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Fluid Overload in Pediatric Acute Respiratory Distress Syndrome after Allogeneic Hematopoietic Cell Transplantation

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Abstract

The aim of the study is to examine the relationship between fluid overload (FO) and severity of respiratory dysfunction in children posthematopoietic cell transplantation (HCT) with pediatric acute respiratory distress syndrome (PARDS). This investigation was a secondary analysis of a multicenter retrospective cohort of children (1month to 21 years) postallogeneic HCT with PARDS receiving invasive mechanical ventilation (IMV) from 2009 to 2014. Daily FO % (FO%) and daily oxygenation index (OI) were calculated for each patient up to the first week of IMV (day 0 = intubation). Linear mixed-effect regression was employed to examine whether FO% and OI were associated on any day during the study period. In total, 158 patients were included. Severe PARDS represented 63% of the cohort and had higher mortality (78 vs. 42%, $p < 0.001$), fewer ventilator free days at 28 (0 [IQR: 0–0] vs. 14 [IQR: 0–23], $p < 0.001$), and 60 days (0 [IQR: 0–27] v. 45 [IQR: 0–55], $p < 0.001$) relative to nonsevere PARDS. Increasing FO% was strongly associated with higher OI ($p < 0.001$). For children with 10% FO, OI was higher by nearly 5 points (adjusted β, 4.6, 95% CI: [2.9, 6.3]). In subgroup analyses, the association between FO% and OI was strongest among severe PARDS ($p < 0.001$) and during the first 3 days elapsed from intubation ($p < 0.001$). FO% was associated with lower PaO_2/FiO_2 (adjusted β, −1.92, 95% CI: [−3.11, −0.73], $p = 0.002$), but not mean

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- hematopoietic cell transplantation
- mechanical ventilation

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airway pressure ($p = 0.746$). In a multicenter cohort of children post-HCT with PARDS, FO was independently associated with oxygenation impairment. The associations were strongest among children with severe PARDS and early in the course of IMV.

Introduction

Hematopoietic cell transplantation (HCT) is an established and accepted treatment for a variety of malignant and nonmalignant disorders.[1] In the last few decades, reported pediatric intensive care unit (PICU) mortality for this population has substantially decreased, but the burden of critical illness remains high.[2] Indeed, acute respiratory failure occurs in up to 25% of pediatric allogeneic-HCT recipients with incidence of mortality around 40 to 60% when invasive mechanical ventilation (IMV) is required.[3,4] Pulmonary complications after allogeneic-HCT may be infectious or noninfectious, vary by phase of transplant, and be characterized by nonspecific, but overlapping lung injury syndromes like diffuse alveolar hemorrhage, engraftment syndrome, and idiopathic pneumonia syndrome.[5] Children post-HCT may progress to severe hypoxemic respiratory failure and develop pediatric acute respiratory distress syndrome (PARDS). Unfortunately, children post-HCT with PARDS appear to manifest a more severe phenotype with high morbidity and mortality.[6] In fact, HCT status remains an independent risk factor for poor outcomes in PARDS even after controlling for the severity of hypoxemia.[7] The contemporary risk factors that drive respiratory morbidity and outcomes in these vulnerable children remain an area of active investigation.

Fluid overload (FO) is traditionally thought of as the inappropriate expansion of extracellular fluid volume. The current definitions of FO require fluid balance assessment by fluid or weight-based methods, duration of fluid balance assessment, and quantification of percentage FO.[8] HCT recipients may be uniquely at risk for FO. The conditioning regimen that includes combinations of radiotherapy and chemotherapy can induce microvascular injury and capillary leak.[9,10] Additionally, given the high burden of concurrent organ injury, need for high volume medications, frequent transfusions, and infection, these children are even more vulnerable to fluid accumulation and its consequences.[11,12]

It has long been recognized that FO is an important toxicity in both pediatric and adult ARDS.[13,14] Whether FO impacts respiratory dysfunction and outcomes in children post-HCT with PARDS is not well described. One report found early FO was associated with higher mortality and lower rates of extubation in intubated children postallogeneic HCT with hypoxemic respiratory failure.[15] However, the mechanisms by which FO drives outcomes in PARDS are unclear. ARDS is defined pathologically by loss of the alveolar capillary permeability barrier and protein-rich edema in the alveoli.[16] The severity of pulmonary edema has been linked to important outcomes including oxygenation index (OI), length of IMV, and mortality.[17,18] Efforts to presumptively minimize pulmonary edema and therefore, improve oxygenation through conservative fluid management has gained acceptance as an important therapeutic strategy in ARDS.[19] OI is considered the standard by which PARDS is evaluated as it combines both oxygenation indices and ventilator pressure.[20] OI has risk stratified outcomes not only in the general PICU population with PARDS, but also in children post-HCT with mortality around 75% in the most severe patients.[6,7]

Therefore, we sought to evaluate the associations between FO and respiratory dysfunction in children postallogeneic HCT with PARDS. We hypothesized that increasing FO would be independently associated with OI. Additionally, we aimed to understand if the relationship between FO and OI differed relative to PARDS severity and time elapsed from intubation.

Materials and Methods

Design, Setting, and Patients

Twelve centers contributed data to a retrospective, multicenter cohort of allogeneic HCT recipients admitted to the PICU post-transplant with the diagnosis of acute respiratory failure between 2009 and 2014.[4] The present investigation represents a secondary analysis of this retrospective cohort. The parent study was coordinated by the HCT-Cancer Immunotherapy subgroup of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network. Institutional Review Board approval was obtained at each center with informed consent waived. Each institution contributed up to 25 of their most recent consecutive HCT recipients receiving IMV.

Inclusion criteria for the parent study were patients post-allogeneic HCT between the ages $\geq$1 month to $<$21 years receiving IMV for acute respiratory failure. Patients with autologous transplants, intubated for reasons other than critical illness, and with transplantation prior to January 1, 2009 were excluded. In the present study, we additionally excluded patients with IMV courses $<$1 day and patients with clear data entry errors or missing renal replacement, oxygenation, or fluid balance data.

Data Collection

Demographic data including age, sex, and weight were collected. HCT-related variables such as time (in days) from HCT to PICU admission, diagnosis leading to transplant, source of hematopoietic progenitor cells, related donor status, and conditioning regimens were recorded. Relevant clinical variables included length of PICU stay (days); length of IMV (days); survival to PICU discharge; treatment with corticosteroids, renal replacement therapy (RRT), vasopressors/inotropes, and inhaled nitric oxide (iNO). Granular details regarding vasopressors/inotropes (dose and duration) and RRT (modality, timing, indication, and duration) were not recorded in the parent study. Vasopressor/inotropic agents included: epinephrine, dobutamine, dopamine, milrinone, and norepinephrine. Finally, initial ventilator mode (pressure control [PC]; pressure

regulated volume control [PRVC]; high frequency oscillatory ventilation [HFOV]; APRV [airway pressure release ventilation]; and VDR [volumetric diffusive respirator]) were recorded.

Definitions of Fluid Overload

Raw intake and output (milliliters) were recorded daily for the first week of IMV (day 0–7) for each patient. Day 0 represented the day of intubation. Weight at admission to the PICU (in kilograms, kg) was the reference weight. Daily fluid balance was defined as the total 24-hour (midnight to midnight) input minus output in liters normalized per kg. The primary exposure, daily FO (%), referred to hereafter as FO%, was calculated using the following equation[21]:

$$\textit{Fluid overload \%(FO\%)} = \textit{(Fluid in – Fluid out [in liters]/kg)} * 100$$

Each patient had a daily FO% calculation from intubation (day = 0) through the earliest of day 7 of IMV, death, or extubation. Additionally, each patient had a peak FO% calculation (highest daily FO% during the study period).

Oxygenation Assessment

Ventilator settings including tidal volume (Vt; mL), positive end-expiratory pressure (PEEP; cmH_2O), peak inspiratory pressure (PIP; cmH_2O), and mean airway pressure (Paw; cmH_2O) were documented every 6 hours for the first 5 days of IMV and then daily for all remaining days of IMV. Additionally, markers of oxygenation including fractional concentration of inspired oxygen (FiO_2), oxygen saturation from pulse oximeter (SpO_2; %), and partial pressure of arterial oxygen (PaO_2; mm Hg) were recorded in a similar fashion to relevant ventilator variables. These data were used to calculate OI respectively based upon the equations below:

$$\textit{Oxygenation index (OI)} = (FiO_2 * Paw * 100)/PaO_2$$

Each patient had a daily OI from intubation up to the first week of IMV lest they died or were extubated before day 7. Peak OI (highest OI during the study period) was also recorded. The severity of PARDS was categorized by the Pediatric Acute Lung Injury Consensus Conference (PALICC) OI index groups for patients receiving IMV.[22] PARDS severity was determined by the peak OI during the study period. Patients were dichotomized into nonsevere PARDS (at-risk of PARDS and mild/moderate PARDS, peak OI <16) and severe PARDS (peak OI ≥ 16).

Statistical Analysis

Data were analyzed using STATA SE (Version 16.1 College Station, Texas, United States) and R (Version 4.1.2 Vienna, Austria). Continuous variables were expressed as mean $\pm$ standard deviation (SD) when normally distributed or median with interquartile range (IQR) otherwise. Differences between nonnormally and normally distributed continuous variables were tested using Wilcoxon rank sum and unequal variances *t*-tests, respectively. Categorical variables were displayed as frequencies and percentages and were compared using Chi-square tests.

Linear regression models were employed to test the relationship between peak FO% and peak OI. Linear mixed-effect regression was then utilized to analyze the repeated measures of data, FO% and OI. Linear mixed-effect models include fixed and random effects. Random effects account for sources of correlated data. As each patient had daily FO% and daily OI calculations up to the first week of IMV, a single patient's measurements were correlated. These models indicated if increasing FO% was associated with a higher OI on any given day for the first week of IMV. Subgroup analyses for severity of PARDS and time elapsed from intubation were also performed. Nonsevere PARDS was compared relative to severe PARDS. To test the relationship between FO% and OI by time elapsed from intubation, the cohort was restricted to two groups: IMV days 0 to 3 and days 4 to 7.

Several sensitivity analyses were performed to test the strength of our associations. First, per a prior analysis of this database, patients with short IMV courses (<4 days) were known to have severe lung injury and higher mortality.[15] Due to potential bias introduced by patients with short IMV courses, high illness severity, and presumptively, high early resuscitation needs, the analyses were repeated excluding these patients. Second, to address bias associated with fluid resuscitation needs on day of intubation (day 0), the analyses were repeated excluding day 0 data. Third, to assess whether there was bias evaluating respiratory dysfunction exclusively as a composite metric of oxygenation and ventilator pressure in OI, we repeated analysis separating OI into its individual constituents (1) PaO_2 to FiO_2 ratio (P/F) and (2) Paw. Fourth, to elucidate the relationship between FO% and respiratory mechanics, we assessed PEEP and dynamic respiratory system compliance (C_{RS} [-mL/cmH_2O]: [Vt] (mL)/[PIP-PEEP] cmH_2O).

Covariates were adjusted for *a priori* in the multivariate models (age, sex, days from HCT to PICU admission, use of iNO, RRT, and vasopressors/inotropes). Specifically, we used treatment with iNO, RRT, and vasoactives as surrogates of illness severity since illness severity scores were lacking in the original dataset. Additionally, to potentially account for fluid accumulation in a non-ICU hospital setting (as pre-PICU weight was not recorded), we adjusted for time from HCT to PICU admission. Unadjusted and adjusted β regression coefficients with 95% confidence intervals (CI) were reported. A *p*-value based upon robust standard error measurements of less than 0.05 was considered statistically significant.

Results

Cohort Characteristics

In total, 158 patients with complete OI data were included in the final analysis (►**Fig. 1**). Median age was 11.2 years, and proportion female was 42%. The majority of patients were transplanted for underlying malignancy. Conditioning with fludarabine and total body irradiation occurred in 47 and

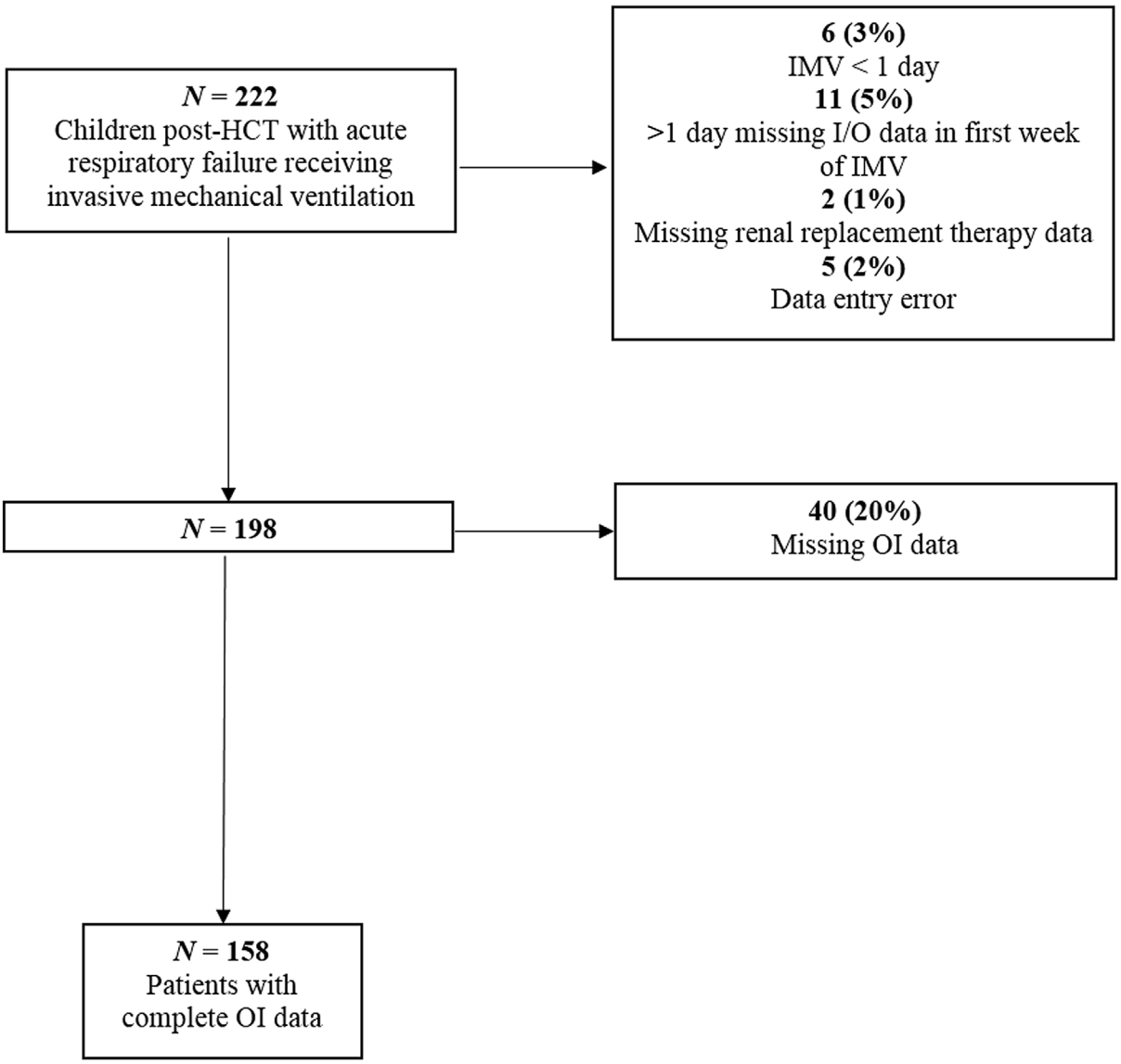

Fig. 1 Patient flow diagram.

38% of patients, respectively. Median time to PICU admission was 47 days (IQR: 19–118). Admission to the PICU for respiratory distress and use of iNO, RRT, vasoactives, and HFOV were common. Nearly all patients received corticosteroids (►**Table 1**).

Nonsevere PARDS ($n = 59$) included patients with at-risk of PARDS ($n = 9$), mild PARDS ($n = 12$), and moderate PARDS ($n = 38$) based upon the PALICC criteria. Age, weight, and sex did not vary relative to PARDS severity. Patients with severe PARDS were more likely to receive cord blood transplants ($p = 0.024$). Otherwise, HCT characteristics were similar between groups (►**Table 1**). Relative to nonsevere PARDS, children with severe PARDS were admitted to the PICU more frequently with respiratory distress ($p < 0.001$). However, admission indication for RRT ($p = 0.268$) and eventual treatment with RRT ($p = 0.191$) were similar between groups. Severe PARDS was treated with more PICU interventions including iNO ($p < 0.001$), vasoactives ($p = 0.005$), and HFOV ($p < 0.001$; ►**Table 1**).

Ventilator Characteristics and Outcomes by PARDS Severity

Overall PICU mortality was 66% ($n = 104/158$). Median OI was 25 (IQR: 12–44). Relative to nonsevere PARDS, severe PARDS had higher OI ($p < 0.001$), lower P/F ($p < 0.0001$), were managed with higher PEEP ($p < 0.001$), and had lower C_{RS} ($p = 0.029$). Initial ventilator mode did not statistically differ ($p = 0.059$), but severe PARDS was treated with HFOV more frequently (►**Table 2**). Additionally, children with severe PARDS had higher mortality ($p < 0.001$) and fewer VFDs at 28 ($p < 0.001$) and 60 days ($p < 0.001$). PICU length of stay was not significantly different between groups ($p = 0.172$; ►**Table 2**).

Fluid Overload and Oxygenation Index

Applying unadjusted (data not shown) and adjusted linear regression, higher peak FO% was associated with higher peak OI. OI was higher, on average, by nearly 1 point on adjusted models (β, 0.81, 95% CI: [0.28, 1.34], $p < 0.001$) for every 1% increase in FO%. To address the repeated measures data, in all

Table 1 Cohort characteristics

	Total cohort ($n = 158$)	Nonsevere PARDS ($n = 59$)	Severe PARDS ($n = 99$)	*p*-Value
Demographics				
Age (y)	11.2 (3.6–16.7)	12.7 (2.1–16.9)	11.1 (4.3–16.1)	0.899
Weight (kg)	40.2 (15.3–63.4)	40 (12.7–61.9)	40.4 (16.2–64)	0.624
Female	67 (42)	21 (36)	46 (47)	0.181
HCT characteristics				
Transplant for malignancy	92 (58)	32 (54)	60 (61)	0.432
Source of transplant				
Bone marrow	74 (47)	33 (56)	41 (42)	**0.024**
Cord blood	56 (35)	12 (22)	43 (43)	
Peripheral blood	28 (18)	12 (22)	15 (15)	
Related donor	38 (24)	19 (32)	19 (19)	0.064
Fludarabine conditioning	74 (47)	22 (37)	52 (52)	0.063
Total body irradiation	60 (38)	20 (34)	40 (40)	0.415
HCT to PICU (days)	47 (19–118)	48 (15–118)	46 (20–119)	0.831
PICU characteristics				
Diagnoses at PICU admit,				
Respiratory distress	123 (78)	39 (66)	86 (87)	**0.002**
Hemodynamic instability	32 (20)	16 (27)	15 (15)	0.067
Neurologic dysfunction	14 (9)	7 (12)	7 (7)	0.596
Dialysis at admission	7 (4)	4 (7)	3 (3)	0.268
Corticosteroids	145 (92)	54 (92)	91 (92)	0.931
ECMO	3 (2)	0 (0)	3 (3)	0.272
HFOV	69 (44)	8 (14)	61 (62)	**<0.001**
iNO	52 (33)	8 (14)	44 (44)	**<0.001**
RRT	64 (41)	20 (34)	44 (44)	0.191
Surfactant	4 (3)	0 (0)	4 (4)	0.114
Vasopressor/Inotropes	130 (82)	42 (71)	88 (89)	**0.005**

Abbreviations: ECMO, extracorporeal membrane oxygenation; HCT, hematopoietic cell transplant; HFOV, high frequency oscillatory ventilation; iNO, inhaled nitric oxide; RRT, renal replacement therapy; TBI, total body irradiation.
Note: Values presented as frequency and percentage or median and interquartile range where appropriate. Categorical variables compared using Chi-square and continuous variables compared Wilcoxon rank sum test; Bold, statistically significant at alpha <0.05.

analyses, increasing FO% was associated with higher OI on any given day during the first week of IMV (►**Table 3**). This indicated FO% was associated with that day's OI. After adjusting for the covariates, for every 1% increase in FO%, OI was higher by nearly 0.5 (β, 0.46, 95% CI: [0.29, 0.63], p <0.001). Comparing patients whose FO% differed by 5, 10, or 20% on any given day during the study period, OI was estimated to be higher by 2.3, 4.6, and 9.2 points, respectively (►**Table 3**).

Fluid Overload and Oxygenation Index by PARDS Severity

After restricting the data to those with severe PARDS there were strong associations between FO% and OI on unadjusted (data not shown) and adjusted analyses among severe PARDS (β, 0.62, 95% CI: [0.38, 0.87], p <0.001). Although the effect size was smaller in the nonsevere PARDS group, increasing FO% was associated with higher OI on unadjusted (data not shown) and adjusted analyses (β, 0.15, 95% CI: [0.07–0.22], p <0.001).

Fluid Overload and Oxygenation Index by Time Elapsed from Intubation

After adjustment for the covariates, there was an association between FO% and OI (β, 0.36, 95% CI: [0.11, 0.60], p <0.001) during IMV days 0 to 3. There was no strong evidence of an association between FO% and OI when the analysis was restricted to days 4 to 7. The effect size was close to the null, but this estimate was imprecise (β, 0.16, 95% CI: [−0.13, 0.45], $p = 0.271$). Unadjusted data was similar (data not shown).

Table 2 Ventilator characteristics and outcomes by PARDS severity

	Nonsevere PARDS ($n = 59$)	Severe PARDS ($n = 99$)	*p*-Value
Ventilator characteristics			
Mode of ventilation[a]			
Conventional-PC	18 (31)	35 (35)	0.059
Conventional-PRVC	40 (68)	47 (47)	
HFOV	1 (2)	15 (15)	
VDR	0 (0)	1 (1)	
APRV	0 (0)	1 (1)	
Oxygenation index[b]	10 (5–13)	37 (27–53)	<0.001
PaO_2/FiO_2	144 (115–186)	69 (55–86)	<0.001
Paw (cmH_2O)	12 (10–15)	22 (17–28)	<0.001
PEEP (cmH_2O)[d]	7 (6–9)	10 (8–12)	<0.001
C_{RS} (mL/[cmH_2O])[c,d]	21 (6–31)	13 (7–21)	0.029
Outcomes			
PICU mortality	25 (42)	77 (78)	<0.001
VFDs (28 d)	14 (0–23)	0 (0–0)	<0.001
VFDs (60 d)	45 (0–55)	0 (0–27)	<0.001
Length of PICU stay	15 (9–38)	21 (11–36)	0.172

Abbreviations: APRV, airway pressure release ventilation; Conventional-PC, pressure control; Conventional-PRVC, pressure regulated volume control; C_{RS}, dynamic respiratory system compliance; FiO_2, fractional concentration of oxygen; HFOV, high frequency oscillatory ventilation; PaO_2, partial pressure of oxygen; Paw, mean airway pressure; PEEP, positive end-expiratory pressure; VDR, volume diffusive respirator; VFDs, ventilator free days (at 28 and 60 d).

[a]Mode of ventilation = mode at intubation (day = 0).

[b]Oxygenation index = (FiO_2 * Paw [cmH_2O]/PaO_2 [mm Hg]) * 100.

[c]Dynamic respiratory system compliance (C_{RS} = Vt [tidal volume]/PIP [peak inspiratory pressure] – PEEP [positive end-expiratory pressure]).

[d]$n = 139$ for children initially treated with conventional mechanical ventilation.

Note: Values displayed are frequencies with percentages or as medians with interquartile ranges. Categorical variables compared using Chi-square and continuous variables compared Wilcoxon rank sum test; Bold = statistically significant at an $\alpha < 0.05$.

Sensitivity Analyses

Many patients experienced their peak OI (48%) and peak FO % (39%) on day of intubation (day 0). By day 3 of IMV, 84% had reached their peak OI (►**Fig. 2A**) and 85% had experienced their peak FO% (►**Fig. 2B**). 19% ($n = 30/158$) of patients had courses of IMV <4 days. Among these patients, 57% ($n = 17/30$) had severe PARDS with an overall mortality of 77% (23/30). To address potential bias introduced by the 30 patients with short IMV courses, they were excluded and analyses were repeated. After removal, increasing FO% was associated with worse oxygenation (β, 0.44, 95% CI: [0.26, 0.61), p <0.001). Furthermore, day 0 (day of intubation) data was excluded given the high proportion of patients experiencing their peak OI and FO% on day 0. After exclusion of the day 0 data, increasing FO% was associated with higher OI on any day during IMV days 1 to 7 (β, 0.38, 95% CI: [0.21, 0.56], p <0.001). Unadjusted data was similar (data not shown).

Table 3 Linear mixed effects regression: FO% and OI, P/F

	1% FO	5% FO	10% FO	20% FO
OI Unadjusted[a]	0.45 [0.28–0.62]	2.3 [1.4–3.1]	4.5 [2.8–6.2]	9.0 [5.6–12.4]
OI Adjusted[a]	0.46 [0.29–0.63]	2.3 [1.5–3.2]	4.6 [2.9–6.3]	9.2 [5.8–12.6]
P/F Unadjusted[a]	−2.02 [−3.22, −0.83]	−10.1 [−16.1, −4.2]	−20.2 [−32.2, −8.3]	−40.4 [−64.4, −16.6]
P/F Adjusted[b]	−1.92 [−3.11, −0.72]	−9.6 [−15.6, −3.6]	−19.2 [−31.2, −7.2]	−38.4 [−62.4, −14.4]

Abbreviations: FO%, fluid overload %; OI, oxygenation index; P/F, PaO_2/FiO_2.

Note: Regression coefficients (β) represented with 95% confidence interval (CI). Adjusted for age, sex, days from HCT to PICU admission, use of nitric oxide, renal replacement therapy, and vasoactives.

[a]All values statistically significant at an α of <0.001.

[b]All values statistically significant at an $\alpha = 0.002$.

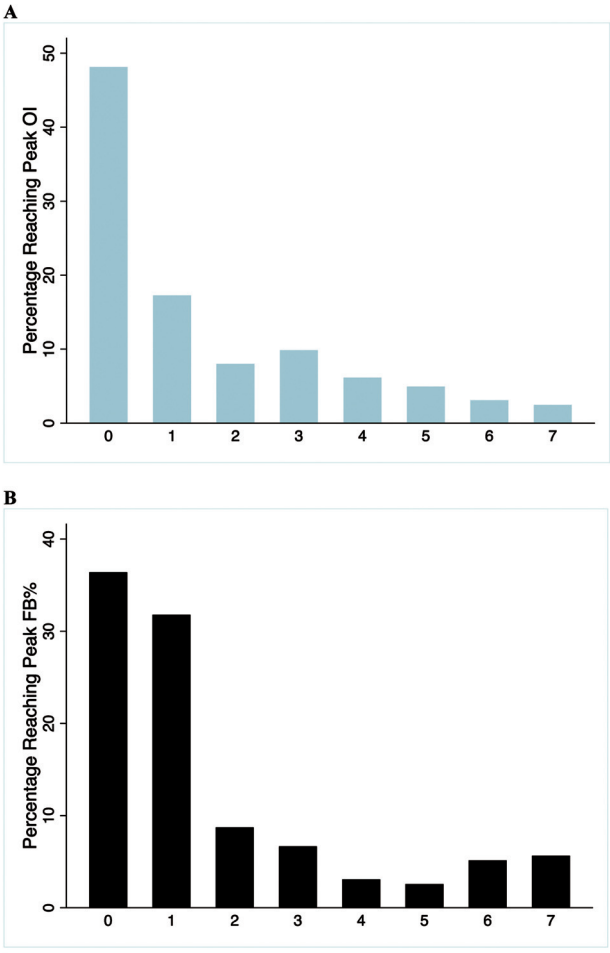

Fig. 2 (**A**) Percentage reaching peak OI by day of invasive mechanical ventilation. Day 0 = day of endotracheal intubation; (**B**) Percentage reaching peak fluid overload % by day of invasive mechanical ventilation.

To address the sensitivity of our results using a composite measure of oxygenation failure in OI, we evaluated the relationship between FO% and (1) P/F and (2) Paw. Lower P/F was strongly associated with increasing FO% on unadjusted and adjusted analyses (β, −1.92, 95% CI: [−3.11, −0.72], $p = 0.002$; ►**Table 3**). For any given day during the study period, P/F would be expected to be lower by almost 20 for a 10% difference in FO% (β, −19.2, 95% CI: [−31.1, −7.2]). However, there was no strong evidence of an association between FO% and Paw on unadjusted (data not shown) and adjusted analyses (β, 0.014, 95% CI: [−0.071, 0.098], $p = 0.746$). Among patients initially managed with conventional mechanical ventilation data ($n = 139$), we did not observe an association with FO% and PEEP (β, −0.010, 95% CI: [−0.040, 0.019], $p = 0.487$), but did observe a weak association with FO% and lower C_{RS} (β, −0.278, 95% CI: [−0.553, −0.002], $p = 0.049$). All analyses were stratified by the severity of PARDS and timing elapsed from intubation and produced similar results to the main analyses (data not shown).

Discussion

In this multicenter retrospective cohort of children with PARDS post-HCT, we demonstrated independent associations between FO and oxygenation impairment. First, we showed that increasing FO was associated in a dose-dependent fashion with higher OI on any given day during the study period. Second, we demonstrated that the associations were strongest among children with severe PARDS and during the first 3 days elapsed from intubation. These relationships persisted after adjustment for potential confounders, including treatment with RRT. Third, FO and OI remained associated (1) after removal of children with short IMV courses and high mortality and (2) after removal of day 0 (day of intubation) data. These results suggest that high illness severity and/or high early fluid resuscitation needs do not alone account for the observed relationship between FO and oxygenation impairment. Fourth, when OI was distilled into its individual constituents, FO was strongly associated with lower P/F, but not Paw. This analysis strengthens the potential link between FO, elaboration of pulmonary edema, and impaired gas exchange in children post-HCT with PARDS. Taken together, given the poor outcomes observed in these children, FO remains an important clinical variable to both prevent and appropriately manage to decrease pulmonary morbidity in the critical care setting.

This is one of the first studies to address FO and measures of respiratory dysfunction in children post-HCT with PARDS applying the PALICC definition. OI has become a standard by which PARDS patients are assessed and risk stratified.[7] Given the time-varying nature of both FO and OI, an analytical strategy was employed to establish temporality between FO and OI. The clinical relevance of our effect sizes was demonstrated by an OI increase of 2, 5, and 9 for patient's differing by FO of 5, 10, and 20%, respectively. Additionally, the independent association with lower P/F with more FO increases the sensitivity and supports the veracity of our findings. Nonetheless, OI is impacted by ventilator management and settings as represented by both Paw and PEEP. This cohort, as per prior analyses, and confirmed in this study, was exposed to high, and potentially, toxic ventilator settings.[23] Inadequate Paw or PEEP alone as an explanation for worse oxygenation deficits seems unlikely particularly in a severe PARDS cohort with a median Paw of 22 (IQR: 17–28) and PEEP of 10 (IQR: 8–12). Furthermore, we did not observe strong associations between FO and respiratory mechanics (Paw and PEEP), and therefore, these variables did not seem to impact our overall findings. Interestingly, among children treated with conventional mechanical ventilation, the finding that FO was weakly associated with lower C_{RS} may, in part, be driven by higher PIPs (as a prior analysis demonstrated that Vt did not vary between nonsurvivors and survivors, but PIPs did).[23]

Data on the relationship between FO and poor outcomes in children with hypoxemic respiratory failure and PARDS is well established.[8,13] However, there is a scarcity of studies evaluating how FO contributes to respiratory dysfunction, oxygenation, and respiratory mechanics. In one study, the investigators applied a similar analytic approach to the present study, and found associations between FO and OI in children with hypoxemic respiratory failure.[24] However, effect sizes were small relative to our study or not reported.

While we recognize this is a historical cohort of patients and fluid management may not reflect current practice, these results are novel in their attempt to address a potential mechanistic contribution of FO to respiratory dysfunction in a patient population with a severe PARDS phenotype.

Nonetheless, we do interpret our findings with caution. This was a profoundly ill cohort with likely high early resuscitation needs to correct intravascular volume deficits and reestablish tissue perfusion in states of circulatory shock (vasopressors/inotropes were needed in 82% of cohort). Furthermore, fluid accumulation during the transition from the resuscitative phase to the de-resuscitative phase of critical illness may merely reflect illness severity and even considered a biomarker for it.[25,26] However, we are reassured that our sensitivity analyses to address this potential issue supported our overall findings. Furthermore, the high proportion of patients receiving RRT (41%) perhaps reflects a high burden of renal dysfunction in this PARDS cohort. Debate continues regarding the role of RRT in addressing FO in critically ill patients.[27–29] Interestingly, treatment with RRT did not significantly vary between nonsevere and severe PARDS. This perhaps both limits confounding related to RRT, but more importantly, calls into question *when* and for *whom* this therapy may be most effective. In one study of post-HCT children with acute lung injury receiving RRT, RRT improved P/F at intervals of 24 (median change of 30.5, $p < 0.0008$) and 48 hours (median change of 43, $p < 0.0062$) after initiation and correlated with reductions in fluid balance.[30] However, the above analysis could not address if the oxygenation benefits were sustained or provided any improvements in outcomes. Nonetheless, certain subgroups, particularly patients with severe PARDS, may benefit from early initiation of RRT to mitigate FO with the hope of improving downstream outcomes.

Although the associations observed were more prominent in severe PARDS, they still persisted in the nonsevere PARDS cohort. This underscores that FO may increase pulmonary morbidity in all degrees of PARDS, but is potentially *most* problematic in the *severe* patients. In the parent study of this database, nonsurvivors were more likely to have multiple, consecutive days with OI's meeting severe criteria.[6] These data suggest that the degree of FO may serve as a catalyst for ongoing oxygenation deficits. These results additionally support our previous investigation indicating that increasing *early* FO was associated with lower survival and rates of successful extubation.[15] However, the clinical significance of the timing of FO in PARDS and relationship with outcomes remains a matter of debate.[13,31]

We recognize we cannot establish causality between FO, oxygenation impairment, pulmonary edema, and subsequent outcomes. However, it remains instructive to explore the possible conceptual framework by which FO may exacerbate pulmonary edema, and ultimately, impair oxygenation. Endothelial cell-derived angiopoietin-2 (Ang-2), a modulator of endothelial barrier function, has been recognized as an important prognostic biomarker and may even predict FO in ARDS.[31–33] In a subset of 18 children post-HCT with PARDS, those with rising Ang-2 levels from day 1 to day 3 were 16 times more likely to die (95% CI: 1.3–197.8).[32] This same cohort also had a higher Ang-2 level at baseline relative to the general PICU population. This suggests the possibility of preexisting endothelial barrier dysfunction and/or higher susceptibility to endothelial injury related to PARDS triggers in this population.[12] These factors in children post-HCT are likely compounded by known pathological derangements in ARDS of impaired alveolar fluid clearance, propensity of ARDS lungs to develop pulmonary edema at lower hydrostatic pressure, and the proinflammatory response to increases in vascular hydrostatic pressure.[34–36]

There are some limitations. Given the observational nature of this study, there is risk for residual confounding. Illness severity scores were not measured in the original collection of these data. We attempted to mitigate this through adjustment of variables including use of iNO, vasopressors/inotropes, and RRT. Previous data suggest that immunocompromised status and fluid balance on day 0 of PARDS diagnosis are important prognostic markers.[37] Another study indicated increasing OI on either day 1 or day 3 of PARDS and a history of cancer/HCT were highly associated with mortality with severity of illness offering no independent prognostic value.[38] Nonetheless, this analysis could have been strengthened by a better understanding of the burden of cardiac and renal dysfunction. Future studies regarding the etiology and impact of FO in this population would be wise to include known organ dysfunctions. Lastly, pre-PICU admission fluid balance and/or weight was not available. Efforts to curb fluid accumulation before it becomes clinically relevant may alter transplant-related complications. Further prospective studies are needed to better define the pathobiology and, downstream phenotypes of PARDS in children post-HCT. It is then we may better understand children most at risk for FO and its impact on respiratory dysfunction in this population.

Despite these limitations, we were able to define a relationship between FO and respiratory dysfunction in a multicenter cohort of pediatric HCT recipients with PARDS. Results of this analysis could be generalizable to children post-allogenic HCT with PARDS. Our repeated measure analysis argues for further mechanistic studies addressing how FO develops, propagates, and potentially drives oxygenation deficits and outcomes in children post-HCT with PARDS.

Conclusion

We investigated the association between FO and respiratory dysfunction in a multicenter retrospective cohort of pediatric HCT recipients with PARDS. We found independent associations between FO and impaired oxygenation as measured by OI and PaO_2/FiO_2. These associations were strongest among severe PARDS and early in the course of IMV. Prevention and timely management of FO in children post-HCT with PARDS may improve outcomes. Further studies and contemporary cohorts are needed to determine if FO exists along the causative pathway of driving pulmonary morbidity and subsequent outcomes in this vulnerable population with PARDS.

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Conflict of Interest
None declared.

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