98]	1.29 [0.70 – 2.37]
Brain/CNS tumor	*Reference*	*reference*
HSCT, n (%)	9.26 [3.17 – 27.07]	1.66 [0.52 – 5.22]
Infection or sepsis at baseline, n (%)	4.83 [3.10 – 7.53]	1.63 [0.93 – 2.88]
Neutropenia at baseline	3.50 [2.16 – 5.66]	0.46 [0.21 – 1.02]
HFNC preceding admission	4.27 [2.67 – 6.84]	1.17 [0.67 – 2.03]
Previous relevant PICU admission	2.54 [1.63 – 3.99]	1.07 [0.63 – 1.83]
Unplanned PICU admission	11.74 [7.55 – 18.27]	**5.82 [3.37 – 10.07]**
Number of failing organs at baseline		
0	*Reference*	*reference*
1	3.26 [2.07 – 5.14]	**2.18 [1.30 – 3.67]**
>= 2	6.88 [4.38 – 10.81]	**2.39 [1.18 – 4.83]**

CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; HFNC, high flow nasal cannula oxygen therapy.
Significant covariates in the model are in bold.

TABLE 4 Clinical and demographic characteristics of unplanned PICU admissions, by occurrence of new or progressive multi organ dysfunction (defined according to PODIUM criteria).

Characteristic	Unplanned PICU admissions (n = 288)	Unplanned PICU admissions without NPMOD (n = 163)	Unplanned PICU admissions with NPMOD (n = 125)
General characteristics per PICU admission			
Age at admission (years), median [IQR]	5.8 [2.3 – 13.1]	7.2 [2.6– 13.5]	4.1 [1.9 – 11.4]
Female sex, n (%)	143 (49.7)	70 (42.9)	73 (58.4)
PICU admission reason, n (%)			
Respiratory failure	106 (36.8)	49 (30.1)	57 (45.6)
Sepsis	40 (13.9)	25 (15.3)	15 (12.0)
Neurological deterioration	36 (12.5)	27 (16.6)	9 (7.2)
Cardiovascular failure	33 (11.5)	20 (12.2)	13 (10.4)
Renal failure	7 (2.4)	1 (0.6)	6 (4.8)
Liver failure	2 (0.7)	1 (0.6)	1 (0.8)
Unplanned post-operative care	24 (8.3)	16 (9.8)	8 (6.4)
Other	40 (13.9)	24 (14.7)	16 (12.8)
Covariates			
Oncological diagnosis groups			
Hemato-oncological	168 (58.3)	84 (51.5)	84 (67.2)

(Continued)

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TABLE 4 Continued

Characteristic	Unplanned PICU admissions (n = 288)	Unplanned PICU admissions without NPMOD (n = 163)	Unplanned PICU admissions with NPMOD (n = 125)
Solid tumor	88 (30.6)	56 (34.4)	32 (25.6)
Brain/CNS tumor	32 (11.1)	23 (14.1)	9 (7.2)
HSCT, n (%)	16 (5.6)	5 (3.1)	11 (8.8)
Infection or sepsis at baseline, n (%)	86 (29.9)	40 (24.5)	46 (36.8)
Neutropenia at baseline, n (%)	75 (26.0)	41 (25.2)	34 (27.2)
HFNC preceding admission, n (%)	79 (27.4)	40 (24.5)	39 (31.2)
Previous relevant PICU admission, n (%)	71 (24.7)	38 (23.3)	33 (26.4)
Number of failing organs at baseline, n (%)			
0	107 (37.2)	75 (46.0)	32 (25.6)
1	65 (22.6)	30 (18.4)	35 (28.0)
>= 2	116 (40.3)	58 (35.6)	58 (46.4)
Outcome			
Maximum number of concomitantly failing organs during first week of PICU stay			
0	59 (45.5)	59 (36.2)	0 (0)
1	58 (27.5)	58 (35.6)	0 (0)
2	53 (10.2)	23 (14.1)	30 (24.0)
3	48 (7.4)	15 (9.2)	33 (26.4)
4	33 (4.5)	5 (3.1)	28 (22.4)
>= 5	37 (12.8)	3 (1.8)	34 (27.2)
PICU length of stay (days), median [IQR]	2.2 [1.0 – 6.0]	1.4 [0.7 – 2.8]	5.6 [2.2 – 10.9]
PICU mortality, n (%)	27 (9.4)	6 (3.7)	21 (16.8)

IQR, interquartile range; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; HFNC, high flow nasal cannula oxygen therapy; NPMOD, new or progressive multi-organ dysfunction; PICU, paediatric intensive care unit.

unplanned PICU admission. PICU mortality rate was slightly higher compared to the total cohort, 4% in the patients without NPMOD and 17% in patients with NPMOD. The most frequently failing organ systems at admissions were similar to what was found in the total cohort, including hematological dysfunction (47%), immunological dysfunction (27%), and respiratory dysfunction (23%) (Figure 2A). In the multivariable logistic regression model, the number of failing organs at PICU baseline was significantly associated with NPMOD (Table 5).

Using our PONC-PODIUM criteria in the cohort of unplanned admissions, NPMOD was present in 123 unplanned PICU admissions (43%) (Supplementary Table S5). In the unplanned admissions with NPMOD, the most frequent failing organ systems at admission included renal dysfunction (22%), endocrine dysfunction (20%), and severe cardiovascular dysfunction (12%) (Figure 2B). Consistent with the application of the original PODIUM criteria, the multivariable model showed that the number of failing organs was a significant risk factor associated with the occurrence of NPMOD (Supplementary Table S6).

Discussion

This is the first study using the recently published PODIUM criteria for organ dysfunction (18) in pediatric oncology patients to identify risk factors for new or progressive multi-organ failure during the first week of PICU admission. Considering all PICU admissions, we found that hemato-oncological diagnosis, unplanned PICU admission and number of failing organs at PICU baseline were independent risk factors. In the subgroup of

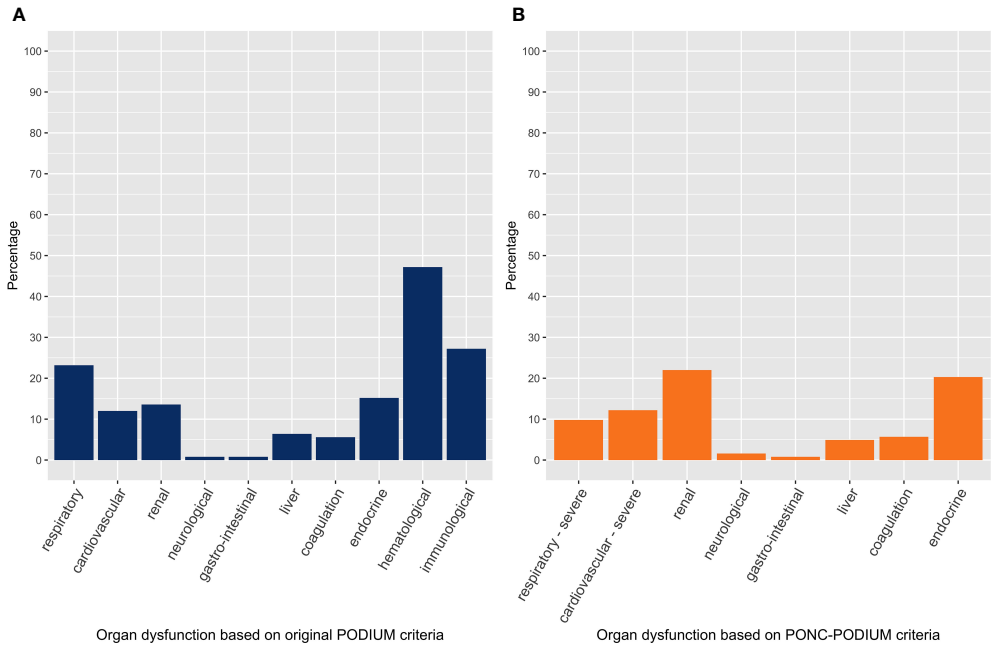

FIGURE 2
Organ dysfunction at PICU baseline in unplanned PICU admissions with new or progressive multi-organ dysfunction. The left panel **(A)** considers organ dysfunction based on the original PODIUM criteria, whereas the right panel **(B)** considers organ dysfunction based on the PONC-PODIUM criteria.

the unplanned PICU admissions, we found that the number of failing organs at PICU baseline was independently associated with NPMOD.

Our finding that hemato-oncological diagnosis is a significant risk factor for developing NPMOD is in line with other studies showing that hemato-oncological patients have greater illness severity at PICU admission, experience multi-organ failure more often, require more PICU resources and have a higher PICU mortality compared to solid tumor patients (11, 12, 24, 25). The high risk for organ dysfunction may be attributed to the combination of generally more dose-intense chemotherapy and glucocorticoids, that may result in increased toxic side-effects and profound and prolonged myelosuppression (11, 12, 26). Yet, upon analysis in only unplanned PICU admissions, we found that

TABLE 5 Results of the univariate and multivariable logistic regression model, with estimated odds ratio (OR) along with the 95% confidence interval (CI), for outcome of new or progressive multi organ dysfunction in unplanned PICU admissions (defined according to the PODIUM criteria).

Covariate	Univariate OR (95% CI)	Multivariable OR (95% CI)
Oncological diagnosis groups		
Hemato-oncological	2.56 [1.12 – 5.85]	1.89 [0.78 – 4.58]
Solid tumor	1.46 [0.60 – 3.54]	1.24 [0.49 – 3.12]
Brain/CNS tumor	*Reference*	*reference*
HSCT, n (%)	3.05 [1.03 – 9.01]	1.76 [0.55 – 5.57]
Infection or sepsis at baseline, n (%)	1.79 [1.08 – 2.98]	1.66 [0.90 – 3.03]
Neutropenia at baseline	1.11 [0.65 – 1.89]	0.45 [0.20 – 1.02]
HFNC preceding admission	1.39 [0.83 – 2.34]	1.21 [0.69 – 2.14]
Previous relevant PICU admission	1.18 [0.69 – 2.02]	0.97 [0.54 – 1.74]
Number of failing organs at baseline		
0	*Reference*	*reference*
1	2.73 [1.44 – 5.18]	**2.19 [1.13 – 4.28]**
>= 2	2.34 [1.35 – 4.07]	**2.55 [1.17 – 5.66]**

CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; HFNC, high flow nasal cannula oxygen therapy.
Significant covariates in the model are in bold.

although a hemato-oncological diagnosis was associated with NPMOD in the univariate analysis, it was not a significant risk factor for NPMOD in the multivariable analysis.

Surprisingly, neutropenia was not a significant risk factor both in the total cohort and cohort of unplanned admissions. Some other studies in adult and pediatric oncology patients also failed to demonstrate an association of neutropenia with worse outcomes, in a multivariable analysis (27–29). Advances in the diagnosis and treatment of infections, the prescription of prophylactic antibiotics and antifungals, and antibiotic stewardship may have limited the role of neutropenia in worse outcome in critically ill oncology patients. A recent study including only pediatric hemato-oncology patients with unplanned PICU admissions showed that neutropenia was an independent risk factor for PICU mortality (30). Our study differs in that we also included patients with a solid or a brain or central nervous system tumor. The degree of multi-organ dysfunction during PICU admission is a significant prognostic factor for PICU mortality in pediatric oncology patients (12). We found that the presence of MOD already at PICU admission is an independent risk factor for progressive MOD, in both the total cohort as in the subgroup including only unplanned PICU admissions. These findings are in line with a study in general pediatric patients, showing that the presence of MOD on day 1 of PICU admission was associated with death or poor neurologic outcome (8). Our finding that PICU mortality in patients with NPMOD in the unplanned admissions was only slightly higher compared to the total cohort including also planned post-operative patients, emphasizes the pivotal role of MOD in the outcome of these patients. Early recognition of deteriorating organ functions before PICU admission followed by early initiation of appropriate treatment may be important to reduce morbidity and mortality in critically ill pediatric oncology patients (12, 16, 31, 32).

In the present study, we tailored the PODIUM criteria to pediatric oncology patients. The adjustments in renal criteria can be valuable to prevent missing AKI, as it was shown that AKI, even stage 1, is significantly associated with short- and long-term complications in critically ill children (33). Second, according to PODIUM, neutropenia is a classifier for dysfunction of two different organ systems (hematologic and immunologic), where we included dysfunction that is more likely to be part of a shared underlying pathway for MOD (e.g. in sepsis) instead of chemotherapeutic treatment. Furthermore, we found a high percentage of endocrine dysfunction. The threshold for glucose ≥ 8.3 mmol/L (150 mg/dL) might be a threshold at which particularly hemato-oncology patients are easily flagged, due to steroid-induced adrenal insufficiency or hyperglycemia (34). This threshold could be considered to be fine-tuned and validated in future studies.

Using our PONC-PODIUM criteria, we found different organ systems that frequently failed at PICU admissions. Endocrine, renal and severe cardiovascular dysfunction emerged as the most frequently failing organ systems in patients who develop NPMOD. This finding may merely have implications for early surveillance at the inpatient ward, prior to PICU admission. Particularly renal and cardiovascular dysfunction can be recognized in an early phase, and timely, appropriate interventions may potentially halt progression to irreversible organ damage. For example, the development of acute kidney injury (AKI) can be monitored at the ward, and substitution or adjustments of nephrotoxic medication and prevention of fluid overload can be easily implemented (35). This may lead to decreased AKI rates and better outcomes (33, 35). In addition, closely monitoring the fluid balance and prevention of fluid overload in patients with cardiovascular failure could provide an opportunity to prevent further deterioration.

Our study revealed several challenges in applying predefined criteria for organ dysfunction to a dataset with continuous data at a frequency of 1 minute and interval data. We accounted for measurement errors and missing data. We thereupon defined age-based limits for artefacts in vital signs, carried last observations forward for a limited time defined per variable and classified organ dysfunction within 1-hour timeframes, to minimize that a single value could immediately flag organ dysfunction. Last observation carried forward to deal with missing data was similarly used in a retrospective study on the early prediction of organ dysfunction in children (36). We used the 24 hours preceding PICU admission to classify organ dysfunction at PICU admission. As PODIUM criteria did not incorporate a specific time period required to fulfil the criteria for organ dysfunction, we classified the concurrent number of failing organ systems within 24-hour windows. Yet, for future studies, a validated time period required to fulfil the criteria especially for respiratory and cardiovascular dysfunction may further optimize defining (concurrent) organ dysfunction.

This is the first study including all organ systems of the PODIUM criteria, as we extracted free text field data using an automatized process of text mining with standardized search terms to, for example, identify gastro-intestinal dysfunction. In addition, our study evaluated a PICU cohort that encompasses all subgroups of pediatric oncology patients, including HSCT patients, from a national referral center where oncology care has been nationally centralized.

Our study has several limitations. First, the data retrieved from patients' medical records were primarily captured for clinical care. Consequently, selective measurements, such as laboratory values only assessed upon clinical suspicion of organ dysfunction, may bias the timing of onset of (multiple) organ dysfunction. Therefore, we summarized to NPMOD within 24-hour-time frames. Second, our study is a single-center study. Consequently, our findings may not be generalizable due to international differences in PICU policies regarding admission and care. Third, we did not have data on morbidity following prior PICU admissions. We therefore defined a relevant prior PICU admission as any prior unplanned admission, or a prior planned admission with a protracted course. For future studies, to assess the effect of a prior PICU admission on the risk of developing NPMOD in a current PICU admission, it would be beneficial to include data on relevant comorbidity following a prior admission. Last, in this retrospective study, we could not differentiate between underlying mechanisms of organ dysfunction and could thus not define MOD syndrome (MODS). The identification of a common underlying pathobiology, such as in MODS, may be helpful to evolve from isolated organ specific to more holistic strategies that target a common pathobiology (4).

This study shows that hemato-oncological diagnosis, number of failing organs and an unplanned admission are significant risk

factors at PICU admission for the development of NPMOD in pediatric oncology patients. For future perspectives, we see opportunities to further refine the PODIUM criteria for pediatric oncology patients. Currently, the PODIUM criteria have been validated in general pediatric patients (5), and are yet to be validated in pediatric oncology patients. We provided a first step towards further refinement of these criteria for pediatric oncology patients. Yet, the criteria introduced in this study need to be validated, preferably in a large multi-center cohort incorporating all subgroups of pediatric oncology patients. The results of the present study may help to guide both intensivists and oncologists in risk stratification for critically ill pediatric oncology patients and to identify patients who may benefit from closer monitoring and early interventions at the ward prior to PICU admission.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by IRB protocol number 16-572/C. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

MS, WT and RW-vA designed the project. MS, JN, CB, MM and EK collected the data. MS, MF, and TK conducted the data analyses. MS, MF, JN, EN, TK, WT, and RW-vA drafted the manuscript. MS prepared the tables and figures. MS, MF, TK, WT, and RW-vA had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1192806/full#supplementary-material

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Diffuse alveolar hemorrhage after hematopoietic cell transplantation- response to treatments and risk factors for mortality

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Diffuse alveolar hemorrhage (DAH) is a life-threatening complication of hematopoietic cellular therapy (HCT). This study aimed to evaluate the effect of DAH treatments on outcomes using data from consecutive HCT patients clinically diagnosed with DAH from 3 institutions between January 2018-August 2022. Endpoints included sustained complete response (sCR) defined as bleeding cessation without recurrent bleeding, and non-relapse mortality (NRM). Forty children developed DAH at a median of 56.5 days post-HCT (range 1-760). Thirty-five (88%) had at least one concurrent endothelial disorder, including transplant-associated thrombotic microangiopathy (n=30), sinusoidal obstructive syndrome (n=19), or acute graft versus host disease (n=10). Fifty percent had a concurrent pulmonary infection at the time of DAH. Common treatments included steroids (n=17, 25% sCR), inhaled tranexamic acid (INH TXA,n=26, 48% sCR), and inhaled recombinant activated factor VII (INH fVIIa, n=10, 73% sCR). NRM was 56% 100 days after first pulmonary bleed and 70% at 1 year. Steroid treatment was associated with increased risk of NRM (HR 2.25 95% CI 1.07-4.71, p=0.03), while treatment with INH TXA (HR 0.43, 95% CI 0.19-0.96, p=0.04) and INH fVIIa (HR 0.22, 95% CI 0.07-0.62, p=0.005) were associated with decreased risk of NRM. Prospective studies are warranted to validate these findings.

KEYWORDS

diffuse alveolar hemorrhage (DAH), steroids, inhaled tranexamic acid (INH TXA), inhaled recombinant activated factor VIIa (INH fVIIa), transplant-associated thrombotic microangiopathy (TA-TMA), sinusoidal obstructive syndrome (SOS), non-relapse related mortality

Highlights

1. In 40 children with DAH after HCT, steroid treatment was associated with an increased risk of NRM (HR 2.25 95% CI 1.07-4.71, p=0.03).
2. Treatment with INH TXA (HR 0.43, 95% CI 0.19- 0.96) and INH fVIIa (HR 0.22, 95% CI 0.07-0.62) was associated with a lower risk of NRM.

Background

Diffuse alveolar hemorrhage (DAH) is a rare complication of hematopoietic cell transplantation (HCT) associated with with high mortality (1–3). The pathophysiology of DAH is poorly understood but hypothesized to involve injury to the pulmonary endothelium from preparative agents, inflammation, and cytokine release (4, 5). There are no standard therapies for DAH (6). Historically, treatment included high-dose corticosteroids (3, 7, 8), though recent reports suggest this approach is associated with poorer survival after HCT (9–11).

Red blood cells are prone to hemolyze in patients with lung injury, and free heme released from these cells is highly reactive, contributing to additional lung damage (12–14). Thus, in addition to targeting drivers of DAH, cessation of bleeding may be an important component of treatment. Emerging evidence supports inhaled approaches to treat DAH, which minimize the risk of systemic thrombosis. Inhaled (INH) tranexamic acid (TXA) prohibits the conversion of plasminogen to plasmin, inhibiting fibrinolysis, and stabilizing clots and has shown excellent cessation of DAH (15), including in small cohorts of pediatric HCT recipients (2, 16). Recombinant activated factor VIIa (fVIIa) promotes hemostasis *via* tissue factor-dependent and independent pathways. Intrapulmonary administration of fVIIa has also halted pulmonary bleeding (17–20). While these studies demonstrate bleeding cessation, they have not shown an impact on survival in the HCT setting. This study aimed to evaluate the effect of DAH treatments on outcomes in a contemporary pediatric HCT cohort.

Methods

In this IRB-approved retrospective study data were extracted from consecutive HCT patients clinically diagnosed with DAH between January 2018-August 2022 from 3 institutions, Children's Healthcare of Atlanta, Cincinnati Children's Medical Center, and the University of California, San Francisco. A sustained complete response (sCR) to treatment was defined as bleeding cessation without recurrent bleeding, a CR as bleeding cessation for ≥24 hours but with a subsequent recurrent bleed, and no response (NR) was continued bleeding or death with active bleeding. Acute graft versus host disease (aGVHD) was staged and graded using Glucksberg criteria. Systemic and pulmonary infections were identified by culture, PCR, or next-generation sequencing. Descriptive statistics were used to compare groups. Sub-distribution hazard models were used to generate hazard ratios (HR) for non-relapse mortality (NRM), treating relapse as a competing risk. SAS 9.4 (Cary, NC) was used, and statistical significance was set at 0.05.

Results/discussion

Forty children developed DAH a median of 56.6 days post HCT (range 1-760). Each patient experienced 1-4 separate pulmonary bleeds with 27 (68%) incurring only one bleed. The first pulmonary bleed was diagnosed by bronchoscopy (n=24), blood in the endotracheal tube (n=14), hemoptysis (n=1), and lung tissue (n=1). The majority 35/40 of patients underwent allogeneic HCT; all 5 autologous recipients developed DAH post-second tandem HCT for neuroblastoma. Eighty- eight percent of patients (35/40) had at least one concurrent endothelial disorder, including transplant-associated thrombotic microangiopathy (n=30, 75%), sinusoidal obstructive syndrome (n=19, 48%) and acute graft versus host disease (n=10, 29%). Sixty percent (21/35) of patients had more than one endothelial disorder (Supplemental Figure 1). Twenty-three (58%) had a systemic infection within four weeks of DAH, and 20 (50%) had documented pulmonary infection at the time of bleed (Table 1).

There were 60 separate pulmonary bleeds. Most patients received multiple treatments for each bleed (Figure 1A). Patients were most commonly treated with steroids (n=17), INH TXA (n=26), and INH fVIIa (n=10). While response rates varied, steroids had an overall sCR/CR of 55%, INH TXA 89%, and INH fVIIa 92% (p= 0.002, Figure 1B). NRM was 56 ± 8% and 70 ± 7% at 100 days and 1-year post first pulmonary bleed, respectively (Figure 1C). TA-TMA and grade III-IV GVHD were not associated with NRM. However, SOS (HR 2.44 95% CI 1.11-5.39, p=0.03) and steroid treatment (HR 2.25 95% CI 1.07-4.71, p=0.03) were associated with an increased risk of NRM. Treatment with INH TXA (HR 0.43, 95% CI 0.19- 0.96, p=0.04) and INH fVIIa (HR 0.22, 95% CI 0.07-0.62, p=0.005) were associated with decreased NRM (Figure 2). After adjusting for SOS, the only other variable significantly associated with NRM, the HR of NRM in those treated with steroids remained significantly higher (HR 2.35, 95% CI 1.14-4.88). To determine if infection impacted NRM risk in those treated with steroids, we adjusted for an identified systemic or pulmonary infection; the HR of NRM in children remained significantly higher in those treated with steroids (HR 2.2, 95% CI 1.0-4.81, p=0.05).

In this multi-institutional study, INH TXA and INH fVIIa led to bleeding cessation and were associated with a decreased mortality risk. These inhaled agents can be administered *via* nebulization in most ventilators although alveolar delivery is poor with the high-frequency oscillatory ventilator (HFOV). Alternatively, these can be directly instilled in bronchi *via* bronchoscopy (Figure 3). Institutional preference to use HFOV could result in bias as HFOV use would preclude these therapies. While the use of

HFOV was rare and similar between therapies (1/17 with steroids, 1/26 with INH TXA, 0/11 INH fVIIa), it's possible that the severity of illness differed in other ways not captured in our data.

Children treated with steroids for any pulmonary bleed had a lower response rate and an increased risk of NRM, even after controlling for SOS, the other NRM risk factor. Our study extends the work of others that linked high-dose steroids with increased mortality in DAH post HCT (9–11).

The current paradigm of DAH pathophysiology is derived from the non-HCT setting, where alveolar damage is thought to be driven by immune-mediated mechanisms. However, 50% of children in this cohort had an identified pulmonary infection at the time of bleed, consistent with other literature in HCT (11). Further, prior studies have demonstrated that currently available diagnostic approaches to detect infections in immune compromised patients may be missing a significant number of

TABLE 1 Characteristics of children with DAH post HCT by NRM versus Alive or Relapsed.

Variable	Alive/Relapsed (n=13, 34%), N (%)	NRM (n=27, 68%), N (%)	p-value
Age years (median, range)[+]	**3 (0-24)**	**11 (0.28- 20.5)**	**0.02**
Sex[^]			0.29
Female	10 (40)	15 (60)	
Male	3 (20)	12 (80)	
Race[^]			**0.02**
White	**4 (17)**	**19 (83)**	
Black/African	**4 (40)**	**6 (60)**	
American Asian	**2 (67)**	**1 (33)**	
Other/Declined	**3 (75)**	**1 (25)**	
Ethnicity[^]			1.0
Hispanic	2 (33)	4 (67)	
Non-Hispanic	11 (32)	23 (68)	
HCT Indication[^]			0.16
Heme Malignancy Immune	6 (32)	13 (68)	
Def/Dys	1 (13)	7 (88)	
Non-malignant Heme	1 (20)	4 (80)	
Solid Tumor	4 (80)	1 (20)	
Neuro/Metabolic	1 (33)	2 (67)	
HCT Type[^]			**0.03**
Allogeneic	**9 (28)**	**26 (74)**	
Autologous	**4 (80)**	**1 (20)**	
Cell Source*[^]			**0.02**
Bone Marrow	**3 (14)**	**18 (86)**	
Peripheral Blood	**3 (30)**	**7 (70)**	
Umbilical Cord	**3 (75)**	**1 (25)**	
Donor*[^]			0.71
Related	3 (21)	11 (79)	
Unrelated	6 (29)	15 (71)	
HLAMismatch*[@^]			0.51
8/8	3 (15)	17 (85)	
7/8	1 (17)	5 (83)	
≤6/8	2 (40)	3 (60)	
Preparative Intensity[^]			**0.04**
Myeloablative	**12 (44)**	**15 (56)**	
RIC	**1 (8)**	**11 (92)**	
Non-myeloablative	**0 (0)**	**1 (100)**	
Acute GVHD Prophylaxis*^			0.88
CNI	6 (21)	23 (79)	
Methotrexate	3 (20)	12 (80)	
MMF	3 (21)	11 (79)	
Abatacept	1 (33)	2 (67)	
T-cell depletion	2 (40)	3 (60)	
TA-TMA[^]	9 (30)	21 (70)	0.70
Eculizumab[^]	9 (35)	17 (65)	1.0

(Continued)

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TABLE 1 Continued

Variable	Alive/Relapsed (n=13, 34%), N (%)	NRM (n=27, 68%), N (%)	p-value
SOS^	4 (21)	15 (79)	0.19
Defibrotide^	4 (22)	14 (78)	0.31
Maximum aGVHD*^ Grade 0-2 Grade 3-4	 7 (28) 2 (20)	 18 (72) 8 (80)	0.69
Concurrent Systemic Infection#%^	8 (35)	15 (65)	1.0
Concurrent Pulmonary Infection#%^	7 (35)	13 (65)	1.0
Day first pulmonary bleed (median, range)	59 (52)	36 (163)	0.74
Number of pulmonary bleeds (median, range)+	1 (1-4)	1 (1-4)	0.53

*Allogeneic HCT recipients only (n=35), #within 4 weeks of first pulmonary bleed, %diagnosed via bacterial, viral, or fungal culture or next generation sequencing of BAL fluid. @excluding cord blood, ^Fishers Exact Test, +Wilcoxon-Rank Sum Test, Abbreviations: human leukocyte antigen (HLA), reduced intensity conditioning (RIC), graft versus host disease (GVHD), calcineurin inhibitor (CNI), mycophenolate mofetil (MMF), transplant associated thrombotic microangiopathy (TA-TMA), sinusoidal obstructive syndrome (SOS), graft versus host disease (GVHD), hematologic malignancy (heme malignancy), immune deficiency/dysregulation (immune def/dys), non-malignant blood disorder (non-malignant heme). Bold indicates significant differences.

clinically important pathogens (22). Infections can invade the endothelium directly inducing damage, and infections can worsen after corticosteroid administration. We hypothesize that infections (diagnosed and/or undiagnosed) are a key driver of the association of increased NRM and steroid treatment for DAH in the HCT setting.

Neither SOS nor defibrotide, which 18/19 (95%) of patients with SOS received, are associated with DAH. While defibrotide has a bleeding warning, in clinical trials, hemorrhagic events in patients with SOS treated with defibrotide were not significantly different than untreated patients (23). However, TA-TMA, present in 75% of our cohort, is associated with both clinical DAH and DAH on

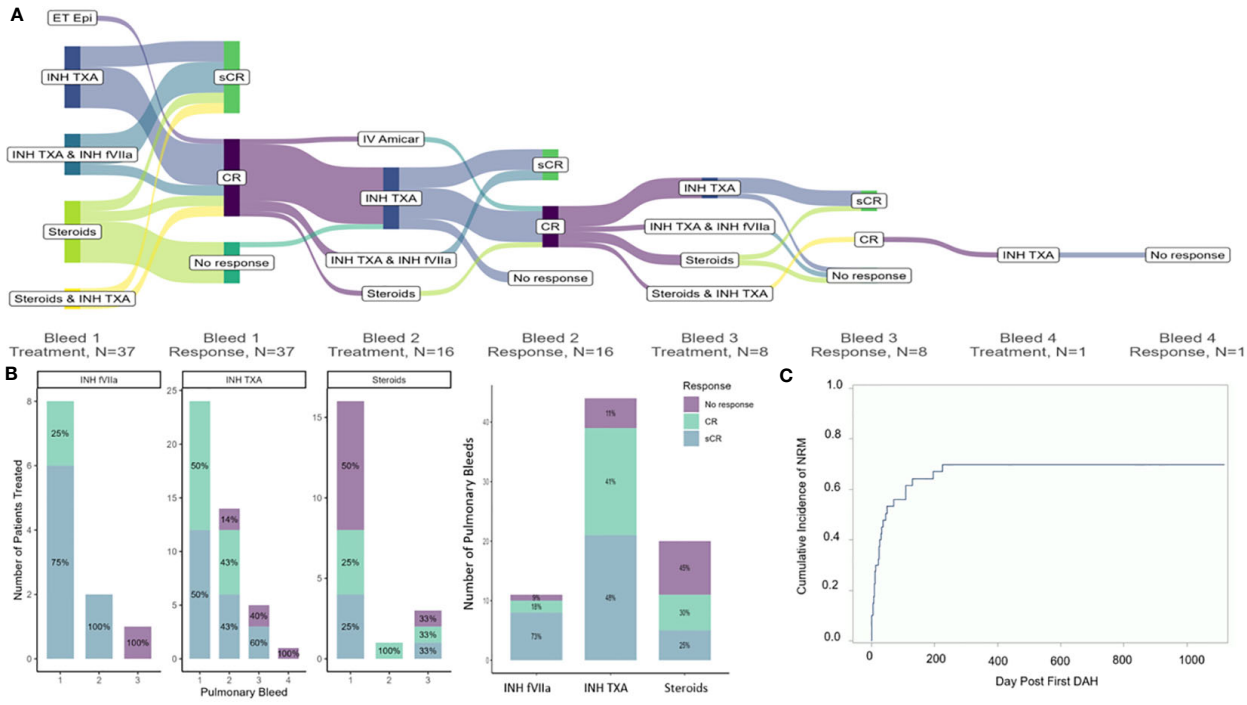

FIGURE 1
Treatment approaches **(A)**, response of pulmonary bleeds **(B)** and non-relapse related mortality **(C)**. **(A)** In this sankey diagram, combinations of treatments for DAH and the response of treatments are indicated for each pulmonary bleed. Not all bleeds were treated; 37 patients received treatment for first pulmonary bleed. Sustained complete response (sCR) was defined as cessation of bleeding without a rebleed. CR as cessation of bleeding for ≥24 hours, but with a recurrent bleed, and no response (NR) as continued bleeding or death with bleeding. **(B)** Response rates of each pulmonary bleed to each agent; notably, many patients received multiple agents. **(C)** Overall response to each agent. As above, multiple drugs were given concurrently; assessment of response was the same for all concurrently administered drugs.

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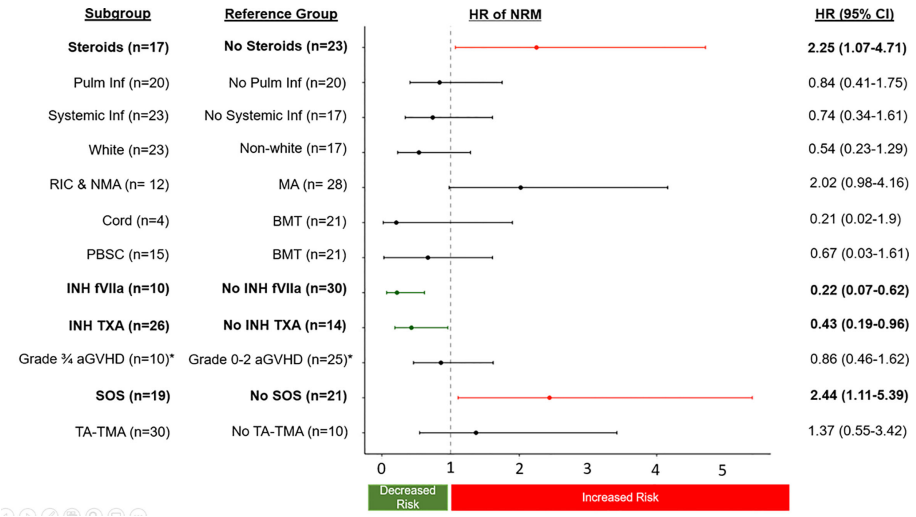

FIGURE 2
The sub-distribution HR of NRM (relapse competing risk) of transplant complications and treatment approaches for DAH. HR greater than 1 are associated with an increased risk of NRM, and less than 1 associated with a decreased risk of NRM. *only allogeneic patients were at risk and used in the analysis (n=35).

autopsy, and is increasingly being recognized as a pulmonary manifestation of TA-TMA (24–26). We noted that all autologous HCT recipients had an underlying diagnosis of neuroblastoma, and attribute this to the known association of TA-TMA and children with this disease and treatment approach (27–29). There is emerging evidence that patients with both SOS and TA-TMA are at higher risk for multi-organ failure, including DAH (25).

Given the shared endothelial injury and thrombotic changes of these three diseases, it is possible that DAH in the HCT setting may be part of a continuum of endothelial injury as most of the cohort

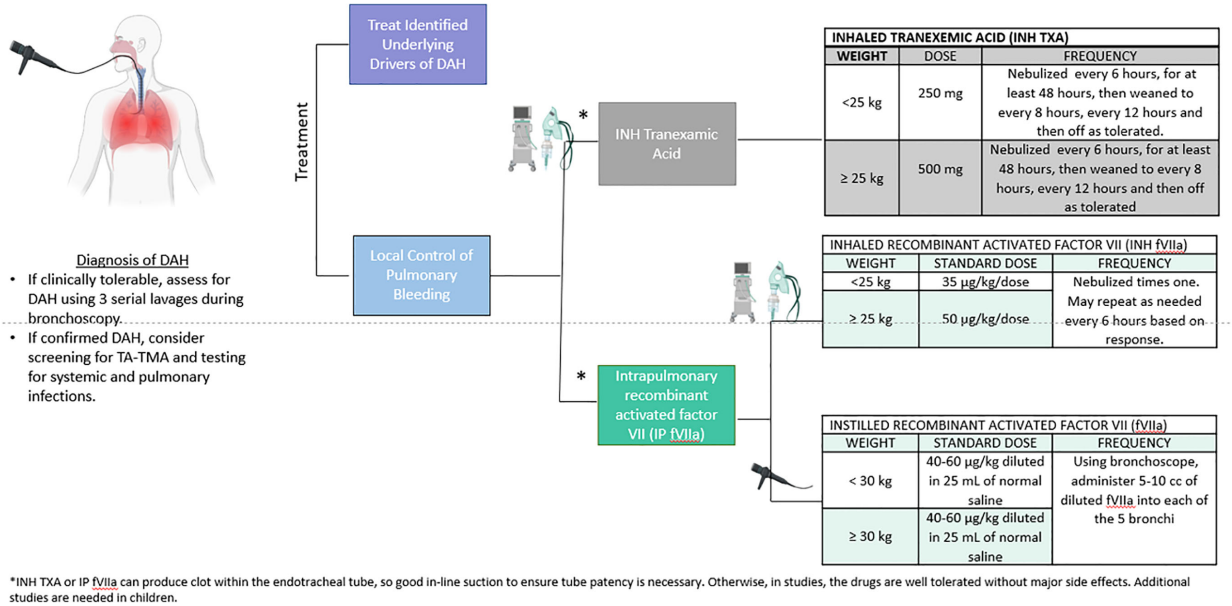

FIGURE 3
Proposed diagnosis and treatment schema with doses supported by our findings and previous literature. The ideal diagnostic approach includes bronchoscopy and evidence of persistent bleeding after 3 washes. Once DAH is confirmed, consider screening for TA-TMA, pulmonary and systemic infections and treating all identified drivers of DAH. Our data and others support treatment with INH TXA and INH or instilled recombinant active factor VIIa at the doses on the right side of the panel. While there are limited data of appropriate doses for INH TXA and intrapulmonary fVIIa for DAH, these doses were used in published in a small single center clinical trial (19) and are reported in the pediatric HCT population (17, 18, 21). In this study, only INH fVIIa was given (19), but instilled factor VIIa *via* a bronchoscope is also described (17, 18). While the data are limited, there are not severe side effects of these drugs reported in the literature. However, intrapulmonary administration of INH TXA or IP fVIIa can result in clot formation, so if patients are intubated, vigilance and intervention to ensure the tube remains patent are important.

had another concurrent endothelial syndrome, TA-TMA, SOS, or aGVHD. Endothelial damage is thought to be a major driver of other lung injuries, including COVID19 induced acute respiratory distress syndrome (30). Our data suggest that this primary endothelial injury could be a major driver in DAH post HCT which could inform treatment.

Small numbers, a retrospective approach, the lack of tissue in most patients, and the potential center effect (2 centers used INH TXA, and 1 center used INH fVIIa) are all limitations of this study. However, finding statistically significant associations with NRM in a multi- institutional study is compelling to drive future studies of treatment with INH TXA and/or INH fVIIa for DAH after HCT. While a multi-institutional large clinical trial may not be feasible, a pragmatic approach could be taken, similar to other HCT complications (31). Despite the cessation of pulmonary bleeding, outcomes remain poor in children with DAH. However, our study compares favorably to the published registry data, with 44% surviving 100 days after first bleed versus 21% (32). Our data promote local approaches to treat DAH in addition to the management of severe coincident complications, including TA-TMA, SOS, GVHD, and infections.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by IRBs at Children's Healthcare of Atlanta, University of California San Francisco, and Cincinnati Children's Medical Center. The requirement for written informed consent was waived given the low risk and the fact that most patients were deceased.

Author contributions

MS, CCD, MZ, and KW designed the study. AH, MC, JO, CH, CCD, and MZ extracted clinical data. MS and AW completed the statistical analysis. MZ and MC designed an institutional protocol for INH fVIIa, and all authors participated in the clinical care of patients and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

MS is a consultant for Alexion and Omeros. MZ is a consultant for Sobi. CCD is a consultant for Alexion and Jazz. CH is a consultant for Omeros. MQ has honorarium from Novartis and Vertex.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1232621/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Multiple Complications of Endothelial Dysfunction 35/40 (88%) of children with DAH had another disease of endothelial dysfunction including transplant-associated thrombotic microangiopathy (TA-TMA), sinusoidal obstructive syndrome (SOS) or grade ¾ acute graft versus host disease (aGVHD). Twenty-one (60%) had multiple early endothelial diseases.

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Benefit of continuous kidney replacement therapy for managing tumor lysis syndrome in children with hematologic malignancies

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Introduction: Tumor lysis syndrome (TLS) is often diagnosed in children with hematological malignancies and can be life threatening due to metabolic disturbances. Continuous renal replacement therapy (CKRT) can reverse these disturbances relatively quickly when conventional medical management fails. Our objective was to investigate the benefit of CKRT in the management of TLS in children admitted to the intensive care unit with hematologic malignancies. In addition, we sought to assess risk factors for acute kidney injury (AKI) in the setting of TLS.

Methods: Retrospective review of all children admitted to the intensive care unit with TLS who received CKRT from January 2012 to August 2022.

Results: Among 222 children hospitalized with TLS from January 2012 to August 2022, 20 (9%) underwent CKRT to manage TLS in the intensive care unit. The patients' median age was 13 years (range 3-17 y), and most were males (18/20). T-cell acute lymphoblastic leukemia was the most common diagnosis (n=10), followed by acute myeloid leukemia (n=4), Burkitt lymphoma (n=4), and B-cell acute lymphoblastic leukemia (n=2). Five patients required mechanical ventilation, and 2 required vasopressors. The most common indication for CKRT was hyperphosphatemia, followed by, hyperuricemia, and hyperkalemia. All metabolic abnormalities corrected within 12 h of initiation of CKRT. CKRT courses were brief, with a median duration of 2 days (range 1-7 days). Having higher serum phosphorus levels 12 h preceding CKRT was significantly associated with severe acute kidney injury (AKI). The median phosphorus level was 6.4 mg/dL in children with no/mild AKI and 10.5 mg/dL in children with severe AKI (p=0.0375). Serum uric acid levels before CKRT were not associated with AKI. All children survived to hospital discharge, and the one-year survival rate was 90%.

Conclusion: CKRT is safe in children with hematologic malignancies with severe TLS and reverses metabolic derangements within 6-12 h. Most patients had AKI at the initiation of CKRT but did not require long-term kidney replacement therapy. Hyperphosphatemia before initiation of CKRT is associated with higher risk of AKI.

KEYWORDS

TLS, tumor lysis, CKRT, AKI, dialysis, pediatrics, hematologic malignancy

1 Introduction

Tumor lysis syndrome (TLS) is a serious and life-threatening condition that is associated with hematologic malignancies. TLS occurs due to rapid breakdown of malignant cells either spontaneously or after the initiation of chemotherapy. This rapid breakdown leads to the release of intracellular potassium, phosphate, nucleic acids at a high rate that overwhelm the normal homeostatic mechanism for removing these byproducts. As a result, children will manifest laboratory TLS characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. The ensuing metabolic derangements can result in serious complications (Clinical TLS) such as acute kidney injury (AKI), arrhythmias, and seizures (1). AKI is typically induced by the deposition of uric acid or xanthine crystals in the renal tubules or by calcium-phosphate crystals deposition due to hyperphosphatemia. Therefore, prevention and prompt management of TLS is warranted, especially in patients at high risk of TLS. Medical management includes aggressive hydration at 1.5-2 times normal maintenance rate, with close monitoring of serum levels of potassium, phosphorus, calcium, and uric acid. In addition, rasburicase, a recombinant urate oxidase that converts uric acid to allantoin which is 10 times more soluble in water than uric acid, is prescribed to children with hyperuricemia. Management and outcome data about TLS in children is scarce (2, 3). Continuous kidney replacement therapy (CKRT) is utilized in severe cases of TLS to remove these solutes. CKRT provides slow and continuous removal of solutes which is more physiologic than intermittent hemodialysis and has less risk of rebound hyperphosphatemia and hyperkalemia.

Our objective was to investigate the benefit of CKRT in the management of TLS in children admitted to the intensive care unit (ICU) with hematologic malignancies. In addition, we sought to assess risk factors for AKI in the setting of TLS.

2 Methods

All children with hematologic malignancies admitted to St. Jude Children's Research Hospital, a specialized pediatric hematologic-oncology hospital, from January 2012 to August 2022 were screened for TLS. Patients were included in the study if CKRT was initiated to manage TLS. This study was approved by our institutional review board. Laboratory TLS and clinical TLS were defined based on daily recorded laboratory and clinical values by using Cairo-Bishop criteria, (Supplemental Figure 1) (4). Clinical TLS was diagnosed in patients who had Laboratory TLS and one of these clinical findings: AKI, cardiac arrhythmias, or symptomatic hypocalcemia. AKI was defined and staged according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines (Supplemental Table 1) (5). Severe AKI was defined as serum creatinine ≥ 2 times baseline (grade 2 and 3 per KDIGO guidelines).

The PrismaFlex CRRT system (Gambro/Baxter) was used with the continuous veno-venous hemodiafiltration (CVVHDF) treatment modality for all patients. All patients received continuous regional citrate infusion for anticoagulation and continuous systemic calcium infusion. Post-filter ionized calcium (Ica) levels were monitored every 2-4 hours.

2.1 Data collection

Daily collected laboratory test data included white blood cell count (WBC) and lactic dehydrogenase (LDH). In addition, the following laboratory values were measured at 6-hour intervals from 24 hours prior to 48 hours after CKRT initiation: uric acid, potassium, phosphorus, calcium, bicarbonate, blood urea nitrogen, and creatinine. Baseline serum creatinine level, when unknown, was imputed by the bedside Schwartz formula with an estimated glomerular filtration rate of 120 mL/min/1.73 m^2 and the patient's height (2).

2.2 Statistical analysis

Descriptive statistics are expressed in percentage for categorical variables and median (range) for continuous variables. The exact Wilcoxon rank-sum test was used to compare distributions of lab values by AKI status. The Wilcoxon signed-rank test was used to compare the differences between matched lab values before and post-CKRT. Spearman's correlation was used to test the relationship between WBC and LDH at 1 and 2 days pre-CKRT and laboratory values pre-CKRT. Median (range) are reported for all statistical tests, and distribution-free 95% confidence intervals of the median difference between laboratory values are presented for comparisons of matched observations at different time points, as described by Hahn and Meeker (1991).

3 Results

Between January 2012 and August 2022, 222 children with hematologic malignancies were hospitalized with TLS. Of those, 20 (9%) required CKRT for management of their TLS in the ICU. Table 1 summarizes the clinical characteristics of our cohort. The median age was 13 years (range, 3-17 y), and interestingly, most were male (18/20). The hematologic malignancy was T-cell acute lymphoblastic leukemia (ALL) in 10 children, acute myeloid leukemia (AML) or Burkitt lymphoma in 4 children each, and B-cell ALL in 2 children. A mediastinal mass was present in 8 children.

Of the 20 patients who underwent CKRT for TLS, 20 had laboratory TLS, and 18 had clinical TLS. At the time of initiation of CKRT, the most common chemical derangement was hyperphosphatemia in 95%, hypocalcemia in 90%, hyperuricemia in 35%, and hyperkalemia in 10%. Median serum phosphorus level was 9.7 mg/dL (range, 3.8-14.9 mg/dL) before start of CKRT (Table 1). LDH levels were elevated, with a median level of 2790 U/L (range, 439-10065 U/L).

TLS management included hydration with a median fluid volume of 2597 mL per m^2 daily. In addition, rasburicase was administered to 19 of the 20 patients (95%), allopurinol to 9 (45%), and phosphate binders to 17 (85%).

3.1 CKRT course

In our cohort, 2 children had intermittent hemodialysis (IHD) before CKRT. Following the course of CKRT, 2 patients had one session of IHD, and one patient received IHD for 15 days. The median duration of CKRT course in our cohort was 2 d (range 1-7 d). Potassium, phosphorus, and uric acid levels dropped significantly within 6 h after starting CKRT (Table 2). Compared to the level 6 h before initiation, the median phosphorus level declined 2.7 mg/dL (p-value <0.0001) in 6 h and 5.05 mg/dL (p-value <0.0001) in 18 h post CKRT. All serum levels of potassium, phosphorus, uric acid levels normalized within 12 hours of CKRT initiation (Figure 1). None of the patients had CKRT-related complications.

3.2 Risk factors for TLS

We investigated whether WBC or LDH levels one day before the start of CKRT were associated with hyperkalemia, hyperphosphatemia, duration of CKRT, or duration of ICU stay (Supplemental Tables 2, 3). Higher LDH levels correlated with higher uric acid levels 12 h prior to CKRT (p-value 0.0803 | Rho = 0.45).

3.3 Risk factors for AKI

Severe AKI (grade 2 and 3) was present in 17 patients (85%). Risk factors for development of AKI were examined. Uric acid,

TABLE 1 Characteristics of patients with TLS and CKRT.

Clinical/Laboratory features	N (%) or Median (Min-Max)
Age (y)	13 (3–17)
Weight (Kg)	53.7 (17.3-130)
Sex	
Female	2 (10)
Male	18 (90)
Race	
African American	4 (21)
Caucasian	15 (79)
Primary diagnosis	
T-ALL	10 (50)
AML	4 (20)
Burkitt lymphoma	4 (20)
B-ALL	2 (10)
Chemical derangement	
Hyperphosphatemia	19 (95)
Hypocalcemia	18 (90)
Hyperuricemia	7 (35)
Hyperkalemia	2 (10)
Lab values 6 hours before CKRT	
BUN (mg/dL)	35.00 (17.0-81.0)
Cr (mg/dL)	1.28 (0.6-5.9)
Potassium (mmole/L)	4.60 (3.6-7.0)
Calcium (mg/dL)	6.70 (4.9-9.7)
Phosphorus (mg/dL)	9.70 (3.8-14.9)
Uric acid (mg/dL)	3.80 (0.2-29.7)
Peak Lab values	
Potassium (mmole/L)	5.5 (4-7.2)
Phosphorus (mg/dL)	10.7 (6.2-14.9)
Uric acid (mg/dL)	6 (2-29.7)
WBC† ($10^3/mm^3$)	41.60 (1.2-470.4)
LDH† (U/L)	2790 (439-10065)
Treatment prior to CKRT	
Fluid rate/BSA (mL/m^2)	2597 (1193-3703)
Rasburicase	19 (95)
Allopurinol	9 (45)
Phosphate binders	17 (85)
Mechanical ventilation	5 (25)
Vasopressor support	2 (10)
Duration of ICU stay (days)	6.5 (3-36)

(Continued)

TABLE 1 Continued

Clinical/Laboratory features	N (%) or Median (Min-Max)
Duration of hospital stay (days)	12 (7-42)
Time from ICU admission to CKRT (days)	1.5 (0-7)
Duration of CKRT (days)	2 (1-7)

TLS, tumor lysis syndrome; CKRT, continuous kidney replacement therapy; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; BUN, blood urea nitrogen; Cr, creatinine; WBC, white blood cell count; LDH, lactate dehydrogenase; BSA, base surface area; ICU, intensive care unit.
† level one day prior to CKRT.

phosphorus, and LDH serum levels in patients with no/mild AKI were compared to those of patients with severe AKI (Table 3). Serum uric acid levels 12 h and 6 h preceding CKRT were not associated with AKI. However, higher serum phosphorus levels 12 h preceding CKRT were significantly associated with severe AKI. The median phosphorus level was 6.4 mg/dL in children with no/mild AKI but 10.5 mg/dL in children with severe AKI (p-value 0.0375). Furthermore, ROC analysis revealed that phosphorus level at 18 h prior to CKRT was the best predictor of severe AKI (ROC = 0.9 SE = 0.075 95% CI = 0.77 – 1.07) (Figure 2). Children in whom severe AKI developed had similar durations of ICU or hospital stay as those in whom severe AKI did not develop.

3.4 ICU course

Five children (25%) received invasive mechanical ventilation for acute respiratory failure, with a median duration of 4 days. Two patients (10%) were on vasopressor support. The median duration of ICU stay was 6.5 d, whereas the median duration of hospital stay was 12 d. All children survived to ICU and hospital discharge. The overall survival rate at one year was 90%. Renal function improved in all patients, and none required long-term dialysis.

4 Discussion

This study analyzed CKRT courses and outcome in a cohort of 20 children admitted to the ICU with hematologic malignancies and severe TLS. Of all 222 children hospitalized with hematologic malignancies and TLS, only 9% required CKRT. CKRT was successful in abating the metabolic derangements within 6 hours of initiation, and serum levels of potassium, phosphorus, and uric acid declined to normal levels within 12 h of the CKRT course. There is limited data on the use of CKRT for TLS especially for pediatric patients. In an adult cohort of 153 patients with newly diagnosed hematologic malignancies who were at high risk for TLS, 30.7% developed TLS. Of those in whom TLS developed, 27 required kidney replacement therapy (KRT) (17.6%), and 17 required CKRT (11%) (6). In another cohort of adults with TLS admitted to ICU, KRT was utilized in 54.2% of patients, and the incidence of AKI was 80.4% (7). In our cohort, the most common indication for CKRT was hyperphosphatemia, and only one-third had hyperuricemia at the initiation of CKRT. This is not surprising in the rasburicase era, as most patients receive rasburicase early during a TLS course to prevent renal damage induced by uric acid crystal deposition in the renal tubules. Indeed, 95% of our cohort received rasburicase before CKRT. A prospective pediatric study of 76 patients with B-cell non-Hodgkin lymphoma found rasburicase to be effective at normalizing 86% and 100% of the uric acid levels in patients at 24 and 72 h respectively (8). In addition, Darmon et al. reported serum phosphorus level to be the main risk factor for clinical TLS,

TABLE 2 Median difference in serum levels 6 h before and up to 24 h post CKRT.

Serum level	Median Difference (95% CI)	p-value
K (mmole/L)		
6 h pre vs. 6 h post CKRT	0.70 (0.5, 0.9)	0.0040
6 h pre vs. 12 h post CKRT	0.80 (0.5, 1.3)	0.0010
6 h pre vs. 18 h post CKRT	0.65 (0.3, 1.1)	0.0143
6 h pre vs. 24 h post CKRT	0.80 (-0.3, 1.2)	0.1533
Phosphorus (mg/dL)		
6 h pre vs. 6 h post CKRT	2.70 (1.9, 3.7)	<.0001
6 h pre vs. 12 h post CKRT	4.80 (2.8, 5.7)	0.0001
6 h pre vs. 18 h post CKRT	5.05 (3.1, 6.2)	<.0001
6 h pre vs. 24 h post CKRT	4.80 (1.5, 7.6)	0.0015
Uric acid (mg/dL)		
6 h pre vs. 6 h post CKRT	1.80 (0.1, 7.7)	0.0090
6 h pre vs. 12 h post CKRT	3.10 (-0.2, 8.8)	0.0023
6 h pre vs. 18 h post CKRT	3.40 (0.6, 8.8)	0.0010
6 h pre vs. 24 h post CKRT	3.00 (-0.2, 10.2)	0.0210
Calcium (mg/dL)		
6 h pre vs. 6 h post CKRT	0.0057	
6 h pre vs. 12 h post CKRT	-2.60 (-3.6,-1.1)	<.0001
6 h pre vs. 18 h post CKRT	-3.35 (-3.8, -1.9)	<.0001
6 h pre vs. 24 h post CKRT	-3.00 (-3.8, -1.4)	0.0012
BUN (mg/dL)		
6 h pre vs. 6 h post CKRT	4.00 (-4.0, 13.0)	0.0927
6 h pre vs. 12 h post CKRT	16.00 (7.0, 23.0)	0.0010
6 h pre vs. 18 h post CKRT	17.00 (6.0, 27.0)	0.0004
6 h pre vs. 24 h post CKRT	12.00 (1.0, 30.0)	0.0039
Cr (mg/dL)		
6 h pre vs. 6 h post CKRT	0.25 (0.1, 0.4)	0.0002
6 h pre vs. 12 h post CKRT	0.48 (0.2, 0.8)	0.0017
6 h pre vs. 18 h post CKRT	0.68 (0.4,0.9)	0.0005
6 h pre vs. 24 h post CKRT	0.89 (0.4, 2.3)	0.0043

CKRT, continuous kidney replacement therapy; K, potassium; BUN, blood urea nitrogen; Cr, creatinine.

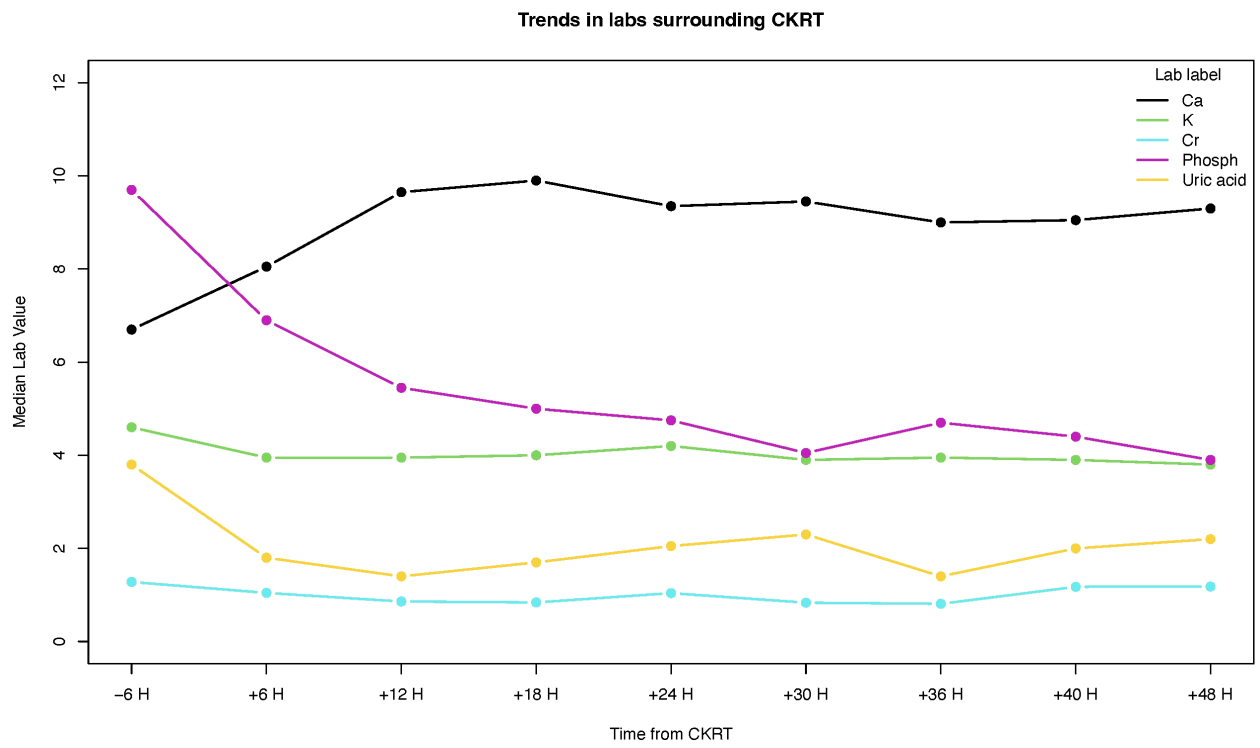

FIGURE 1
Changes in serum levels of calcium (Ca), potassium (K), creatinine (Cr), phosphorus (phosph), and uric acid.

TABLE 3 Comparison of patients with no/mild AKI and those with severe AKI.

Laboratory measure	Median (min, max)		P value
	No/Mild AKI (Stage 0,1) n=3	Severe AKI (Stage 2,3) n=17	
Uric acid (mg/dL)			
6 h pre CKRT	3.70 (2.3, 9.0)	3.90 (0.2, 29.7)	0.723
12 h pre CKRT	2.40 (1.1, 7.7)	5.00 (0.9, 17.7)	0.3643
Phosphorus (mg/dL)			
6 h pre CKRT	8.20 (7.3, 8.9)	10.65 (3.8, 14.9)	0.1785
12 h pre CKRT	6.40 (5.1,7.1)	10.50 (5.8, 12.4)	0.0375
Calcium (mg/dL)			
6 h pre CKRT	7.30 (6.6, 7.5)	6.65 (4.9, 9.7)	0.3199
12 h pre CKRT	7.40 (7.3, 7.5)	7.10 (5.6, 9.0)	0.2964
LDH 1 d pre CKRT (U/L)	2303.00 (2147.0, 2790.0)	2340.50 (351.0, 10065.0)	0.9577
Duration of hospital stay (d)	16.00 (9.0, 21.0)	12.00 (7.0, 42.0)	0.4825
Duration of ICU stay (d)	7.00 (4.0, 8.0)	6.00 (3.0, 36.0)	0.8491

AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; LDH, lactate dehydrogenase; ICU, intensive care unit.

with a 5-fold increase in risk of clinical TLS with each1 mmole increase in phosphorus level (6).

In our cohort of severe TLS requiring CKRT, most patients were males (90%). This observation was reported in previous TLS cohorts: in a cohort of 8 children who required renal replacement therapy due to TLS, 87.5% were male (9). In addition, in a cohort of 153 adults with cancer and TLS admitted to the ICU, 69% were male, and AKI occurred at a rate of 86% in male patients. Being male is associated with higher risk of AKI (OR=6.79, IC 95% 2.59-19.44) (7, 9). Prospective large cohorts are needed to examine and confirm the association of male sex with severe TLS and AKI. If confirmed, then being male should be considered a risk factor for severe clinical TLS. Of note, male sex has been reported in previous studies to confer a higher risk of AKI requiring dialysis (10, 11). In a large cohort of hospitalized patients with AKI, AKI-D was 2.19 times more likely to develop in men than in women (11).

The reported prevalence of AKI in the setting of TLS is high and ranges from 64-80% (6, 7). Severe AKI was observed in 85% of our cohort. Our findings indicate that hyperphosphatemia contributes to AKI in this pediatric cohort. Children with AKI had significantly higher phosphorus levels before initiation of CKRT (6.4 mg/dL in children with no/mild AKI vs.10.5 mg/in those with severe AKI, p-value 0.0375). These findings are similar to those previously described in adult cohorts. In a large cohort of 120 adults with hematologic malignancies and TLS, AKI developed in 56, and phosphate was strongly associated with AKI (Hazard ratio of 1.76 per 0.5 mmole/L increase in phosphate) (12). As in our cohort, uric acid levels did not

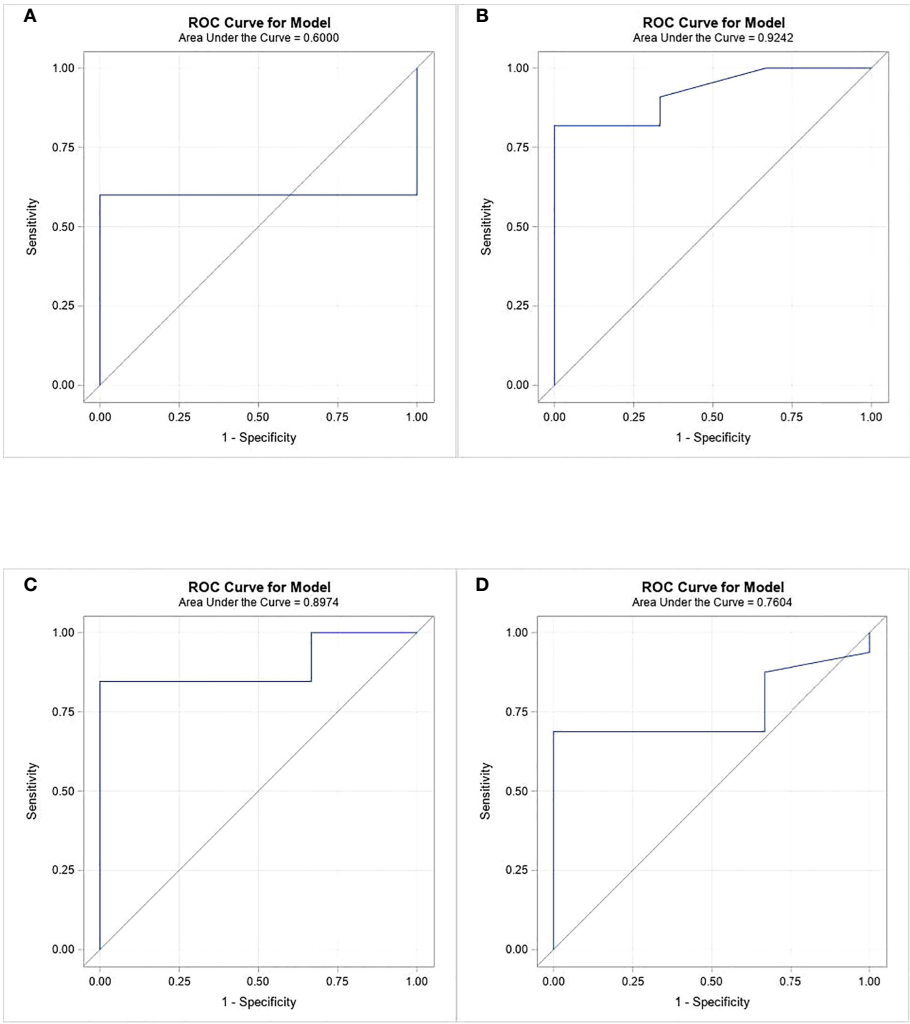

FIGURE 2
ROC analysis of phosphorous levels at 4 time periods prior to CKRT initiation as a predictor of severe AKI. **(A)** at 24 hours, **(B)** at 18 hours, **(C)** at 12 hours, **(D)** at 6 hours.

contribute to AKI. On the basis of these findings, we suggest that rapid rise in phosphorus levels should alert clinicians to consider the initiation of CKRT in these situations to prevent developing AKI or progression of an existing AKI. Abdel-Nabey et al. reported the practice of KRT initiation in patients with TLS admitted to the ICU with a phosphorus level of > 7.7 mg/dL or when the phosphorus level increase is >3 mg/dL every 6 h (7). This practice is reasonable considering the strong association of hyperphosphatemia with AKI in this pediatric cohort and in adult cohorts (6, 12).

The reported overall mortality rate of patients with TLS ranges from 15 to 35% (6, 13, 14). In our cohort, all patients survived to ICU and hospital discharge even though 85% had severe AKI and 25% had acute respiratory failure. This outcome suggests that early intervention and CKRT provide benefit and improve outcome in this population. In addition, in our cohort, the overall mortality at 1 year was low (10%).

The limitations of our study include its retrospective design, small population, and absence of a control group. However, our study describes the largest cohort of children with TLS and hematologic malignancies who were treated by CKRT. Prospective randomized, controlled studies are needed to outline the benefit of early KRT initiation to prevent AKI in this high-risk population.

5 Conclusion

CKRT is safe in children with hematologic malignancies with severe TLS and reverses metabolic derangements within 6-12 h. Most patients had AKI at the time of initiation of CKRT but did not require long-term KRT. Hyperphosphatemia before initiation of CKRT was associated with AKI; thus, rapidly rising phosphorus level can indicate the need for CKRT. Male sex seems to be associated with a higher risk of TLS requiring dialysis. The results of prospective multicenter studies may identify a cut-off phosphorus value at which to start CKRT.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by IRB at St. Jude Children's Research Hospital. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: Retrospective data collection.

Author contributions

LE contributed to planning, writing, and editing the manuscript. AA and LS contributed to data collection, writing, and editing the manuscript. VJ contributed to data collection and editing the manuscript, CC and EA contributed to data analysis and manuscript writing, RR contributed to planning and editing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1234677/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Definition of laboratory and clinical TLS.

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Prognostic factors and predictive scores for 6-months mortality of hematopoietic stem cell transplantation recipients admitted to the pediatric intensive care unit

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Objective: Despite advances in hematopoietic stem cell transplantation (HSCT), a considerable number of pediatric HSCT patients develops post-transplant complications requiring admission to the pediatric intensive care unit (PICU). The objective of this study was to evaluate clinical findings, PICU supportive therapy and outcome as well as predictive factors for 6-months survival after discharge of HSCT patients from PICU.

Study design: This retrospective single-center analysis investigated patient characteristics, microbiological findings, reasons for admission and death of 54 cases accounting for 94 admissions to the PICU of the University Children's Hospital Tuebingen from 2002 to 2017. We compared clinical characteristics between children with and without 6-months survival after discharge from PICU following HSCT. Finally, we assessed the potential prognostic value of the oncological Pediatric Risk of Mortality Score (O-PRISM), the Pediatric Sequential Organ Failure Assessment Score (pSOFA) and the pRIFLE Criteria for Acute Kidney Injury for 6-months survival using Generalized Estimating Equations (GEE) and Receiver Operating Characteristic curves.

Results: Respiratory insufficiency, gastroenterological problems and sepsis were the most common reasons for PICU admission. Out of 54 patients, 38 (70%) died during or after their last PICU admission, 30% survived for at least six months. When considering only first PICU admissions, we could not determine prognostic factors for 6-months mortality. In contrast, under consideration of all PICU admissions in the GEE model, ventilation (p=0.03) and dialysis (p=0.007) were prognostic factors for 6-months mortality. Furthermore, pSOFA (p=0.04) and O-PRISM (p=0.02) were independent risk factors for 6-months mortality considering all PICU admissions.

Conclusion: Admission of HSCT patients to PICU is still associated with poor outcome and 69% of patients died within 6 months. Need for respiratory support and dialysis are associated with poor outcome. Prediction of 6-months survival is difficult, especially during a first PICU admission. However, on subsequent PICU admissions pSOFA and O-PRISM scores might be useful to predict mortality. These scores should be prospectively evaluated in further studies to verify whether they can identify pediatric HSCT recipients profiting most from transferal to the PICU.

KEYWORDS

pediatric, HSCT, PICU, survival, outcome, pSOFA, O-PRISM

1 Introduction

Treatment and outcome of children with cancer have substantially improved during the last two decades. Mortality among hematopoietic stem cell transplantation (HSCT) recipients admitted to pediatric intensive care units (PICUs) has dropped significantly from 91% to about 25% within the last 30 years. However, this is still one of the highest mortality rates among PICU patients (1–4). Survival is determined by different factors such as age, type of HSCT, immune reconstitution, graft versus host disease (GvHD), infections, organ failure and need for organ replacement therapies (1–14).

In stark contrast, the six months survival rate of pediatric patients after HSCT on PICUs has remained relatively unchanged at only 21% to 25% (1, 10).

Advances in PICU patient care including protective ventilation strategies, early and aggressive therapy in sepsis and different options in renal replacement therapy have contributed to the drop in PICU mortality in HSCT patients (1, 5). Other approaches to reduce mortality and morbidity focus on increased pre-PICU symptom surveillance like the Pediatric Early Warning Score (PEWS) (3). Furthermore, changes in oncological treatment such as reduced intensity conditioning, targeted treatment protocols, graft manipulation, patient and donor selection, and advanced supportive therapies contribute to mortality reduction (1, 4, 7).

Around 10% to 40% of all pediatric HSCT recipients are admitted to the PICU at least once (2–5, 9, 15). Besides treatment- or condition-related risk factors, respiratory failure, multiple organ failure and septic shock are major causes for PICU admission (5, 14, 15).

Admission of oncological pediatric patients often raises sensitive questions and ethical issues in parents and healthcare practitioners. Clinical decision-making, e.g. whether a patient should be admitted to PICU at all or intubated or inotropic support should be escalated, is difficult because the outcome after PICU interventions is hard to predict. Furthermore, aggressive interventions need to be balanced against the provision of best end-of-life care through palliative care in the ward or parental support at home. Therefore, data that helps to determine which children may benefit from PICU supportive therapy is crucial to decide the best treatment approach for pediatric HSCT recipients.

Suitable scoring systems for post-HSCT pediatric patients provide a possibility to estimate outcome and the individual mortality risk and may be used to guide clinical decision making. Pediatric Critical Illness Score (PCIS), Pediatric Logistic Organ Dysfunction (PELOD) and the updated version of Pediatric Risk of Mortality (PRISM-3) were of prognostic value for HSCT recipients on PICUs (6, 12, 13, 16), whereas others such as the Pediatric Multiorgan Dysfunction score (PMOD) or the Pediatric Index of Mortality score (PIM-2) showed conflicting data (2, 6, 10, 16). The Oncological Pediatric Risk of Mortality (O-PRISM) score was found to be superior to the Pediatric Risk of Mortality score (PRISM) in a number of studies (1). In PICU patients with acute kidney injury (AKI), the pRIFLE classification (pediatric Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, End-stage kidney diseases) (17, 18) is an important tool to predict hospital mortality and PICU length of stay (19). In 2017, Matics et al. adapted and validated the Sequential Organ Failure Assessment (SOFA) score, which was originally developed for Sepsis outcome, specifically for critically ill children (20). This pediatric SOFA score (pSOFA) had excellent discrimination for in-hospital mortality, with an area under the curve of 0.94 (95% CI, 0.92-0.95). However, to the best of our knowledge, only three studies have applied pSOFA for pediatric HSCT patients to predict PICU mortality and none of them looked at long-term (6-months) survival (21–23). Here, we describe patient characteristics, clinical features, critical care interventions and outcome in a cohort of pediatric HSCT patients, admitted to the PICU of the University Children's Hospital Tuebingen. This is the first study which explicitly discriminates between first and subsequent PICU admissions to evaluate risk factors for 6-months mortality. The objective is to evaluate the predictive ability of different critical care interventions and scoring systems (O-PRISM, pSOFA and pRIFLE) for the individual mortality risk considering all PICU admissions of a patient by applying a Generalized Estimating Equations (GEE) model. We focus not only on PICU mortality but on long-term (6-months) mortality.

This new approach reveals unique insight into long-term prognosis of pediatric HSCT recipients and can support pediatric intensivists and oncologists in clinical decision making.

2 Methods

2.1 Patient population and study setting

We performed a retrospective, single-center analysis in HSCT patients admitted to the PICU of the University Children's Hospital Tuebingen during the period from January 2002 to December 2017. This 14-bed PICU cares for critically ill infants and children with up to 920 admissions per year. The main reason for admission is the need for cardiac surgery in about half of all patients, followed by general pediatric surgery and pediatric medical conditions that require intensive care treatment, including patients after HSCT. HSCT is performed by the department of pediatric hematology and oncology at the University Children's hospital Tuebingen, where about 50 pediatric HSCTs per year are undertaken with a special focus on re-transplantation and haploidentical HSCT. We selected all pediatric HSCT-patients with at least one non-scheduled PICU admission during the observation period and followed them up for any PICU readmission up to two years after HSCT. All PICU admissions due to scheduled post-operative care or interventions such as bronchoscopy, other endoscopies or catheter implantations were excluded from the analysis. The study was approved by the local ethical review board at the University Hospital Tuebingen (project No. 562/2010A) with a waiver of informed consent.

2.2 Data acquisition

Demographic, clinical and microbiological data was retrospectively retrieved from patient medical records of the hospital information system (i.s.h. med, SAP). Pediatric patients were included, if they were admitted to the PICU during conditioning or after up to two years after HSCT. Data obtained included age, sex, weight, underlying condition, disease status prior to HSCT, conditioning intensity, type of transplantation and conditioning, transplant-related complications, timing of PICU admission in HSCT, time after HSCT until PICU admission, PICU supportive therapy, number of PICU admissions, duration of PICU stays, reason for PICU admission, 6-months survival, date and cause of death. Microbiological and virological findings were extracted from the hospital laboratory order communication system (LAURIS, nexus/Swisslab). O-PRISM, pSOFA and pRIFLE Scores were determined for the day of PICU admission. Presence of graft-versus host disease (GvHD), thrombotic microangiopathy (TMA) and veno-occlusive disease (VOD) was assessed for every PICU stay and the highest grade of severity was documented. All HSCT patients are routinely monitored for frequent viral pathogens via blood PCR at least once a week. ADV, bacteria and fungi in stool, candida and aspergillus antigen in serum, a swab from the central vascular catheter entrance and a throat swab for bacteria and funguses is performed once a week. BKV in urine is screened once before HSCT. In case of symptoms (e.g. diarrhea, cough), further bacterial and viral diagnostics are performed. All these screening results were evaluated in the analysis presented. The main reason for PICU admission was independently identified by two pediatric oncologists and intensivists after screening of the patient's history. In case of dissent the two specialists discussed the case and agreed upon one main reason for admission. Cause of death was grouped in accordance with the CLASS system (Classification of death causes after transplantation) (24).

2.3 Statistical methods

Patient data was analyzed using Microsoft® Excel, Version 16.12 and IBM® SPSS Statistics Version 22 for Windows. Results are presented as numbers for categorical variables. Normally and not normally distributed quantitative variables are presented as mean ± standard deviation and median (minimum and maximum or interquartile range), respectively. The Kaplan Meier survival analysis was performed using Microsoft® Excel. To determine potential clinically relevant scores and risk factors for 6-months survival, we first applied univariate logistic regression using data from every first PICU admission. Influence of univariate factors with $p<0.05$ and clinically impactful factors of PICU treatment, known from a previous study (25) were then assessed by generalized estimating equation (GEE) models in order to generally determine the odds ratio of 6-months survival for each risk factor. By adjusting for PICU admission number, the GEE models allow for analysis of repeated measurements or correlated observations, which is the case in multiple PICU admissions of a single patient in our cohort. Every model additionally adjusted for clinically meaningful covariates known from the literature [age group (26), type of transplant, GVHD (27)]. Receiver operating characteristics were constructed and the most appropriate cut-off values for each marker or combination of markers were chosen from the ROC curve by using the point of the curve where the product of the two indices (sensitivity x specificity) is maximum. Cut-off points were used for the calculation of the positive and the negative predictive values.

3 Results

A total of 710 patients underwent HSCT during the study period. Of these patients, 54 accounted for a total of 94 admissions to PICU during the study period. 31 boys (57%) and 23 (43%) girls with a median age of 10 years (IQR 5.0-14.8) were admitted to PICU (Additional Table 1). 19 patients (35%) died during or after the first PICU admission. Eleven patients (20%) were discharged from PICU and survived and 24 (44%) were readmitted at least once more. Eleven (20%) died during or after the second PICU admission, three (6%) were discharged from PICU after the second admission and survived and ten (19%) were admitted three or more times to PICU. Out of these ten patients only two (4%) survived. In total 31 patients (57%) died during one of their

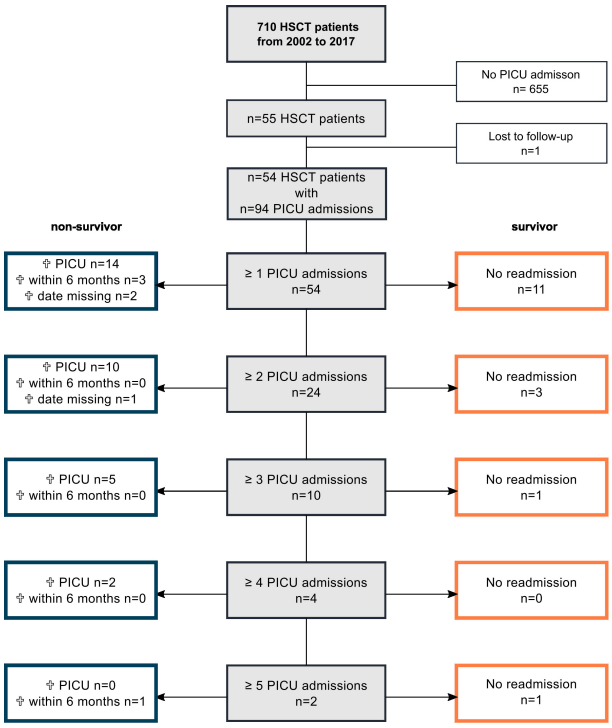

FIGURE 1
Overview of the study cohort of post-HSCT patients (n=54), their admissions, readmissions and survival. One patient who was lost to follow-up was excluded from the analysis; missing information on 6-months survival in n=3 patients. Analysis requiring 6-months survival data was performed with an n=51.

stays on the PICU and 7 died after discharge. The overall 6-months survival rate was 30% (16/54) (Figure 1, Additional Table 1). The Kaplan-Meier curve demonstrates that almost all non-survivors died during the first six months after HSCT (Figure 2).

3.1 Reasons for admission to PICU

The most frequent reason for admission to PICU after HSCT was respiratory problems (29.2%) followed by gastroenterological problems including GvHD of the gut or liver, VOD and intestinal bleedings (14.6%) and sepsis (13.5%). The most common reason for PICU admission in 6-months survivors was sepsis, whereas respiratory failure, gastroenterological and neurological problems were most common in 6-months non-survivors. Of note, 6-months non-survivors represented the highest proportion (75-85%) among patients with respiratory failure, gastroenterological and neurological problems, cardiocirculatory failure, renal dysfunction and cardiorespiratory failure as reason for PICU admission. In contrast, sepsis was the main reason for PICU admission in 6-months survivors (28%, Figure 3A).

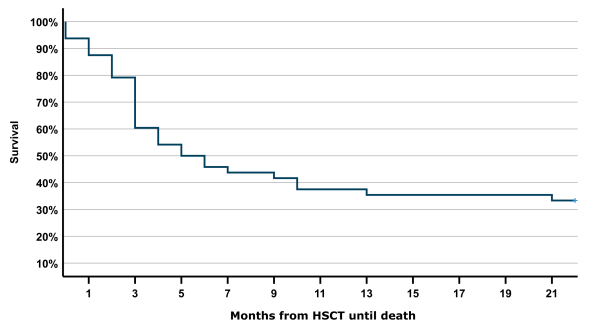

FIGURE 2
Kaplan-Meier analysis of mortality after pediatric HSCT. Probability of survival (in months) after HSCT and at least one PICU admission. Missing information on 6-months survival in n=3 patients.

3.2 Microbiological and virological findings

Rates of bacterial, viral and fungal organisms per admission group were detected by routine screening on each PICU admission (or up to one week before) (Additional Figures 1A–C, Additional Table 2). Cumulative rates and rates of each detected organism are displayed for each PICU admission without readmission, with readmission or non-survival during or after the respective PICU stay. Overall, bacterial isolates were detected most frequently when no further PICU admission was required. Enterococci and coagulase-negative Staphylococci accounted for about 50% of detected organisms when readmission was required or only one admission was necessary. On the contrary, in non-survivors *Clostridioides difficile* and *Pseudomonas/Stenotrophomonas spp* were isolated in about 50% of admissions (Additional Figure 1A). In non-survivors during or after PICU admission *Adenovirus* (ADV) was found most frequently, followed by *BK-Virus* (BKV) and *Human Herpesvirus 6* (HHV 6). In the case of readmission to PICU a similar distribution of viruses was found. However, ADV was less frequent. In patients without readmission, *BK-Virus* was most commonly isolated (Additional Figure 1B). In contrast to the decreasing rate of bacterial isolates with readmission and non-survival, fungal isolates were almost twice as common in non-survivors as in patients who required no further readmission to PICU. Distribution of fungal isolates was clearly dominated by *Candida* and *Aspergillus spp* in all admission groups (Additional Figure 1C).

3.3 Cause of death

35 out of 51 patients, for whom data on 6-months survival is available, died. Multi-organ failure was the most common cause of death (34%) followed by cardiac or vascular organ dysfunction (20%) and infections (17%). This distribution is rather similar in patients dying during or after the first or second PICU admission. In total, just 4 (11%) patients died due to the underlying malignancy/relapse (relapse-related mortality). The relapse-related mortality was more relevant after or during the second PICU admission. However, with 89% the transplant-related (non-relapse-related) mortality was by far more relevant in the presented cohort (Figure 3B).

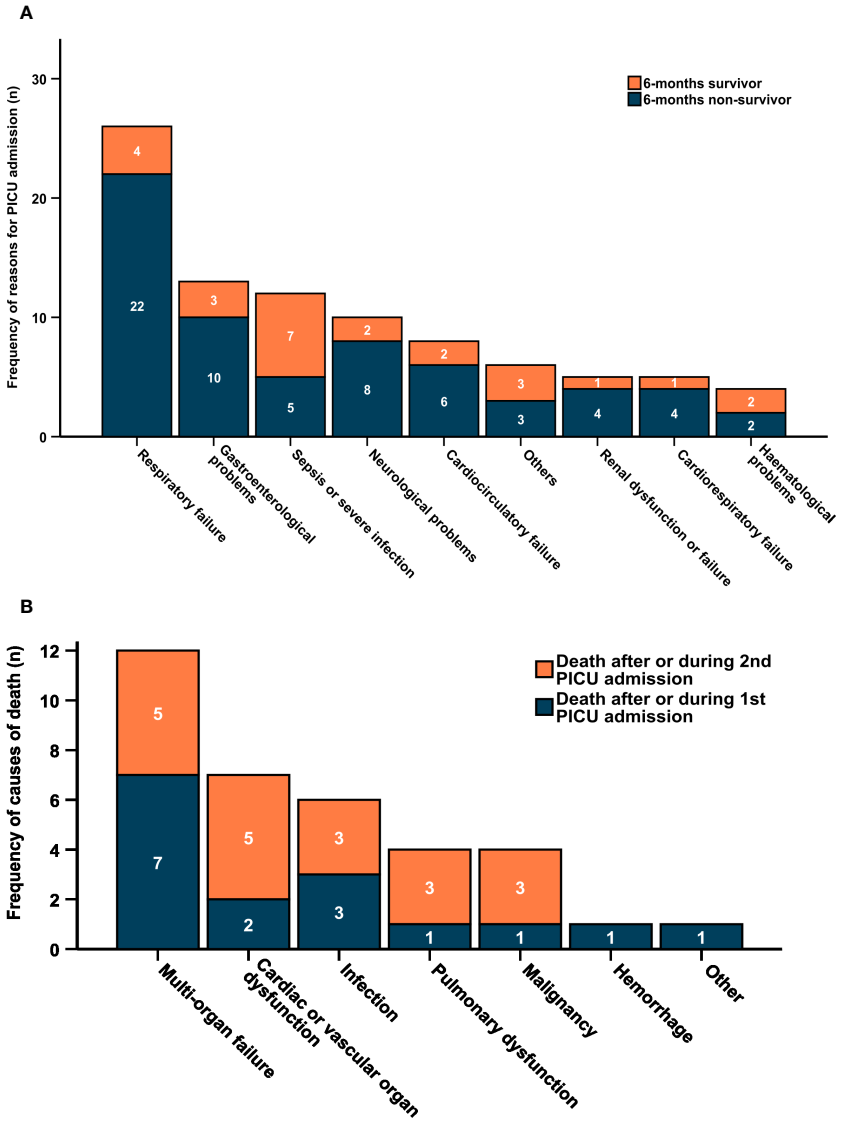

FIGURE 3
(A) Reasons for PICU admission according to 6-months mortality. **(B)** Reasons of death by PICU admission. **(A)** Frequency of main reasons for PICU admission (n=89) after HSCT by 6-months survival. **(B)** Frequency of causes of death (n=35) within 6 months after last PICU admission. Dark blue bars indicate death after or during 1st PICU admission (missing cause of death in n=2), orange bars indicate death after or during 2nd PICU admission.

3.4 Comparison of 6-months survivors and 6-months non-survivors

All transplant-related details for 51 patients in which data on 6-months mortality was available are listed in Table 1. ALL (n=15), primary immunodeficiency (n=7) and solid tumors (n=7) were the most frequent underlying diseases. Six (12%) patients had undergone autologous transplantation. 45 (88%) had received allogeneic HSCT, including 20 (39%) haploidentical HSCT. The median period until first PICU admission after HSCT was 50 days with a wide range from -15 to 378 days. Median length of PICU stay was 6 days. In regards to HSCT related side effects GvHD was present in 26 (51%) patients, thrombotic microangiopathy in 10 patients and VOD in 9 patients.

All patients with JMML (juvenile myelomonocytic leukemia), MDS (myelodysplastic syndrome) and WAS (Wiskott-Aldrich-syndrome) as well as the vast majority of patients with primary immunodeficiency (5/7) and AML (4/5) died during or within 6 months after PICU admission. 83% of all patients being transplanted with an active malignancy died (details see Table 1).

Three patients underwent Extracorporeal Membrane Oxygenation (ECMO) on their first PICU admission, but all died. It is worth to mention one additional patient, who was readmitted

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TABLE 1 Patient, disease, HSCT and PICU treatment characteristics of 6-months survivors and 6-months non-survivors (n=51*).

	6-months survivor (n=16)	6-months non-survivor (n=35)	Total (n=51*)
Patient characteristics			
Sex m/f	10/6	21/14	31/20
Median age in years; [IQR]	10 [5-16]	9 [4-15]	10 [5-15]
Weight (kg) before HSCT; mean ± SD	39 ± 23	35 ± 23	36 ± 23
Weight (kg) on PICU admission; mean ± SD	37 ± 22	34 ± 21	34 ± 21
Underlying disease			
ALL	5	10	15
AML	1	4	5
CML	2	0	2
JMML	0	2	2
MDS	0	3	3
Lymphoma	1	1	2
Solid tumor	3	4	7
PID	2	5	7
AA	1	0	1
WAS	0	1	1
Others	1	5	6
Disease status prior to HSCT			
Complete remission **Active malignancy** **Non-malignant disease**	8 2 4	11 10 11	19 12 15
Received therapy before HSCT and conditioning			
No conditioning **Myeloablative** **Reduced intensity**	1 11 3	0 28 5	1 39 8
Donor type			
Autologous	3	3	6
Allogeneic[1], total	13	32	45
- haploidentical	6	14	20
- matched related donor	0	6	6
- matched unrelated donor	6	10	16
- cord blood	0	2	2
Complications			
TMA	3	7	10
VOD	2	7	9
GvHD (any)	7	19	26
GvHD gut	3	13	26
GvHD liver	2	5	7
GvHD skin	5	14	19
Occurrence of aGVHD[2]	7	18	25

(Continued)

TABLE 1 Continued

	6-months survivor (n=16)	6-months non-survivor (n=35)	Total (n=51*)
I-II aGVHD	3	7	11
III-IV aGVHD	3	9	12
Occurrence of cGVHD[2]	2	2	4
Mild cGVHD	1	0	1
Moderate cGVHD	0	1	1
Severe cGVHD	1	1	2
First PICU admission and treatment			
PICU admission after 1st HSCT	11	29	40
PICU admission after 2nd HSCT	5	6	11
Timepoint of first PICU admission			
Conditioning **Pre-engraftment** **Post-engraftment**	1 4 11	4 6 24	5 10 35
Days after HSCT until first PICU admission; median, [range]	29 [-15; 246]	51 [-10; 378]	50 [-15;378]
Length of first PICU admission; median days, [range]	4 [1; 34]	6 [1; 39]	6 [1;39]
MOF	13	32	45
Ventilation	6	16	22
Circulatory support	8	16	24
Dialysis	1	11	12
ECMO	0	3	3
pSOFA; median [range]	9 [3; 13]	10 [5; 17]	10 [3;17]
O-PRISM; median [range]	22 [7; 39]	26 [10; 48]	26 [7;48]
pRIFLE; median [range]	2 [0; 3]	2 [0; 4]	2 [0;4]
Cause of death			
Relapse-related mortality **Non-relapse-related mortality**	0	4 31	35

IQR, interquartile range; SD, standard deviation; TMA, thrombotic microangiopathy; GvHD, graft versus host disease; VOD, veno-occlusive disease; MOF, multi-organ failure; ECMO, extracorporeal membrane oxygenation; pSOFA, pediatric Sequential Organ Failure Assessment Score; O-PRISM, Oncological Pediatric Risk of Mortality Score; pRIFLE, pediatric Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, End-stage kidney diseases. Patient characteristics, underlying disease, disease status, received therapy and donor type are displayed for every first PICU admission. Scores were determined for the day of PICU admission and medians are shown for every patient's first PICU admission. GvHD, TMA and VOD were counted if present during any PICU stay and the highest grade of severity was documented. There is missing information on 6-months survival in 3 patients (*), therefore total n=51. [1]in one patient, only allogeneic but not special type is known. Missing data on disease status prior to HSCT in 5 patients, in received therapy in 3 patients and timepoint of first PICU admission is unknown in one patient. [2]includes patients with the combination of acute and chronic GVHD.

twice to the PICU beyond the pre-defined observation period of this study (>3 years after HSCT), who underwent ECMO and survived.

3.5 Prediction of 6-months mortality

pSOFA and O-PRISM scores increased with number of PICU admission, although less data could be evaluated due to a decreasing number of patients for every additional readmission (Figures 4A, B). Differences in median scores between 6-months survivors and non-survivors could not be detected when only considering all first PICU admissions of our cohort, but in all patients' last admissions (Table 1, Figures 4C, D, Additional Table 3). Furthermore, univariate logistic regression analysis did not reveal any of the disease scores or critical care interventions as predictive for 6-months mortality in this patient subset (Table 2). In contrast, consideration of all admissions to the PICU of a single patient confirmed pSOFA and O-PRISM as well as respiratory support and dialysis as predictive factors for 6-months mortality (Table 2). Due to the longitudinal data structure with different numbers of admissions for every patient, generalized estimating equations were applied and models corrected for admission number, age-group, type of transplant and GVHD. Overall, pSOFA and O-PRISM were associated with 6-months mortality with an adjusted

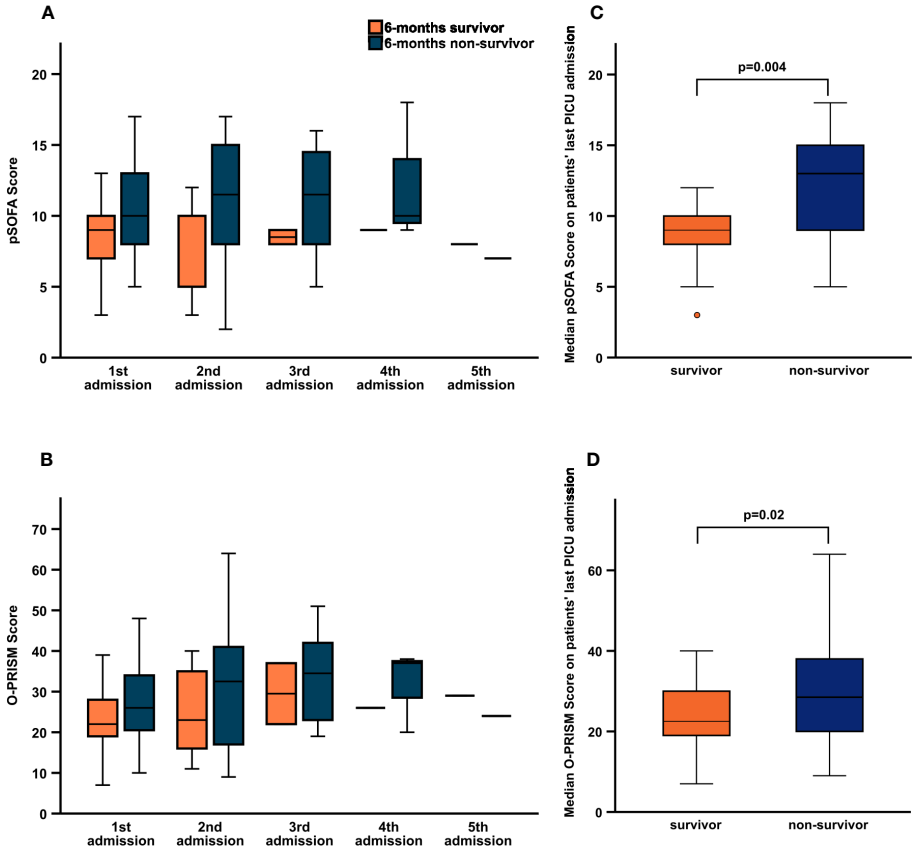

FIGURE 4
Comparison of pSOFA and O-PRISM score between 6-months survivors and 6-months non-survivors. Median pSOFA **(A)** and O-PRISM **(B)** score distributed by number of PICU admission and median pSOFA **(C)** and O-PRISM **(D)** score of patients' last PICU admission for 6-months survivors (orange) and non-survivors (blue). For numbers (median, range) see Additional Table 3.

OR of 1.04 (95% CI 1.00-1.07, p=0.04, QIC 113.48) and 1.01 (95% CI 1.00-1.02, p=0.02, QIC 114.44). When examining the different PICU interventions, respiratory support and dialysis increased the risk for 6-months mortality with an adjusted OR of 1.21 (95% CI 1.02-1.44, p=0.03, QIC 113.60) and 1.67 (95% CI 1.15-2.44, p=0.007, QIC 106.67), respectively. This was not true for cardiocirculatory support (Table 2).

Receiver operating characteristic curves (ROC) analysis of both scores was performed separately for every PICU admission in order to identify an optimal cut-off for prediction of 6-months mortality (Additional Figures 2A, B). During the second PICU admission sensitivity and PPV of pSOFA, was highest (94.44%, 95% CI 72.7-99.9, PPV 89.5%, 95% CI 74.3-96.2) with an area under the ROC curve (AUC) of 0.78 and cut-off of 6.0, O-PRISM showed a maximum sensitivity of 75.0% (95% CI 34.9-96.8) and PPV 85.7% (95% CI 58.6-96.2) with an AUC of 0.59 and a cut-off of 24.5 during the third admission (Table 3). No single optimal cut-off could be identified for both scores.

4 Discussion

During the last decades there has been remarkable progress in pediatric oncology with increasing life expectancy and improving prognosis in many areas. However, the prognosis of children that are admitted to PICU after HSCT is still quite poor. Here, we describe a pediatric HSCT cohort of 54 children admitted to the PICU in more detail and analyze potential prognostic factors for 6-months mortality.

In line with other contemporary studies (5, 28), PICU mortality of our cohort was 57% (31/54) and 6-months mortality was 65% (35/54). This means an additional 6% of patients died within 180 days after their last PICU discharge. Compared to a study that was performed at our hospital 18 years ago (25), 6-months survival rate has increased from 23% to 30%. With five times the observation period in the current study (3 vs. 15 years), the number of PICU patients only doubled (23 vs. 54 patients) compared to the previous study. However, the average number of PICU admissions decreased from 9 PICU admissions per year in the former study (26 admissions in 23 patients) compared to 6 PICU admissions per year (94 admissions in 54 patients). This result could be related to a different PICU admission strategy at earlier timepoints, a shorter time per admission to the PICU in line with the availability of moving patients between PICU and HSCT intermediate care wards. Consistent with the patient structure in previous studies, the most common underlying disease for HSCT was ALL (6, 25). Solid tumors and primary immunodeficiency disorders (PID) represented the second largest group, which might be due to

TABLE 2 Relationship between main variables and 6 months mortality after PICU discharge using logistic regression analysis and Generalized estimating equations (GEE) models.

		Univariate logistic regression		Generalized estimating equations		
Variable	n	Every 1st PICU admission OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	QIC
pSOFA	50	1.12 (0.94-1.35)	0.21	1.04 (1.00 – 1.07)	0.04	113.48
O-PRISM	50	1.05 (0.98-1.13)	0.15	1.01 (1.00 – 1.02)	0.02	114.44
Respiratory support	50	1.77 (0.53-5.92)	0.36	1.21 (1.02 – 1.44)	0.03	113.60
Cardiocirculatory support	50	0.89 (0.27-2.92)	0.85	1.07 (0.95 – 1.20)	0.29	116.32
Dialysis*	48	7.17 (0.84-61.46)	0.07	1.67 (1.15 – 2.44)	0.007	106.67

Univariate logistic regression on every first PICU admission of each patient and Generalized estimating equations model of n=85 PICU admissions (n=83 for analysis of dialysis). Each model was adjusted for the following covariates: number of admissions and patient-specific confounders (age group, type of transplant and GVHD). *Dialysis was not adjusted for type of transplant due to multicollinearity. Respiratory support includes invasive ventilation or non-invasive ventilation. P-value for adjusted OR. OR: odds ratio; CI: confidence interval; QIC: Quasi-likelihood under the independence model criterion (QIC) for choosing the best correlation structure.

improved diagnostics and the expertise in our center. Of note, haploidentical transplantation represented the most frequent transplant mode followed by matched unrelated donor in the current study. 18 years ago haploidentical HSCT was the most common type of transplantation as well (25).

The most important cause for PICU admission in our cohort was respiratory failure, followed by gastrointestinal problems and sepsis. Importantly, respiratory failure or the combination of respiratory and cardiocirculatory failure as well as renal dysfunction or failure and neurological problems were present in the vast majority (75-85%) of

TABLE 3 Predictability of pSOFA and O-PRISM during 1st - 4th PICU admission.

Variable	n	AUC	Cut-off	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)
pSOFA 1st PICU admission	49	0.62	9.5	53.12 (34.7-70.9)	58.8 (32.9-81.6)	70.8 (55.8-82.4)	40.0 (27.9-53.4)	55.1 (40.2 – 69.3)
pSOFA 2nd PICU admission	23	0.78	6.0	94.44 (72.7-99.9)	60.0 (14.7-94.7)	89.5 (74.3-96.2)	75.0 (28.2-95.8)	87.0 (66.4-97.2)
pSOFA 3rd PICU admission	10	0.69	8.5	62.5 (24.5-91.5)	50.0 (1.26-98.7)	83.3 (53.1-95.7)	25.0 (6.0-63.4)	60.0 (26.2-87.8)
pSOFA 4th PICU admission	4	0.83	9.5	66.7 (9.4-99.2)	100.0 (2.5-100.0)	100.0	50.0 (16.8-83.2)	75.0 (19.4-99.4)
pSOFA every last PICU admission	50	0.76	9.5	71.4 (53.7-85.4)	60.0 (32.3-83.7)	80.7 (68.4-88.9)	47.4 (31.6-63.7)	68.0 (53.3-80.5)
O-PRISM 1st PICU admission	49	0.63	22.5	71.9 (53.3-86.3)	58.8 (32.9-81.6)	76.7 (64.1-85.8)	52.6 (36.0-68.7)	67.4 (52.5-80.1)
O-PRISM 2nd PICU Admission	23	0.64	25.0	61.1 (35.8-82.7)	60.0 (14.7-94.7)	84.6 (63.9-94.5)	30.0 (14.6-51.8)	60.9 (38.5-80.3)
O-PRISM 3rd PICU admission	10	0.59	24.5	75.0 (34.9-96.8)	50.0 (1.3-98.7)	85.7 (58.6-96.2)	33.3 (7.4-75.8)	70.0 (34.8-93.3)
O-PRISM 4th PICU admission	4	0.67	23.0	66.7 (9.43-99.2)	0.0 (0.0-97.5)	66.7 (47.3-81.7)	0	50.0 (6.8-93.2)
O-PRISM every last PICU admission	50	0.71	23.5	68.6 (50.7-83.2)	60.0 (32.3-83.7)	80.0 (67.4-88.6)	45.0 (30.1-60.8)	66.0 (51.2-78.8)

AUC and Cut-off for pSOFA and O-PRISM on 1st – 4th admission N for every number of PICU admission is given, missing data on scores in n=1 patient. Sensitivity, specificity, positive and negative predictive values are expressed as percentages. Confidence intervals for sensitivity and specificity are "exact" Clopper-Pearson confidence intervals. Confidence intervals for the predictive values are standard logit confidence intervals. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

patients that died within 6-months after PICU admission. On the contrary, 6-months survivors accounted for the majority of patients admitted with sepsis. The striking role of respiratory failure as the main reason for admission to PICU in our study is well known from HSCT and non-HSCT hemato-oncologic patients (5, 8). However, compared to the past, when almost all PICU admissions resulted in mechanical ventilation, less than half of the HSCT recipients (22/51) needed mechanical ventilation and half of all patients needed circulatory support in our current cohort. In this context the role of non-invasive ventilation (NIV) strategies in HSCT patients is still under investigation with several conflicting study results. On the one hand, invasive mechanical ventilation considerably increases the risk of mortality (3, 4, 13, 14). Early use of NIV to prevent intubation might be a promising option and is associated with lower mortality rate in some studies (3, 14). In other analysis non-invasive ventilation use pre-intubation was associated with increased mortality in pediatric HSCT patients (28, 29). Further studies are required to evaluate NIV in HSCT patients. Although not systematically assessed, the distribution and cumulative rate of bacterial, viral and fungal isolates among patients without and with PICU readmission compared to non-survivors revealed some interesting insights. Gram-negative rods, *Pseudomonas spp* and *Clostridioides difficile* were overrepresented in 6-months non-survivors. Furthermore, among viral isolates ADV clearly dominated in 6-months non-survivors. This is consistent with the current literature stating the highest infection-associated mortality rate of 42% if ADV is present at admission (compared to a total mortality rate of 16.2% of all PICU admissions in the same cohort) (3). The frequency of fungal isolates was highest in six months non-survivors and dominated by *Candida spp* and *Aspergillus* spp.

In order to gain a better understanding of why patients died early during or after the first PICU admission compared to later during or after a second or further PICU admissions, we analyzed the frequency of causes of death. In general the relapse-related mortality (RRM) was rather low (4/51), however the non-relapse but transplant-related mortality was considerable high with 31/51. Multi-organ failure and cardiac or vascular organ dysfunction were given reasons in more than half of all deaths, followed by infections. These findings are consistent with other reports from the literature (11).

4.1 Prediction of outcome and value of pSOFA

Overall, when considering every first PICU admission, no difference of demographic features, type of treatment, frequency of GvHD, presence of MOF and need for supportive therapy was found between 6-months survivors and 6-months non-survivors. Only the frequency of dialysis, reflecting renal failure seemed to be more frequent in six months non-survivors. Sustained renal failure and failed negative fluid management have already been identified as significant mortality risk factors in the previous study in our center (25). Of note, 3 patients received PICU supportive therapy via ECMO on their first admission, all of whom died. This is supported by a high PICU mortality rate of 77.8% for HSCT patients on ECMO given in the literature (4). On the other hand, there are a few case reports of successful ECMO treatment in non-malignant HSCT patients (1). Thus, it is debatable whether ECMO-therapy should be offered to HSCT patients due to unfavorable prognosis. To that end, an international and multidisciplinary consensus statement on the use of ECMO in children receiving HSCT has been published only recently as a clinical decision support tool in these difficult situations (30). In order to find a suitable prognostic tool to predict 6-months survival, we assessed the predictive ability of O-PRISM and pSOFA as well as the need for PICU supportive therapy for 6-months survival within our cohort. To account for multiple PICU admissions of each patient, we used GEE models. The adjusted odds ratio confirmed pSOFA and O-PRISM as prognostic factors for 6-months survival, although cut-offs determined by ROC curves did not perform well. A recent study including 110 pediatric oncology patients found a cut-off value of pSOFA of ≥ 8 for discriminating mortality (22). Furthermore, serial evaluation of SOFA score during the first few days after PICU admission was a good predictor of prognosis and correlated with mortality in pediatric oncology patients requiring mechanical ventilation (31). This supports our finding, that pSOFA is useful in pediatric HSCT patients requiring repetitive PICU admissions. However, here we could not determine a clear cut-off of pSOFA or O-PRISM to decide which children may benefit from repetitive PICU admissions or escalation of therapy as opposed to supportive or palliative care outside the PICU.

Interestingly, when we specifically assessed all PICU admissions of each patient using GEE models, we also found a significantly higher risk of 6-months mortality in patients undergoing dialysis or with the need for ventilatory support. Therefore, we hypothesize that long-term need for PICU supportive therapy, in particular mechanical ventilation and dialysis are predictors of poor outcome.

The present study has some limitations. First, this study is limited by its retrospective, single-center design with a rather small cohort size. Transfer and admission criteria of HSCT recipients to a PICU may differ between hospitals and countries and thus our results may not be applicable in different settings. Second, changes in clinical patient care or criteria for PICU admission during the study period might have an impact on the presented results. Third, the retrospective evaluation of predictive scoring system is always dependent on the quality of clinical data. It should be kept in mind that regardless of which score is applied, they anticipate population mortality risk and not individual prognosis. Additionally, pSOFA focuses on organ malfunction in sepsis including thrombocyte count and hyperbilirubinemia. These two factors are often pathological in post HSCT patients as thrombocytopenia might be present due to delayed hematopoietic reconstitution and hyperbilirubinemia based on transient VOD or drug toxicity. Considering these causes not being associated with high mortality, thrombocytopenia and hyperbilirubinemia seem not to be adequate parameters to predict outcome in HSCT patients. Furthermore, O-PRISM was established for the presented target group of children requiring ICU treatment following HSCT. The score and its parameters are based on a retrospective analysis in a single center setting and a prospective evaluation in the same center (32, 33) and includes the standard PRISM score and three additional variables (CRP, GVHD and hemorrhage). As with pSOFA, PRISM also includes liver function presented by PTT and bilirubin which might not be suitable

parameters in HSCT patients. Finally, we did not take into consideration quality of life and disease burden in this study. Nevertheless, our analysis provides an important approach for a further prospective assessment of the predictive ability of the pSOFA and O-PRISM score, including a larger number of pediatric oncology patients from multiple centers with more than one PICU admission.

In conclusion, admission of HSCT patients to PICU is still associated with poor outcome since 65% of patients died within six months. In particular, mechanical ventilation and dialysis seem to be associated with poor outcome. In contrast to the first PICU admission of HSCT patients, pSOFA and O-PRISM might be of particular predictive value in repetitive PICU admissions. However, further research is certainly required to disentangle whether pSOFA and O-PRISM can predict which patients benefit most from continued PICU supportive therapy and whether these scores can inform end of life decisions.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Informed consent was not obtained to make single pseudonymized participant data publicly available. Requests to access these datasets should be directed to hanna.renk@med.uni-tuebingen.de.

Ethics statement

The study was approved by the local ethical review board at the University Hospital Tuebingen (project No. 562/2010A) with a waiver of informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

FN, HR, and SS are responsible for the conception and design of the study. SS and HR performed the statistical analysis and drafted the manuscript. SH and NB have made substantial contributions to the acquisition of the data. FN, MD, PL, and MH revised this manuscript critically for important intellectual content. All authors finally approved this version of the manuscript for submissions. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CritCom: assessment of quality of interdisciplinary communication around deterioration in pediatric oncologic patients

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Background: High-quality clinical care requires excellent interdisciplinary communication, especially during emergencies, and no tools exist to evaluate communication in critical care. We describe the development of a pragmatic tool focusing on interdisciplinary communication during patient deterioration (CritCom).

Methods: The preliminary CritCom tool was developed after a literature review and consultation with a multidisciplinary panel of global experts in communication, pediatric oncology, and critical care to review the domains and establish content validity iteratively. Face and linguistic validity were established through cognitive interviews, translation, and linguistic synthesis. We conducted a pilot study among an international group of clinicians to establish reliability and usability.

Results: After reviewing 105 potential survey items, we identified 52 items across seven domains. These were refined through cognitive interviews with 36 clinicians from 15 countries. CritCom was piloted with 433 clinicians (58% nurses, 36% physicians, and 6% other) from 42 hospitals in 22 countries. Psychometric testing guided the refinement of the items for the final tool.

CritCom comprised six domains with five items each (30 total). The final tool has excellent reliability (Cronbach's alpha 0.81-0.86), usability (93% agree or strongly agree that the tool is easy to use), and similar performance between English and Spanish tools. Confirmatory factor analysis was used to establish the final 6-domain structure.

Conclusions: CritCom is a reliable and pragmatic bilingual tool to assess the quality of interdisciplinary communication around patient deterioration for children in diverse resource levels globally. Critcom results can be used to design and evaluate interventions to improve team communication.

KEYWORDS

communication, interdisciplinary, critical care, quality care, assessment

Introduction

Effective team communication is critical for improving the quality of care in medical settings (1). Effective communication is when information has been exchanged and is understood in the manner intended by all members of the clinical team. The quality, relevance, and clarity of interdisciplinary communication are essential for collaborative work in the hospital environment.

Interdisciplinary communication in hospitalized children involves the development of integrated communication across disciplinary boundaries, such as intensive care, oncology, nurses, general medicine, etc. (2) Interdisciplinary communication is essential for providing quality care, especially in critical situations where the potential for error is higher (3–6). The Joint Commission (a United States-based nonprofit organization that accredits more than 22,000 US healthcare organizations and programs) has identified communication as one of three major causes of sentinel events (unforeseen events leading to severe injuries or death). Poor communication is the leading cause of treatment delays, preventable harm, and death (4, 6–12). Accordingly, the Joint Commission identified improving communication as a high priority among the National Patient Safety Goals (7).

Communication failures can be caused by a lack of psychological safety, ineffective methods, time pressures, language barriers, and a lack of standardized procedures (11). Contributing factors include poor leadership and relationships in the healthcare team, fear of reprisal, and concerns about appearing incompetent in complex or ambiguous clinical situations (4). Additionally, differences in the organizational context and professional roles contribute to communication failures, although this relationship to communication has yet to be fully understood (13). These communication failures have significant consequences for patient care, especially in patient deterioration, defined as the "evolving, predictable and symptomatic process of worsening physiology towards critical illness" (14) when communication needs directly translate to necessary patient decision-making (15, 16).

Developing strategies to improve interdisciplinary communication is critical for improving the quality of care; however, measuring communication quality in the healthcare setting remains challenging. While multiple healthcare communication measures exist (1, 3, 5, 6, 17–24), they focus on aspects such as safety climate, teamwork, collaborative environment, and perception of quality care. There has been no focus on the characteristics of interdisciplinary communication quality, and few have been studied in multiple languages and across internationally diverse healthcare settings (17, 22, 23, 25–27). The lack of valid, reliable, and multilingual measurement tools presents a barrier to understanding how organizational climate impacts communication quality. Even when tools have been developed, they have often been developed within the setting of high-resource English-speaking contexts and do not apply in a global setting with varying resource levels and languages, and they may not accurately measure the intended construct.

This study aimed to develop and pilot a bilingual (English and Spanish) measure to assess the quality of interdisciplinary communication around patient deterioration in any resource setting. The goals of this study are to (1) describe the process for development, content validity, face validity, and pilot testing of this measure in English and Spanish and (2) describe the reliability testing of the survey instrument.

The analysis this tool provides is needed in any healthcare setting because there is a direct impact on patient care and safety that can be improved by enhancing interdisciplinary communication. The benefit will be reflected in improved patient safety, a higher level of staff satisfaction due to better interpersonal relationships, and better patient outcomes.

Methods

This was a measurement development study to assess interdisciplinary communication quality in the setting of pediatric patient deterioration. This study included (1) the use of an expert group and literature review to draft an initial measure, (2) cognitive interviewing for tool refinement, and (3) a pilot quantitative study of the draft measure to assess reliability, refine domain structure, and produce a final measure. This tool was designed for easy use by

interdisciplinary clinicians, evaluators, and researchers in clinical care.

Human subjects

The St. Jude Children's Hospital (St. Jude) Institutional Review Board approved this study as an exempt, minimal-risk study. Additional local approvals were obtained from centers participating in the CritCom pilot when required.

CritCom initial development

The preliminary version of CritCom was developed using a 7-step method (1. Literature Review, 2. Measure Development, 3. Cognitive Interviews (English), 4. Translation, 5. Cognitive Interviews (Spanish); 6. Language Synthesis, and 7. Final Review), which has been previously described (28) and is briefly summarized below. This methodology, specifically the rigorous translation process, was used to ensure that the measure was usable in multiple contexts and languages. Throughout the process, we aimed to design a pragmatic measure, which has been defined as a measure that is "important to stakeholders in addition to researchers, low burden, broadly applicable, sensitive to change, and actionable" (29).

First, a literature review was conducted to identify existing tools developed or utilized in healthcare settings to evaluate inter-professional communication. Literature on teamwork was also included at this stage, as these tools often contain domains of communication. Studies with measures addressing communication elements in healthcare were reviewed for common themes, and all relevant survey items were collated. A database comprising 421 questions and 45 domains of communication was obtained from this literature review. The initial domain selection included the constructs with the most significant evidence, frequency of occurrence, and relevance to clinical care. This database of items was then iteratively reviewed by a 21-member panel of global experts in pediatric oncology, interdisciplinary communication, and measure development from 21countries (Supplemental Table 1) to establish content validity and improve cultural sensitivity, producing a draft measure with 52 items across seven domains. This measure focused on childhood cancer care due to the high risk of clinical deterioration in hospitalized children. During these events, interdisciplinary care is necessary for efficient care and improved clinical outcomes.

We conducted cognitive interviews with 36 clinicians from 15 countries. Interviews in English were conducted with nurses and physicians working in the intensive care unit (ICU) or medical wards to identify problematic survey items and to establish face validity. Interviews were conducted by JR, KP, and SM using a standardized interview guide (28) in phases of 3-5 interviews, with changes to the survey based on feedback. Interviews were stopped after eight rounds of weekly meetings when no further changes were needed for the English survey version. To address regionalism, CritCom was translated into Spanish using a forward-back translation process with iterative review by a group of five native Spanish speakers from different countries. Cognitive interviews were then conducted in Spanish using the same techniques as in English (JR and MPT). During this round of cognitive interviews, changes were made to the Spanish and English instruments based on feedback. As edits and clarifications were made, the bilingual research team worked to ensure that the intent of the original items was preserved. (See Supplemental Table 2 for participant demographics of cognitive interviews).

The bilingual expert panel completed a final review to confirm that the measures reflected all relevant communication components identified in the initial review. Additionally, bilingual members of the expert panel reviewed the two versions to ensure that the meaning was maintained between the two languages. This process resulted in a preliminary CritCom tool with 52 items across seven domains (see Supplemental Figure 1 for a summary of the initial CritCom development process).

CritCom pilot

We piloted a preliminary 52-item CritCom measure globally among hospital staff (ICU and ward nurses and physicians) providing childhood cancer care. Participants were recruited from the St. Jude Global Critical Care Program (30) network of collaborators and pediatric critical care research networks such as Proyecto EVAT (31), POKER (PICU Oncology Kids Europe Research Group) (32), and PALISI (Pediatric Acute Lung Injury and Sepsis Investigators) (33). Recruitment asked clinicians to fill out an application indicating interest in participating individually or as a hospital; those selecting hospital participation were instructed to provide a list of emails for eligible participants at their center. Eligible participants included any clinical staff involved in the clinical care of hospitalized children with cancer who may have experienced deterioration. Those who do not take care of children with cancer or do not care for these children during deterioration were excluded from this study.

After identifying the eligible participants, CritCom was administered electronically via an anonymous Qualtrics survey in English or Spanish (based on the participant's country). The participants were given six weeks to respond and receive weekly reminders. Participants provided demographic information about themselves and their organizations. Finally, they were asked to complete a set of questions regarding CritCom usability (see Supplemental Figure 2 for the demographic and usability questions of the pilot measure).

Pilot analyses

The data for the Spanish and English versions of the tool were managed and analyzed using R, a programming language for statistical computing (34). Data were explored and described before performing psychometric analyses, which focused on the

measure's reliability. Within R, the packages used for psychometric analysis were Classical Test Theory (CTT) and lavaan, which were used for latent variable analysis. Our team has expertise in quantitative measurement development, and these analytical methods were informed by our prior work (35).

After initial data cleaning and descriptive analyses, psychometric data analysis was performed, and these results provided further measurement refinement. Confirmatory factor analysis (CFA) was initially used to confirm the hypothesized domain structure that emerged from earlier development stages (36). Confirmatory factor analysis consists of developing a statistical model to test the pre-identified factor (domain) structure compared to a structure where all items exist within one domain. These analyses helped identify poorly performing domains and items and understand if our proposed subscale structure was correct. We anticipated that some CritCom domains would have intercorrelations because of their conceptual overlap. Additionally, we used a robust full-information maximum likelihood to handle non-normality in the data appropriately. These psychometric analyses were then used to exclude the items and restructure the domains. Items were dropped if they had poor loadings on the construct or required more variability. One domain was dropped from the instrument due to poor performance in the CFA, and the other was re-conceptualized after dropping poorly performing items.

After the final tool was developed, we re-conducted CFA (37). These analyses were used to assess the final conceptual structure of the domains. We assessed three measures of fit: comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) (38). The CFI ranges from 0-1, where larger values indicate a better model fit. RMSEA assesses the covariance between the models, and the ideal output is less than 0.05. Finally, the SRMR is an analysis of the residuals in the model, with a desired output less than 0.05.

The usability of the Critcom tool was assessed through descriptive statistics of the usability questions. Additionally, we used the pragmatic scale of the Psychometric and Pragmatic Evidence Rating Scale (PAPERS) to assess the quality of the developed measure (39). This scale consists of five categories and provides a Likert scale assessment ranging from -1 (poor) to 4 (excellent).

Results

Participants

A total of 433 participants from 42 Spanish- and English-speaking hospitals in 22 countries completed the pilot CritCom (Table 1), representing a response rate of 62.8%. Participants included nurses (57.9%), physicians at all levels of training (36.1%), and other clinical staff, including respiratory therapists. The participants performed clinical work across a range of hospital units/ward types, including the ICU (34.9%), oncology ward (26.3%), and general medical ward (18.7%). The participants were primarily from upper-income countries (50%; Table 1; Supplemental Figure 3).

TABLE 1 CritCom pilot participant demographics (n=433).

Characteristic	Frequency	Percent
Profession		
Nurse	250	57.9%
General nurses	48	
Oncology nurses	65	
PICU nurses	74	
Other/admin	63	
Physician	156	36.1%
General physicians	29	
Oncology physicians	44	
PICU physicians	67	
Other/admin	16	
Other	26	6.0%
Unit		
General Medicine Ward	81	18.7%
Oncology Unit	114	26.3%
Intensive Care Unit	151	34.9%
Other/Non-clinical	87	20.1%
Gender		
Male	86	19.9%
Female	340	78.5%
Other	7	1.6%
Years at current hospital		
5 years or less	146	33.7%
6-10 years	163	37.6%
11-15 years	62	14.3%
16-20 years	21	4.9%
More than 20 years	41	9.5%
Country Income classification		
Low income	8	1.8%
Low middle income	28	6.5%
Upper middle income	342	79.0%
High income	55	12.7%

Instrument refinement

After the initial development, the 52-item preliminary CritCom measure was assessed for its structure using CFA and individual item analyses. The results of the CFA during this process are shown in Table 2. The initial baseline model included 52 original items in one domain, and the original pilot included all original items in the seven-domain structure. After assessing these models, 14 items were dropped because of poor performance, such as items with low item-

TABLE 2 Confirmatory Factor Analysis (CFA).

Model	Domains	Items	df	CFI	RMSEA	SRMR
Baseline single model	1	52		0.71	0.71	0.06
Original pilot, all items	7	52		0.83	0.05	0.06
Original domain structure, reduced items	7	38		0.89	0.052	0.051
Revised domain structure, reduced items	8	38		0.92	0.046	0.047
Final Structure, reduced items	**6**	**30**		**0.94**	**0.045**	**0.049**

total correlations or those loaded poorly onto the domain structure (Table 2). One of the domains (systems) was split into two as the items did not fit within a single construct, resulting in eight domains. Two domains (mechanisms, modes, and systems) were dropped due to conceptual ambiguity and poor psychometric performance, resulting in a final instrument that included 30 items within six domains.

The final CritCom tool measured the quality of clinical communication using the following domains: (1) actionable, (2) clarity, (3) tone, (4) empowerment, (5) collaboration and teamwork, and (6) leadership (Table 3; Supplemental Figure 4). CFA results demonstrated an improvement in the overall structure throughout the refinement of the measure. This culminated in the results for the final structure, which had a good fit with the model. This is illustrated through the CFI = 0.94 (desired statistic greater than.90), RMSEA = 0.045 (desired statistic less than 0.05), and SRMR = 0.049 (desired statistic less than 0.05). These indices indicate a good fit of the measurement model (i.e., the six domains of CritCom) to the observed data (28) (Table 2). The CFA approach we used here follows established analytical and reporting best practice guidelines (40).

Domain reliability

Table 4 presents the number of items and Cronbach's alpha, which measures the internal consistency (reliability) for each domain in the original measure and after-measure refinement.

TABLE 3 Final critCom domain definition.

Actionable	Using language that is timely, relevant, and contains the necessary information to act.
Clarity	A language that is clear, complete, structured, and communicates a shared mental model.
Tone	Understanding communication styles and wording, including non-verbal communication, and being ignored.
Empowerment	Assesses a team member's ability and comfort to evaluate patients proactively, make decisions, speak up, and escalate concerns without fear of consequences.
Collaboration and teamwork	The ways that team members work together and have mutual respect and role clarity.
Leadership	A domain that assesses the influences of organizational leadership and reporting structures that impede or facilitate communication.

These scores highlighted the internal consistency of each domain. The final measure had excellent internal consistency, with Cronbach's alpha ranging from 0.81 – 0.86, suggesting good subscale reliability. This indicates that the items fit well within one domain and target the same underlying component (i.e., the construct) of communication quality.

CritCom scale results

CritCom results were calculated by computing the average of each item within a domain and then calculating the overall average for the total score. Table 4 presents the pilot's final measure scores, with overall scores ranging from one (representing poor-quality communication) to five (high-quality communication) in each domain. Overall, tone had the lowest and actionable the highest domain scores, respectively. Figure 1 illustrates the distribution of the overall CritCom scores, showing good variability in the sample, although most total scores ranged from 3 to 5.

Additionally, we assessed domain scores by language (English or Spanish) to understand how CritCom performed in each language (Figure 2). The profile plot shows that the pattern of domain scores did not vary appreciably between assessment languages, indicating similar measure performances in English and Spanish.

CritCom usability

After completing the CritCom measure, the participants were asked to assess the instrument's usability (Figure 3). The vast majority of the participants agreed or strongly agreed that the survey was easy to use (94.0%), described the questions as clear (94.7%), felt it correctly described communication in their setting (89.8%), and agreed to cover concepts that are important within their clinical setting (96.1%). Overall, these findings demonstrate that participants found the tool usable and that it resonated with the concept they believed to be important.

In the PAPERS categories, CritCom scored good (3) on brevity (30 items), readability (between 8th and 12th-grade reading levels), and burden (manual calculation, although it provides recommendations for handling missing data). It scored excellent (4) for cost (free) and training (no training required). Overall, this resulted in a PAPERS score of 17 out of 20, indicating that this tool is usable and practical for clinicians and researchers (41). (Supplemental Figure 5).

TABLE 4 Subscale reliabilities and descriptive statistics.

Domain	Draft Item Number	Draft Alpha	Final Item Number	Final Alpha	Domain Mean	Domain SD*
Actionable	6	0.81	5	0.81	4.25	0.57
Clarity	6	0.81	5	0.82	4.11	0.60
Tone	7	0.79	5	0.84	3.75	0.69
Mechanisms and Modes	7	0.67	–	–	–	–
Empowerment	7	0.84	5	0.81	4.08	0.69
Collaboration and teamwork	9	0.88	5	0.83	4.13	0.63
Systems (renamed Leadership)	10	0.87	5	0.86	4.09	0.76
Overall Tool	**52**		**30**		**4.07**	**0.53**

* The range of all domains was 1–5.

Discussion

In this study, we developed CritCom, a valid, reliable, pragmatic bilingual tool to evaluate the quality of interdisciplinary communication regarding patient deterioration, using 30 items across six distinct domains. This measure consists of a Likert scale from 1-5, where individuals rate the extent to which their setting has or does each aspect of high-quality communication. This tool performed well across diverse cultures, languages, and various resource settings and has broad applicability in diverse clinical contexts. This global sample of clinicians felt that the CritCom tool was important and usable, and the tool performed well using an established assessment of measurement quality. We could not find in the literature a tool that could be compared in content, development, or pilot testing that could help us compare final results.

CritCom addresses the global need for a measurement tool to assess the quality of team communication in clinical settings. While previously available measures (6, 18–24, 27) include components of communication quality, none focus exclusively on distinct conceptual elements of communication, nor were they developed for use in multilingual, variably resourced settings.

Despite multiple studies demonstrating the relationship between communication quality and clinical outcomes (3–5), the lack of valid measures limits the evaluation and assessment of interventions to improve communication on a global scale. Similarly, while team dynamics and communication networks are accepted components of the clinical setting that influence the implementation of other evidence-based interventions to improve patient care (42, 43), the lack of dedicated measurement tools has prevented an empirical investigation of this relationship. These concepts are especially fundamental in resource-limited settings, where human and material resources to provide acute and critical care are not always available (20, 44) and high-quality communication faces additional challenges (25).

The CritCom tool can be used by clinicians, hospital leadership, evaluators, and researchers to assess communication quality, identify areas of strengths and opportunities for improvement,

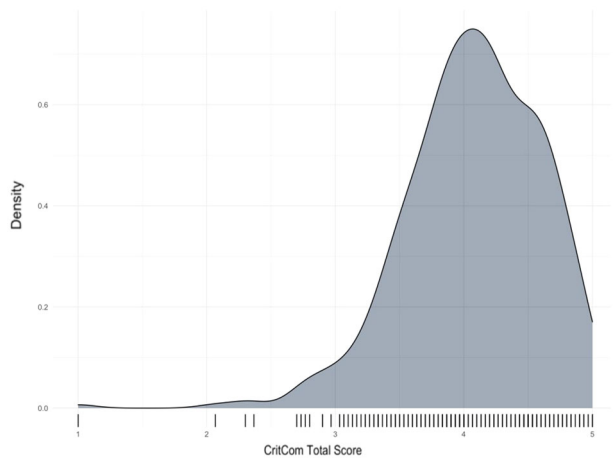

FIGURE 1
Overall CritCom scores pilot results. Density plot.

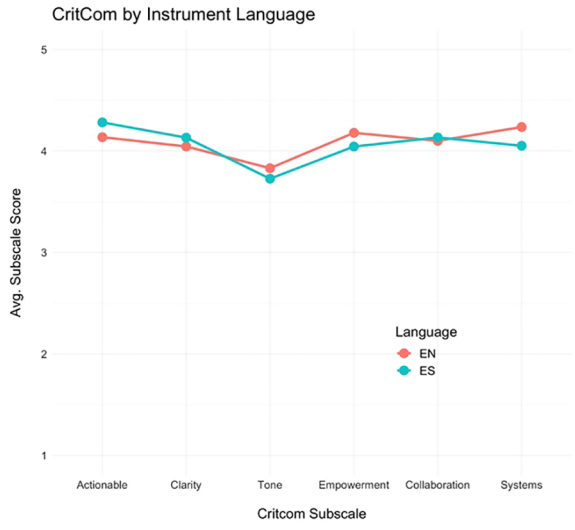

FIGURE 2
Responses comparing English and Spanish language tool.

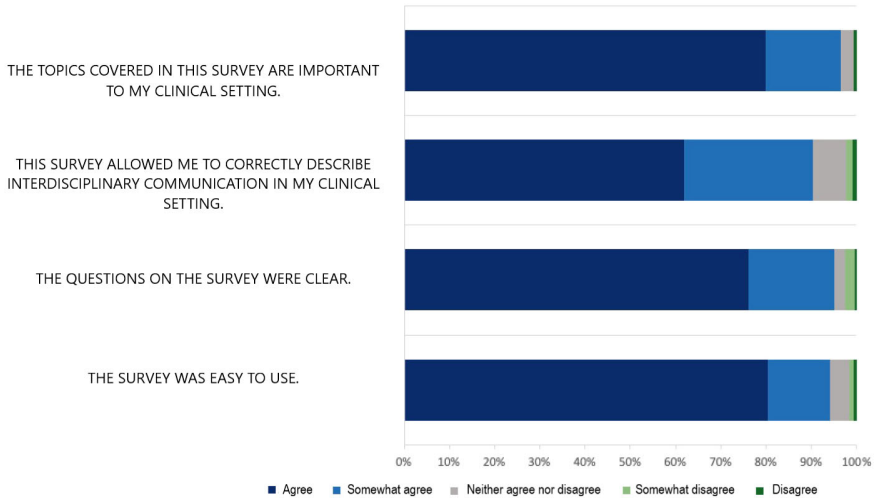

FIGURE 3
Usability results.

and track changes in communication over time. Similarly, clinicians and researchers can use CritCom as an outcome measure for quality improvement projects to improve communication, provide a baseline assessment, and post-intervention reassessment to supplement clinical data on errors and sentinel events. Finally, CritCom provides an opportunity to understand the modifiable determinants of high-quality team communications.

To promote the future global use of CritCom, our team is currently working on supplementing the English and Spanish versions of the tool with other languages, including Portuguese and Arabic, using the same rigorous linguistic validation methodology described in this study. We want to use the global CritCom results to further explore the landscape of interdisciplinary communication quality in hospitals from diverse cultures and resource levels to identify common characteristics and challenges. These findings can guide the development of tailored interventions to improve communication applicable to various resourced settings. Additionally, the methods used to develop this measure can be applied to other tools. The consideration of language, resources, and cultural differences is necessary as we outline the tools that will ultimately be used to measure outcomes.

This study had several limitations. For the pilot study to refine the CritCom tool, we selected an individual-based rather than a center-based recruitment strategy. This means that some, but not all, individuals completing the pilot participated as part of a hospital group. While appropriate for the objectives of the current study to refine CritCom through psychometric testing, future work should focus on the center-based evaluation of communication quality to more broadly understand common challenges and explore individual-level variations (i.e., nurse versus physician perspectives on team communication).

As a bilingual tool, our sample size included a more robust sample of Spanish clinicians than English-speaking clinicians, preventing us from evaluating each language tool individually. The methodology for developing the two language versions, with a focus on linguistic validity, however, and the near-identical performance of the two tools across CritCom domains suggests that the constructs described are conceptually similar in both languages. Expanding the use of CritCom in future studies will allow us to address some of the limitations related to the small sample size in the current study.

High-quality communication between providers and families of patients is also an integral part of pediatric care, particularly during clinical deterioration. However, the barriers identified in previous work (45) have shown that they cover different domains than those addressed in the present work, for which the development and analysis of this tool are entirely focused on communication between clinical staff.

Finally, this tool was developed to focus on interdisciplinary communication around childhood cancer care, potentially limiting its generalizability to other patient populations. However, this tool provides a structure that can be applied in different settings. Future studies should examine the validity of this measure across other care settings and the impact of the demographic variables on the perceived quality of communication.

Conclusion

CritCom is a valid, reliable, and pragmatic measurement tool developed in English and Spanish to evaluate the quality of interdisciplinary communication regarding deterioration in hospitalized children. The CritCom results provide a quantitative, center-specific assessment of communication quality that can identify areas for improvement, facilitate tailored interventions related to the findings, assess the efficacy of targeted interventions, and serve as a routine evaluation in hospitals to improve communication continuously and enhance the quality of care in hospitals at all resource levels.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AsA, JR, SM, DL, and DG conceptualized and designed the study, coordinated data collection, supervised data analyses, drafted the initial manuscript, and reviewed and revised the manuscript. MP-T, KP, LC, AnA, and FS, helped design and pilot the data collection instruments, collected data, contributed and reviewed and revised the manuscript. JA and LM contributed to the literature review, study design, and manuscript review. SJ, EK, BM, JS, and ES assisted with the study design and critically reviewed and revised the manuscript. ZZ, PB, SG, JK, AM, and RS-C contribute to the content validity and survey design. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1207578/full#supplementary-material

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Hospital survival following pediatric HSCT: changes in complications, ICU therapies and outcomes over 10 years

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Introduction: Hematopoietic stem cell transplantation (HSCT) is an increasingly utilized therapy for malignant and non-malignant pediatric diseases. HSCT complications, including infection, organ dysfunction, and graft-versus-host-disease (GVHD) often require intensive care unit (ICU) therapies and are associated with mortality. Our aims were to identify the HSCT characteristics, complications and ICU therapies associated with (1) survival, and (2) survival changes over a ten-year period in a national dataset.

Methods: A national sample from the Health Facts (Cerner Corporation, Kansas City, MO) database from 2009 to 2018 was utilized. Inclusion criteria were age 30 days to <22 years and HSCT procedure code. For patients with >1 HSCT, the first was analyzed. Data included demographics, hospital length of stay (LOS), hospital outcome, transplant type and indication. HSCT complications included GVHD and infections. ICU therapies were positive pressure ventilation (PPV), vasoactive infusion, and dialysis. Primary outcome was survival to discharge. Statistical methods included bivariate analyses and multivariate logistic regression.

Results: 473 patients underwent HSCT with 93% survival. 62% were allogeneic (89% survival) and 38% were autologous (98% survival). GVHD occurred in 33% of allogeneic HSCT. Infections occurred in 26% of all HSCT. ICU therapies included PPV (11% of patients), vasoactive (25%), and dialysis (3%). Decreased survival was associated with allogeneic HSCT ($p < 0.01$), GVHD ($p = 0.02$), infection ($p < 0.01$), and ICU therapies ($p < 0.01$). Survival improved from 89% (2009–2013) to 96% (2014–2018) ($p < 0.01$). Allogeneic survival improved (82%–94%, $p < 0.01$) while autologous survival was unchanged. Survival improvement over time was associated with decreasing infections (33%–21%, $p < 0.01$) and increasing vasoactive infusions (20%–28%, $p = 0.05$). On multivariate analysis, later time period was associated with improved survival ($p < 0.01$, adjusted OR 4.28).

Discussion: Hospital survival for HSCT improved from 89% to 96% from 2009 to 2018. Factors associated with mortality included allogeneic HSCT, GVHD, infections and ICU therapies. Improving survival coincided with decreasing infections and increasing vasoactive use.

KEYWORDS

bone marrow transplant, hematopoietic stem cell transplantation, survival, outcomes, intensive care, infection, GVHD

Abbreviations

HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LOS, length of stay; GVHD, graft-versus-host-disease; PPV, positive pressure ventilation.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an established therapy for children with malignant and non-malignant diseases, including hematologic and solid tumors, bone marrow failure syndromes, immunodeficiencies, and genetic and metabolic disorders (1). As indications for HSCT broadened, transplant volumes have increased by 5%–10% per year; approximately 2,500 children currently undergo HSCT each year in the United States (1–3). However, HSCT carries substantial risk of treatment-related morbidity and mortality, including infectious complications, graft-versus-host disease (GVHD), and organ toxicity induced by preparatory regimens (1, 4, 5).

Approximately one third of patients require intensive care unit (ICU) management for HSCT complications (6–12). Mortality in the first 100 days is as high as 11% for allogeneic transplant and 4% for autologous transplant (1, 3, 5), an improvement from 15% and 7% respectively before 1991 (3). Other studies have revealed similar trends of improving survival over time (5, 13–17). Tracking change is particularly relevant given improvements in human leukocyte antigen-matching, reduced-intensity pre-transplant regimens, GVHD management, infection prophylaxis and treatment (5, 14, 15, 18) and ICU care. Importantly, the contribution of ICU care to these temporal trends has not been evaluated.

Our aims were to associate HSCT characteristics, HSCT complications and ICU therapies with (1) survival, and (2) survival changes over a ten-year time period in a national sample from 2009 to 2018 to assess if survival improved and if there are any changes in HSCT complications or practice associated with improvement.

Methods

Database and study design

This is a retrospective multicenter study using the Health Facts™ database (Cerner Corporation, Kansas City, MO). This database has de-identified clinical data from academic and nonacademic hospitals of varied sizes and locations in the United States with a Cerner data use agreement. The database includes demographic and admission information, diagnostic and procedure codes, laboratory results, medication and respiratory data, and hospital outcome. Health Facts™ has been successfully used in other longitudinal studies examining pediatric trends and practice (19, 20). This study was approved by the Children's National Hospital Institutional Review Board (Pro00009282) and granted a waiver of consent for de-identified data.

Inclusion criteria included encounters for patients age 30 days to less than 22 years admitted between January 1, 2009 and June 1, 2018 with at least one HSCT procedure code, indicating receipt of HSCT during the admission. The procedure codes used to define HSCT, associated diagnoses and some therapies are detailed in the **Supplementary Appendix A**. For patients with more than one HSCT encounter during the study period, only the first was included. Encounters were excluded if they had incomplete data (below).

Variables and outcome measures

The primary outcome was survival to hospital discharge. Demographic variables included age, sex, race, ethnicity, and hospital length of stay (LOS). HSCT variables included transplant type (autologous and allogeneic), year of transplant, underlying diagnoses necessitating the transplant and complications including GVHD and infection. ICU therapies included positive pressure ventilation (PPV), dialysis, and vasoactive agent infusion. Transplant type, GVHD and underlying diagnosis/indication for HSCT were identified from diagnostic and/or procedure codes. Diagnoses and transplant indications were grouped into categories including malignant hematologic diseases, solid tumors, non-malignant hematologic diseases, immunodeficiencies, and non-malignant other diseases. If more than one diagnosis was present, one was chosen based on clinical expertise and likelihood to necessitate HSCT by T.O and B.D. Infectious complications were identified from microbiology results and were categorized by the culture site as blood, respiratory, urine, skin and soft tissue, or other. Organism types included bacteria (gram positive and gram negative), viruses, and other (fungus, yeast, and mycobacteria); patients could have more than one organism identified. PPV (non-invasive and invasive) was determined from procedure codes and respiratory care data. Respiratory care data indicating PPV included >8 h of recorded ventilator settings. Dialysis (hemodialysis, peritoneal dialysis, urinary filtration, and vascular access for dialysis) was determined from procedure codes. Vasoactive agent infusion (epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and/or vasopressin) was determined from medication administration data.

Statistical analysis

Variables were assessed individually for their association to hospital survival using bivariate analysis. Bivariate tests included Pearson's χ^2 or Fisher's Exact for categorical variables and Wilcoxon rank sums tests for continuous variables. Post hoc multiple comparisons were performed if the primary comparison was significant.

The study period was divided into two 5-year intervals to assess change over time, 2009–2013 and 2014–2018. Bivariate analyses were performed for demographic, HSCT, ICU care variables, and survival to assess changes between the two time periods.

Multivariable logistic regression was used to investigate the effect of time period, selected demographics, HSCT, and ICU therapy variables on hospital survival. Variables significant at the 0.2 level in the bivariate analyses of survival were included in the multivariable logistic regression model.

Odds ratios and adjusted odds ratios are reported. Statistical significance was declared at the 0.05 alpha level. Results were

expressed as medians with 25th–75th percentiles or counts with percentages. All statistical analyses were conducted using JMP® (version 16.1, SAS, Cary, North Carolina, USA).

Results

A total of 586 encounters met the study inclusion criteria. Fifty-seven encounters were excluded for incomplete data (**Figure 1**). Only the first HSCT procedure for each patient was included, with 56 subsequent HSCT encounters excluded. The final sample had 473 patients with hospital survival of 93%. Demographic and HSCT variable data are shown in **Table 1**. Median age was 8 years [3–15]. There were 284 (60%) males, and 322 (68%) patients were Caucasian. Transplant type was allogeneic for 293 patients (62%). Underlying diagnoses and HSCT indications included malignant hematologic diseases (47%), solid tumors (33%), non-malignant hematologic diseases (14%), immunodeficiency syndromes (4%) and other non-malignant diseases (2%). Hospital LOS was 32 days [23–47] and differed between survivors [31 days (23–43)] and deaths [85 days (63–116)] ($p < 0.01$).

Survival to hospital discharge for allogeneic HSCT was 89% compared to 98% for autologous HSCT [$p < 0.01$, OR 0.19 (0.07–0.55)] (**Table 1**). Compared to malignant hematologic diseases with 90% survival (reference group), solid tumors had improved survival of 97% [$p < 0.01$, OR 4.23 (1.43–12.53)]. There were no differences in survival between the other HSCT indication groups and the malignant hematologic reference group.

The major complications of GVHD and infections were associated with decreased survival to discharge. GVHD occurred in 96 patients (33% of allogeneic HSCT) and infections in 125 (26% of all HSCT) (**Table 2**). Survival for allogeneic HSCT patients with GVHD was 83% compared to 92% survival for those without GVHD [$p = 0.02$, OR 0.41 (0.19–0.87)]. Infectious complications were associated with decreased survival [$p < 0.01$, OR 0.27 (0.13–0.54)], with 85% survival if one or more infectious complication occurred and 95% survival if no infectious complications occurred. Among the infectious complication types, positive blood [$p < 0.01$, OR 0.23 (0.11–0.47)], respiratory [$p < 0.01$, OR 0.10 (0.04–0.23)], and urine cultures [$p = 0.05$, OR 0.39 (0.15–1.02)] were associated with decreased survival. The lowest survival (63%) was in patients with a positive respiratory culture.

ICU therapies included PPV in 53 patients (11%), vasoactive agent infusion in 116 patients (25%), and dialysis in 16 patients (3%) (**Table 2**). Survival was 53% for those receiving PPV, 78% for those receiving vasoactive agent infusions, and 38% for those receiving dialysis. Receiving one or more ICU therapies was associated with decreased survival [$p < 0.01$, OR 0.03 (0.01–0.11)]. An increasing number of ICU therapies was associated with worse survival, with 91% survival for one ICU therapy, 41% survival for two ICU therapies, and 14% survival for three ICU therapies ($p < 0.01$).

There was a significant improvement in survival over the 10-year period, from 89% in the early time period (2009–2013) to 96% in the late time period (2014–2018) [$p < 0.01$, OR 2.72 (1.32–5.61)] (**Table 3**). In particular, allogeneic HSCT survival increased from 82% to 94% [$p < 0.01$, OR 3.51 (1.59–7.77)], while autologous HSCT survival remained unchanged at 98%. The demographic and transplant variables were similar between the time periods with no significant differences in age, sex, transplant type, transplant indication, or LOS. GVHD was not different between the time periods but infectious complications were significantly reduced from 33% to 21% [$p < 0.01$, OR 0.54 (0.36–0.81)]. Of the ICU therapies, there was a trend towards an

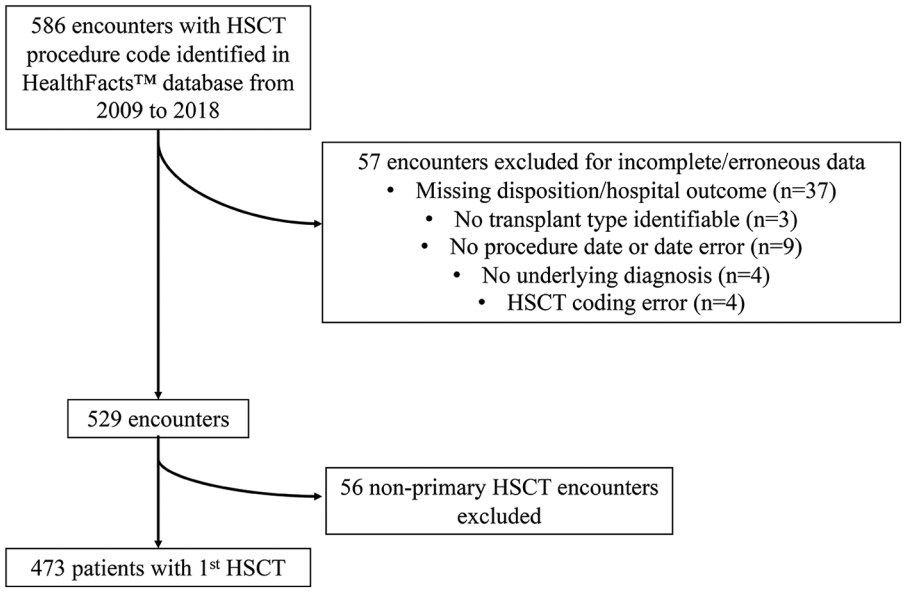

FIGURE 1
Patient inclusion diagram. HSCT, hematopoietic stem cell transplantation.

TABLE 1 Demographic and hematopoietic stem cell transplant variables and their association with survival.

	All patients ($n = 473$)	Survivors ($n = 438$)	Deaths ($n = 35$)	p (1)	OR of Survival [95% CI]
Demographic					
Age, median [25%ile–75%ile], years	8 [3–15]	8 [3–15]	6 [1–15]	0.41 (2)	
Male, *n* (%)	284 (60)	265 (93)	19 (7)	0.47 (3)	1.29 [0.65–2.58]
Female, *n* (%)	189 (40)	173 (92)	16 (8)		
Race and ethnicity, *n* (%)					
Caucasian	322 (68)	299 (93)	23 (7)	0.96 (4)	
African American	69 (15)	63 (91)	6 (9)		
Asian/Pacific Islander	21 (4)	20 (95)	1 (5)		
Hispanic	26 (6)	24 (92)	2 (8)		
Other/Unknown	35 (7)	32 (91)	3 (9)		
Hospital LOS, median [25%ile–75%ile], days	32 [23–47]	31 [23–43]	85 [63–116]	<0.01 (5)	
Transplant Type					
Allogeneic, *n* (%)	293 (62)	262 (89)	31 (11)	<0.01 (6)	0.19 [0.07–0.55]
Autologous, *n* (%)	180 (38)	176 (98)	4 (2)		
Transplant Indication				0.02 (7)	
Malignant Hematologic, *n* (%)	221 (47)	199 (90)	22 (10)	REF (7)	
Solid tumor, *n* (%)	157 (33)	153 (97)	4 (3)	<0.01 (7)	4.23 [1.43–12.53]
Non-malignant Hematologic, *n* (%)	64 (14)	59 (92)	5 (8)	0.81 (7)	1.30 [0.47–3.59]
Immunodeficiency, *n* (%)	21 (4)	18 (86)	3 (14)	0.46 (7)	0.66 [0.18–2.43]
Non-malignant other, *n* (%)	10 (2)	9 (90)	1 (10)	1.00 (7)	0.99 [0.12–8.23]

OR, odds ratio; CI, confidence interval; NS, not significant, LOS, length of stay; REF, reference group.
(1) Continuous variables compared with Wilcoxon rank sums tests. Categorical variables were compared with Pearson's χ^2 or Fisher's Exact, and *post hoc* multiple comparisons were performed when the primary comparison was significant (see Methods).
(2) Comparison of age medians, survivors vs. deaths.
(3) Comparison of sex distributions, survivors vs. deaths.
(4) Comparison of race and ethnicity distributions, survivors vs. deaths.
(5) Comparison of hospital LOS medians, survivors vs. deaths.
(6) Comparison of transplant type distributions, survivors vs. deaths.
(7) Comparison of transplant indication distributions, survivors vs. deaths. Malignant hematologic subgroup served as reference group for *post hoc* multiple comparisons. See Supplementary Appendix for individual diagnoses included in each transplant indication subgroup.

increase in vasoactive agent infusions from 20% to 28% [$p = 0.05$, OR 1.54 (1.00–2.37)] and a decrease in the use of PPV from 14% to 9% [$p = 0.07$, OR 0.59 (0.33–1.05)].

The results of the multivariable logistic regression investigating the effect of time period on hospital survival, controlled for HSCT type, indication, GVHD, infectious complications and ICU therapies, are shown in **Table 4** (Online). The adjusted OR for survival in the late time period relative to the early time period was 4.44 [1.43–13.77] ($p < 0.01$). ICU therapies were associated with decreased survival on multivariate analysis including PPV [$p < 0.01$, adjusted OR 0.07 (0.02–0.19)], vasoactive infusion [$p < 0.01$, adjusted OR 0.08 (0.03–0.24)], and dialysis [$p = 0.01$, adjusted OR 0.12 (0.02–0.68)].

Discussion

We observed a 93% survival after hospital admission for pediatric HSCT in a large multicenter sample in the United States from 2009 to 2018. Survival was 89% for allogeneic HSCT and 98% for autologous HSCT. Clinical variables associated with decreased survival included allogeneic HSCT, complications of GVHD and infection, and indicators of severity of illness post-HSCT including ICU therapies of PPV, vasoactive agent infusion and dialysis. Survival significantly improved from 89% (2009–2013) to 96% (2014–2018); in particular allogeneic HSCT survival improved (82%–94%) while autologous HSCT survival remained unchanged. Survival improvement was accompanied by decreasing infectious complications and increasing vasoactive agent use over time. After adjusting for HSCT variables, HSCT complications, and ICU therapies in a multivariable regression, time period was a significant predictor of survival ($p < 0.01$) with an adjusted OR of 4.44 [1.43–13.77].

Early treatment-related mortality, often standardized to 100 days following HSCT, is generally attributable to organ toxicity from the transplant conditioning regimen, infection during the period of immunosuppression, and GVHD, as opposed to relapse-related mortality which generally occurs later post-transplant. Since there is no risk of GVHD for autologous HSCT, there is no need for prophylactic immunosuppression with decreased risk of infection as a result (21). Mortality at 100 days is as high as 11% for allogenic HSCT and 4% for autologous HSCT (1, 3, 5) which has improved over time (3, 5, 13–16). We observed 11% and 2% hospital mortality for allogeneic and autologous HSCT respectively at median hospital day 85 [63–116]. Because these data were acquired from a multi-institutional database, we used HSCT admission hospital survival as a proxy for early (100-day) treatment-related mortality.

These findings support the trends of decreasing HSCT complications and improving survival noted over the last several

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TABLE 2 Hematopoietic stem cell transplant complications and ICU therapies and their association with survival.

	N (%) (Total $n = 473$)	Survival (%)	p (1)	OR of Survival [95% CI]
Complication				
GVHD (2)	96 (33)	80 (83)	0.02	0.41 [0.19–0.87]
No GVHD	197 (67)	182 (92)		
Any infectious complication	125 (26)	106 (85)	<0.01	0.27 [0.13–0.54]
No infectious complication	348 (74)	332 (95)		
Blood culture positive	87 (18)	71 (82)	<0.01	0.23 [0.11–0.47]
No blood culture positive	386 (82)	367 (95)		
Respiratory culture positive	30 (6)	19 (63)	<0.01	0.10 [0.04–0.23]
No respiratory culture positive	443 (94)	419 (95)		
Urine culture positive	39 (8)	33 (85)	0.05	0.39 [0.15–1.02]
No urine culture positive	434 (92)	405 (93)		
Skin/soft tissue culture positive	10 (2)	8 (80)	0.16	0.31 [0.06–1.50]
No skin/soft tissue culture positive	463 (98)	430 (93)		
Other culture positive	11 (2)	9 (82)	0.19	0.35 [0.07–1.67]
No other culture positive	462 (98)	429 (93)		
GVHD plus infectious complication (3)	39 (27)	29 (74)	0.08	0.45 [0.18–1.11]
GVHD or infection alone	105 (73)	91 (87)		
ICU Therapies				
Any ICU Therapy	143 (30)	111 (78)	<0.01	0.03 [0.01–0.11]
No ICU Therapy	330 (70)	327 (99)		
PPV (4)	53 (11)	28 (53)	<0.01	0.03 [0.01–0.06]
No PPV	420 (89)	410 (98)		
Vasoactive infusion (5)	116 (25)	91 (78)	<0.01	0.10 [0.05–0.23]
No vasoactive infusion	357 (75)	347 (97)		
Dialysis (6)	16 (3)	6 (38)	<0.01	0.03 [0.01–0.10]
No Dialysis	457 (97)	432 (95)		
Number of ICU Therapies			<0.01	
1 ICU Therapy (7)	109 (76)	99 (91)	REF	1
2 ICU Therapies	27 (19)	11 (41)	<0.01	0.07 [0.03–0.19]
3 ICU Therapies	7 (5)	1 (14)	<0.01	0.02 [0.002–0.15]

ICU, intensive care unit; OR: odds ratio; CI, confidence interval; GVHD, graft-versus-host-disease; PPV, positive pressure ventilation.
(1) Categorical variables were compared with Pearson's χ^2 or Fisher's Exact.
(2) Reported as percent of allogeneic transplants (total $n = 293$).
(3) For allogeneic transplant recipients, those with both GVHD and infectious complication were compared to those with GVHD or infectious complication alone (total $n = 144$).
(4) PPV includes invasive and non-invasive modalities.
(5) Vasoactive infusions include epinephrine, norepinephrine, dopamine, dobutamine, milrinone, and/or vasopressin.
(6) Dialysis includes hemodialysis, peritoneal dialysis, urinary filtration and related procedures (see Supplementary Methods and Appendix).
(7) For patients receiving ICU therapies ($n = 143$), receipt of 1, 2, or 3 therapies were compared.

decades (3–5, 13, 14, 16, 17, 22–25). Outcome improvement over time is presumably related, in part, to advancements in HSCT care including reduced intensity conditioning (3, 5, 15, 24, 26) higher resolution human leukocyte antigen-matching (18, 27, 28), expanded agents for bacterial, viral and fungal prophylaxis and treatment, enhanced detection of infection (29–36), and novel GVHD prophylaxis and treatment strategies (14, 24, 37–42). In particular, we identified that infectious complications were significantly reduced over time which was temporally associated with improving survival over time. However, infectious complications were still frequent and were associated with decreased survival, with the worst survival seen for respiratory infections (63%). Respiratory infections have a high mortality in HSCT patients (43, 44) and both animal and human data suggest defects in the pulmonary immune response following HSCT may be contributing (45).

A total of 17%–35% of children require ICU care following HSCT (9–12) and outcomes for post-HSCT ICU patients have improved over time in parallel with HSCT survival (46, 47). For instance, survival of mechanically ventilated HSCT patients has steadily increased from 9%–14% in the 1970–1980s (48–50), to 12%–47% in the 1980–1990s (51–54), and to 18%–58% in the 1990s to early 2000s (6, 10, 17, 47, 55, 56) with current estimates of 39%–58% survival (8, 9, 11, 57–60). In our 2009–2018 cohort, 30% of patients received at least one ICU therapy in the immediate post-HSCT period. Survival was 53% for patients receiving PPV, 78% for patients receiving at least one vasoactive agent infusion, and 38% for patients receiving dialysis, comparable to other recent studies (8, 9, 57, 58). We also found that survival decreased with an increasing number of ICU therapies received: 91% of patients receiving only one therapy survived, while 41% of those receiving two therapies survived, and 14% of those receiving all three therapies survived.

Our observation that increased vasoactive agent use was temporally associated with improvement in survival is novel and may represent a practice shift towards more liberal vasoactive

TABLE 3 Trends over time in hematopoietic stem cell transplant indications, complications, intensive care unit therapies and outcomes.

	Early Time Period (2009–2013) (*n* = 204)	Late Time Period (2014–2018) (*n* = 269)	*p* (1)	Odds Ratio [95% CI]
Demographics				
Age, median [25%ile–75%ile], years	7 [3–15]	8 [3–14]	0.73	
Male (*n*, column %)	116 (57)	168 (62)	0.22	0.79 [0.55–1.15]
Female (*n*, column %)	88 (43)	101 (38)		
Transplant type				
Allogeneic (*n*, column %)	119 (58)	174 (65)	0.16 (2)	0.76 [0.53–1.11]
Autologous (*n*, column %)	85 (42)	95 (35)		
Hospital outcome				
Overall				
Survivors (*n*, column %)	181 (89)	257 (96)	<0.01 (3)	2.72 [1.32–5.61]
Deaths (*n*, column %)	23 (11)	12 (4)		
Allogeneic				
Survivors (*n*, %allogeneic/column)	98 (82)	164 (94)	<0.01 (4)	3.51 [1.59–7.77]
Deaths (*n*, %allogeneic/column)	21 (18)	10 (6)		
Autologous				
Survivors (*n*, % autologous/column)	83 (98)	93 (98)	1.00 (5)	1.12 [0.15–8.13]
Deaths (*n*, % autologous/column)	2 (2)	2 (2)		
Hospital LOS, median [25%ile–75%ile], days	31 [23–47]	33 [24–48]	0.47	
Transplant Indication (6)			0.10	
Malignant Hematologic (*n*, column %)	83 (41)	138 (51)		
Solid tumor (*n*, column %)	76 (37)	81 (30)		
Non-malignant Hematologic (*n*, column %)	29 (14)	35 (13)		
Immunodeficiency (*n*, column %)	9 (4)	12 (4)		
Non-malignant other (*n*, column %)	7 (3)	3 (1)		
Transplant Complication				
GVHD (*n*, %allogeneic transplant/column) (7)	39 (33)	57 (33)	1.00	1.00 [0.61–1.64]
No GVHD (*n*, %allogeneic transplant/column) (7)	80 (67)	117 (67)		
Any infectious complication (*n*, column %)	68 (33)	57 (21)	<0.01	0.54 [0.36–0.81]
No Infectious complication (*n*, column %)	136 (67)	212 (79)		
ICU Therapies				
Any ICU Therapy (*n*, column %)	58 (28)	85 (32)	0.46	0.16 [0.78–1.73]
No ICU Therapy (*n*, column %)	146 (72)	184 (68)		
PPV (*n*, column %)	29 (14)	24 (9)	0.07	0.59 [0.33–1.05]
No PPV (*n*, column %)	175 (86)	245 (91)		
Dialysis (*n*, column %)	8 (4)	8 (3)	0.57	0.75 [0.28–2.04]
No Dialysis (*n*, column %)	196 (96)	261 (97)		
Vasoactive infusion (*n*, column %)	41 (20)	75 (28)	0.05	1.54 [1.00–2.37]
No Vasoactive infusion (*n*, column %)	163 (80)	194 (72)		

CI, confidence interval; NS, not significant; LOS, length of stay; GVHD, graft-versus-host-disease; ICU, intensive care unit; PPV, positive pressure ventilation.
(1) Variable distributions in the early versus late time periods were compared. Continuous variables were compared with Wilcoxon rank sums tests, and categorical variables were compared with Pearson's χ^2 or Fisher's Exact.
(2) Comparison of transplant type distribution (allogeneic/autologous), early vs. late time periods.
(3) Comparison of survival distribution for all transplant types, early vs. late time periods.
(4) Comparison of survival distribution for allogeneic transplants, early vs. late time periods.
(5) Comparison of survival distribution for autologous transplants, early vs. late time periods.
(6) See Supplementary Appendix for individual diagnoses included in each transplant indication subgroup.
(7) GVHD reported as percent of allogeneic transplants (total *n* = 293).

use. Emphasis on early recognition of sepsis with prompt initiation of vasoactive treatments, including peripheral delivery (a modification to guidelines in 2007) (61), may have contributed to increasing use and be partly responsible for this observation. This finding may also relate to the potential harmful effects of fluid overload post-HSCT and recommendations for conservative fluid management (62–66) which could have influenced increasing use of vasoactive agent infusions. Additionally, we observed a trend towards decreasing use of PPV over time during the study period. Decreasing use of mechanical ventilation in this population has been previously reported (17, 67) in conjunction with improving survival. Decreasing infections (that may manifest as deterioration requiring PPV) may be contributing. The impact of non-invasive PPV use on this trend is unclear. In our cohort,

TABLE 4 Hematopoietic stem cell transplant variables including transplant time period and their association with survival: A multivariable logistic regression.

Variable	*p*	aOR Survival (95% CI)
PPV	<0.01	0.07 [0.02–0.19]
Vasoactive infusion	<0.01	0.08 [0.03–0.24]
Time period (2014–2018)	<0.01	4.44 [1.43–13.77]
Dialysis	0.01	0.12 [0.02–0.68]
Transplant type/GVHD		
Autologous transplant	REF	1
Allogeneic transplant without GVHD	0.61	0.41 [0.01–12.71]
Allogeneic transplant with GVHD	0.36	0.19 [0.01–6.51]
Infectious Complication	0.56	0.72 [0.24–2.15]
Transplant Indication		
Malignant Hematologic	REF	1
Solid tumor	0.84	0.70 [0.02–22.21]
Non-malignant Hematologic	0.50	0.60 [0.14–2.61]
Immunodeficiency	0.61	1.60 [0.26–10.00]
Non-malignant other	0.43	2.99 [0.20–45.37]

aOR, adjusted odds ratio; CI, confidence interval; PPV, positive pressure ventilation; GVHD, graft-versus-host-disease; REF, reference group.

only 3 patients received only non-invasive PPV, limiting our inferences on the overall PPV trend.

There are limitations to this study. First, national databases, while providing large samples from multiple sites, usually lack the granularity present in single site data. Therefore, some important HSCT variables could not be analyzed, including donor source, matching, and conditioning regimen. Second, our use of positive culture results as evidence of infectious complications did not include clinical corroboration and presumably missed culture-negative infections or mis-assigned instances of contamination. Third, respiratory cultures may be more likely sent for mechanically ventilated patients, contributing to the low survival seen in this group. Fourth, while we were able to assess ICU therapies (PPV, vasoactive agent infusion, dialysis), we were not able to assess other details of ICU care such as admission and discharge dates, indications for admission or therapies, or other measures of severity of illness. Comorbid diagnoses and some therapies were deduced from diagnosis and procedure codes, potentially missing those that were not coded/billed. For example, the specific diagnostic code for hepatic veno-occlusive disease was introduced in 2015 and therefore was not assessed in this study. Finally, we could not ascertain cause of death or outcome after discharge (including 100-day mortality for survivors discharged before 100 days).

Conclusion

Hospital survival following HSCT was 93% in a recent multicenter national sample from 2009 to 2018. Factors associated with decreased survival included allogeneic HSCT, GVHD, infectious complications and ICU therapies. Survival significantly improved over time, from 89% to 96%, particularly for allogeneic HSCT. In addition, improving survival was associated with decreasing infectious complications and increasing vasoactive agent use.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

TO, AP, BD, and MP contributed to the study design, methodology, data curation, and formal analysis. TO and MP contributed to drafting of the initial manuscript. TO, AP, BD, and MP contributed to reviewing and editing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1247792/full#supplementary-material

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Intrapulmonary administration of recombinant activated factor VII in pediatric, adolescent, and young adult oncology and hematopoietic cell transplant patients with pulmonary hemorrhage

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Introduction: Diffuse alveolar hemorrhage (DAH) is a devastating disease process with 50-100% mortality in oncology and hematopoietic cell transplant (HCT) recipients. High concentrations of tissue factors have been demonstrated in the alveolar wall in acute respiratory distress syndrome and DAH, along with elevated levels of tissue factor pathway inhibitors. Activated recombinant factor VII (rFVIIa) activates the tissue factor pathway, successfully overcoming the tissue factor pathway inhibitor (TFPI) inhibition of activation of Factor X. Intrapulmonary administration (IP) of rFVIIa in DAH is described in small case series with successful hemostasis and minimal complications.

Methods: We completed a single center retrospective descriptive study of treatment with rFVIIa and outcomes in pediatric oncology and HCT patients with pulmonary hemorrhage at a quaternary hematology/oncology hospital between 2011 and 2019. We aimed to assess the safety and survival of patients with pulmonary hemorrhage who received of IP rFVIIa.

Results: We identified 31 patients with pulmonary hemorrhage requiring ICU care. Thirteen patients received intrapulmonary rFVIIa, while eighteen patients did not. Overall, 13 of 31 patients (41.9%) survived ICU discharge. ICU survival (n=6) amongst those in the IP rFVIIa group was 46.2% compared to 38.9% (n=7) in those who did not receive IP therapy (p=0.69). Hospital survival was 46.2% in the

IP group and 27.8% in the non-IP group (p=0.45). There were no adverse events noted from use of IP FVIIa.

Conclusions: Intrapulmonary rFVIIa can be safely administered in pediatric oncology patients with pulmonary hemorrhage and should be considered a viable treatment option for these patients.

KEYWORDS

pulmonary hemorrhage, diffuse alveolar hemorrhage (DAH), hematopoietic cell transplant (HCT), recombinant factor VIIa, pediatric oncologic emergencies, critical care

Introduction

Pulmonary hemorrhage, specifically, diffuse alveolar hemorrhage (DAH), is a devastating disease process with 50-100% mortality in oncology and hematopoietic cell transplant (HCT) recipients. It is characterized by a pattern of clinical and radiological findings including hypoxemic respiratory failure, anemia, hemoptysis, diffuse interstitial infiltrates on chest radiography, and progressively bloody return on bronchoalveolar lavage (1–4). The pathogenesis, while not fully elucidated, is thought to occur from direct lung injury of varying etiologies, leading to alveolar inflammation, dysregulated cytokine release, and subsequent widespread injury to the alveolar-capillary basement membrane (1, 2, 5). Pulmonary inflammation causes increased intra-alveolar expression of tissue factor (TF) with high concentrations detected in the alveolar wall in patients with acute respiratory distress syndrome (ARDS), pneumonia, and DAH. Tissue factor pathway inhibitors (TFPIs) also increase significantly. TFPIs prevent binding of activated Factor VII (FVIIa) and TF, ultimately preventing Factor X activation and downstream activation of fibrin to achieve hemostasis. This phenomenon offers a hypothesis for increased risk of bleeding in the inflamed lung as well as rationale for local administration of hemostatic agents (6–8). In addition to overcoming the TFPI, Factor VIIa is useful in patients who lack abnormalities on traditional coagulation studies. Factor VIIa not only directly activates Factor X, but it also increases thrombin production on the surface of activated platelets without the need of VIII and IX, and even in the face of in thrombocytopenia (9–13).

As DAH in oncology and HCT patients is thought to be propagated from dysregulated inflammation, glucocorticoids have been the mainstay of therapy, though its use has not resulted in significantly improved outcomes (2, 4, 14–16). Novel administration of hemostatic agents, such as inhaled tranexamic acid (TXA) and activated recombinant factor VII (rFVIIa), in oncology and post-HCT DAH has yielded promising preliminary outcomes in few adult and pediatric case reports and case series (7, 8, 17–23). These potentially promising results prompted the recent incorporation of these agents into our clinical practice for patients at very high risk of death. We present a retrospective review of patients over 8 years during which our treatment practice has evolved. We hypothesized that the use of intrapulmonary rFVIIa would be safe and improve survival.

Abbreviations: DAH, Diffuse Alveolar Hemorrhage; rFVIIa, Recombinant Factor VIIa; HCT, Hematopoietic cell transplant; ARDS, Acute respiratory distress syndrome; IP, intrapulmonary; TF, Tissue factor; TFPI, Tissue factor pathway inhibitors; TXA, Tranexamic acid.

Methods

We completed a single-center, retrospective descriptive study of treatment regimens and outcomes in pediatric, adolescent, and young adult oncology and HCT patients diagnosed with pulmonary hemorrhage, including DAH, at a quaternary pediatric hematology/oncology hospital (St. Jude Children's Research Hospital, Memphis, TN, USA) between August 2011 and December 2019. The study underwent expedited review approval by the local Institutional Review Board. Patients were identified by ICU admission log diagnoses and electronic medical record survey of codes for pulmonary hemorrhage and diffuse alveolar hemorrhage. Treatment regimens were extracted from the medical record including date, time, route of administration, and dose of rFVIIa as well as additional adjuvant therapies with steroids, immunomodulators and inhaled TXA. Dose routes were characterized as intravenous (IV) or intrapulmonary. Intrapulmonary was defined as nebulized, direct instillation via ETT with or without bronchoscopy. Demographic and outcome data were collected including primary diagnosis, history, and type of HCT, ventilator free days, ICU and hospital length of stay, platelet counts and coagulation panels at onset of hemorrhage. We also collected safety data including need for reintubation for endotracheal tube obstruction from thrombosis or secretions. The primary outcome was defined as survival to ICU discharge.

Drug preparation and administration

Activated human recombinant factor VII (rFVIIa) solutions were aseptically prepared by the inpatient pharmacy and dispensed to the ICU. For direct intrapulmonary administration during

bronchoscopy procedures patients received rFVIIa 50mcg/kg/dose (rounded to nearest vial size). As previously described, the dose was diluted with 25-50 ml of sterile 0.9% sodium chloride solution and divided into 5 aliquots of approximately 5-10 ml to facilitate ease of administration into the five lobes of the lung (7, 18). For nebulization, rFVIIa 50-75 mcg/kg/dose (rounded to nearest vial size) was prepared in 3-5 ml of sterile 0.9% sodium chloride and administered at varying frequency from every 6 hours to once daily at the discretion of the prescribing physician. The Aerogen Solo™ vibrating mesh nebulizer was placed inline before the humidifier on the inspiratory side of the ventilator circuit. After encountering problems with ventilator malfunction during inhaled TXA delivery in prior patients, the following procedure was implemented. Despite nebulized delivery of rFVIIa not reported to have the same effects as TXA on the ventilator circuit, to ensure safe delivery, we employed the following precautions with administration of all inhaled agents including rFVIIa. Two Maquet Servo Duo guard filters were placed on the expiratory limb of the ventilator circuit and exchanged immediately upon completion of medication delivery (Supplementary Figure 1A). A one-way valve was placed between the nebulizer and inspiratory outlet to protect the inspiratory arm of the ventilator circuit. (Supplementary Figure 1B)

Statistical methods

All coding and data analyses were done using SAS version 9.4 or R version 4.3.2. Continuous variables were summarized as number, mean (standard deviation [SD]), and median (range). The Shapiro-Wilk's test was used to test for normality within groups, and group comparisons were made using either a Wilcoxon Rank Sum Test or two-sample t-test, as appropriate. Categorical variables were summarized as count and percent, and group comparisons were made using either Pearson's chi-square test or Fisher's exact test. Kaplan-Meier and exact log-rank tests were used to compare PICU and hospital survival of those treated and not treated with IP rFVIIa.

Results

Over the eight-year retrospective period, we identified 31 patients with pulmonary hemorrhage requiring ICU care (Table 1). Of the 31 patients, thirteen patients received intrapulmonary IP rFVIIa treatment. Eighteen patients did not receive IP rFVIIa. There were no identified systemic thrombotic events and no obstructed endotracheal tubes requiring exchange in the cohort.

Pulmonary hemorrhage was diagnosed by bronchoalveolar lavage in 18 (58.1%) patients and clinically in the remaining patients (defined as hemoptysis, blood visualized from vocal cords on direct laryngoscopy during intubation, bloody secretions from endotracheal tube with diffuse patchy infiltrates on chest radiographic findings and/or hypoxemic respiratory failure).

Overall, 13 of 31 (41.9%) survived to ICU discharge and 11 patients (35.5%) survived to hospital discharge. Severity of illness was evaluated by oxygenation index (OI) or oxygenation saturation index (OSI) when arterial blood gas was not available for OI calculation. The mean OI and OSI in the overall cohort were 32 (SD 18.7) and 17.7 (SD 12.1) respectively. Amongst ICU survivors, the mean OI was 23.4 (SD 29.4) compared to 37.4 (SD 14.5) in non-ICU survivors (p=0.82) and mean OSI was 15.8 (SD 9.6) versus a mean OSI of 19.1 (SD 13.9) in non-survivors (p=0.73). Mean platelet count at time of hemorrhage was 98,000/mm3 (SD 55,400/mm3), with a median of 81,000/mm3 (range 26,000-230,000/mm3) and did not differ significantly between ICU survivors and non-survivors (p=0.15). Mean prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen was 17.5 seconds, 38.1 seconds, 1.6 and 374 mg/dL respectively. Ventilator free days was significantly higher in ICU survivors with a mean of 13.1days (SD 10.2) compared to zero days in non-survivors (p=<0.001). PICU length of stay did not differ significantly (Table 1).

Thirteen patients received intrapulmonary rFVIIa, and eighteen patients did not receive IP treatment. Patient characteristics by ICU survival for each treatment group, IP rFVIIa and no IP FVIIa are shown in Tables 2, 3, respectively. Of the 13 patients treated with IP rFVIIa, 6 (46%) survived both ICU and hospital discharge. There was no significant difference in PICU survival between patients treated and not treated with IP-rFVIIa (p=0.1) (Figure 1A); however, patients who received IP rFVIIa had lower hospital mortality than patients who were not treated with IP rFVIIa (p=0.029) (Figure 1B).

As we began to implement the use of inhaled TXA clinically after the initiation of study period, a *post hoc* analysis was completed of the patients who received therapy with inhaled TXA. Five patients received inhaled TXA three of whom also received inhaled rFVIIa. All survived to ICU discharge and 80% (n= 4) survived to hospital discharge. There were no adverse events in this group either.

Discussion

Pulmonary hemorrhage, specifically diffuse alveolar hemorrhage, is a well-recognized pulmonary complication of hematopoietic cell transplantation, occurring in approximately 5% of post-transplant patients (4, 14). It has also been described in the setting of acute myelogenous leukemia (24). Its exact pathogenesis has not been well elucidated but is thought to be from a direct injury to the lung parenchyma followed by a combination of alveolar inflammation and dysregulated cytokine release leading to further damage of the alveolar-capillary membrane (3). The initial lung injury may be secondary to various factors, such as conditioning agents, occult infection, transplant-associated thrombotic microangiopathy, graft-versus-host disease, or idiopathic pneumonia syndrome (3, 15, 25). In patients with acute myelogenous leukemia, this lung injury results from lysis of leukemic cells, which release lysozymes and other enzymes into the circulation (26).

The pathogenesis of DAH is thought to be inflammation-mediated. Therefore, glucocorticoids have historically been the mainstay of therapy, along with other supportive measures such as mechanical ventilation, transfusion of blood products, treatment of

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TABLE 1 Entire Cohort (N=31) by PICU Survival.

Variable	Total (n=31)	Survived ICU (n=13)	Died ICU (n=18)	P Value
Age, years				0.475
Mean (SD)	9.6 (6.8)	10.7 (6.9)	8.9 (6.9)	.
Median (Range)	10.0 (0.8~23.0)	12.0 (0.8~20.0)	9.5 (0.8~23.0)	.
Gender				0.409
Female	17 (54.8%)	6 (46.2%)	11 (61.1%)	.
Male	14 (45.2%)	7 (53.8%)	7 (38.9%)	.
Diagnosis Pulmonary Hemorrhage				0.284
BAL	18 (58.1%)	9 (69.2%)	9 (50.0%)	.
Clinical	13 (41.9%)	4 (30.8%)	9 (50.0%)	.
Primary Dx				0.288
Brain tumor	1 (3.2%)	1 (7.7%)		.
Non-malignant hematologic disorder	3 (9.7%)	1 (7.7%)	2 (11.1%)	.
Leukemia	21 (67.7%)	7 (53.8%)	14 (77.8%)	.
Lymphoma	1 (3.2%)		1 (5.6%)	.
Primary HLH	1 (3.2%)	1 (7.7%)		.
Solid tumor	4 (12.9%)	3 (23.1%)	1 (5.6%)	.
Post HCT				0.111
No	4 (12.9%)	2 (15.4%)	2 (11.1%)	.
Autologous	3 (9.7%)	3 (23.1%)		.
MSD	1 (3.2%)	1 (7.7%)		.
MUD	8 (25.8%)	3 (23.1%)	5 (27.8%)	.
Haploidentical	15 (48.4%)	4 (30.8%)	11 (61.1%)	.
IP rFVIIa				0.686
No	18 (58.1%)	7 (53.8%)	11 (61.1%)	.
Yes	13 (41.9%)	6 (46.2%)	7 (38.9%)	.
Vent-free days				<.001
Mean (SD)	5.5 (9.2)	13.1 (10.2)	0 (0)	.
Median (Range)	0 (0~25)	17 (0~25)	0 (0~0)	.
PICU LOS, days				0.795
Mean (SD)	41.9 (50.3)	48.3 (71.4)	37.2 (28.4)	.
Median (Range)	25 (1~262)	19 (3~262)	41.5 (1~93)	.
Hospital LOS, days				0.471
Mean (SD)	65.9 (63.8)	73.1 (90.1)	60.8 (37.3)	.
Median (Range)	46 (3~333)	37 (3~333)	61.5 (4~138)	.
OSI, pre				0.733
N	23	10	13	.
Mean (SD)	17.7 (12.1)	15.8 (9.6)	19.1 (13.9)	.
Median (Range)	12.7 (4.5~58.8)	13.7 (4.5~38.8)	12.6 (5.6~58.8)	.

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TABLE 1 Continued

Variable	Total (n=31)	Survived ICU (n=13)	Died ICU (n=18)	P Value
OI pre				0.817
N	6	2	4	.
Mean (SD)	32.7 (18.7)	23.4 (29.4)	37.4 (14.5)	.
Median (Range)	30.8 (2.6~59.0)	23.4 (2.6~44.2)	30.8 (29.0~59.0)	.
PLT count				0.150
N	29	11	18	.
Mean (SD)	98.3 (55.4)	113.0 (55.1)	89.3 (55.3)	.
Median (Range)	81 (26~230)	103 (41~230)	76 (26~215)	.
PT				0.810
Mean (SD)	17.6 (4.0)	17.5 (3.8)	17.8 (4.2)	.
Median (Range)	16.6 (13.0~27.3)	17.1 (13.2~24.9)	16.0 (13.0~27.3)	.
INR				0.840
N	29	11	18	.
Mean (SD)	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)	.
Median (Range)	1.4 (1.0~2.8)	1.5 (1.0~2.3)	1.4 (1.1~2.8)	.
PTT				0.619
N	28	11	17	.
Mean (SD)	38.1 (11.5)	36.8 (10.4)	39.0 (12.4)	.
Median (Range)	35.6 (22.7~64.7)	35.5 (24.3~57.5)	36.1 (22.7~64.7)	.
Fibrinogen				0.997
N	28	10	18	.
Mean (SD)	374.1 (170.3)	374.0 (127.8)	374.2 (193.5)	.
Median (Range)	369 (67~722)	399 (96~531)	338 (67~722)	.

ICU, intensive care unit; HCT, hematopoietic cell transplant; auto, autologous; haplo, haploidentical; MSD, matched sibling donor; MUD, matched unrelated donor; BAL, bronchoalveolar lavage; OSI, oxygenation saturation index; OI, oxygenation index; SD, standard deviation; LOS, length of stay; Vent, ventilator; PLT, platelet; PT, prothrombin time; PTT, partial thromboplastin time; INR, internationalized standard ratio.

TABLE 2 PICU Survival for Patients Treated with Intrapulmonary FVIIa.

Variable	Total (n=13)	Survived ICU (n=6)	Died ICU (n=7)	P Value
Age, years				0.603
N	13	6	7	.
Mean (SD)	9.4 (7.5)	8.1 (7.5)	10.4 (7.9)	.
Median (Range)	9.0 (0.8~23.0)	5.0 (0.8~18.0)	10.0 (1.0~23.0)	.
Gender				1.000
Female	5 (38.5%)	2 (33.3%)	3 (42.9%)	.
Male	8 (61.5%)	4 (66.7%)	4 (57.1%)	.
Primary Diagnosis				1.000

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TABLE 2 Continued

Variable	Total (n=13)	Survived ICU (n=6)	Died ICU (n=7)	P Value
Non-malignant Hematologic disorder	2 (15.4%)	1 (16.7%)	1 (14.3%)	.
Leukemia	7 (53.8%)	3 (50.0%)	4 (57.1%)	.
Lymphoma	1 (7.7%)		1 (14.3%)	.
Solid tumor	3 (23.1%)	2 (33.3%)	1 (14.3%)	.
HCT source				0.125
No	1 (7.7%)	1 (16.7%)		.
Autologous	2 (15.4%)	2 (33.3%)		.
MSD	1 (7.7%)	1 (16.7%)		.
MUD	3 (23.1%)	1 (16.7%)	2 (28.6%)	.
Haploidentical	6 (46.2%)	1 (16.7%)	5 (71.4%)	.
Diagnosis Pulmonary Hemorrhage				0.103
BAL	7 (53.8%)	5 (83.3%)	2 (28.6%)	.
Clinical	6 (46.2%)	1 (16.7%)	5 (71.4%)	.
OSI, pre				0.219
N	11	5	6	.
Mean (SD)	17.2 (6.7)	14.4 (4.2)	19.6 (7.8)	.
Median (Range)	17.5 (8.2~29.6)	14.7 (8.2~19.0)	20.4 (9.0~29.6)	.
OI, pre				NA
N	2	1	1	.
Mean (SD)	44.6 (0.6)	44.2 (.)	45.0 (.)	.
Median (Range)	44.6 (44.2~45.0)	44.2 (44.2~44.2)	45.0 (45.0~45.0)	.
PICU LOS, days				0.306
N	13	6	7	.
Mean (SD)	62.5 (67.3)	86.5 (94.0)	42.0 (25.3)	.
Median (Range)	47 (3~262)	66.5 (8~262)	47 (3~74)	.
Hospital LOS, days				0.464
N	13	6	7	.
Mean (SD)	92.7 (86.2)	114.5 (120.6)	74 (43)	.
Median (Range)	67 (13~333)	75 (13~333)	67 (17~138)	.
Vent free days				0.053
N	13	6	7	.
Mean (SD)	4.7 (9.0)	10.2 (11.4)	0.0 (0.0)	.
Median (Range)	0.0 (0.0~24.0)	8.5 (0.0~24.0)	0.0 (0.0~0.0)	.
PLT count				0.561
N	13	6	7	.
Mean (SD)	64.5 (32.3)	70.5 (42.5)	59.4 (22.7)	.
Median (Range)	56 (30~130)	52 (30~130)	74 (31~84)	.

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TABLE 2 Continued

Variable	Total (n=13)	Survived ICU (n=6)	Died ICU (n=7)	P Value
PT				0.287
N	13	6	7	.
Mean (SD)	17.7 (4.7)	16.1 (3.4)	19.0 (5.4)	.
Median (Range)	15.4 (13.2~27.3)	15.0 (13.2~22.0)	15.4 (14.1~27.3)	.
PTT				0.695
N	13	6	7	.
Mean (SD)	36.1 (12.1)	34.6 (9.0)	37.4 (14.8)	.
Median (Range)	33.4 (22.7~60.0)	34.5 (24.3~50.6)	31.7 (22.7~60.0)	.
INR				0.277
N	13	6	7	.
Mean (SD)	1.5 (0.6)	1.4 (0.4)	1.7 (0.6)	.
Median (Range)	1.3 (1.0~2.8)	1.2 (1.0~2.1)	1.3 (1.2~2.8)	.
Fibrinogen				0.667
N	13	6	7	.
Mean (SD)	367.0 (136.0)	385.7 (95.9)	351.0 (169.3)	.
Median (Range)	358 (197~694)	395.5 (249~531)	309 (197~694)	.

ICU, intensive care unit; HCT, hematopoietic cell transplant; auto, autologous; haplo, haploidentical; MSD, matched sibling donor; MUD, matched unrelated donor; BAL, bronchoalveolar lavage; OSI, oxygenation saturation index; OI, oxygenation index; SD, standard deviation; LOS, length of stay; Vent, ventilator; PLT, platelet; PT, prothrombin time; PTT, partial thromboplastin time; INR, internationalized standard ratio.

TABLE 3 PICU Survival for Patients Not Treated with Intrapulmonary FVIIa.

Variable	Total (n=18)	Survived ICU (n=7)	Died ICU (n=11)	P Value
Age (years)				0.196
N	18	7	11	.
Mean (SD)	10.4 (6.3)	12.9 (6.1)	8.9 (6.1)	.
Median (Range)	11.5 (0.8~20.0)	13.0 (1.0~20.0	10.0 (0.8~19.0	.
Gender				0.627
Female	12 (66.7%)	4 (57.1%)	8 (72.7%)	.
Male	6 (33.3%)	3 (42.9%)	3 (27.3%)	.
Primary Diagnosis				0.137
Brain tumor	1 (5.6%)	1 (14.3%)		.
Non-malignant Hematologic disorder	1 (5.6%)		1 (9.1%)	.
Leukemia	14 (77.8%)	4 (57.1%)	10 (90.9%)	.
Primary HLH	1 (5.6%)	1 (14.3%)		.
Solid tumor	1 (5.6%)	1 (14.3%)		.
Post HCT				0.881
No	3 (16.7%)	1 (14.3%)	2 (18.2%)	.
Autologous	1 (5.6%)	1 (14.3%)		.

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TABLE 3 Continued

Variable	Total (n=18)	Survived ICU (n=7)	Died ICU (n=11)	P Value
MUD	5 (27.8%)	2 (28.6%)	3 (27.3%)	.
Haploidentical	9 (50.0%)	3 (42.9%)	6 (54.5%)	.
Diagnosis Pulmonary Hemorrhage				1.000
BAL	11 (61.1%)	4 (57.1%)	7 (63.6%)	.
Clinical	7 (38.9%)	3 (42.9%)	4 (36.4%)	.
OSI, pre				1.000
N	12	5	7	.
Mean (SD)	18.2 (15.8)	17.4 (13.4)	18.7 (18.3)	.
Median (Range)	11.4 (4.5~58.8)	11.5 (4.5~38.8)	11.3 (5.6~58.8)	.
OI, pre				NA
N	4	1	3	
Mean (SD)	23.3 (13.8)	2.6 (NA)	30.2 (1.6)	
Median (Range)	29.25 (2.6, 32.0)		29.5 (29.0, 32.0)	
PICU LOS, days				0.093
N	18	7	11	.
Mean (SD)	26.9 (26.4)	15.6 (11.4)	34.2 (31.0)	.
Median (Range)	18.5 (1.0~93.0)	11.0 (3.0~36.0)	23.0 (1.0~93.0)	.
Hospital LOS, days				0.348
N	18	7	11	.
Mean (SD)	46.6 (31.6)	37.6 (30.2)	52.4 (32.5)	.
Median (Range)	34.5 (3.0~109.0)	29.0 (3.0~99.0)	46.0 (4.0~109.0)	.
Vent free days				0.004
N	18	7	11	.
Mean (SD)	6.1 (9.6)	15.6 (9.3)	0.0 (0.0)	.
Median (Range)	0.0(0.0~25.0)	19.0(3.0~25.0	0.0(0.0~0.0)	.
PLT count				0.770
N	18	7	11	.
Mean (SD)	64.3 (35.6)	68.1 (52.2)	61.8 (22.6)	.
Median (Range)	64.5 (8~130)	81 (8~130)	62 (32~112)	.
PT				0.295
N	18	7	11	.
Mean (SD)	17.4 (3.7)	18.6 (4.0)	16.7 (3.4)	.
Median (Range)	16.5 (13.0~24.9)	17.7 (14.3~24.9)	15.5 (13.0~22.5)	.
PTT				0.406
N	17	7	10	.
Mean (SD)	53.4 (26.2)	44.7 (17.0)	59.6 (30.5)	.
Median (Range)	41.2 (25.1~101.0)	41.1(27.9~76.0)	46.1 (25.1~101.0)	.
INR				0.365

(Continued)

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TABLE 3 Continued

Variable	Total (n=18)	Survived ICU (n=7)	Died ICU (n=11)	P Value
N	18	7	11	.
Mean (SD)	1.5 (0.4)	1.6 (0.5)	1.5 (0.4)	.
Median (Range)	1.4 (1.1~2.3)	1.5 (1.2~2.3)	1.3 (1.1~2.2)	.
Fibrinogen				0.934
N	17	6	11	.
Mean (SD)	351.4 (182.3)	346.2 (148.5)	354.2 (205.2)	.
Median (Range)	381 (67~646)	388.5 (96~511)	317 (67~646)	.

ICU, intensive care unit; HCT, hematopoietic cell transplant; auto, autologous; haplo, haploidentical; MSD, matched sibling donor; MUD, matched unrelated donor; BAL, bronchoalveolar lavage; OSI, oxygenation saturation index; OI, oxygenation index; SD, standard deviation; LOS, length of stay; Vent, ventilator; PLT, platelet; PT, prothrombin time; PTT, partial thromboplastin time; INR, internationalized standard ratio.

potential infections, and extracorporeal membrane oxygenation in rare cases (2–4, 14, 27). While glucocorticoids remain a foundational therapy, optimal dosing is unknown and efficacy is unclear with various publications showing conflicting data. Recently, Chopra et al. showed a survival benefit in the population of pediatric HCT patients who received steroids for management of DAH, while Schoettler et al. found steroids associated with worse survival (23, 28). Steroid use may subject this vulnerable patient population to untoward side-effects such as infection, hypertension, hyperglycemia, and myopathy (4, 14, 29, 30). Therefore, other management strategies are needed.

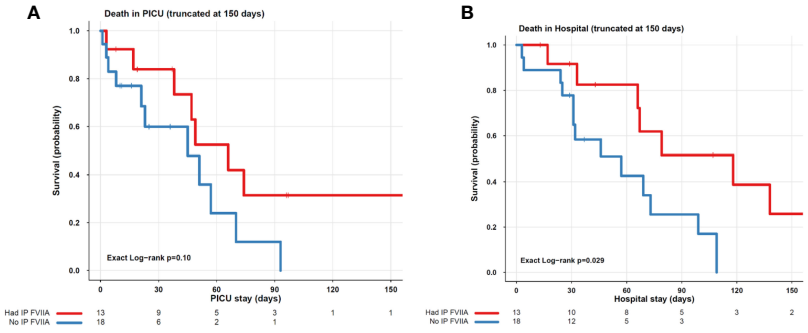
In recent years, therapies such as rFVIIa and TXA have been used as novel agents in the treatment of post-HCT DAH (17, 18, 23, 31, 32). We report on the use of rFVIIa in the treatment of pulmonary hemorrhage/DAH in the largest cohort of pediatric HCT and oncology patients published to date. We found the use of intrapulmonary rFVIIa both safe. Though not statistically significant, there was a trend towards improved ICU and hospital survival.

Severity of pulmonary illness, defined by OI and OSI at time of pulmonary hemorrhage diagnosis, did not differ significantly between ICU survivors and non-survivors. Propensity for bleeding, as evidenced by mean and median platelet counts at onset of hemorrhage also did not differ between survivors and non-survivors. Although OI may be useful in determining needs for escalating respiratory support, including high frequency oscillatory therapy and/or extracorporeal membrane oxygenation (ECMO), it may not offer insight into chance of survival. The mean and median PLT count at time of diagnosis was 98,000/mm3 and 81,000/mm3, respectively, and did not differ significantly between survivors and non-survivors.

The practice of maintaining PLT count >50,000/mm3 was insufficient to prevent bleeding as 61% (n=19) of pulmonary hemorrhages occurred with a PLT count >50,000/mm3 and furthermore, 39% (n=12) occurred with a PLT count >75,000/mm3. Therefore, normalizing the platelet count is not sufficient to manage pulmonary hemorrhage in this population.

There were no obvious safety issues noted with intrapulmonary administration of the drug. There was no evidence of worsening of oxygenation as the OI remained stable after instillation. There were no episodes of clot formation blocking endotracheal tubes and no patient required reintubation. Systemic levels of rFVIIa were not evaluated as this was not part of our routine practice.

Recombinant activated factor VIIa (rFVIIa) is an intravenous hemostatic agent indicated for the treatment of bleeding episodes



PICU = pediatric intensive care unit; IP FVIIA = intrapulmonary recombinant activated factor VII

FIGURE 1
PICU **(A)** and Hospital **(B)** Mortality for Patients Treated and Not Treated with IP FVIIa. PICU, pediatric intensive care unit; IP FVIIA, intrapulmonary recombinant activated factor VII.

and peri-operative management in patients with inherited and acquired hemophilia (33). Hemostasis is achieved by both TF-tissue factor dependent (extrinsic pathway) and independent pathways. The former occurs as rFVIIa binds to TF and activated platelets at sites of tissue injury, thus activating Factor X and Factor IX resulting in thrombin generation and successfully overcoming the TFPI inhibition of activation of factor X. In a TF- independent manner, rFVIIa directly activates Factor X on the surface of activated platelets (34). Recombinant activated factor VII was initially developed for hemophilia A/B patients who also had the presence of an inhibitor (34, 35). Its use is described in a variety of clinical scenarios, such as congenital factor VII deficiency, hepatic dysfunction, post-operative bleeding, and qualitative platelet disorders (36). More recently, nebulized use of rFVIIa has been reported in the treatment of DAH post-HCT. It is thought to promote hemostasis by overcoming an excess of tissue factor pathway inhibitors in inflamed alveoli, thereby restoring thrombin generation (17, 18, 22).

Tranexamic acid (TXA) is a potent anti-fibrinolytic agent, a derivative of the amino acid lysine, that binds to plasminogen, inhibiting its binding to fibrin and thus preventing plasmin activation and subsequent degradation of fibrin clots (37). It has been used as a preventative measure and hemostatic therapy in various clinical conditions including hemophilia, immune thrombocytopenia, trauma, and intraoperatively (38, 39) Its use in pulmonary hemorrhage has been described in a handful of adult and pediatric patients with promising hemostatic results. When administered directly into the airway, it is thought to act by enhancing the activity of remaining anti-fibrinolytic factors at sites of ongoing bleeding while decreasing the risk of adverse effects such as thromboembolic events and neurotoxicity associated with systemically administered TXA (17, 40, 41). Additionally, Schoettler, et al. demonstrated decreased non-relapse mortality with inhaled rFVIIa and inhaled TXA in a retrospective analysis of pediatric HCT patients (23). TXA was delivered by inhalation only, undiluted at either 250 mg (patients < 25 kg) or 500 mg (patients ≥ 25 kg) per dose. All aerosol solutions were delivered using the Aerogen Solo^{TM} vibrating mesh nebulizer, which was placed inline before the humidifier on the inspiratory side of the ventilator circuit. As noted, after encountering problems with ventilator malfunction during inhaled TXA delivery, two Maquet Servo Duo guard filters were placed on the expiratory limb of the ventilator circuit and exchanged immediately upon completion of medication delivery (Supplementary Figure 1A). A one-way valve was placed between the nebulizer and inspiratory outlet to protect the inspiratory arm of the ventilator circuit. (Supplementary Figure 1B). All filters and equipment were routinely inspected for proper function by the respiratory therapists.

The use of locally instilled, intrapulmonary TXA and rFVIIa for DAH post pediatric HCT was first reported by Bafaqih, et al., in 2015. They reported a series of 18 pediatric patients with post-HCT DAH who were not responsive to conventional therapies and were subsequently treated with IP TXA +/- IP rFVIIa. Of these, 16 patients (89%) achieved hemostasis and 16 patients (89%) survived to ICU discharge. Park, et al., reported a series of 6 pediatric patients with DAH post-HCT treated with intrapulmonary rFVIIa, of which all achieved hemostasis and 4 (67%) were liberated from mechanical ventilation within 7 days.

Although our study demonstrated slightly lower ICU survival rate (58.8%) in comparison to prior studies, our cohort was nearly twice as large as many of the previous reports. Furthermore, both ICU and hospital survival were greater in those who received intrapulmonary procoagulant therapy compared to those who did not. Intrapulmonary therapy with TXA and rFVIIa are components of our comprehensive approach described in Supplementary Figure 2. In addition, we institute early bronchoscopy, high mean airway pressure to tamponade alveolar bleeding, glucocorticoid therapy to control inflammation when indicated, and treatment of co-morbidities such as TA-TMA, graft versus host disease, and idiopathic pneumonia syndrome. This two-step hemostasis regimen has also enabled us to support two patients who were refractory to pharmacologic management with rescue cardiopulmonary support (ECMO) (42).

Our study has several important limitations. As a retrospective, single center study our data is limited by chart review and may be incomplete. Additionally, throughout this 8-year review, we lacked a standard treatment approach. As such, clinical practices, and use of TXA and FVIIa were varied, and individual physician decision making factors to offer inhaled treatment or not were not clearly documented to include in the analysis, thereby limiting the interpretation of our results. Furthermore, our population is limited to pediatric oncology and HCT patients, and results may not be generalizable to other populations. Despite these limitations, this study is the largest single center retrospective report of the use of intrapulmonary instillation of rFVIIa in pulmonary hemorrhage seen in oncology and HCT recipients. Our standardized approach is based upon pathophysiological reasoning. There were no safety concerns identified in our patient population and there was a trend towards improved survival. The limited number of subjects likely prevented this trend from being statistically significant as well as the selection of ICU survival as the primary outcome.

This patient population often has co-morbid diagnoses increasing mortality as well as death from underlying cancer and related therapies. Future well designed, multi-center prospective studies evaluating the use of both intrapulmonary TXA and FVIIa are warranted.

We conclude that the use of IP rFVIIa is a safe and feasible therapy in oncology and HCT-associated pulmonary hemorrhage in children. We believe these therapies can be safely used and have the potential to improve survival. They are a welcome addition to the armamentarium of therapies for managing this devastating disease process.

Conclusion

The use of IP FVIIa is both safe and feasible for the treatment of pulmonary hemorrhage in pediatric oncology and HCT patients. This safety and feasibility were also noted in an exceedingly small cohort of patients treated with inhaled TXA. Intrapulmonary administration of antifibrinolytic therapies should be considered

as a treatment option for patients with pulmonary hemorrhage. However, larger prospective studies are warranted to further evaluate the effectiveness and impact on patient outcomes of the aforementioned therapies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by St. Jude Children's Research Hospital IRB. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

CH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JM: Writing – original draft, Writing – review & editing. JG: Formal analysis, Methodology, Writing – review & editing. EH: Writing – review & editing. PB: Investigation, Resources, Writing – review & editing. DH: Writing – review & editing. MH: Writing – review & editing. GK: Formal analysis, Methodology, Writing – review & editing. JR: Investigation, Resources, Writing – review & editing. SS: Investigation, Writing – review & editing. AS: Writing – review & editing. AQ: Investigation, Writing – review & editing. SG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Supplementary material

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Risk factors predicting need for the pediatric intensive care unit (PICU) post-hematopoietic cell transplant, PICU utilization, and outcomes following HCT: a single center retrospective analysis

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Hematopoietic cell transplant (HCT) is a curative treatment for multiple malignant and non-malignant disorders. While morbidity and mortality have decreased significantly over the years, some patients still require management in the pediatric intensive care unit (PICU) during their HCT course for additional respiratory, cardiovascular, and/or renal support. We retrospectively reviewed pediatric patients (0–18 years) who underwent HCT from January 2015–December 2020 at our institution to determine risk factors for PICU care and evaluate PICU utilization and outcomes. We also assessed pulmonary function testing (PFT) data to determine if differences were noted between PICU and non-PICU patients as well as potential evolution of pulmonary dysfunction over time. Risk factors of needing PICU care were lower age, lower weight, having an underlying inborn error of metabolism, and receiving busulfan-based conditioning. Nearly half of PICU encounters involved use of each of respiratory support types including high-flow nasal cannula, non-invasive positive pressure ventilation, and mechanical ventilation. Approximately one-fifth of PICU encounters involved renal replacement therapy. Pulmonary function test results largely did not differ between PICU and non-PICU patients at any timepoint aside from individuals who required PICU care having lower DLCO scores at one-year post-HCT. Future directions include consideration of combining our data with other centers for a multi-center retrospective analysis with the goal of gathering and reporting additional multi-center data to work toward continuing to decrease morbidity and mortality for patients undergoing HCT.

KEYWORDS

hematopoietic cell transplant (HCT), hematopoietic stem cell transplant (HSCT), pediatric intensive care unit (PICU), utilization, outcomes, pulmonary function tests (PFTs)

Introduction

Hematopoietic cell transplant (HCT) is a potentially curative therapy for a variety of conditions including hematologic malignancies, non-malignant hematologic disorders, immunodeficiencies, and several inherited metabolic disorders. Over the past several decades, there have been significant advances resulting in lower rates of relapse, graft failure, and other complications with resultant improved survival (1, 2). Despite this, there is still morbidity and mortality from transplant-related complications in the peri-transplant period. Pediatric intensive care unit (PICU) utilization during HCT in general is known to increase the risk of mortality post-HCT, particularly if it involves multisystem organ failure (3). However, it is unclear which specific components of PICU care (e.g., any respiratory support vs. intubation, types of dialysis) in more recent years are associated with the greatest risk for different short- and long-term outcomes (3–5). Data from a variety of prior studies suggests that stem cell transplant patients and immunocompromised patients have higher mortality than other critically ill children post-intubation and have higher mortality when they are difficult to oxygenate, require high frequency oscillatory ventilation and/or are fluid overloaded (6–9). Further risk assessment remains challenging given advances in practice and supportive care changing rapidly over time in addition to institutional variability in HCT and PICU practices.

To date, some single-center retrospective studies of risk factors for PICU care post-HCT have been published (3–5) and multiple older prospective and multi-center studies also available (10–12). However, recent prospective and multi-center experiences are lacking aside from two recently published multi-center retrospective studies (13, 14). Further, utilization of different supports in the PICU (e.g., types of respiratory support, types of dialysis) during HCT needs to be better described as HCT centers often have different approaches and institutional practices for interventions necessitating a PICU transfer and ongoing PICU care. Additionally, information linking long-term outcomes to physiologic instability during the HCT process is not readily available. For pulmonary dysfunction in particular, delay in diagnosis of later complications and dysfunction post-HCT, specifically chronic graft vs. host disease involving the lungs, has led to creation of the TRANSPIRE study (NCT04098445) which aims to enhance and develop further screening and early detection of late pulmonary complications post-HCT to improve the post-HCT management (15). Herein, we report our single center experience of transplant related risk factors for PICU care and utilization as well as ascertain short- and long-term outcomes after PICU care. Additionally, we aim to further characterize long-term lung disease by comparing pulmonary function test (PFT) results of individuals throughout their HCT course.

Methods

We retrospectively reviewed pediatric patients (0–18 years) who underwent HCT at the University of Minnesota from January 2015–December 2020. HCT and PICU databases were queried for demographic data in addition to pre-HCT, HCT and post-HCT data. These databases are prospectively collected and longitudinally monitored with data validity and quality checks. For the PICU data, local data was obtained from the Virtual Pediatric Systems (VPS, LLC). VPS is a prospectively collected cohort of consecutive PICU admissions and chart abstraction is undertaken by a trained coordinator. Variables evaluated included type of respiratory support and duration as well as need for dialysis. Only PICU encounters which occurred after the transplant date were assessed. Further information was extracted from the electronic medical record via chart review for missing data.

For PFT data, number of PFTs per patient and timing of PFTs in relation to HCT were evaluated (baseline prior to HCT, 100 days post-HCT, 6 months post-HCT, 1-year post-HCT, and greater than 1-year post-HCT). PFTs were assigned to the category closest to their time of completion (80–110 days for 100 days post-HCT, 130–281 days for 6 months post-HCT, and 328–499 days for 1-year post-HCT). Variables assessed on PFTs included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, mid-forced expiratory flow volumes between 25% and 75% of vital capacity (FEF25–75), forced residual capacity (FRC), residual volume (RV), total lung capacity (TLC), and diffusing capacity for carbon dioxide (DLCO). PICU and non-PICU patient PFT data were then imported into the Global Lung Function Initiative (GLI) Calculator (https://gli-calculator.ersnet.org/) to determine z-scores and assess for statistically significant differences with alpha level of 0.05.

Statistical methods

University of Minnesota's pediatric transplant and PICU databases were queried for pediatric allogeneic HCTs and PICU encounters from January 2015–December 2020. Descriptive statistics, including mean, median, IQR, and range, were employed to characterize demographic, clinical, laboratory variables and the Global Lung Function Initiative (GLI) calculated PFT data across the two groups. Categorical variable comparisons between groups were conducted using chi-square test or Fisher's exact test in cases of limited expected counts, and continuous variable comparisons between groups were conducted using Wilcoxon rank-sum tests. Overall survival was estimated by Kaplan-Meier curves (16). Log-rank test was used to compare the estimates between groups. Multivariate logistic regression analysis was also conducted to further characterize risk factors for PICU admission post-HCT. Variables with $p < 0.1$ in univariate analysis were evaluated for multivariate analysis (Supplementary Tables S1, S2). Odds ratios were determined with odds ratios >1 indicating more risk of needing PICU care.

All statistical tests were two-sided, and significance was established at $p < 0.05$. The statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 277 children underwent HCT between January 2015 and December 2020. Median age at time of transplant was 6.2 years

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(IQR 1.1–11.4 years). Over half of children were male (58.1%) with most children of White race (76.5%). Most common indications for HCT were non-malignant disorders (41.2%), followed by malignant disorders, and underlying inborn errors of metabolism (Table 1). Umbilical cord blood was the predominant donor source (42.2%), followed by matched unrelated donor, and matched sibling donor (Table 1).

PICU admission and resource use

A total of 77 children (38.5%) needed PICU care. Of these, most patients had one PICU stay (66.2%). Median time from HCT to first PICU admission was 51 days (IQR 13–323 days).

Univariate analysis

Patients needing PICU care were more likely to be younger ($p < 0.01$). Lower weight was also associated with higher risk of PICU admission ($p < 0.01$). BMI was not significantly different between the two groups. Patients with underlying inborn errors of metabolism were more likely than individuals with non-malignant or malignant underlying diagnoses to need PICU care ($p = 0.01$). Patients with busulfan-based conditioning regimens were also more likely to need PICU care ($p = 0.01$). Individuals with underlying pulmonary and/or cardiac disease (moderate or severe pulmonary co-morbidity sub score, arrhythmia, heart valve, other cardiac condition) were not found to be at a higher risk to need PICU care. Donor type was not a significant risk factor for PICU care. Potential metrics of patient complexity or fragility (i.e., performance status, comorbidity index [HCT-CI], and disease-risk index [DRI]) were not associated with needing PICU care.

Patients that required PICU care were more likely to have detectable adenoviremia at some point during their HCT course ($p < 0.01$), while there was no difference in detectable CMV and EBV viremia between the two groups. CMV matching was different amongst the two groups with donor negative, recipient positive status noted in the highest proportion of individuals who needed PICU care. Additional demographic and clinical data can be found in Table 1.

Multivariate analysis

Based on univariate analysis results (Table 1), age, weight, race, underlying diagnosis, CMV matching and conditioning regimen were considered for multivariate analysis (Supplementary Tables S1, S2). A final multivariate model incorporating both age and underlying diagnosis found that for every one year increase in age while controlling for underlying diagnosis, the odds of needing PICU care decreased (odds ratio 0.92, 95% CI 0.87–0.97).

Of the 77 individual patients who received PICU care, there were a total of 127 ICU encounters. Median length of PICU stay was 5.1 days (IQR 1.6–15.9 days). Most patients were neutrophil engrafted prior to PICU stay (83.5%), while some achieved

TABLE 1 Demographic and clinical characteristics of included patients.

Characteristics	PICU	No PICU	*P* value
N	77	200	
Number of PICU Encounters			–
1	51 (66.2%)	–	
2	14 (18%)	–	
3	12 (16%)	–	
Day of Transplant to 1st PICU Event (Days)			–
Median (IQR)	51 (310)	–	
Age at Transplant (years)			
Median (IQR)	2.5 (8.8)	7.1 (10.4)	<0.01
Weight (kg)			
Median (IQR)	13.3 (20.9)	22.5 (31.4)	<0.01
BMI (kg/m^2)			
N	76[a]	200	0.25
Median (IQR)	17.2 (3.6)	17.6 (4.6)	
BMI Group			
≤25	72 (94.7%)	182 (91.0%)	0.31
>25	4 (5.3%)	18 (9.0%)	
Race			0.02
Unknown	5 (6.5%)	23 (11.5%)	
Caucasian	58 (75.3%)	154 (77.0%)	
African American	3 (3.9%)	15 (7.5%)	
American Indian	2 (2.6%)	3 (1.5%)	
Asian	9 (11.7%)	5 (2.5%)	
Gender			0.84
Male	44 (57.1%)	117 (58.5%)	
Female	33 (42.9%)	83 (41.5%)	
Underlying Disease			0.01
Inherited metabolic disorders	29 (37.7%)	43 (21.5%)	
Non-malignant	23 (29.9%)	91 (45.5%)	
Malignant	25 (32.5%)	66 (33.0%)	
Cell source			0.20
Bone marrow	35 (45.5%)	110 (55.0%)	
PBSC	3 (3.9%)	12 (6.0%)	
UCB	39 (50.7%)	78 (39.0%)	
Donor Type (Bone marrow + PBSC)			0.18
Matched sibling	10 (26.3%)	49 (40.2%)	
Matched URD	19 (50.0%)	42 (34.4%)	
Mismatched Sibling/URD + Haploidentical	9 (23.7%)	31 (25.4%)	
CMV matching			0.04
Donor+ Recipient+	5 (6.5%)	38 (19.0%)	
Donor+ Recipient-	8 (10.4%)	11 (5.5%)	
Donor- Recipient+	36 (46.8%)	79 (39.5%)	
Donor- Recipient-	28 (36.8%)	72 (36.0%)	
Conditioning Regimen			0.01
Cyclophosphamide + Fludarabine + TBI	9 (11.7%)	50 (25.2%)	
Cyclophosphamide + TBI	14 (18.2%)	39 (19.7%)	
No TBI	4 (5.2%)	23 (11.6%)	
Busulfan with no TBI	50 (64.9%)	86 (43.4%)	
LPS/KPS			0.20
≤80	23 (29.9%)	45 (22.5%)	
>80	54 (70.1)	155 (77.5%)	
HCT-CI			0.32
0	39 (50.7%)	121 (60.5%)	
1–2	24 (31.7%)	48 (24.0%)	
>=3	14 (18.2%)	31 (15.5%)	

(*Continued*)

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TABLE 1 Continued

Characteristics	PICU	No PICU	*P* value
DRI			0.54
Very Low	0	5 (2.5%)	
Low	12 (15.6%)	33 (16.5%)	
Intermediate	12 (15.6%)	21 (10.5%)	
High	1 (1.3%)	2 (1.0%)	
Very high	52 (67.5%)	134 (67.0%)	
Missing	0	5 (2.5%)	
Cardiopulmonary comorbidity prior to HCT			0.74
Yes	14 (18.2%)	33 (16.5%)	
No	63 (81.8%)	167 (83.5%)	
CMV status			0.86
Yes	20 (26.0%)	54 (27.0%)	
No	57 (74.0%)	146 (73.0%)	
EBV status			0.27
Yes	11 (14.3%)	40 (20.0%)	
No	66 (85.7%)	160 (80.0%)	
Adenovirus status			<0.01
Yes	10 (13.0%)	7 (3.5%)	
No	67 (87.0%)	193 (96.5%)	
Adenovirus time (days)			
N	10	7	
Median (range)	77 (71)	76 (62)	0.47
Transplant year			0.33
2015	12 (15.6%)	41 (20.5%)	
2016	20 (26.0%)	32 (16.0%)	
2017	13 (16.9%)	37 (18.5%)	
2018	11 (14.3%)	33 (16.5%)	
2019	14 (18.2%)	28 (14.0%)	
2020	7 (9.1)	29 (14.5%)	
ANC engraftment status at last follow-up			0.50
Alive without engrafted	0	1 (0.5%)	
Dead without engrafted	2 (2.6%)	2 (1.0%)	
ANC > 500 × 3 days	75 (97.4%)	197 (98.5%)	
Follow-up Status			<0.01
Alive	40 (52.0%)	181 (90.5%)	
Dead	37 (48.0%)	19 (9.5%)	
Alive patients follow up time (days)			<0.01
N	40	181	
Median (IQR)	1,790.5 (737.5)	1,812 (1,067)	
Relapse status at last follow-up			<0.01
Alive without relapse	37 (48.1%)	173 (86.5%)	
Dead without relapse	32 (41.6%)	7 (3.5%)	
Relapse	8 (10.4%)	20 (10.0%)	

BMI, body mass index; UCB, umbilical cord blood; LPS, Lansky Performance Score; KPS, Karnofsky Performance Score; HCT-CI, hematopoietic cell transplant comorbidity index; DRI, disease-risk index; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ANC, absolute neutrophil count.
[a]One patient had missing height information and BMI unable to be calculated.

TABLE 2 Characteristics of PICU encounters.

Factor	PICU Encounters (*N* = 127)
Time from BMT to PICU (days)	
Median (IQR)	87 (292)
Engraftment status at PICU admission	
Engrafted before PICU	106 (83.5%)
Engrafted after PICU	19 (15.0%)
Failed to engraft	2 (1.6%)
Age at time of PICU Encounter (Years)	
Median (IQR)	3.9 (9.3)
Weight at time of PICU Encounter (kg)	
Median (IQR)	15.7 (19.8)
PICU_PRISM_3	
Median (IQR)	10.0 (10.0)
PIM_3 Logit	
Median (IQR)	−2.6 (1.5)
Tracheostomy	
No	126 (99.2%)
Yes[a]	1 (0.8%)
HFNC	
Yes	59 (46.5%)
No	68 (53.5%)
HFNC Duration (Days)	
N	59
Median (IQR)	1.1 (1.4)
ECMO	
No	124 (97.6%)
Yes	3 (2.4%)
ECMO Duration (Days)	
N	3
Median (IQR)	10.8 (20.6)
NIPPV	
Yes	66 (52.0%)
No	61 (48.0%)
NIPPV Duration (Days)	
N	66
Median (IQR)	3.4 (5.2)
MV	
Yes	65 (48.8%)
No	62 (51.2%)
MV Duration (Days)	
N	65
Median (IQR)	8.9 (12.4)
RRT	
Yes	22 (17.3%)
No	105 (82.7%)
RRT Duration (Days)	
N	22
Median (IQR)	10.5 (21.3)
PICU LOS (Days)	
Median (IQR)	5.1 (14.3)

Organ support duration above only includes that while in PICU.
HFNC, high flow nasal cannula; ECMO, extracorporeal membrane oxygenation; NIPPV, non-invasive positive pressure ventilation; MV, mechanical ventilation; RRT, renal replacement therapy; LOS, length of stay.
[a]Additional details of this patient are not included as they may be identifying.

neutrophil engraftment following PICU admission (15.0%). A small proportion of these patients failed to engraft (1.6%). Additional details of PICU encounters are listed in Table 2.

Regarding respiratory support utilization, multiple modalities were utilized in the PICU with some patients utilizing more than one modality. In approximately half of encounters (46.5%), high flow nasal cannula support (HFNC, which can commonly occur in the general ward in our hospital) was used, non-invasive positive pressure support (NIPPV) was used in over half of encounters (52.0%), and mechanical ventilation (MV) was utilized in just under half of encounters (48.8%). Median duration of HFNC support was 1.1 days (IQR 0.5–1.9 days) while

median duration of NIPPV was 3.4 days (0.8–6 days), and median duration of mechanical ventilation was 8.9 days (IQR 2.9–15.3 days). Additional organ support included extra-corporeal membrane oxygenation (ECMO) in three encounters (2.4%), with a median duration of 10.8 days (IQR 3.5–24.1 days) and renal replacement therapy in 22 encounters (17.3%), with a median duration of 10.5 days (IQR 0.6–21.9 days).

Mortality outcomes

At last follow-up, individuals needing PICU care experienced higher mortality, but had similar rates of relapse when compared to patients not needing PICU care (Table 1). Overall survival at three years was 51% in PICU group and 92% in non-PICU group ($p < 0.01$; Figure 1). When PICU care was combined with the need for mechanical ventilation, a further decrease in overall survival at three years was found (77% without mechanical ventilation and 35% with mechanical ventilation; Figure 2). More than one PICU stay was also found to negatively impact three-year overall survival (63% for single PICU stay and 31% for two or more PICU stays; Figure 3). Lastly, all three patients where ECMO was utilized died.

Pulmonary function tests (PFTs)

Of the total cohort of 277 patients, 108 patients completed PFTs at any time point. The 169 patients that were excluded from PFT analysis did not have PFTs at any time point pre-BMT and up to one-year post-BMT. Of these 169 patients, 131 were less than 6 years-old at time of BMT and unable to complete PFTs due to age. Pulmonary function testing was completed for 91 patients at baseline, 21 patients at Day 100 post-HCT, 9 at six months post-HCT, 74 at one-year post-HCT, and 59 patients had PFTs after one-year post-HCT. Of note, 6 patients of the 108 patients who completed any PFTs died prior to the six-month post-HCT timepoint.

There were no statistically significant differences in the PFT variables of interest between PICU and non-PICU patients at baseline (Supplementary Table S3). At one-year post-HCT, DLCO was lower in patients who required PICU support during HCT ($p = 0.03$; Supplementary Table S4). At all other timepoints, there were no statistically significant differences in PFT variables between PICU and non-PICU patients.

Discussion

In this single-center retrospective review of nearly 300 pediatric patients undergoing HCT during the study period, we demonstrated that a variety of risk factors are associated with need for PICU care post-HCT as well as demonstrating the importance of younger age increasing risk for need for PICU care when controlling for underlying disease. We also highlighted that NIPPV and mechanical ventilation were the most utilized PICU therapies by HCT patients transferred to the PICU post-HCT as well as reviewed outcomes of post-HCT patients who needed PICU care. Finally, we demonstrated a difference in diffusing capacity measurements at one-year post-HCT in patients admitted to the PICU. Spirometry and plethysmography findings did not demonstrate any statistically significant changes from pre-transplant studies to post-transplant follow-up. Our study and its results add to the growing body of literature to inform the care and management of HCT patients going forward.

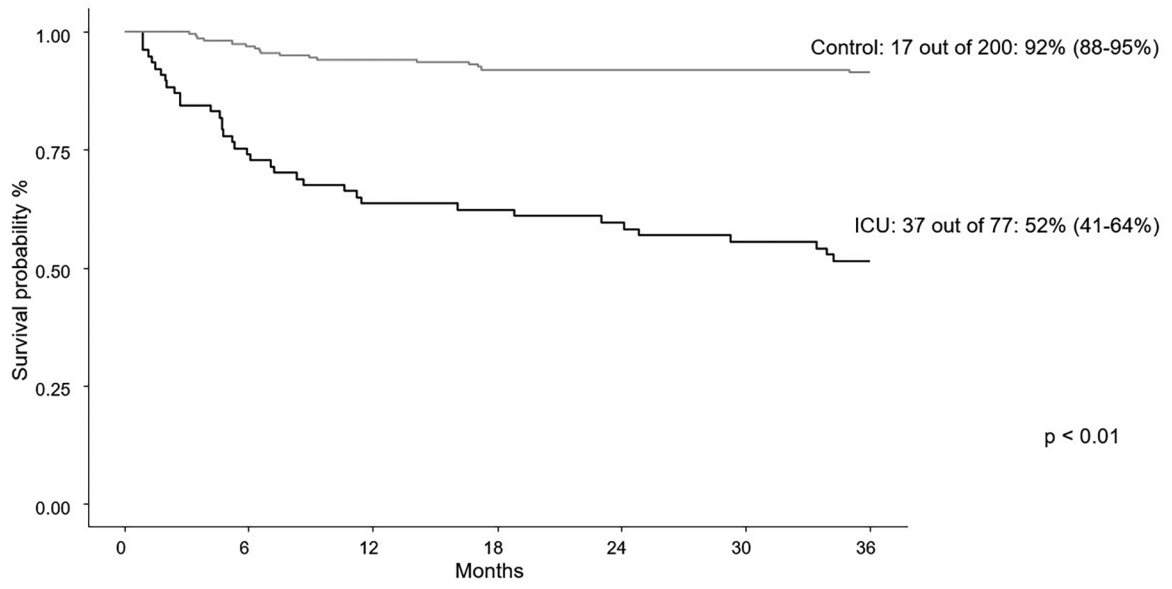

FIGURE 1
Three-year survival curves for first PICU encounter vs. control patients.

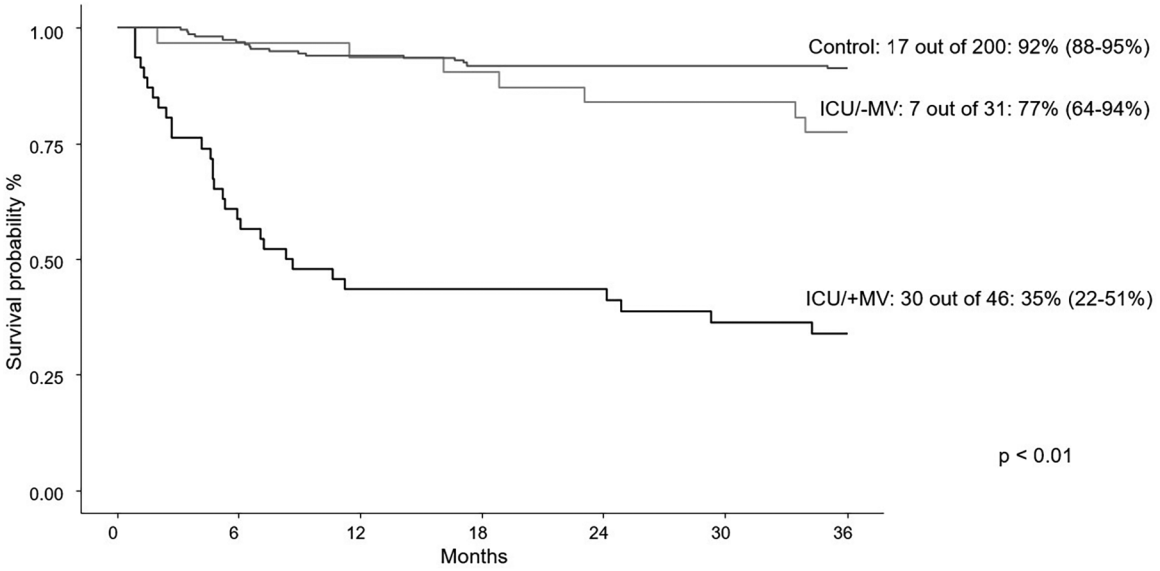

FIGURE 2
Three-year survival curves for first PICU encounter +/– mechanical ventilation (MV) vs. control patients.

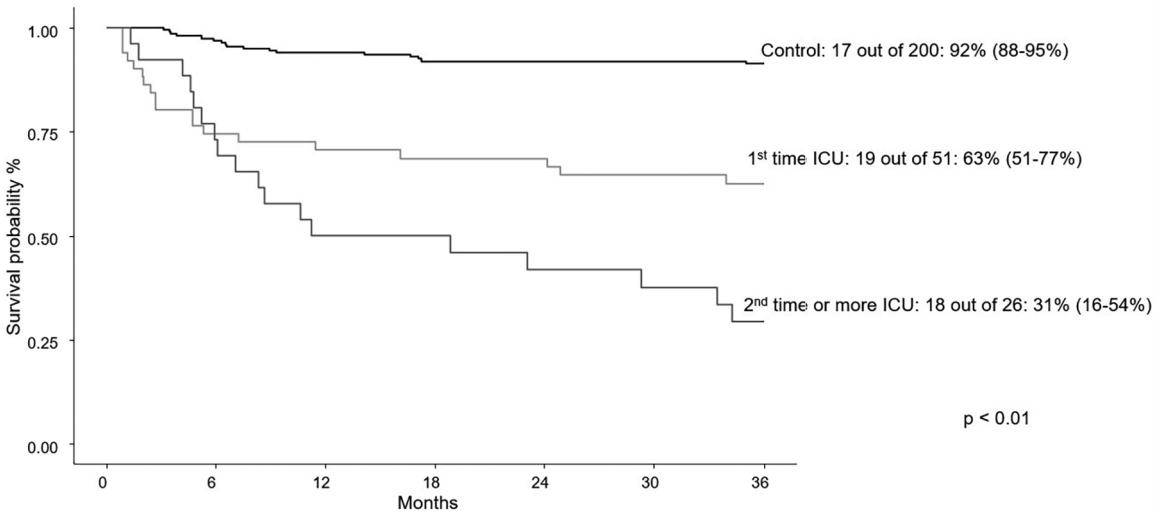

FIGURE 3
Three-year survival curves for PICU encounter(s) vs. control.

Our study found that younger patients (and patients with lower weights) were more likely to need ICU care, which is not surprising given patients with smaller airways have a higher risk of increased respiratory needs and intubation post-HCT (17). Our cohort had a higher proportion of patients needing PICU care compared to previously reported retrospective cohorts (38.5% vs. 10%–15%; 3–5, 13, 14) and is likely the result of our patient cohort being younger, lower weight and having a high proportion of patients with underlying inborn errors of metabolism, who are also have a higher risk of complications peri-transplant (17–19). Further, when evaluating PICU care risk by multivariate logistic regression and adjusting for underlying disease, increasing age was found to have a lower odds of needing PICU care, which is in keeping with lower age (and likely smaller weight patients) experiencing higher risk of PICU need peri-HCT (17).

Additionally, by univariate analysis, racial identity differences were noted with a higher portion of Asian individuals utilizing PICU care. While the racial demographics in our study are felt to closely approximate our geographic area, the small numbers of non-White individuals and our study occurring at a single center

make this data difficult to interpret. Further, race is likely a proxy for a variety of other factors and putting significant weight on race, which is largely now accepted as a social construct, is not appropriate. However, race could be a more important factor in multi-institutional studies with more granular multivariate analyses that consider socioeconomic status, proximity to transplant center, insurance status, etc.

A variety of respiratory supports were the most utilized PICU resources in our study with escalating durations of support with more invasive modalities of respiratory assistance. The relatively short PICU stay duration of 5.1 days is likely influenced by high percentage of patients transferring to PICU for HFNC and NIPVV support. The median time to first PICU admission was 51 days post-HCT in our cohort. While that timing post-HCT explains the high percentage of patients who were neutrophil engrafted prior to PICU transfer, it also illustrates that significant organ dysfunction can occur weeks following engraftment, including after discharge from the initial HCT hospitalization. This is consistent with reports from a recent multi-center study, which demonstrated ICU exposure for patients post-HCT increased across the measured time points of day +100, 1-year and 5-years post-HCT (14). Additionally, our institutional practice of allowing advanced respiratory support on the HCT unit (HFNC and some NIPPV) potentially led to PICU transfer later in the post-HCT course than in institutions with more restrictive policies. Post-HCT PICU 3-year overall survival from our cohort (52.0%) is higher in comparison to a recently published study (14.9%; 13) that evaluated post-HCT outcomes and is similar to another recent multi-center study's 1-year survival post-ICU transfer (52.5%; 14). This discrepancy is at least partially due to improvement in supportive care over time. However, it should also be noted that despite our higher proportion of patients needing PICU care compared to other cohorts, survival in our cohort is at least the same or better than in other studies, highlighting our PICU's management of our patients and our comfort as a transplant center taking higher risk HCT patients.

Our study demonstrated no significant differences between longitudinal pulmonary function testing in children exposed to the PICU during their transplant course compared to those who were not aside from lower DLCO at one-year post-HCT in children exposed to PICU (Supplementary Tables S3, S4). It is also important to specifically note around one-third of patients had an abnormal DLCO at baseline, but DLCO abnormality increased at one-year post-HCT for patients who required PICU care during the peri-HCT period (Supplementary Tables S3, S4). Decreased diffusing capacity demonstrates a decline in gas exchange with parenchymal lung changes consistent with pulmonary interstitial lung disease. In our cohort, we did not demonstrate an association between obstructive or restrictive lung disease after PICU admissions. The PFT data are limited in number and highlights the importance of studies like TRANSPIRE to further evaluate standard PFTs at multiple time points as well as evaluate additional markers of lung dysfunction in the HCT setting (15). Due to the need for patients to be developmentally capable of participating in PFTs, which generally are difficult to perform in children under 6 years of age, alternative measurements are being explored. Some of these include airway oscillometry (which is performed during normal tidal volume breathing, and therefore does not require the same level of participation) and multiple breath washout to determine lung clearance index (a testing modality that requires only tidal breathing), which are being evaluated in TRANSPIRE and are important for future study in this cohort (15, 20, 21). Despite our limited PFT data, there is a paucity of this data published in the HCT population, and having serial PFTs for some HCT patients is a strength of our study.

Given the retrospective nature of our study, there are study limitations. As one example of retrospective limitations in our study, adenoviremia was found to be associated with higher risk for PICU care. However, we do not have data on additional details of adenoviremia (sites of involvement, highest viral load, end-organ dysfunction thought to be specifically related to adenoviremia, etc.). Additionally. transplant-related risk factors and PICU utilization and outcomes can have inherent institutional variability requiring larger and multi-center studies to establish stronger associations. There is also an inherent limitation of lack of availability of PFT data in the younger cohort who are typically not developmentally capable of performing standard PFTs until they reach 6 years of age, so other modalities should continue to be explored and used to address this concern.

Understanding the risk factors, peri-HCT PICU utilization and long-term pulmonary outcomes in children undergoing HCT is critical to develop a long-term monitoring and management plan. As transplant conditioning and post-transplant management continues to evolve, a deeper understanding and assessment is critical for optimal pre- and post-transplant care. Along with other recent studies (3–5, 13, 14), creation of a pre-HCT PICU and outcome risk scoring system as more studies are published would be an important tool for clinicians to predict outcomes for pediatric HCT patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AJ: Writing – original draft, Writing – review & editing. SC: Writing – original draft, Writing – review & editing. SG: Writing – original draft, Writing – review & editing. QC: Formal

Analysis, Writing – original draft, Writing – review & editing. JH: Writing – original draft, Writing – review & editing. AG: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1385153/full#supplementary-material

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Timing of intubation of pediatric hematopoietic cell transplant patients: an international survey

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Introduction: Retrospective data suggest that pediatric hematopoietic cell transplant (HCT) patients placed on non-invasive ventilation (NIV) prior to intubation have increased risk of mortality compared to patients who are intubated earlier in their course. The HCT-CI subgroup of the PALISI Network set out to gain a better understanding of factors that influence clinician's decisions surrounding timing of intubation of pediatric HCT patients.

Methods: We validated and distributed a brief survey exploring potential factors that may influence clinician's decisions around timing of intubation of pediatric HCT patients with acute lung injury (ALI).

Results: One hundred and four of the 869 PALISI Network's members responded to the survey; 97 of these respondents acknowledged caring for HCT patients and were offered the remainder of the survey. The majority of respondents were PICU physicians (96%), with a small number of Advanced Practice Providers and HCT physicians. As expected, poor prognosis categories were perceived as a factors that delay timing to intubation whereas need for invasive procedures was perceived as a factor shortening timing to intubation. Concerns for oxygen toxicity or NIV-associated lung injury were not believed to influence timing of intubation.

Discussion: Our survey indicates increased risk of ALI from prolonged NIV and oxygen toxicity in HCT patients are not a concern for most clinicians. Further education of pediatric ICU clinicians around these risk factors could lead to improvement in outcomes and demands further study. Additionally, clinicians identified concerns for the patient's poor prognosis as a common reason for delayed intubation.

KEYWORDS

hematopoietic cell transplant, intubation, mechanical ventilation, palliative care, non-invasive ventilation associated lung injury, oxygen toxicity

Introduction

Delayed intubation and prolonged use of NIV and supplemental oxygen have been implicated as potential risk factors for poor outcome in pediatric hematopoietic cell transplant patients with Pediatric Acute Respiratory Distress Syndrome (PARDS) (1–3). Additionally, recent data has shown that lung injury from NIV may be underappreciated and contribute to the suboptimal outcomes for HCT patients who develop PARDS (4, 5). While much discussion has centered on the need for earlier intervention in this high-risk population (6), retrospective data suggests pediatric intensivists may intubate this population late in their PARDS course as evidenced by the very high rate of cardiac arrest during intubation when compared to the general pediatric population (1, 2, 7, 8). The Hematopoietic Cell Transplant and Cancer Immunotherapy (HCT-CI) subgroup of the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network performed a survey of pediatric intensivists and pediatric HCT clinicians within the PALISI Network to gain a better understanding of clinician's beliefs surrounding the timing of intubation for pediatric HCT patients with PARDS. The purpose of the survey is to better inform future educational efforts as well as guide research efforts of the group aimed at improving outcomes for pediatric HCT patients with PARDS.

Methods

Survey questions were written by members of the PALISI Network's HCT-CI subgroup and validated through the following process: 1) potential questions drafted by working group to address possible factors influencing decision making around timing of intuabtion; 2) questions sent to 8 members of the HCT-CI subgroup's Executive Committee for comments and revision; 3) questions asked to the University of Minnesota and St Jude Childrens Research Hospitals' critical care teams including 10 physicians, 7 Advanced Practice Providers, one research coordinator, and 3 fellows resulting in 3 revisions to achieve uniformity in question interpretation. The final survey contained 19 questions which included 3 demographic questions regarding the respondent, 1 question addressing the respondent's self-assessment of their own timing of intubation of HCT patients, 2 case scenarios developed to test whether engraftment status influenced decision making, and thirteen 5-point Likert scale questions investigating the factors the HCT-CI subgroup identified as potential influencers of decision making around timing of intubation. The survey was approved by the PALISI Network's scientific review committee for distribution to its members. A cross sectional survey was undertaken with distribution to all members of the general PALISI Network, including the HCT-CI subgroup, through email with a link to RedCAP. Prior to distribution the survey was approved by the University of Minnesota IRB. Survey responses were anonymous and data were presented collectively through RedCAP. Statistical analysis is descriptive.

Results

A total of 869 surveys were sent via email to members of the PALISI Network. One hundred and four members from 33 centers in 4 countries and 3 continents responded for a response rate of 12%. Of the 104 respondents, 97 cared for HCT patients and were then given the remainder of questions through branching logic. Of these 97 respondents, 82 were PICU attending physicians, 9 PICU fellows, 1 PICU advanced practice provider (APP), 3 HCT attending physicians, 1 HCT APP and 1 "other".

After determining if respondents cared for HCT patients, they were asked to report their assessment of their own timing of intubation of HCT patients. The most popular answer was "depends on the situation" (44.8% of respondents) while 27.1% answered they intubate HCT patients earlier and 12.5% answered they intubated HCT patients later than the general PICU population (Figure 1).

The survey then presented the following clinical scenarios:

Scenario 1: Patient is a 6-year-old male who is Day +28 after allogeneic HCT. He is admitted to the PICU with respiratory distress. His current VS are T 37.2 P 140 R 50 BP 100/60 Oxygen Saturation 86%. He has been on the current BiPap settings (IPAP 18/EPAP 10 FiO2 0.7) for 6 hours. VBG shows pH 7.32/PCO2 58/HCO3 32. He is engrafted. What would most likely be your next plan?

Scenario 2: Patient is a 6-year-old male who is Day +40 after allogeneic HCT. He is admitted to the PICU with respiratory distress. His current VS are T 37.2 P 140 R 50 BP 100/60 Oxygen Saturation 86%. He has been on the current BiPap settings (IPAP 18/EPAP 10 FiO2 0.7) for 6 hours. VBG shows pH 7.32/PCO2 58/HCO3 32. He is not engrafted and there is concern he may have relapsed. What would most likely be your next plan?

In the first scenario, 86 (89.6%) respondents indicated they would intubate the patient and place on conventional mechanical ventilation (CMV) with no respondents recommending limitation of support. In the second scenario where relapse was a consideration, 66 respondents (68.8%) elected to intubate and place on CMV with 18 (18.8%) recommending limitation of support (Figure 2).

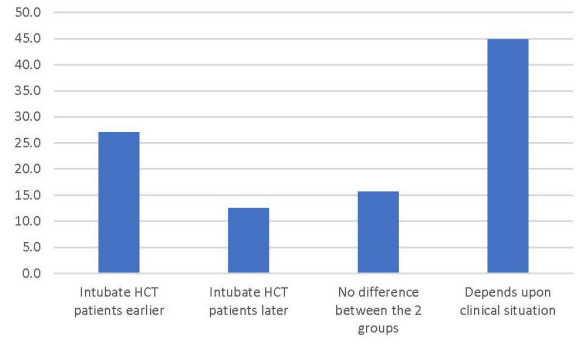

FIGURE 1
Percentage of respondents answering the survey prompt "In general, when comparing the timing of intubation for children who have respiratory failure after an HCT to the general pediatric population, I tend to...".

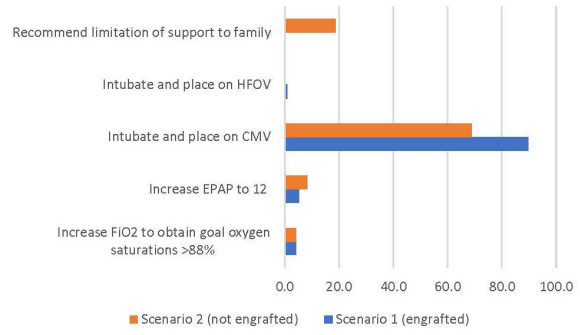

FIGURE 2
Percentage of respondents giving the survey response for clinical scenarios 1 and 2 (see text for description).

We then asked questions regarding the role that different clinical factors played in determining timing of intubation (Table 1). Answers were on a 5-point Likert scale. The 2 factors that respondents most commonly responded "definitely plays a role" or "somewhat played a role" in delaying intubation were 1) patient with a poor prognosis that they felt should have limitations of support, but they hadn't had time for discussion (89.78); and 2) patients they felt would not be able to extubated (93.8). While the 2 most common factors respondents answered "definitely" or "somewhat played a role" in intubating HCT patients earlier were 1) need for CRRT (63.5%) and 2) need for bronchoscopy (79.2%).

The 2 factors which the PALISI HCT-CI subgroup have identified in previous retrospective studies to increase risk for poor outcomes in HCT patients requiring mechanical ventilation,

TABLE 1 Effect of specific clinical factors on timing of intubation in HCT patients.

	Definitely plays a role in delaying intubation	Slightly plays a role in delaying intubation	No impact	Slight role in decision to intubate earlier	Definite role in decision to intubate earlier
Medical team (PICU and/or HCT) feels patient should be DNR/DNI but there has not yet been a discussion of code status with patient/family	50 (51.5%)	37 (38.1%)	10 (10.3%)	0 (0%)	0 (0%)
Medical team (PICU and/or HCT) does not feel patient will be extubated once intubated, worried about loss of communication for patient with family	56 (57.7%)	35 (36.1%)	6 (6.2%)	0 (0%)	0 (0%)
Disagreement between family members regarding code status	17 (17.5%)	51 (52.6%)	29 (29.9%)	0 (0%)	0 (0%)
Disagreement between medical providers regarding appropriateness of invasive mechanical ventilation	18 (18.8%)	58 (60.4%)	16 (16.7%)	3 (3.1%)	1 (1%)
Concern for difficult airway and/or cardiac arrest with intubation procedure - waiting for additional help for procedure	25 (26%)	35 (36.5%)	18 (18.8%)	12 (12.5%)	6 (6.3%)
Concern for infection from invasive endotracheal tube/ventilator associated pneumonia	1 (1%)	13 (13.5%)	77 (80.2%)	3 (3.1%)	2 (2.1%)
Patient has not engrafted and engraftment unlikely	17 (17.7%)	36 (37.5%)	40 (41.7%)	2 (2.1%)	1 (1%)
Patient may have relapsed/have persistent primary disease for which HCT performed	23 (24%)	30 (31.3%)	39 (40.6%)	4 (4.2%)	0 (0%)
Concern for increased risk of oxygen toxicity in HCT patients	0 (0%)	2 (2.1%)	73 (76%)	18 (18.8%)	3 (3.1%)
Concern for cardiac arrest during intubation of HCT patients - better chance of survival without intubation & use NIV instead	7 (7.3%)	24 (25%)	45 (46.9%)	14 (14.6%)	6 (6.3%)
Concern for increased risk of lung injury with non-invasive ventilation in HCT patients	0 (0%)	7 (7.3%)	53 (55.2%)	28 (29.2%)	8 (8.3%)
Need for bronchoscopy to obtain diagnosis	0 (0%)	0 (0%)	20 (20.8%)	44 (45.8%)	32 (33.3%)
Need for CRRT to optimize fluid balance	0 (0%)	1 (1%)	34 (35.4%)	40 (41.7)	21 (21.9%)

prolonged oxygen exposure and NIV exposure prior to intubation, were not commonly identified as influencing behavior. Most respondents (76%) stated concern for increased risk of oxygen toxicity in HCT patients had no impact of their decision regarding timing of intubation with only 3.1% stating it "definitely plays a role" in the decision to intubate earlier. Additionally, 55.2% of respondents stated risk of lung injury from NIV had no impact on their decisions surrounding timing of intubation with only 8.3% stating it "definitely played a role" in their decision to intubate HCT patients earlier. Increased risk of peri-intubation cardiac arrest in the HCT population, also did not seem to play a significant role in decisions surrounding timing of intubation with nearly half (46.9% saying it had no impact and only 6.3% stating it "definitely played a role" in deciding to intubate earlier (Table 1).

Discussion

It is well known that HCT patients requiring mechanical ventilation are at high risk of poorer outcomes than general medical PICU patients requiring mechanical ventilation (2, 3, 7). The PALISI Network's HCT-CI subgroup has been committed to improving these outcomes since its inception in 2005. We and others have shown that HCT patients exposed to high levels of oxygen support or NIV prior to intubation are associated with worse outcomes (1, 2, 7, 9, 10). It is unclear if this is a causative relationship. However, given the high level of inflammatory response and oxidative stress that plague the HCT population, it is feasible these patients could be more susceptible to oxygen toxicity and NIV-induced lung injury than the general population. These factors do not seem to play a role in determining an earlier timing of intubation according to our survey results. Therefore, these are areas which may be important for our group and others to focus resources for research and education on in order to improve outcomes in this vulnerable population.

The factors most associated with delaying intubation center around physician concerns for a poor patient prognosis – that patients should have limitations of support or that they will be unable to extubate them. While this is understandable, it can be a self-fulfilling prophecy, preventing us from advancing the field. If we believe these patients can't be saved, we don't provide them with aggressive care, and they do poorly as we expect reinforcing our belief that they cannot be saved.

Limitations of the survey are the small number of respondents as well as few responses from HCT physicians. The small number of total respondents may be related to the requirement that respondents personally provide care to HCT patients, which is an unknown number, but likely a minority of PALISI members. HCT physicians also are an even smaller minority of PALISI members. However, the decisions around timing of intubation are mostly made by ICU physicians so lack of HCT clinician response likely does not have a large impact on the results. Additionally, actual clinician practice is often not concordant with their self-report. A prospective observational study is therefore warranted to provide more accurate results.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Minnesota Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Participants checked a box while taking the survey that they understood that by submitting the survey their informed consent was implied.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Pulmonary hypertension in the intensive care unit after pediatric allogeneic hematopoietic stem cell transplant: incidence, risk factors, and outcomes

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Objective: To determine the incidence, risk factors, and outcomes of pulmonary hypertension (PH) in the pediatric intensive care unit (PICU) after pediatric hematopoietic stem cell transplant (HCT).

Methods: This was a retrospective study of pediatric patients who underwent allogeneic HCT between January 2008-December 2014 at a center contributing to the Center for International Blood and Marrow Transplant Research data registry. Incidence of PH was assessed from PICU diagnostic codes from records merged from the Virtual Pediatric Systems database. Regression and survival analyses identified factors associated with post-HCT PH. Additional post-HCT morbidities and survival after PH were also assessed.

Results: Among 6,995 HCT recipients, there were 29 cases of PH, a cumulative incidence of 0.42% (95% CI 0.27%-0.57%) at 60 months post-HCT. In the sub-cohort of 1,067 patients requiring intensive care after HCT, this accounted for a PH prevalence of 2.72% (95% CI 1.74–3.69%). There was an increased risk of developing PH associated with Black/African American race, metabolic disorders, partially HLA-matched or cord blood allografts, graft-versus-host prophylaxis regimen, and lower pre-HCT functional status. Patients who developed PH had significant PICU comorbidities including heart failure, pulmonary hemorrhage,

respiratory failure, renal failure, and infections. Survival at 6 months after diagnosis of post-HCT PH was 51.7% (95% CI 32.5%-67.9%).

Conclusions: PH is a rare but serious complication in the pediatric post-HCT population. A significant burden of additional comorbidities, procedural interventions, and risk of mortality is associated with its development. Close monitoring and prompt intervention for this severe complication are necessary in this vulnerable population.

KEYWORDS

pulmonary hypertension, stem cell transplant, pulmonary vascular disease, critical care, pediatrics

Introduction

Endothelial injury is a dominant pathologic process underlying a number of severe post-hematopoietic stem cell transplant (HCT) complications, including transplant-associated thrombotic microangiopathy (TA-TMA), hepatic veno-occlusive disease, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, and graft-versus-host disease (GVHD) (1). Endothelial dysfunction in the pulmonary vasculature in many disease states may manifest as pulmonary hypertension (PH), a pathology characterized by pulmonary vascular remodeling, elevated pulmonary arterial and right ventricular pressure, and eventually right heart failure leading to death. While cardiovascular diseases are reported to develop following pediatric HCT, pulmonary hypertension is one of the lesser studied despite contributing significantly to morbidity and mortality when arising in the post-transplant period (2, 3).

There are few studies that have examined post-HCT PH among children. These have focused primarily on high-risk populations and reported concerning outcomes. In 2013, Jodele, et al. reported a case series of 5 patients who were diagnosed with PH after developing hypoxemic respiratory failure post-HCT (4). Four of these patients died and all 3 who underwent autopsy demonstrated significant pulmonary vascular remodeling in the setting of TA-TMA. A 2019 study from Levy, et al. reported a retrospective review of 70 children who presented with unexplained respiratory symptoms after HCT, of which 22 (31%) were diagnosed with PH and 7/22 (32%) of these children suffered a fatal outcome (5). Finally, in 2023, a review of lung biopsy and postmortem samples from children with TA-TMA and respiratory failure identified 10 children with pulmonary vascular changes consistent with pulmonary arterial hypertension and/or pulmonary venous microthrombi, 9 (90%) of whom died (6). Each of these studies focused specifically on patients presenting with respiratory failure, but less is known about the incidence of PH and its outcomes among a broader representation of the transplant population.

Importantly, advanced medical therapies including novel therapeutic agents and critical care support technologies have improved outcomes in childhood PH (7). However, early identification and management of PH will be key in mitigating the poor outcomes that have been demonstrated among those who progress to respiratory failure prior to diagnosis of PH. Thus, a better understanding of the complication's true epidemiology and identification of potential risk factors for PH among HCT recipients is needed. As such, we sought to address three aims. First, to report the cumulative incidence of PH during a PICU admission amongst a large, clinically diverse population of HCT recipients. Second, to describe the factors associated with its development in the post-HCT period. And lastly, to examine how PH affects long term survival following HCT.

Methods

Patient cohort

Two large administrative databases were merged to create the cohort analyzed in the present study. The Center for International Blood and Marrow Transplant Research (CIBMTR) comprises over 450 transplant centers worldwide and collects thorough data on consecutive allogeneic HCT patients. In addition to transplant-related data, high quality longitudinal follow up is included in the CIBMTR data collection. The Virtual Pediatric Systems (VPS) database documents consecutive PICU admissions to over 140 hospitals across North America. VPS records include patient demographics, International Classification of Diseases (ICD), Ninth and Tenth Revision and STAR diagnosis codes, severity of illness scores including the Pediatric Risk of Mortality-III (PRISM-III) score (8), and critical care interventions. STAR is the proprietary diagnosis classification schema of VPS. Trained VPS analysts assign diagnoses to patients based on review of attending

physician documentation and ICD codes. Analysts collect admission information at each site with >95% inter-rater reliability.

Details of the CIBMTR and VPS database merge have been described previously (9, 10). In brief, CIBMTR records were collected for patients ≤21 years old who received a first allogeneic HCT between January 1, 2008 and December 31, 2014. Patients were excluded if they underwent HCT outside of the United States/Canada, had an identical twin donor, or lacked at least 100-day follow-up. Those who died within 100 days of HCT were included. VPS was then queried for patients ≤21 years of age admitted to a PICU between January 1, 2008 and December 31, 2014 with a diagnosis indicating prior HCT to derive a sub-cohort of post-transplant patients with critical illness. Short term semi-elective admissions (i.e., scheduled or perioperative admissions <2 days) were excluded. The HCT-related details from CIBMTR records were matched to patient records from the VPS database based on identical date of birth, sex, and transplant indication. This method was approved by the University of California, San Francisco (UCSF) institutional review board. An unblinded review of the matching results was performed from records at the UCSF Benioff Children's Hospital and confirmed validity of matching (9).

Outcomes

The primary outcome assessed was clinically significant PH, defined as PH requiring management in the PICU. Instances of the primary outcome were identified from STAR diagnosis codes. STAR codes included in the primary outcome were "416 Pulmonary Hypertension, Primary", "416.8A Pulmonary Hypertension, Secondary", and "416.9A Pulmonary Circulatory Disease" coded at any time during a PICU stay. Survival analyses examined all-cause mortality post-transplant.

Predictors

Demographics, patient clinical characteristics, including HCT Comorbidity Index and Karnofsky/Lansky Performance Scores (11–13), and transplant-related factors were assessed as potential predictors of post-HCT PH.

Statistical analysis

Descriptive statistics are reported as means with standard deviations and medians with interquartile ranges (IQR) as appropriate. Cumulative incidence of significant PH after HCT was determined using a cumulative incidence function, treating death as a competing event. Hazard ratios with 95% confidence intervals (CI) describing the risk of developing PH were derived for each predictor via univariate Cox proportional hazard models. Lastly, Kaplan-Meier curves were used to estimate the overall survival probabilities following HCT and following diagnosis of post-HCT PH.

Results

Baseline characteristics

There were 6,995 HCT recipients included in the final analyses. Patient demographics are reported in Table 1. Most patients underwent HCT for malignant diseases (57.4%), followed by non-malignant hematologic diseases (26.2%) and primary immunodeficiencies (11.5%). Most patients received bone marrow grafts (57.5%). Pre-transplant functional status was generally high, with most patients having a pre-transplant comorbidity index (11) of 0 (66.3%) and Karnofsky/Lansky performance score (12, 13) of 100 (53.1%). Median follow-up of survivors was 73 months (IQR 60–96 months).

Cumulative incidence and risk factors for PH

There were 29 total cases of the primary outcome of PH managed in the PICU. Among all HCT recipients, 5-year cumulative incidence of significant PH was 0.42% (95% CI 0.27%-0.57%; Figure 1). Variables associated with the development of post-HCT PH are depicted in Figure 2 (Supplementary Table 1). There was an increased risk of developing significant PH in Black/African American patients relative to White (HR 2.44, 95% CI 1.10–5.40 p=0.027), patients being transplanted for metabolic disorders relative to malignancies (HR 3.30, 95% CI 1.09–9.93, p=0.034), those who received partially HLA-matched unrelated or cord blood grafts relative to grafts from HLA-identical siblings (HR 5.89, 95% CI 1.52–22.79, p=0.010; HR 4.76, 95% CI 1.36–16.72, p=0.015, respectively), as well as those who received cord blood grafts relative to bone marrow (HR 2.30, 95% CI 1.07–4.97, p=0.033). Those with worse pre-transplant functional status had higher risk of significant PH. Patients with a comorbidity index of 3+ demonstrated 3.98 times the risk (95% CI 1.86–8.51, p<0.001) compared to those with a comorbidity index of 0, and those with a Karnofsky/Lansky score of ≤80 demonstrated 2.99 times the risk (95% CI 1.33–6.74, p=0.008) compared to a score of 100. Patients who received GVHD prophylaxis with a calcineurin inhibitor plus mycophenolate mofetil (MMF) had an increased risk of significant PH compared to those treated with a calcineurin inhibitor and methotrexate (HR 2.93, 95% CI 1.23–6.98, p=0.015). There were no statistically significant differences in the risk of developing significant PH based on age, sex, insurance status, BMI classification, conditioning regimens, sex matching, or post-HCT GVHD status.

PICU characteristics of PH patients

There were 1,067 patients admitted to the PICU post-transplant for a total of 2,107 admissions. The 29 patients diagnosed with significant PH were admitted to the PICU for a total of 37 admissions. Among the sub-cohort of post-HCT patients with

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TABLE 1 Baseline patient and transplant characteristics.

		Total, 6995	No PH, 6966 (99.6)	PH, 29 (0.4)
Age (mean (SD))		9.14 (6.17)	9.15 (6.17)	6.90 (6.03)
Age group	<1 year	665 (9.5)	659 (9.5)	6 (20.7)
	1–4 years	1598 (22.8)	1590 (22.8)	8 (27.6)
	5–12 years	2505 (35.8)	2496 (35.8)	9 (31.0)
	13–20 years	2227 (31.8)	2221 (31.9)	6 (20.7)
Sex, female		2893 (41.3)	2882 (41.3)	11 (37.9)
Race	White	5008 (75.8)	4989 (75.8)	19 (67.9)
	American Indian or Alaska Native	62 (0.9)	62 (0.9)	0 (0.0)
	Asian	356 (5.4)	356 (5.4)	0 (0.0)
	Black or African American	987 (14.9)	978 (14.9)	9 (32.1)
	Native Hawaiian or other Pacific Islander	17 (0.3)	17 (0.3)	0 (0.0)
	More than one race	179 (2.7)	179 (2.7)	0 (0.0)
	Missing	386	385	1
Ethnicity, Hispanic or Latino		1646 (24.3)	1640 (24.4)	6 (20.7)
	Missing	232	232	0
Insurance	Private/military/dual insurance	1801 (59.6)	1797 (59.6)	4 (36.4)
	Public insurance only	1169 (38.7)	1162 (38.6)	7 (63.6)
	Uninsured	54 (1.8)	54 (1.8)	0 (0.0)
	Missing	3971	3953	18
Neighborhood median household income (median [IQR])		$52,348 [41,323, 68,774]	$52,348 [41,332, 68,795]	$53,298 [38,198, 62,209]
BMI (median [IQR])		18.34 [16.23, 22.06]	18.34 [16.23, 22.06]	18.90 [17.56, 24.31]
BMI Classification	Normal	2159 (58.7)	2153 (58.8)	6 (46.2)
	Overweight	601 (16.4)	598 (16.3)	3 (23.1)
	Obese	643 (17.5)	639 (17.4)	4 (30.8)
	Underweight	272 (7.4)	272 (7.4)	0 (0.0)
	Missing	3320	3304	16
Indication for transplant	Malignant disease	4013 (57.4)	3998 (57.4)	15 (51.7)
	Non-malignant hematologic disease	1833 (26.2)	1827 (26.2)	6 (20.7)
	Metabolic disorders	324 (4.6)	320 (4.6)	4 (13.8)
	Primary immunodeficiency	805 (11.5)	801 (11.5)	4 (13.8)
	Other disease	20 (0.3)	20 (0.3)	0 (0.0)
HCT comorbidity index	0	4638 (66.8)	4623 (66.8)	15 (51.7)
	1	910 (13.1)	910 (13.2)	0 (0.0)
	2	384 (5.5)	382 (5.5)	2 (6.9)
	3+	1016 (14.6)	1004 (14.5)	12 (41.4)
	Missing	47	47	0
Karnofsky score	100	3714 (54.1)	3700 (54.2)	14 (48.3)
	90	2164 (31.5)	2159 (31.6)	5 (17.2)

(Continued)

TABLE 1 Continued

		Total, 6995	No PH, 6966 (99.6)	PH, 29 (0.4)
	<=80	982 (14.3)	972 (14.2)	10 (34.5)
	Missing	135	135	0
Conditioning regimen	RIC/NMA	1793 (25.8)	1788 (25.8)	5 (17.2)
	MAC-No TBI	2675 (38.4)	2662 (38.4)	13 (44.8)
	MAC-TBI	2436 (35.0)	2425 (35.0)	11 (37.9)
	No conditioning	57 (0.8)	57 (0.8)	0 (0.0)
	Missing	34	34	0
ATG/Alemtuzumab conditioning	Neither	2770 (50.5)	2760 (50.5)	10 (45.5)
	ATG alone	2706 (49.3)	2694 (49.3)	12 (54.5)
	Alemtuzumab alone	12 (0.2)	12 (0.2)	0 (0.0)
	Missing	1507	1500	7
Graft type	Bone marrow	4022 (57.5)	4009 (57.6)	13 (44.8)
	Cord blood	1911 (27.3)	1898 (27.2)	13 (44.8)
	Peripheral blood	1062 (15.2)	1059 (15.2)	3 (10.3)
HLA matching	HLA-identical sibling	1860 (26.6)	1857 (26.7)	3 (10.3)
	Well-matched unrelated (8/8)	1888 (27.0)	1885 (27.1)	3 (10.3)
	Partially matched related	429 (6.1)	426 (6.1)	3 (10.3)
	Partially matched unrelated	830 (11.9)	823 (11.8)	7 (24.1)
	Cord blood	1911 (27.3)	1898 (27.3)	13 (44.8)
	Missing	77	77	0
Sex matching	Matched	2762 (39.5)	2756 (39.6)	6 (20.7)
	Mismatch	2311 (33.1)	2301 (33.1)	10 (34.5)
	Cord blood	1911 (27.4)	1898 (27.3)	13 (44.8)
	Missing	11	11	0
Recipient CMV status, positive		3872 (56.3)	3852 (56.2)	20 (71.4)
	Missing	116	115	1
GVH prophylaxis regimen	CNI + MTX	3316 (47.4)	3308 (47.5)	8 (27.6)
	CNI + MMF	2117 (30.3)	2103 (30.2)	14 (48.3)
	CNI +/- others	1049 (15.0)	1044 (15.0)	5 (17.2)
	TCD	349 (5.0)	347 (5.0)	2 (6.9)
	Other/missing	164 (2.4)	164 (2.4)	0 (0.0)
Acute GVHD (max grade)	None	3629 (51.9)	3609 (51.8)	20 (69.0)
	Grade I	926 (13.2)	923 (13.3)	3 (10.3)
	Grade II	1170 (16.7)	1167 (16.8)	3 (10.3)
	Grade III	673 (9.6)	671 (9.6)	2 (6.9)
	Grade IV	373 (5.3)	373 (5.4)	0 (0.0)
	Present, grade unknown	214 (3.1)	214 (3.1)	0 (0.0)
	Missing	10	9	1
Chronic GVHD (max grade)	None	5035 (72.0)	5010 (71.9)	25 (86.2)

(Continued)

TABLE 1 Continued

		Total, 6995	No PH, 6966 (99.6)	PH, 29 (0.4)
	Limited	759 (10.9)	757 (10.9)	2 (6.9)
	Extensive	1180 (16.9)	1178 (16.9)	2 (6.9)
	Present, grade unknown	2 (0.0)	0 (0.0)	0 (0.0)
	Missing	19	19	0

Values represent n (%) unless otherwise indicated. RIC (Reduced Intensity Chemotherapy). NMA (Non-Myeloablative). TBI (Total Body Irradiation). ATG (Anti-Thymocyte Globulin). HLA (Human Leukocyte Antigen). CNI (Calcineurin Inhibitor). MTX (Methotrexate). MMF (Mycophenolate Mofetil). TCD (T Cell Depletion). GVHD (Graft Versus Host Disease).

critical illness, the prevalence of PH was 2.72% (95% CI 1.74–3.69%). The median time from HCT to PICU admission with PH was 3.77 months (IQR l.23–9.57 months) which was comparable to the median time between HCT and PICU admission for non-PH critical illness (p=0.17). Additional PICU-related characteristics of the PH patients at the time of PH diagnosis are described in Supplementary Table 2. The majority of patients were admitted with a PRISM-3 score >10 (n=14, 51.9%), although some patients had low PRISM-3 scores at the time of PICU admission (e.g. score 0–2 in n=7, 25.9%). Comorbidities observed during the PICU stays included heart failure (n=5, 17.2%), pulmonary hemorrhage (n=7, 24.1%), thrombotic microangiopathy (n=1, 3.4%), hepatobiliary failure (n=3, 10.3%), and renal failure (n=11, 37.9%). Infections were relatively common (bacterial n=15, 51.7%; viral n=14, 48.3%; and fungal n=5, 17.2%). Intubation was required in 21 patients (72.4%) and renal replacement therapy occurred in 8 (27.6%).

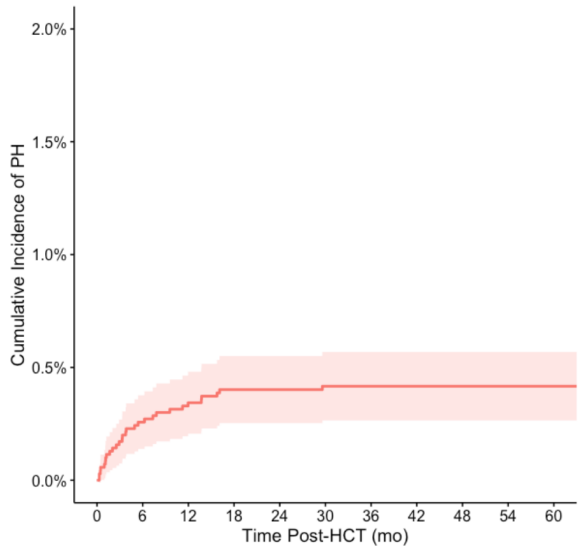

FIGURE 1
Cumulative incidence of pulmonary hypertension in the PICU following stem cell transplant. The cumulative incidence of pulmonary hypertension following HCT was 0.42% (95% CI 0.27%-0.57%) at 60 months post-HCT. Death was treated as a competing event in the cumulative incidence calculation.

Post-transplant mortality

During the study period, 16 of the 29 patients with PH died. Most deaths occurred early, within 3 months after PH onset, and all occurred during a PICU admission, with 15 of the 16 occurring in the patient's first post-HCT PICU admission. The overall survival at 6 months following diagnosis of PH was 51.7% (95% CI 32.5%-67.9%, Figure 3). Death was attributed to primary disease in 5 cases, organ failure or infection in 4 cases each, and GVHD, hemorrhage, or other causes in 1 case each. Among the entire cohort, overall survival at 6 months post-HCT was 84.1% (95% CI 83.2%-85.0%).

Discussion

Our findings provide new insight into the epidemiology, risk factors, and prognosis of significant PH following pediatric HCT. The incidence of significant post-HCT PH is low among the entire allogeneic HCT population, estimated at 0.42% (95% CI 0.27%-0.57%) at 60 months post-HCT. Among the patients requiring PICU care post-HCT, PH was prevalent in 2.72%. Those who developed PH had notable intensive care comorbidities and required significant invasive interventions. Post-PH mortality was significant and occurred early after diagnosis. These findings provide an updated understanding of a rare post-HCT complication and could serve as a benchmark for future studies.

Prior reports examining the overall incidence of post-HCT PH have cited rates as high as 15–28% among children (5, 14, 15). However, these studies focused only on subsets of the HCT population who were transplanted for specific diseases, such as osteopetrosis or CNS tumors. Studies including a wider breadth of transplant recipients have primarily examined PH incidence among those who have already developed cardiorespiratory symptoms and thus represent an enriched population (4, 5, 16). As such, by studying all allogeneic transplant recipients from the time of transplant, our study found a significantly lower cumulative incidence of post-HCT PH.

It is difficult to define a comprehensive pre-transplant risk profile for PH with such a low incidence of disease. Nonetheless, we were able to identify several factors associated with its development. African American patients, patients with a poor pre-HCT Comorbidity Index or Karnofsky/Lansky score, and

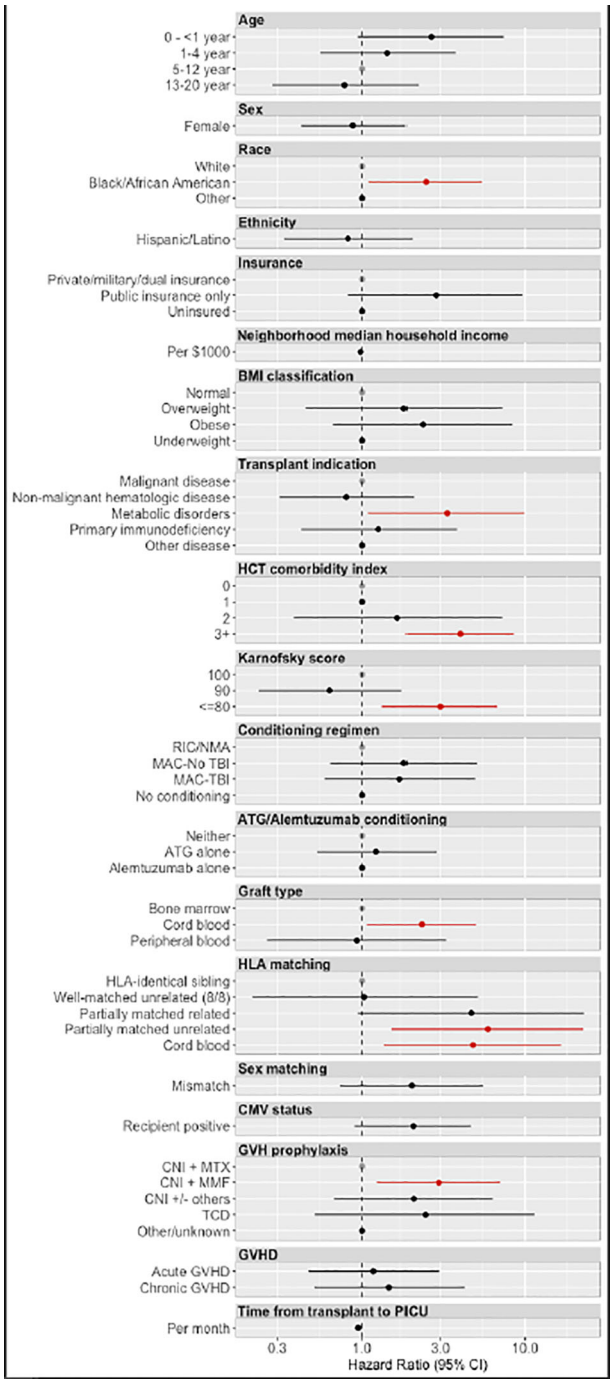

FIGURE 2
Hazard ratios for the development of pulmonary hypertension. Hazard ratios for the development of pulmonary hypertension were derived from univariable Cox regression models. Factors associated with statistically significant increased risk for post-transplant pulmonary hypertension included Black/African American race, metabolic disorders as the primary transplant indication, worse HCT comorbidity index and Karnofsky scores, partial HLA matching in unrelated donors, cord blood transplants, and CNI + MMF GVH prophylaxis regimens. RIC (Reduced Intensity Chemotherapy). NMA (Non-Myeloablative). TBI (Total Body Irradiation). ATG (Anti-Thymocyte Globulin). HLA (Human Leukocyte Antigen). CNI (Calcineurin Inhibitor). MTX (Methotrexate). MMF (Mycophenolate Mofetil). TCD (T Cell Depletion). GVHD (Graft Versus Host Disease).

patients with metabolic disorders had increased risk for PH. Racial differences in pediatric PH have been reported previously, including one study finding that Black children demonstrate an increased odds of lung disease-associated PH (17). PH has also been previously associated with inborn errors of metabolism, primarily those related to mitochondrial dysfunction, cobalamin C defects, and mucopolysaccharidoses (18, 19). Patients with mucopolysaccharidoses carry an increased baseline risk of developing pulmonary vascular disease due to the pathologic deposition of glycosaminoglycans leading to obstructive airway, restrictive lung, and valvular heart diseases (20). The exact reasons underlying the increased risk of PH for these groups in our cohort

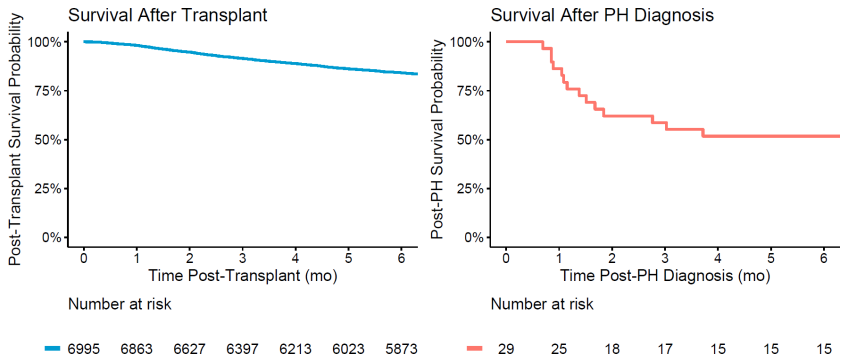

FIGURE 3
Survival following HCT and following diagnosis of post-HCT PH. Overall survival at 6 months following HCT was 84.1% (95% CI 83.2%-85.0%). Overall survival at 6 months following diagnosis of PH was 51.7% (95% CI 32.5%-67.9%).

cannot be elucidated due to the limitations of our data set. Nonetheless, these factors may help guide future investigations.

The contribution of alloreactivity to post-HCT PH remains uncertain. Although neither acute nor chronic GVHD were associated with PH, PH was associated with both the use of partially matched unrelated donors and the use of calcineurin inhibitor and mycophenolate mofetil (CNI + MMF) for GVHD prophylaxis (both of which are associated with greater rates of GVHD (21)). Similar results have been reported previously (6). This alludes to the possibility that GVHD-mediated injury may underlie the endothelial dysfunction that contributes to PH in these rare patients. Prior studies have reported that certain conditioning agents may be associated with increased risk of endothelial dysfunction and PH (1, 5). Unfortunately, we were unable to examine the associations between specific agents and PH in this data set. Further studies examining the mechanisms of endothelial dysfunction and pulmonary vascular disease after HCT are needed to better understand who will be at greatest risk for developing these complications.

Patients with PH experienced notable comorbidities during their PICU stays, including high rates of infection and multiple different organ system failures that often required invasive interventions. Interestingly, PRISM-3 risk of mortality scores for critically ill patients did not universally reflect the severity of the clinical course for all patients. Nine of the 29 patients were admitted with PRISM-3 scores less than 5. The PRISM-3 score is an established tool that has demonstrated excellent predictive power, with an area under receiver operating curve of 0.95 for predicting PICU mortality (8). In the pediatric HCT population, it is included as one of five components of a focused mortality risk prediction model that demonstrated improved performance in this unique sub-population (9). Despite this, it failed to consistently predict the significantly worse prognosis of those with PH in our cohort. Failure to identify high risk patients early on is one of the major limitations in a number of other studies examining this vulnerable population (9, 22–24). Our findings enforce the need for development of alternative prognostication models that incorporate early features of disease, potentially including echocardiographic or blood biomarkers, and transplant-related factors to better identify early organ dysfunction and risk of mortality among this unique subset of the PICU population. This is particularly important in the setting of post-HCT PH, where early PH identification and management has been demonstrated to significantly improve outcomes for these children (5).

Our study has a number of strengths. A large, diverse population of allogeneic transplant recipients from around North America was included for analysis and the merging of VPS PICU data with CIBMTR transplant data provides a valuable and unique level of detail to the analyses. There were also several limitations to our study. First, we were limited in our assessment of post-transplant PH to cases that required PICU admission and specifically documented a PH diagnosis. Detailed echocardiographic or catheterization data were not available nor was there a uniform screening protocol to identify all cases. Therefore, this report likely underestimates the true incidence of post-HCT PH, and probably fails to take into account mild cases. Lastly, the low incidence of disease limited our abilities to form a comprehensive predictive model due to lack of statistical power.

In summary, we have found that the incidence of clinically significant PH developing after pediatric allogeneic HCT is likely low, though prospective studies employing a standardized screening protocol are needed to confirm the true incidence rate. For those who develop PH and require intensive care, there is a significant burden of PICU morbidity and post-transplant mortality. Future studies should continue to focus efforts on understanding the clinical course and underlying pathophysiology of the rare but serious post-HCT complication of PH.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author and CIBMTR at info-request@mcw.edu.

Author contributions

MSm: Writing – original draft, Conceptualization, Formal analysis, Methodology. GC: Conceptualization, Formal analysis, Methodology, Writing – review & editing. RP: Writing – review & editing. RB: Writing – review & editing. JS: Writing – review & editing. KA: Writing – review & editing. BH: Writing – review & editing. AP: Writing – review & editing. BS: Writing – review & editing. HS: Writing – review & editing. MSc: Writing – review & editing. MSo: Writing – review & editing. RK: Writing – review & editing. CH: Writing – review & editing. CD: Writing – review & editing. JF: Writing – review & editing. MZ: Writing – original draft.

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Conflict of interest

RP reports bluebird bio: advisory board and Amgen: research funding. BH reports ad hoc advisory boards for Nkarta, Sanofi, Incyte, Rigel, Maat; consultancy with ACI Group, Therakos/Mallinkrodt speaker fees; data safety monitoring committee for Angiocrine; adjudication committee with CSL Behring. HS reports having received personal fees from Incyte, Janssen, Novartis, Sanofi and from the Belgian Hematological Society BHS paid to her institution; and serves as a volunteer for the EBMT. MSc reports consulting and honorarium from Omeros and Alexion. MSo reports receiving honoraria from JAZZ Pharmaceuticals Canada and research funding per a contract with Massachusetts General Hospital. CD reports consulting for Alexion and Jazz Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1415984/full#supplementary-material

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Assessment of the quality of interdisciplinary communication (CritCom): evaluation and refinement of a center summary report

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Communication failures among clinicians in the ICU (intensive care unit) often lead to worse patient outcomes. CritCom is a bilingual (English and Spanish) tool to evaluate the quality of interdisciplinary communication around patient deterioration for pediatric oncology patients. The use of reports, such as the CritCom report, as dissemination methods lead to quicker knowledge translation and implementation of research findings into policy. Nurses and physicians at participating centers who care for patients at risk of deterioration completed the CritCom survey and center-specific reports were generated to communicate CritCom results. Focus groups were conducted with clinicians receiving CritCom reports in both English and Spanish to evaluate report clarity and usability. Participants found the reports to be useful and described the writing and design as clear and specific. Participants provided feedback to improve report design and requested actionable steps to improve communication at their center. Feedback illustrated that the report was easy to interpret and a useful way to disseminate information. Participants noted the utility of the report, illustrating that the use of reports can be a useful method to disseminate research findings back to participants in a way that is applicable to the local context. Communicating research findings through reports can minimize the significant time lag in knowledge translation and provide participants with actionable steps to implement in their setting.

KEYWORDS

report, interdisciplinary communication, deterioration, pediatric oncology, critical care

1 Introduction

Outcomes for critically ill patients improve when clinicians work together and communicate effectively as a team (1–3). Communication between clinicians is particularly important in the care of children with cancer, who are at higher risk of deterioration and subsequent mortality (2, 3). High-quality interdisciplinary communication has been linked to earlier recognition of adverse events and decreased mortality (4). Communication failures, however, often impact clinicians understanding of patient care plans (4), resulting in worse patient outcomes by delaying treatment and causing injury (5). Thus, enhancing interprofessional communication is important to improve patient outcomes and quality of care delivery (4, 6).

Barriers to teamwork and communication between clinicians include feeling disempowered to speak up, issues with hierarchy, and negative interpersonal communication (7). Few studies have addressed the quality of team communication, especially in resource-diverse settings. The CritCom tool, developed to fill this gap, is a new reliable and valid bilingual survey to assess the quality of interdisciplinary communication around patient deterioration for pediatric oncology patients (8). CritCom is an anonymous electronic provider survey that evaluates communication between clinicians across six domains: actionable, clarity, tone, collaboration and teamwork, leadership, and empowerment. CritCom was initially piloted at 42 hospitals in 22 countries among clinicians who care for children with cancer at risk of deterioration (9). For centers with three or more participants, a center-specific report was created to summarize responses and communicate results. This study explains the development of the report, which includes the initial drafting, review using focus groups, and revision of the report. This study also evaluated the clarity and usability of the CritCom center reports.

Recently, emphasis has been placed on creating dissemination efforts that are adaptable to local contexts, engaging stakeholders and encouraging continuing collaboration between researchers and participants (10). The use of reports can aid in quicker knowledge translation, closing the significant gap between research and practice (11). Further, reports must be developed in a clear manner, tailored to the stakeholder with clear and actionable messages (12). If research findings are not disseminated, then the research efforts themselves are largely considered a waste of effort and resources (13).

Timely report development, publication, and dissemination are important to quickly inform survey participants and hospital administration of the strengths and weaknesses of communication at their center, which can ultimately be used to implement policy focused on interprofessional communication in critical care settings, improving patient outcomes.

2 Methods

2.1 Report development

For centers with three or more participants, a report summarizing all staff responses was generated (see Figure 1) in English or Spanish based on prior experience with center-level reports of staff assessments (14). The report described performance in each domain (average and range), the overall communication score (average of all domains), list of strengths and opportunities (highest and lowest scoring items), detailed performance in each survey item, and suggestions for next steps. This report was modeled after another report created and used by this team for a prior study (15). A first draft of the CritCom report was drafted by the study team and reviewed by all study team members. The CritCom report was distributed to all participants at each center.

2.2 Report assessment

The CritCom report was assessed via focus groups consisting of participants from various centers. Participants were recruited among all individuals who completed the survey and received a hospital-based report. Focus groups were organized by participant profession (nurse vs. physician) and language (English vs. Spanish), with a total of four focus groups. The focus groups were structured using a facilitator guide to evaluate participant understanding about their center-specific report, as well as communication in their hospitals (see Additional File 1). The guide was initially developed in English based on prior work (14). A pilot focus group was conducted with five participants from St. Jude representative of the target audience. The guide was then revised based on feedback and translated to Spanish by bilingual team members (JR and MPT).

Focus groups were held via the web-conferencing platform Zoom. Participants were encouraged to participate with their video and engage as during an in-person discussion. Two individuals (PW and LC) who were not involved in CritCom report development facilitated the English focus groups. Bilingual members of the team (JR and MPT) facilitated the Spanish focus groups. Focus groups were audio-recorded, then were translated and transcribed by a professional service. Transcripts were deidentified and uploaded into MAXQDA for thematic analysis (16, maxqda.com). A codebook was developed from previous work and iteratively revised through review of two transcripts (see Additional File 1) (17). Two investigators (PW and LC) coded all transcripts with discrepancies resolved by two adjudicators (AA and SM). Thematic content analysis focused on participant experiences with communication and CritCom report feedback. The development and assessment process is depicted in Figure 2.

3 Results

Focus groups consisted of 11 English-speaking participants from five countries and 12 Spanish-speaking participants from four countries; these were 57% physicians and 43% nurses with a primary work area in the ward (65%) and intensive care unit (ICU) (35%). Identified themes included experiences with communication in their setting, report interpretation, and recommendations for improvement (Table 1).

Participants noted multiple examples of poor communication in their clinical settings: "*Maybe with nurse and physicians is better, but don't think the multidisciplinary team we don't have the same*

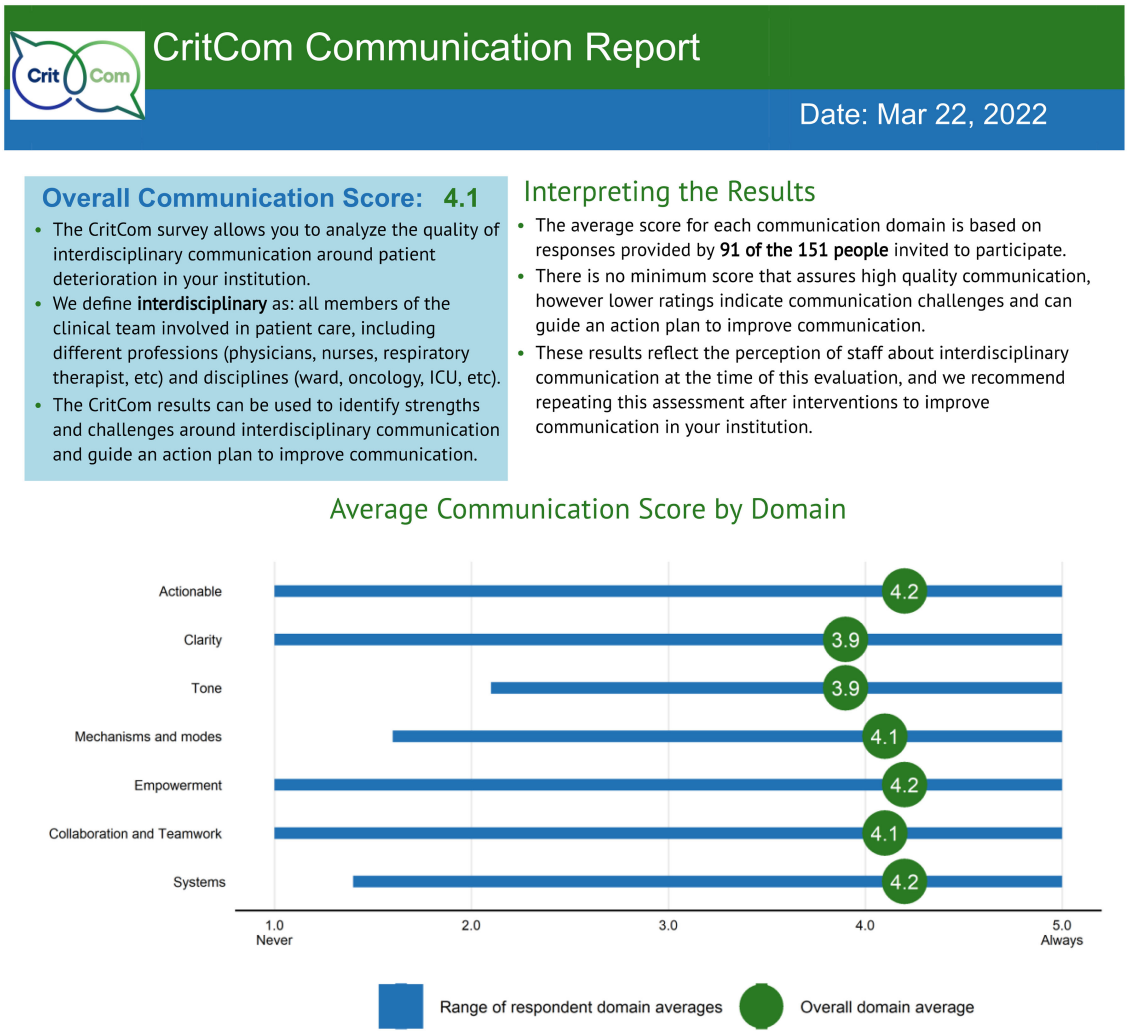

FIGURE 1 (Continued)

CritCom Communication Report:

Date: Mar 22, 2022

Actionable

Score 4.2

Communication that allows the team to get the job done. Communication contains relevant, complete, timely, and the necessary information to act.

1.	Staff in my unit communicate patient information in a timely manner	4.1
2.	In matters concerning patient care, nurses call physicians in a timely manner	4.2
3.	I know when I need to talk to someone about a change in the clinical status of my patient	4.5
4.	When a patient's status changes, staff communicate all relevant information to make management decisions	4.1
5.	During shift changes, staff exchange all essential patient information	4.0
6.	Staff communicate complete information when transferring a patient with deterioration from one unit to another	4.0

Clarity

Score 3.9

Communication that allows for the content to be clear, structured, and to communicate a shared mental model.

1.	Staff follows a structured method (e.g., SBAR, IPASS, or other institutional format) when communicating a patient concern to another team member	3.4
2.	Staff verbally confirm information that they receive from one another	3.9
3.	Our team uses standard medical language to communicate with other staff about a deteriorating patient's status	4.1
4.	Staff seek clarification about unclear information	4.3
5.	After talking about a patient with deterioration, staff have the same understanding about the next steps in management	4.0
6.	Our team communicates clearly	4.0

Tone

Score 3.9

Communication tone, including wording, non-verbal communication, and being ignored.

1.	Communication between staff in my unit has a positive tone	4.0
2.	In my unit, we talk about errors without placing blame	3.8
3.	Staff demonstrate active listening with other team members	4.0
4.	Staff in my unit use approachable non-verbal communication (body language, facial expression)	3.7
5.	Constructive criticism between staff is delivered in a way that promotes positive interactions	3.6
6.	When I speak up about a patient concern, I may be reprimanded or scolded	4.2
7.	When I speak up about a patient concern, I may be ignored or dismissed	4.0

Mechanisms and modes

Score 4.1

Structural elements of communication, including how we communicate, with whom, language barriers, and technology.

1.	We follow a standard protocol to guide escalation of care in a deteriorating patient	3.7
2.	I know who to talk to when I am concerned about the clinical status of a patient	4.5
3.	I can reach someone easily when I need to communicate about a deteriorating patient	4.4
4.	Our team uses written communication (for example patient notes, medical documentation) effectively	4.1
5.	Our team uses electronic communication (for example, phone or pager) effectively	4.1
6.	When there is a deteriorating patient, staff discuss patient care in person (face-to-face)	3.9
7.	There are language barriers (e.g., different languages or dialects) between members of the healthcare team	4.2

Results based on responses to the CritCom Communication Survey, ©2021, St. Jude Children's Research Hospital - Memphis, TN. USA

FIGURE 1 (Continued)

CritCom Communication Report:

Date: Mar 22, 2022

Collaboration and Teamwork

Score 4.1

Communication that allows for interdisciplinary collaboration between staff includes working collaboratively, teamwork, role clarity, and mutual respect.

1.	In my unit, staff treat each other with respect	4.2
2.	In my unit, there is good collaboration between nurses and physicians	4.1
3.	There is good collaboration between the ward and ICU teams	3.8
4.	I feel supported when discussing challenging patient care issues with other staff in my unit	4.3
5.	Staff in my unit work well together as a team	4.2
6.	Constructive criticism is welcome from any member of the team	3.6
7.	I know my role when managing a patient with deterioration	4.4
8.	Decisions regarding patient care are made collaboratively with input from all relevant disciplines (oncology, surgery, ICU, etc.)	4.1
9.	In my unit, both physicians and nurses contribute to decisions regarding escalation of care	4.0

Systems

Score 4.2

Systemic elements that improve or impede communication, including system structure, culture, reporting structures, and hierarchy.

1.	Unit leadership believes interdisciplinary communication is important	4.5
2.	Unit leadership is open to hearing patient safety concerns from staff	4.4
3.	Unit leadership encourages nurses to take initiative	4.2
4.	There is a clear chain of command (leadership structure) in my unit	4.3
5.	The ward nurses in my hospital are approachable	4.3
6.	The ICU nurses in my hospital are approachable	4.1
7.	The ward physicians (trainees, attendings, consultants) in my hospital are approachable	4.1
8.	The ICU physicians (trainees, attendings, consultants) in my hospital are approachable	4.2
9.	Unit leadership intervene if staff act in a way that impedes effective communication.	3.8
10.	In my unit, hierarchy is a barrier to communication	3.8

Empowerment

Score 4.2

Communication that allows team members to proactively evaluate patients, make decisions, speak up, and escalate concerns without the fear of consequences.

1.	I feel empowered to communicate freely with others on my team	4.3
2.	In my unit, nurses speak up to clarify a physician's order when they feel it may be incorrect	4.2
3.	It is easy for staff in my unit to ask questions when there is something that they do not understand	4.2
4.	I feel empowered to advocate for the care plan that I believe is appropriate for my patient	4.3
5.	Staff in my unit are comfortable questioning the decisions or actions of those with more authority	3.7
6.	Staff in my unit are comfortable calling for help for a patient with deterioration	4.5
7.	In my unit, it is easy to speak up if I perceive a problem with patient care	4.2

Next Steps

- These results can guide interventions to improve interdisciplinary communication in your institution.
- Areas with lower ratings indicate that there is room for improvement.
- Address domains that are modiı able and have data available to support the needed changes.
- Develop long-term strategies to tackle the domains that may be more difı cult to modify.
- Make plans to assess institution's quality of interdisciplinary communication on an ongoing basis to monitor changes as you strive for an ongoing impact.

Results based on responses to the CritCom Communication Survey, ©2021, St. Jude Children's Research Hospital - Memphis, TN. USA

FIGURE 1 (Continued)
CRITCOM report.

language for everyone." They also reported instances of good communication: "*how we communicate with other people not only because it is a doctor, a nurse, or staff member. We have to go all on the side of good communication for us to have the results … well positive to be able to assist the patient.*" Poor and good communication were noted to impact patient care: "*Well, I consider that if we take a long time to report on the patient's status, we also lengthen the patient's treatment time.*"

Overall, participants found the CritCom report to be clear, specific, and helpful to the strengths and weaknesses of

FIGURE 2
Report development and assessment process.

communication between clinicians at their center. "*It's very well designed and the information is adequate, concrete and at the same time extensive within two to three pages with a lot of graphics.*" Participants described the report scores and graphs easy to interpret. "*We just have to improve in the few points that we failed and not drop points in those where we did well.*" Participants also recognized the utility of the report to develop strategies to enhance communication within and between units: "*What we must work on and where we can continue to apply the knowledge that we already have but only reinforce them and have greater empowerment which is where we scored the lowest.*"

Additionally, participants offered several recommendations to improve the report, such as providing more information about participant demographics. Many also noted a need to include actionable steps: "*It would also be good to add a box with recommendations from their experience that they elaborated this survey to improve that communication in at least the areas where the scores were the lowest.*"

4 Discussion

This study describes the evaluation of the CritCom report to promote understanding of study findings by centers participating in the CritCom assessment. Our findings demonstrate that participants found the report to be clear, usable, and useful to visualize and understand their results.

The time lag between research and implementing findings into practice is too long (10, 18). Further, the percentage of research results that are implemented into practice is low, at approximately 14% (13, 18). Dissemination of information is necessary to adopt research findings into clinical practice (13).

Adapting research findings through the creation of reports is helpful to minimize this time lag by quickly transferring

TABLE 1 Focus group feedback.

Focus group feedback		
Theme	Code	Example quote
Experiences with communication in their setting	Communication challenges	"I also think that sometimes the other person to whom we are sending that message, does not receive it with the same importance in the way that we are taking the deterioration of the patient and maybe on those occasions is when the patient and the communication is lost."
	Good communication	"But most of all I feel that it is the trust and the empowerment that one has on the tool to communicate with the doctor."
	Impacts on patient care	"That is where the patient could be a transfer from intensive care when we could have performed actions before in the service. I think that bad communication between all would affect a lot."
	Other communication	"And the focus area, because the communication between health workers, physician, nurses, between unit and the unit is very important." "We know when to talk when need to transfer

(Continued)

TABLE 1 Continued

Focus group feedback		
Theme	Code	Example quote
		patients from one place to another there's an adequate amount of concern over the critical state of the patient and all of those mechanisms are functioning well, effective communication."
Report interpretation	Ease of interpretation	"I think that the graphs are very clear and that the extent of the report is obviously enough."
	Report or score interpretation	"I would interpret that in general we are not doing too bad but we can improve in many of the aspects and go through the pages to see what we have to work on to improve."
	Report use	"I consider that the report is good. It gives us the three … well it gives us the opportunities and strengths and under opportunities, we can guide ourselves or we can support ourselves from there to make improvement projects and later if we do the survey again to be able to measure how much we did, what we worked on and in what other things we can continue working."
	Seeking additional guidance	"So, I'm not sure that we'll be able to take specific action without a little bit more guidance based on these areas with room for improvement."
	Written material	"I think that it's very well written and summarized in a form that is very quick and easy because it provides us with all the information that has been collected in the survey so I think that it's okay and just as [Doctor 3] said the extent of it is correct."
	Domain graph	"I think that the graphs are very clear and that the extent of the report is obviously enough"
	Strengths and opportunities	"I think particularly the part that highlights the strengths and opportunities with the highest and lowest scores was helpful in just pulling that information to the front, but then having the opportunity to read and go deeper into the specific questions for each domain was up with scores was also helpful." "Yes, I agree. It is very well broken down in that each item that we are evaluating or that they evaluated us and where it tells us where we had the highest or lowest score of each area … let's say … team collaboration is where we are not doing well. We get to see each item where we were evaluated, and each question is very well explained, and it gives us as the idea of what we have to work. For me, it is quite good."
	Second and third pages	"It's not only about the opportunities that are highlighted two and three but also that we can break down every single item and see what are the aspects that we can also improve on."
	Other components	"I believe, apart from everything that is being said, that in regards to the images that appear at each of the subtitles, I don't know, maybe they should be a little larger or in color."
	Overall report	"To me I do not think that anything else is needed. To me, it was complete and digestible."
Recommendations for improvement	Confusion with the survey details	"Is it going to be for permanent staff or only for rotating substitute personnel? I think it would also be like specifying who the survey is addressed to."

(Continued)

TABLE 1 Continued

Focus group feedback		
Theme	Code	Example quote
	Report feedback	"Yeah, I think just looking at the overall communication score, you can't really tell much from it." "What are some interventions or even further assessments that can be done to look at those areas of opportunities? So what can you give us to help improve the way the constructive criticism is received?"

information from the researchers back to the clinical setting. Clear, easy to read, and descriptive reports describing communication can help hospital administration and unit leaders pinpoint areas of strength and weakness that can be targeted for intervention. Feedback from this report illustrates that participants could use the report to take actionable steps to improve communication at their hospital.

Studies have found that simply publishing research findings is often ineffective in actually changing practice, and thus the gap remains between research and practice (11). Targeted dissemination efforts, such as the CritCom report, are useful methods of translating information back into the hands of clinicians.

This work represents an example of how research findings can be made available to participants to promote local quality improvement and actionable change. Clinicians, researchers, and administrators can utilize the CritCom report to interpret CritCom results and improve interdisciplinary communication and, subsequently, patient outcomes. For example, the report can inform center-specific trainings or other strategies to improve the areas of communication that scored low. Providing clear and contextually appropriate reports of research findings allows participants to use study results to advocate to their hospital administration for local change.

This study has several limitations. Only nurses and physicians were invited to participate; members of the interprofessional team (respiratory therapists, etc.) were not included, as these roles did not exist at all centers. Additionally, this study was limited to English- and Spanish-speaking participants. This limits the generalizability of our findings regarding CritCom report usability to other professions and languages; future work should include these groups.

In summary, participant feedback illustrates that the CritCom report successfully provided clear and relevant findings regarding communication quality at each center. Using dissemination methods such as a summary report is useful to provide participants timely and actionable research data to inform strategies to improve team communication in their setting.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval were waived for this study due to determination of non-human subjects research as defined by the Common Rule at 45 CFR 46.102(I) and the Office for Human Research Protections (OHRP). It is under an exempt IRB from St. Jude Children's Research Hospital. The written informed consent was waived by IRB from St. Jude Children's Research Hospital.

Author contributions

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Transplant-associated thrombotic microangiopathy in pediatrics: incidence, risk factors, therapeutic options, and outcome based on data from a single center

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is a critical complication of hematopoietic stem cell transplantation. Awareness about TA-TMA has increased in recent years, resulting in the implementation of TA-TMA screening in most centers.

Methods: Retrospective analysis of children who underwent autologous or allogeneic hematopoietic stem cell transplantation at our center between January 2018 and December 2022 was conducted to evaluate the incidence, clinical features, and outcomes of TA-TMA following the administration of different therapeutic options.

Results: A total of 45 patients comprised the study cohort, of whom 10 developed TA-TMA with a cumulative incidence of 22% by 100 days after transplantation. Patients with and without TA-TMA in our cohort displayed an overall survival of 80% and 88%, respectively (p = 0.48), and a non-relapse mortality of 0% and 5.7%, respectively (p = 0.12), at 1 year after transplantation. Risk factors for TA-TMA development included allogeneic transplantation and total body irradiation-based conditioning regime. Among the 10 patients with TA-TMA, 7 did not meet the high-risk criteria described by Jodele and colleagues. Of these seven patients, two responded to calcineurin-inhibitor withdrawal without further therapy and five developed multiorgan dysfunction syndrome and were treated with anti-inflammatory steroids (prednisone), and all responded to therapy. The three patients with high-risk TA-TMA were treated with complement blockade or prednisone, and all responded to therapy.

Conclusion: TA-TMA is a multifactorial complication with high morbidity rates. Patients with high-risk TA-TMA may benefit from complement blockade using eculizumab. No consensus has been reached regarding therapy for patients who do not meet high-risk criteria. Our analysis showed that these patients may respond to anti-inflammatory treatment with prednisone.

KEYWORDS

transplant-associated thrombotic microangiopathy, hematopoietic stem cell transplantation, eculizumab, multiorgan dysfunction syndrome, high-risk transplant-associated thrombotic microangiopathy, calcineurin inhibitor

Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) is a serious complication of hematopoietic stem cell transplantation (HSCT) with high mortality and chronic organ injury (1). TA-TMA is a multifactorial complication characterized by endothelial dysfunction or injury, which leads to microangiopathic Coombs-negative hemolytic anemia, refractory thrombocytopenia, and multiorgan damage (2). Multiorgan damage may manifest as renal insufficiency, polyserositis, gastrointestinal bleeding, pulmonary hypertension, and/or encephalopathy (2–7).

TA-TMA can range from mild TA-TMA, which may need no therapy or only withdrawal of trigger medications [such as calcineurin inhibitors or mammalian target of rapamycin (mTOR) inhibitors], to severe TA-TMA, which has high mortality rates (7–9).

Histological confirmation remains the gold standard for TA-TMA diagnosis. The limited feasibility of invasive intervention after HSCT necessitates the development of non-invasive diagnostic criteria (1, 9–12). Most diagnostic criteria include elevated lactate dehydrogenase (LDH), low haptoglobin, thrombocytopenia, and the presence of schistocytes on peripheral blood smears (13).

The incidence of TA-TMA is unclear and varies from 0.5% to 76% according to the published literature (9). TA-TMA may develop after both allogeneic and autologous HSCT. Multiple risk factors mentioned in retrospective studies, including busulfan-based and total body irradiation (TBI)-based myeloablative conditioning, development of graft-versus-host disease (GvHD), GvHD prophylaxis using calcineurin inhibitors or mTOR inhibitors, and viral infection with cytomegalovirus, adenovirus, and human herpes virus 6, are associated with TA-TMA development (1, 8, 14–24).

The pathophysiology behind endothelial injury is still unclear. Recent studies have proposed a three-hit hypothesis: an underlying predisposition to compliment activation, toxic conditioning regimen, and post-transplant factors (14). Conditioning regimen, toxic medication, infections, and other transplant-related factors may induce endothelial injury, leading to increased protein inflammatory cytokine secretion that further promotes endothelial injury and activates the complement cascade (14).

Therapeutic options for treating TA-TMA with variable efficacy include plasma exchange, administration of rituximab, withdrawal of calcineurin inhibitor, and complement blockade (7, 9, 14, 20, 25–29). Newer published reports showed that patients have evidence of complement dysregulation (7, 30). This might suggest that complement blockade may be a therapeutic option for severe TA-TMA (7, 31–34). In recent studies, inhibition of complement activity has demonstrated promising results in selected patients with TA-TMA. The monoclonal antibody eculizumab binds C5 and inhibits terminal complement activation. Jodele and colleagues established a protocol to identify high-risk patients with TA-TMA (25). After administering eculizumab to the high-risk patients identified, 64% of the patients showed partial response (PR) and 56% achieved complete remission. Therefore, Jodele et al. recommend the early initiation of eculizumab and adjustment of its dosing to improve response.

In addition to classical complement pathway activation, the lectin complement pathway is activated by endothelial injury. Activation of lectin pathway also triggers the coagulation cascade, which also leads to the procoagulant phase, platelet adhesion, tissue injury, and finally to organ damage (35). Narsoplimab is a human monoclonal antibody that binds to mannan-binding lectin serine protease 2 (MASP2) and thereby blocks lectin-mediated complement activation without affecting the classical pathway. A phase II study administered narsoplimab in adults with severe TA-TMA and achieved high response rates (74%) in terms of laboratory markers and organ function without serious adverse effects (35, 36). Nevertheless, the lack of consensus on the standard treatment approach for TA-TMA makes it challenging to treat this complication.

In this paper, we describe our clinical experience involving a cohort of children who underwent transplantation at our center between January 2018 and December 2022.

Abbreviations: TA-TMA, transplant-associated thrombotic microangiopathy; MODS, multiorgan dysfunction syndrome; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; VOD/SOS, hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS); MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; BM, bone marrow; pBSC, peripheral blood stem cell; CSA, ciclosporin A; CNI, calcineurin inhibitor; OS, overall survival; Bu, busulfan; TBI, total body irradiation; MMF, mycophenolate-mofetil; NRM, non-relapse mortality; CMV, cytomegalovirus; mTOR, mammalian target of rapamycin; AKI, acute kidney injury; cys-c GFR, cystatin c glomerular filtration rate; LDH, lactate dehydrogenase; MUD, matched unrelated donor; MFD, matched family donor.

Methods

TA-TMA screening

In our cohort, we utilize a screening and diagnosis algorithm according to evidence-based guidelines described in prior studies (1, 2, 9, 12, 30, 37–39) (Figure 1). The pediatric patients at our institution were monitored for TA-TMA before conditioning them and until day 100 after transplantation or until TA-TMA resolves. The routine monitoring for TA-TMA in the first 30 days post-transplant included daily blood count, renal function parameters [creatinine, urea, and cystatin c glomerular filtration rate (cys-c GFR)], blood pressure, LDH measured twice weekly, haptoglobin, the presence of schistocytes, and random urine protein/creatinine ratio in urine specimen. Complement activation (C50, C5b-9, and Anti H) was checked only if TA-TMA was suspected. The standard monitoring after day 30 post-transplant included weekly complete blood count, LDH, cys-c GFR, and the presence of schistocytes in blood smear. The laboratory characteristics are shown in Table 1.

Definition of TA-TMA and risk stratification

We applied the diagnostic criteria published by Jodele et al. in 2014 and Dandoy et al. in 2020 (2, 12, 18, 25, 37, 39–41). TA-TMA was

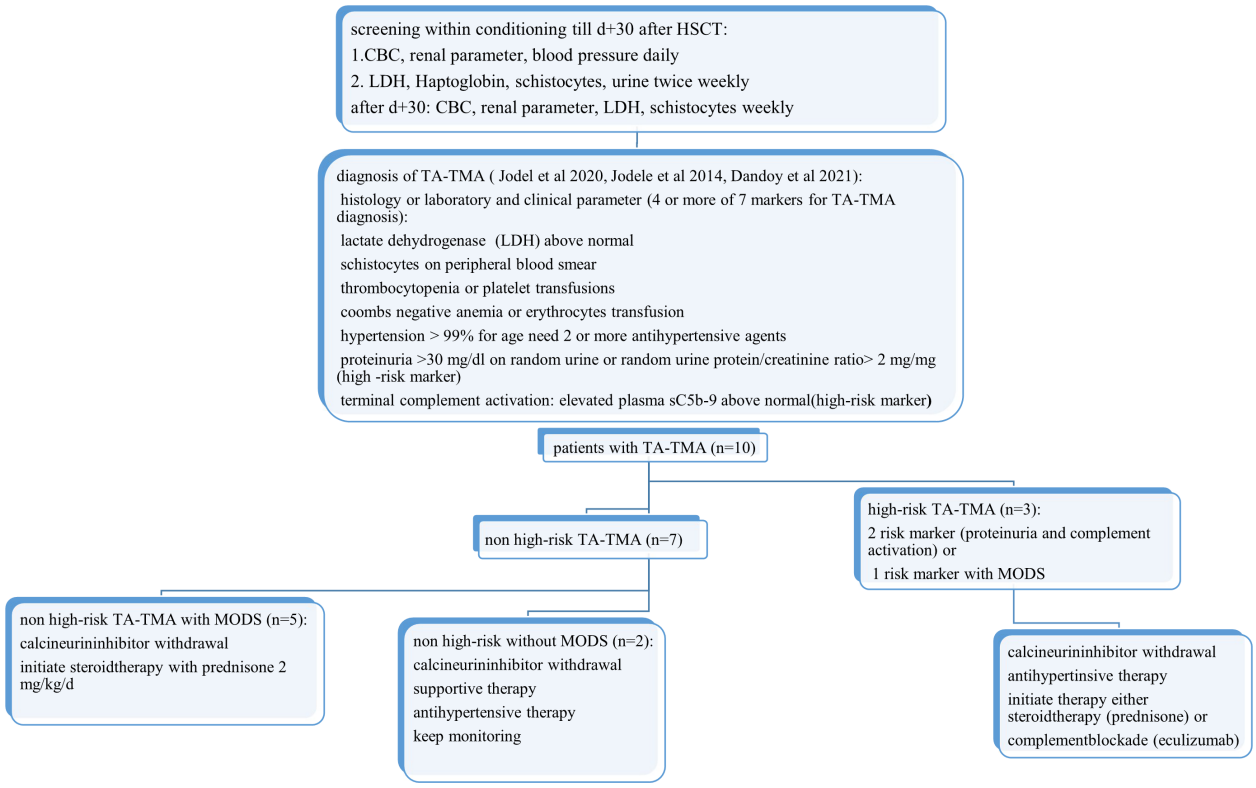

FIGURE 1
Screening and proposed therapy algorithm. LDH, lactate dehydrogenase; CBC, complete blood count. The patients were monitored for TA-TMA before conditioning them and until day 100 after transplantation or until TA-TMA resolves. Monitoring for TA-TMA in the first 30 days post-transplant included the evaluation of CBC, renal retention parameter (creatinine, urea, and cys-c GFR), blood pressure, LDH measured twice weekly, haptoglobin, schistocytes, and random urine protein/creatinine ratio in the urine specimen. The standard monitoring after day 30 post-transplant included weekly CBC, LDH, cys-c GFR, and schistocytes in blood smear. We applied the diagnostic criteria published earlier. TA-TMA was diagnosed either histologically based on a biopsy of affected organs or when four or more out of seven laboratory/clinical markers were simultaneously present and confirmed in two consecutive tests. These markers included elevated LDH, positive schistocytes, *de novo* thrombocytopenia, Coombs-negative hemolytic anemia, hypertension, and two high-risk criteria: proteinuria >30 mg/dL or random urine protein/creatinine ratio >2 mg/mg and terminal complement activation (c5b-9). Patients were classified as high risk if they fulfilled both high-risk criteria at diagnosis, or one high-risk criteria with evidence of multiorgan damage/dysfunction. All patients with TA-TMA received supportive therapy to heal the underlying organ injury, including antihypertensive therapy, minimized transfusion regimen, and management of acute infections and other transplant-related complications. GvHD prophylaxis with calcineurin or mTOR inhibitors were stopped for all patients within 2 weeks after diagnosis considering GvHD risk and time point post-HSCT with or without replacement therapy (mycophenolate-mofetil). High-risk patients with TA-TMA instantly received additional treatment with complement blockade (eculizumab) or high doses of prednisone 1–2 mg/kg/d tapered over 4–6 weeks. All patients with non-high-risk TA-TMA with multiorgan dysfunction syndrome (MODS) received anti-inflammatory therapy with prednisone 1–2 mg/kg/d followed by tapering over 4–6 weeks. Patients with non-high-risk TA-TMA without MODS were monitored closely without further therapy and received prednisone only if they did not respond to withdrawal of calcineurin inhibitors.

diagnosed either histologically based on biopsy of affected organs or when four or more laboratory/clinical markers out of seven markers were simultaneously present and confirmed in two consecutive tests. These markers included (1) elevated LDH, (2) presence of schistocytes in blood smear, (3) *de novo* thrombocytopenia (number of thrombocytes < 50 × 10^9/L) or >50% decrease in platelet count, (4) Coombs-negative hemolytic anemia or increasing need for blood transfusion, and (5) hypertension > 99th percentile for age along with the high-risk criteria: (6) evidence of kidney injury with proteinuria (protein level in urine > 30 mg/dL) or random urine protein/creatinine ratio > 2 mg/mg and (7) terminal complement activation (C5b-9).

Patients were classified as high risk if they fulfilled both high-risk criteria at diagnosis or one high-risk criteria with evidence of multiorgan damage/dysfunction [multiorgan dysfunction syndrome (MODS)] (2, 14, 25, 41–49).

Definition of multiorgan dysfunction syndrome

TA-TMA affects a wide spectrum of organs and may result in acute or chronic organ dysfunction. This includes renal injury, hypertension, intestinal bleeding, encephalopathy, pulmonary hypertension, and polyserositis (1, 2, 14, 25). Patients with TA-TMA with MODS are critically sick and need prompt therapeutic interventions although these patients do not always fulfill the high-risk criteria for TA-TMA.

TABLE 1 Laboratory characteristics and clinical risk factors in patients with and without TA-TMA.

	Patients with TA-TMA $N = 10$	Patients without TA-TMA $N = 35$	p-value
Laboratory findings during the first 100 d after HSCT: LDH (U/L)	507 (287–867)	281 (180–374)	$p < 0.001$
No. of platelet transfusions in the first 100 d	11 (4–32)	10 (1–32)	$p = 0.071$
No. of erythrocyte transfusions in the first 100 d	8 (3–15)	6 (1–13)	$p = 0.087$
Days to platelet engraftment > 20 × 10^9/L	38 (12–150)	25 (11–120)	$p = 0.2$
Days to platelet engraftment > 50 × 10^9/L	49 (12–170)	30 (12–150)	$p = 0.098$
AKI (doubling of creatinine)	8 (80%)	7 (20%)	$p < 0.001$
Clinical risk factors			
aGvHD Grade II–IV	2 (20%)	12 (34.2%)	$p = 0.63$
Viral infection	3 (30%)	11 (31.4%)	$p = 0.74$
VOD/SOS	0	4 (11.4%)	$p = 0.26$

TA-TMA, transplant-associated thrombotic microangiopathy; aGvHD, acute graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; VOD/SOS, hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS); AKI, acute kidney injury; LDH, lactate dehydrogenase (reference 100–250 U/L).

Patients and clinical data

All patients who underwent allogeneic and autologous HSCT at our institution between January 2018 and December 2022 were included in this cohort ($n = 35$ and $n = 10$, respectively). The indication for autologous HSCT was high-risk neuroblastoma in seven cases and relapsed Ewing sarcoma, germ-cell cancer, and relapsed nephroblastoma in one case each. Patient data were collected, including sex, transplant diagnosis, stem cell source, conditioning regimen (50), GvHD prophylaxis, transplantation-related complications, and outcome. GvHD was diagnosed according to the Glucksberg clinical criteria (51). The clinical characteristics are shown in Table 2. We divided the participants with TA-TMA in our cohort according to the high-risk criteria into three groups: (1) high-risk TA-TMA (2, 14, 25), (2) non-high-risk TA-TMA with MODS (1, 14, 25), and (3) non-high-risk TA-TMA without MODS.

The study was approved by the local ethics committee of our institution.

Statistical analysis

SPSS statistical software, version 29 (IBM®, New York, USA) was used to analyze the collected data. Pearson's chi-squared test was used to determine any association between age, gender, cell source, HSCT type, conditioning, etc. as risk factors and TA-TMA development. Moreover, t-test and one-factor analysis of variance were used to test whether the average values of multiple clinical and laboratory factors between the patients with and without TA-TMA and among the TA-TMA groups are different. The results are expressed as an odds ratio (OR) with a 95% confidence interval (CI), and data were considered significant at p-value < 0.05.

Results

Cohort characteristics

We identified 45 pediatric patients who underwent allogeneic or autologous HSCT at our institution from January 2018 to December 2022. The clinical characteristics are shown in Table 2. Malignant diseases were the most common underlying diagnosis ($n = 28$, 62%). Moreover, 35 subjects received allogeneic transplants (77.8%) from 9/10 or 10/10 matched unrelated donor ($n = 30$, 85.8%), matched family donor ($n = 2$, 5.7%), or haploidentical donor ($n = 3$, 8.5%), and the most frequent cell source was peripheral blood stem cells ($n = 37$, 82%). Nearly all transplant recipients (95.5%) received TBI-, busulfan-, or treosulfan-based myeloablative conditioning. Ciclosporin A was the most frequently used GvHD prophylaxis ($n = 32$, 91.4%).

Ten of the 45 patients (22%) met the criteria for TA-TMA diagnosis. High-risk TA-TMA was diagnosed in 6.6% of all HSCT patients ($n = 3$), of which two cases occurred after allogeneic HSCT and one case occurred after autologous HSCT with high-risk neuroblastoma.

All affected patients developed this complication within the first 100 days after transplantation with a median of 49 (11–98) days. Patients with high-risk TA-TMA were more likely to be older in comparison to non-high-risk patients [median age, 14 (8–17) years vs. 8.5 (2–17) years, respectively] and developed pericardial/pleural effusions more frequently ($p = 0.01$). No patient in our cohort had evidence of complement activation (C5b-9 range: 98–191 ng/mL). Patients with or without high-risk TA-TMA showed no difference in conditioning regimen ($p = 0.098$), GvHD rates (30% vs. 31%, $p = 0.63$), and documented infection (20% vs. 34.2%, $p = 0.74$). The demographics and characteristics of patients with TA-TMA are shown in Table 3.

Clinical monitoring

The number of erythrocyte and platelet transfusions was documented for 100 days after transplantation. Red blood transfusion was administered at a hemoglobin level < 7 g/dL and platelet count < 20 × 10^9/L. Hypertension was defined when systolic and/or diastolic values > 99th percentile for age. The number of antihypertensive medications for each patient was also documented. Cytomegalovirus, adenovirus, and Epstein–Barr virus screening via polymerase chain reaction were performed at least once weekly.

TABLE 2 Baseline clinical characteristics of patients who underwent HSCT between January 2018 and December 2022.

	Patients with TA-TMA *N* = 10	Patients without TA-TMA *N* = 35	*p*-value
Male sex	5 (50%)	21 (60%)	0.46
Age, years	11 (2–17)	6 (1–17)	
Age			0.24
>10 years	4 (40%)	8 (22.8%)	
<10 years	6 (60%)	27 (77.2%)	
Initial diagnosis			0.46
Malignancy	5 (50%)	23 (65.7%)	
Bone marrow failure (MDS, SAA)	3 (30%)	5 (14%)	
Immunodeficiency/ metabolic disease	1 (10%)	4 (11.4%)	
Benign hematologic disease	1 (10%)	3 (8.5%)	
HSCT-Typ			0.29
Allogeneic	9 (90%)	26 (74.3%)	
MUD (9 or 10/10)	8 (89%)	21 (80.7%)	
MFD	0	2 (7.7%)	
MMFD (haploidentical)	1 (11%)	3 (11.5%)	
Autologous	1 (10%)	9 (25.7%)	
Stem cell source			0.037
BM	4 (40%)	4 (11.4%)	
PBSC	7 (70%)	30 (85.7%)	
Conditioning regimen			0.098
Bu-based regimen	2 (20%)	10 (28.5%)	
TBI-based regimen	3 (30%)	2 (5.7%)	0.031
Other	5 (50%)	23 (65.7%)	
GvHD prophylaxis			0.75
CSA-based prophylaxis	8 (80%)	24 (68.6%)	
MMF-based prophylaxis	1 (10%)	2 (5.7%)	

TA-TMA, transplant-associated thrombotic microangiopathy; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; BM, bone marrow; pBSC, peripheral blood stem cell; CSA, ciclosporin A; Bu, busulfan; TBI, total body irradiation; MMF, mycophenolate-mofetil.

A diagnosis of acute kidney injury was reached if the creatinine values were doubled compared to the baseline value before transplantation (2, 40, 52).

The occurrences of MODS, GvHD, and transplantation-related complications were noted for the first 100 days after transplantation.

Risk factors for TA-TMA

Among the 45 subjects, TA-TMA was more likely to develop after allogeneic HSCT than after autologous HSCT (25.7% vs. 10%, respectively, $p = 0.29$). All TA-TMA cases that developed after allogeneic HSCT were seen in patients who received transplants from matched unrelated donors. No statistical difference in TA-TMA rates was seen between allogeneic transplantations from 9/10 or 10/10 unrelated donors (40% vs. 24%, $p = 0.4$). The risk was slightly higher in patients with non-malignant disease in comparison to those with malignant diseases in the whole cohort (29.4% vs. 17.8%, $p = 0.46$) and in the allogeneic HSCT (29.4% vs. 22.2%, $p = 0.46$) both without statistical significance. As a cell source, only bone marrow showed a significant difference (50% vs. 18.9%, $p = 0.037$), although the results should be considered carefully considering the low patient numbers in our cohort.

Notably, the risk of developing TA-TMA was higher in older patients (>10 years old), but without statistical significance. Out of 12 patients in our cohort who were older than 10 years, 4 developed TA-TMA, compared to 6 out of 33 who were younger (33.3% vs. 18%, $p = 0.24$). GvHD prophylaxis with ciclosporin A was not an independent risk factor for TA-TMA (33.3% vs. 25%, $p = 0.75$), given that it was used in all cases and there was no comparison group.

Nearly all subjects received myeloablative conditioning (95.5%). We observed that patients who received TBI-based conditioning were more likely to develop TA-TMA (60% vs. 17.5%, $p = 0.031$). Busulfan- and treosulfan-based regimens did not appear to be a significant risk factor for TA-TMA development (16.6% vs. 24.2, $p = 0.7$ and 26% vs. 18.2%, $p = 0.72$, respectively).

Severe acute GvHD (Grades III and IV) was not a significant risk factor for TA-TMA development (30% vs. 31%, $p = 0.63$), and infections in the first 100 days after transplantation were similarly not associated with an increased risk for TA-TMA. Our cohort of patients who developed other types of angiopathy complications (hepatic veno-occlusive disease or sinusoidal obstruction syndrome) do not exhibit a significantly increased risk of developing TA-TMA (0% vs. 11.4%, $p = 0.26$).

Treatment of TA-TMA

Recent studies have tried to develop treatment strategies based on TA-TMA pathophysiology (2, 14, 25, 53). Several have reported that calcineurin inhibitors such as ciclosporin and tacrolimus and mTOR inhibitors such as sirolimus might be probable causal factors for endothelial injury in patients with TA-TMA (1, 8, 9, 23, 54, 55).

All patients with TA-TMA at our institution received supportive therapy to heal the underlying organ injury, which included antihypertensive therapy, minimized transfusion regimen (2, 14, 25, 39), and management of acute infections and other transplant-related complications.

GvHD prophylaxis with calcineurin or mTOR inhibitors were stopped in all patients within 2 weeks after diagnosis considering GvHD risk and the time point after administering HSCT with or

TABLE 3 Demographics and disease characteristics of patients with TA-TMA.

	High-risk TA-TMA			Non-high-risk TA-TMA						
Patients	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10
Age at SCT, years	<10	>10	>10	<10	<10	>10	<10	<10	<10	>10
Diagnosis	M	B	M	M	M	B	B	B	M	B
Stem cell source	pB	pB	pB	BM	BM	BM	pB	pB	BM	pB
Conditioning regimen	TBI/VP16	Treo/Fl/TT	Bu/Mel	TBI/VP16	TBI/VP16	Fl/Cy	Bu/Fl/Mel	Treo/Fl	Treo/ Fl/TT	Treo/Fl
Days after SCT at diagnosis	92	43	16	21	100	11	47	17	54	98
Cys c-GFR mL/ min/1.73 m²	49	62	83	50	91	59	108	66	90	42
Proteinuria (protein level in urine > 30 mg/dL) or protein-creatinine ratio > 2 mg/mg	31 mg/dL	26 mg/dL, P/C ratio: 3.3 mg/mg	30 mg/dL	No	No	6 mg/dL	14 mg/dL	5 mg/dL	11 mg/dL	26 mg/dL
Transplant-related complication	Serositis	Serositis	Serositis	Serositis, encephalopathy	Serositis	Serositis	PHT	Intestinal bleeding, serositis	No	No
Complement C5b-9 (ng/mL)	150	125	191	121	170	156	107	133	98	188
Biopsy	Kidney	ND	ND	ND	ND	ND	ND	Colon	ND	ND
GvHD stage, organ	Grade I, skin	Grade I, skin	NA	Grade II, skin	No	Grade II, skin	No	No	No	No
Infections	No	Herpes simplex	No	EBV/CMV	No	EBV	No	No	No	No
Therapy	Eculizumab CNI withdrawal	Eculizumab + Pred + CNI withdrawal	Pred	CNI withdrawal + Pred	CNI withdrawal + Pred	CNI withdrawal + Pred	CNI withdrawal + Pred	CNI withdrawal + Pred	CNI withdrawal	CNI withdrawal
Response	CR	PR	CR	CR	PR	CR	CR	CR	CR	CR

M, malignant; B, benign; NA, not applicable; ND, not done; CR, complete response; PR, partial response; BM, bone marrow; pB, peripheral blood stem cells; CNI, calcineurin inhibitor; TBI, total body irradiation; VP16, etoposide; Bu, busulfan; Treo, treosulfan; Flu, fludarabine; Mel, melphalan; Cy, cyclophosphamide; Pred, prednisone; GvHD, graft-versus-host disease; complement C5b-9, reference 58–239 ng/mL; PHT, pulmonary hypertension; P/C ratio, protein/creatinine ratio in spontaneous urine sample.

without replacement therapy (mycophenolate-mofetil) (8, 9, 23, 54, 56, 57). Patients with high-risk TA-TMA instantly received additional treatment with complement blockade (eculizumab) (7, 14, 18, 25, 27–29, 58, 59) or high doses of prednisone 1–2 mg/kg/d and tapering over 4–6 weeks.

All patients with non-high-risk TA-TMA with MODS received anti-inflammatory therapy with prednisone 1–2 mg/kg/d followed by tapering over 4–6 weeks (14). Patients with non-high-risk TA-TMA without MODS were monitored closely without further therapy and received prednisone only if they did not respond to calcineurin inhibitor withdrawal.

Classification of treatment response

Response to therapy was evaluated once a week during the therapeutic regimen and after it ended. Overall survival was evaluated at 3, 6, and 12 months after transplantation. Patients were defined as displaying complete response (CR) if MODS, transfusion-dependent anemia, and thrombocytopenia resolved completely (25). Patients with no response (NR) still have active disease with MODS or still need transfusion of erythrocytes and/or thrombocytes. All other patients, who did not meet NR or CR criteria or who had relapsed after therapy stopped, were defined as having PR.

Complications of TA-TMA and therapeutic response

Our cohort showed variability in the clinical presentation and disease management of TA-TMA. Patient demographics and disease characteristics are shown in Table 3.

Renal impairment and chronic kidney disease were the most frequent complications in patients with TA-TMA (n = 8, 80%),

followed by (poly)serositis that resulted in pleural and pericardial effusion and ascites (n = 7, 70%). Pulmonary hypertension (n = 1, 10%), gastrointestinal bleeding (n = 1, 10%), and encephalopathy (n = 1, 10%) were also documented. No patient in our study showed complement activation at TA-TMA diagnosis. The cys-c GFR of most patients with significant renal injury were still below the pretransplantation cys-c GFR after the patients recovered from TA-TMA (n = 6, 60%) and needed long-term follow up.

Cessation of immunosuppression by withdrawing calcineurin inhibitors or switching to mycophenolate-mofetil was the first therapeutic strategy employed in all patients with TA-TMA.

Patients with TA-TMA also received adjunct therapy such as complement blockade with eculizumab or anti-inflammatory agents with prednisone according to high-risk stratification or existing critical organ damage/dysfunction as seen in MODS. Patients with high-risk TA-TMA (n = 3, 30%) were treated with eculizumab (n = 1, 10%) and prednisone (n = 2, 20%). Two patients achieved CR (66%), while one patient showed PR (33%) to therapy with prednisone and was switched to eculizumab. The number of eculizumab doses was 11, and the duration of therapy was 113 days. Therapy was well tolerated without any significant side effects. Response to therapy is described in Table 4.

Patients who did not meet the high-risk criteria were divided into critically sick patients with MODS who received therapy with prednisone (n = 5, 50%) and patients without MODS who did not receive adjunct treatment (n = 2, 20%). All patients with non-high-risk TA-TMA with MODS showed CR to prednisone therapy with a median treatment duration of 38 (30–48) days (Figure 1).

It is worth mentioning that withdrawal of calcineurin inhibitors was initiated in many patients concurrently with the initiation of corticosteroid administration (6/10 patients with TA-TMA, 60%, 1 with high-risk TA-TMA and 5 with non-high-risk TA-TMA) (Table 3). Therefore, it is not clear whether the withdrawal of calcineurin inhibitors by itself possibly resolved TA-TMA without the addition of steroids.

TA-TMA in all patients without MODS (n = 2, 20%) resolved spontaneously approximately 14 (12–21) days after ceasing immunosuppression without adjunct treatment.

The adjusted analysis showed that hematologic resolution occurred in 77 (36–105) days and 77 (26–150) days in high-risk and non-high-risk TA-TMA, respectively.

Eight of 10 patients with TA-TMA in our cohort were alive 1 year after diagnosis with an overall survival of 80% and non-relapse mortality of 0% (Figure 2).

Discussion

In this paper, we report our experience in the diagnosis and management of patients with newly diagnosed TA-TMA after HSCT. The cohort had 45 pediatric transplant recipients who underwent allogeneic or autologous HSCT. The overall incidence of TA-TMA reported in the literature varies widely from 0.5% to 76%. This wide range may be attributed to the fact that most recent studies are retrospective observations; moreover, mild TA-TMA cases may have remained undiscovered (2, 12, 17, 60).

In our cohort, TA-TMA was documented in 22% (n = 10) of all patients based on currently published diagnostic criteria. All cases occurred within 100 days after transplantation with a median time of 49 (11–98) days.

Several studies have observed a high risk of TA-TMA following autologous HSCT in children (2, 7, 61). In our study, only 1 patient out of 10 autologous HSCTs with high-risk neuroblastoma developed TA-TMA, giving rise to a TA-TMA incidence of 10%. A single-centered study by Schoettler et al. described pediatric TA-TMA following autologous HSCT. The incidence of TA-TMA was 3.7%, which occurred most frequently in patients with neuroblastoma (78%), all of whom were conditioned with carboplatin, etoposide, and melphalan. Consistent with our observations, TA-TMA was diagnosed within the first 100 days after transplantation. Most of these patients had normal levels of complement and had renal involvement at presentation. In the study by Schoettler et al., the prevalence of TA-TMA in patients with neuroblastoma was 6%, which is low compared to 14% (1 of 7) in our study and significantly lower than that mentioned in the literature (30%). Considering that all the patients with neuroblastoma in our cohort were conditioned with busulfan and melphalan, we believe that patients with neuroblastoma may have additional risk factors related to the disease itself. These factors may include endothelial injury caused by the initially high levels of catecholamine in combination with standard chemotherapy apart from conditioning regimen (62).

When examining the risk factors associated with TA-TMA, we found a higher incidence of TA-TMA among patients who received a conditioning regimen with TBI (60 vs. 17.5%, p = 0.031), were older than 10 years (33.3 vs. 18%, p = 0.24), and had non-malignant diseases (29.4% vs. 17.8%, p = 0.46) (2); however, GvHD prophylaxis with calcineurin inhibitors did not seem to be an independent risk factor for TA-TMA development (33.3% vs. 25%, p = 0.75). Similar results were reported by Higham et al. in 2021, who described a retrospective analysis of TA-TMA with 257 pediatric patients who underwent 292 allogeneic HSCTs (63). They showed higher incidence of TA-TMA in patients aged >10 years than in those aged <10 years (9.8% vs. 3.1%, p = 0.4) and in patients who received TBI-based myeloablative conditioning regimens compared with non-TBI-based regimens (12.2% vs. 5.7%, p = 0.17) with no impact from the stem cell source.

Contrary to our results, severe aplastic anemia as an underlying disease was found to be a clear risk factor compared with patients with malignancy or other non-malignant diagnoses (17.6% vs. 8.3% vs. 0%, p = 0.006). However, we detected higher rates of TA-TMA in patients with bone marrow failure, including severe aplastic anemia and myelodysplastic syndrome, who underwent allogeneic HSCT compared to malignant or other non-malignant diseases (37.5% vs. 22.2% vs. 22.2%, p = 0.68) (63).

Patients who met the criteria of TA-TMA have a high risk of post-transplant morbidity and may develop multiple clinically significant complications including pulmonary hypertension, severe gastrointestinal bleeding, and pleural and pericardial effusion. This supports the observations of previous studies that TA-TMA may lead to multiorgan damage/dysfunction, which coexist with other HSCT complications (2, 14, 64–69).

TABLE 4 Response to therapy.

	High-risk TA-TMA n=3	Non-high-risk TMA MODS+ n=5	Non-high-risk TMA MODS– n=2	*p*-value
Age, years	14 (8–17)	7.8 (2–17)	10.5 (4–17)	$p = 0.43$
Time until normalization of LDH, d	23.6 (7–44)	27.8 (11–74)	94 (48–140)	$p = 0.095$
Time until normalization of haptoglobin, d	98 (14–225)	99.6 (78–230)	115 (80–150)	$p = 0.922$
Time until disappearance of schistocytes, d	45 (12–75)	19.6 (14–30)	96.5 (43–150)	$p = 0.078$
Time until platelets were recovered to >20 × 10^9/L	25.3 (12–40)	35.2 (12–80)	37.5 (30–45)	$p = 0.8$
Time until TA-TMA resolution, d	65.8 (36–105)	65.8 (26–120)	105 (60–150)	$p = 0.54$

TA-TMA, transplant-associated thrombotic microangiopathy; MODS, multiorgan dysfunction syndrome; MODS+, with MODS; MODS–, without MODS; LDH, lactate dehydrogenase; d, days; Y, years.

The TA-TMA severity in our cohort ranged from mild, self-limiting TA-TMA to severe, high-risk TA-TMA with proteinuria, renal injury, multiorgan damage, and high risk of morbidity and admission to intensive care unit (2). Mild cases resolved with supportive care only, including antihypertensive therapy, minimization of transfusions, and withdrawal of calcineurin inhibitors (9, 14). High-risk TA-TMA has successfully been treated with different medications. Based on recent studies on the efficacy and safety of complement blockade in patients with high-risk TA-TMA, one patient was treated with eculizumab while the other two patients were treated with prednisone in the present study (9, 14, 25, 39, 53, 70, 71). TA-TMA was resolved in one of the two patients who received prednisone; however, prednisone therapy had to be switched to eculizumab therapy in the other patient due to relapse after initial response. This patient showed PR to eculizumab and developed chronic renal insufficiency. It remains unknown why the two patients showed a clinical response with complement blockade despite no evidence of complement activation being detected in the laboratory.

In our cohort, we observed a group of patients with non-high-risk TA-TMA ($n = 5$, 50% of all patients with TA-TMA), who were critically sick with MODS and TA-TMA-related complications. To our knowledge, no consensus exists regarding therapy for these types of patients.

Recent publications examining TA-TMA pathophysiology, which hypothesized that endothelial injury leads to an increase in proinflammatory cytokine, procoagulant factors, and adhesion molecules, led us to consider interrupting the inflammatory cascade with prednisone. Since the stimulation of endothelial injury in most cases is temporary, we tapered prednisone over 4–6 weeks (14, 25).

All five patients responded to therapy with hematological and MODS resolution in 65 (26–120) days. Most patients with TA-TMA with significant renal injury still exhibited a cys-c GFR that

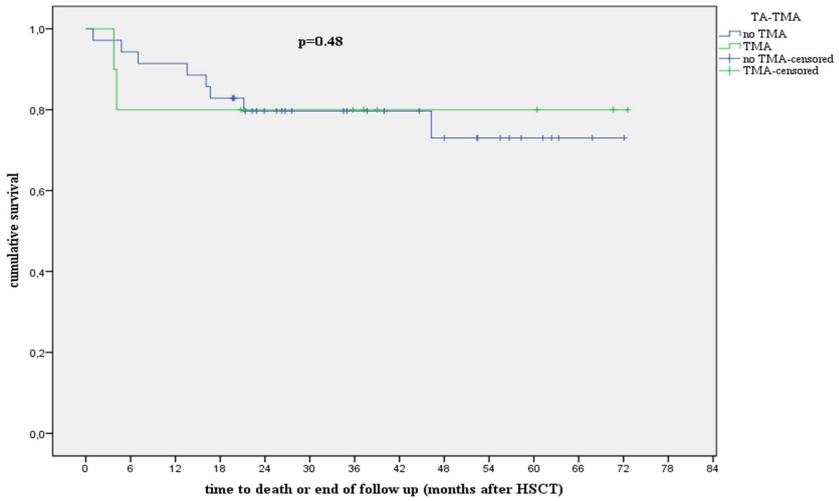

FIGURE 2
Analysis showing survival in patients with and without TA-TMA. hR, high risk; HSCT, hematopoietic stem cell transplantation; TA-TMA, transplant-associated thrombotic microangiopathy. We compared the overall survival (OS) and non-relapse mortality (NRM) 1 year after stem cell transplantation. Patients with and without TA-TMA in our cohort exhibited an OS ($p = 0.48$) of 80% and 88%, respectively, and an NRM ($p = 0.12$) of 0% and 5.7%, respectively, at 1 year after transplantation.

was below the pretransplantation value after TA-TMA recovery and required long-term follow up.

Here, we describe our experience with the risk factors, outcome, and impact of TA-TMA treatment on subsequent transplant outcomes.

We recognize several limitations of our analysis. First, the study represents a small number of patients with TA-TMA with a relatively small total sample size, making it difficult to interpret the results and their significance and to draw definite conclusions. Second, the retrospective design of the cohort may lead to underreporting less severe TA-TMA cases. Furthermore, opportunities for histological confirmation of the TA-TMA diagnosis in this vulnerable population of patients after HSCT with high bleeding risk were limited.

Despite limitations, this retrospective study provides crucial data showing that TA-TMA impairs the quality of life of a significant proportion of pediatric transplant recipients. Additionally, patients undergoing HSCT should have a routine scheduled screening program to identify suspected cases early to prevent lasting organ damage.

Multicenter prospective studies will be needed to construct a consensus recommendation for early recognition and monitoring of children with this common post-transplant complication and for developing a therapeutic approach tailored according to risk.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee, University Halle (Saale). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because purely retrospective analysis performed.

Author contributions

KK: Writing – original draft, Writing – review & editing. JH: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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