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Fluid overload and outcomes in critically ill children: A single center prospective cohort study

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ABSTRACT

Objective: To prospectively evaluate the association between fluid overload (FO) and clinical outcomes, mortality, mechanical ventilation (MV), and duration and length of stay in a pediatric intensive care unit (PICU).
Methods: Over a 12-month period, patients who were on MV for >24 h or vasoactive support were prospectively included. Demographic and clinical data were recorded. Daily FO was calculated as [(fluid in − fluid out) / admission weight] × 100%. Multivariate stepwise logistic regression analysis was used to determine predictors of survival.
Results: 224 patients were included; median age was 3.3 (IQR 0.7, 9.9) years, mortality was 15.6%. The median peak FO (PFO) was 12.5% (IQR 5, 25), PFO > 10% was present in 55.8% of patients, and PFO > 20% was present in 33%. The PFO in non-survivors was 17.8% (IQR 8, 30) and 11% (IQR 4, 23) in survivors ($p = 0.028$). A survival analysis showed no association between PFO and mortality. A multivariate analysis identified vasoactive support, >3 organ failures and acute kidney injury (AKI) but not FO as independent risk factors for mortality. FO was associated with MV duration and PICU length of stay.
Conclusion: FO is frequent in a general PICU population, but PFO is not an independent risk factor for mortality. Future studies of FO should focus on patients with AKI and multiorgan failure for better classification of severity and potential interventions.

1. Introduction

Intravenous fluid is a common treatment for critically ill patients and is thought to be the cornerstone of initial treatment for many conditions. The development of fluid overload (FO) because of therapeutic interventions is common, particularly in critically ill children, who are at higher risk because of systemic inflammation, reduced plasma oncotic pressure and capillary leak, among other factors. Detrimental effects of FO have been recently described, and most experts now recommend caution when generalizing the beneficial effects of the so-called early goal-directed therapy to situations outside the initial resuscitation phase [1-6]. Our group and others have reported an association between the degree of FO and mortality in children requiring renal replacement therapy [7-15]. Recent data support the association between FO and unfavorable outcomes in other subgroups of critically ill children, such as those with pediatric acute lung injury and respiratory failure [16-19], those who have cardiac surgery and are receiving extracorporeal life support after congenital heart disease surgery [20-22] and newborns [23], but there is still debate regarding whether FO is an epiphenomenon in critically ill patients or is independently related to mortality [24,25].

The purpose of this study was to prospectively evaluate the association between fluid overload and mortality in a general pediatric intensive care unit (PICU) population. The secondary outcomes were evaluations of the associations between FO and mechanical ventilation (MV) duration, hospital and PICU length of stay (LOS). Although positive fluid balance has been related to mortality in many critically illnesses, we hypothesize that FO is an indirect marker of severity in the general population of critically ill children and it is not directly related to mortality.

2. Patients and methods

The Institutional Review Board for Human Use at The University of Alabama at Birmingham approved this study, waiving the requirement for informed consent from individual patients.

Abbreviations: FO, fluid overload; PICU, pediatric intensive care unit; AKI, acute kidney injury; MV, mechanical ventilation; LOS, length of stay; MODS, multiple organ dysfunction syndrome; P-MODS, Pediatric Multiple Organ Dysfunction Score; SCr, serum creatinine.

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2.1. Patients

During a 12-month period (January to December 2007), all children admitted to the PICU at Children's of Alabama were screened each day during their admission. Our unit is a general medical and surgical PICU, but children are admitted to another specialized unit after congenital heart surgery.

All patients who received MV for >24 h or required vasoactive support (>5 mcg/kg/min dopamine) were prospectively identified and included in a relational database. Each admission to the PICU was recorded separately for children with multiple admissions. Patients were excluded if their age at admission was younger than 30 days or older than 21 years; if they had preexisting chronic renal insufficiency or end-stage renal disease; or if admission to the PICU was for a renal transplantation.

2.2. Data collection

Data were recorded at time of inclusion and daily until discharge from the PICU or death. All data recorded, including demographic, laboratory and clinical information, were obtained through medical record review. The treating physician determined the primary diagnosis and cause of death. Pediatric Risk of Mortality 2 (PRISM2) scores at the time of admission to the PICU were recorded as calculated by a single data analyst. Admissions were classified as either having or not having sepsis and as either having or not having multiple organ dysfunction syndrome (MODS). Sepsis was defined using the International Pediatric Sepsis Consensus Conference definitions [26]. MODS was defined as the presence of at least 2 failed organs at any time during PICU admission. Organ system failures were defined using the International Pediatric Sepsis Consensus Conference definitions [26]. Acute kidney injury (AKI) was classified according to pRIFLE criteria. The Pediatric Multiple Organ Dysfunction Score (P-MODS) was calculated [27].

The primary outcome was survival to hospital discharge. The secondary outcomes were hospital and PICU LOS. A retrospective analysis of the prospective collected data was done looking for association between peak FO and duration of MV.

2.3. Fluid overload

The daily and total fluid intake and output were recorded during PICU stay. The percent of FO was calculated using the following formula: [(total fluid intake (L) − total fluid output in liters (L)) / (admission weight in kilograms) ∗ 100] [8,9].

Peak FO was defined as the maximum percentage of FO relative to PICU admission on any day during the PICU stay. Twenty percent FO was chosen as a breaking point based on prior studies [7-10]. Peak FO in patients with continuous renal replacement therapy (CRRT) was considered the FO prior to the initiation of CRRT.

2.4. Statistical considerations

Descriptive statistics were used to summarize all continuous and categorical variables. Comparisons between patient groups were performed using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables because of concerns about the normality of the distributions of these variables. Multivariate stepwise logistic regression analysis (with entry criteria of $\alpha = 0.20$ and

Table 1
Demographic and clinical information of all population and survivors. Data as median and interquartile range unless listed. PRISM-2, pediatric risk of mortality score; PICU, pediatric intensive care unit; LOS, length of stay; MV, mechanical ventilation; MODS, multiple organ dysfunction syndrome; PMODS, pediatric multiple organ dysfunction score; AKI, acute kidney injury.

	All $n = 224$	Survivors $n = 189$	Nonsurvivors $n = 35$	*p*-Value
Age (years)	3.3 (0.7,9.9)	2.6 (0.5,9.3)	5.5 (0.9,13.9)	0.035
Weight (kg)	14.3 (6.6–35)	13.1 (6.1–33.3)	19.3 (10.0,47.5)	0.059
Height (cm)	90 (62,136)	89 (60,134)	113 (72,155)	0.044
Gender (%)				0.713
Male	59.8	60.3	57.1	
Female	40.2	39.7	42.9	
Race (%)				0.58
White	48.7	47.6	45.3	
Black	42.4	43.4	37.1	
Hispanic	7.1	7.4	5.7	
Other	1.8	1.6	2.9	
PRISM2 (mean ± SD)	13.2 ± 8.7	11.5 ± 7.2	22.4 ± 10.4	<0.01
PICU LOS (days)	6 (4,9)	6 (4,10)	5 (3,10)	0.84
Hospital LOS (days)	12 (7,22)	14 (5,23)	6 (2,12)	<0.01
MV support (%)	90.6	89.9	94.3	0.542
MV duration (days)	4 (2–7)	4 (2,7)	4 (3,7)	0.324
MODS (%)	92	90.5	100	0.084
PMOD Score	1 (0,3)	1 (0,2)	3 (1,7)	<0.01
≥3 organ failures (%)	70	20.63	100	<0.01
pRIFLE				<0.01
no AKI	17.9	21.2	0	
R or I	64.7	66.2	47.1	
F	17.4	12.7	42.9	
Vasoactive support (%)				
≥1 drug	40.2	30.7	91.4	<0.01
≥2 drugs	25	15.9	77.1	<0.01
Diagnosis (%)				0.067
Respiratory	30.8	34.4	11.4	
Trauma	17.9	16.9	22.9	
Neurological	15.2	15.3	14.3	
Cardiac	11.6	12.2	8.6	
Sepsis	7.6	6.3	14.3	
Oncology	7.6	6.3	14.3	
Liver	2.2	1.6	5.7	
Renal	2.2	2.1	2.9	
other	4.9	4.9	5.6	

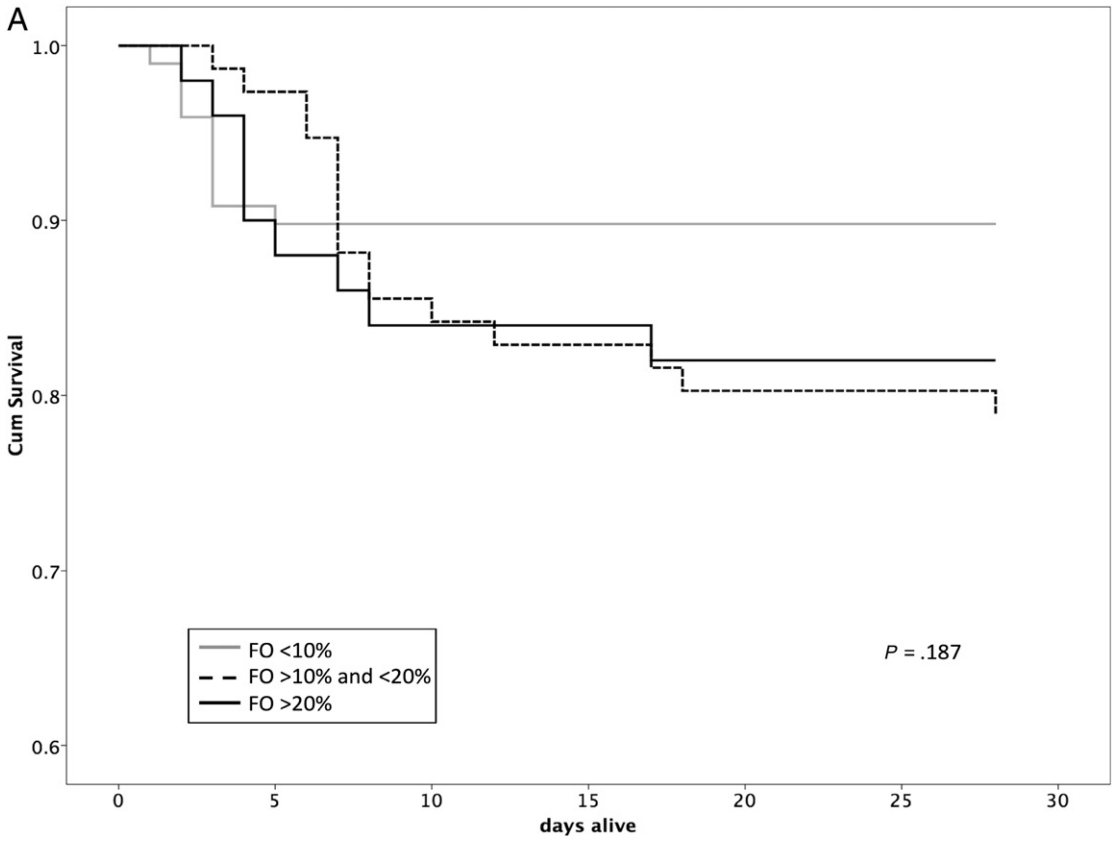

Fig. 1. Kaplan-Meier plots for cumulative survival stratified by percentage of fluid Overload (FO).

exit criteria of $\alpha = 0.10$) was used to determine predictors of survival after controlling for potential confounding variables. Odds ratios (OR) and their corresponding 95% confidence intervals (CIs) were calculated for categorical variables and for statistically significant categorical predictor variables in logistic regression analyses.

The Kaplan-Meier method was used to analyze differences in cumulative survival and the duration of MV according to peak FO, and the distribution was compared using the log-rank test. We divided %FO into the bands (<10%, between 10 and 20% and >20%) for post-hoc analysis.

All statistical tests were 2-sided and were performed with a p value < 0.05 indicating statistical significance. The SPSS software package (version 20.0; SPSS, Chicago, IL, USA) was used for the statistical analyses.

3. Results

Two hundred twenty-four patients met the inclusion criteria during the study period. Mortality was 15.6%. The demographic and clinical characteristics of the survivors and non-survivors are presented in Table 1. The most common primary diseases were respiratory, trauma and neurological, with no differences between the survivors and non-survivors. The most common causes of death were MODS (14 patients), brain death (17 patients) and cardiopulmonary arrest (4 patients). The non-survivors were older, had higher severity scores and more frequently had MODS and required vasoactive support.

3.1. Fluid overload and mortality

Peak FO >10% was present in 55.8% of the patients; it was >20% in 33% of the patients, and 7.1% of the patients had peak FO > 50%. Peak FO was 17.8% (7.5, 30) in the non-survivors and 11.1 (4.2, 22.9) in the survivors ($p = 0.028$). The proportion of patients with peak FO > 20% was 31.7% in the survivors and 45.7% in the non-survivors ($p = 0.122$). The survival analysis showed no association between the percentage of FO and outcomes ($p = 0.187$) (Fig. 1).

Among the survivors, peak FO correlated with PICU LOS ($r = 0.7$, $p < 0.01$) and MV days ($r = 0.67$, $p < 0.01$) but not with hospital LOS. Kaplan-Meier analysis showed that the duration of MV was longer in the patients with peak FO > 20% (Fig. 2).

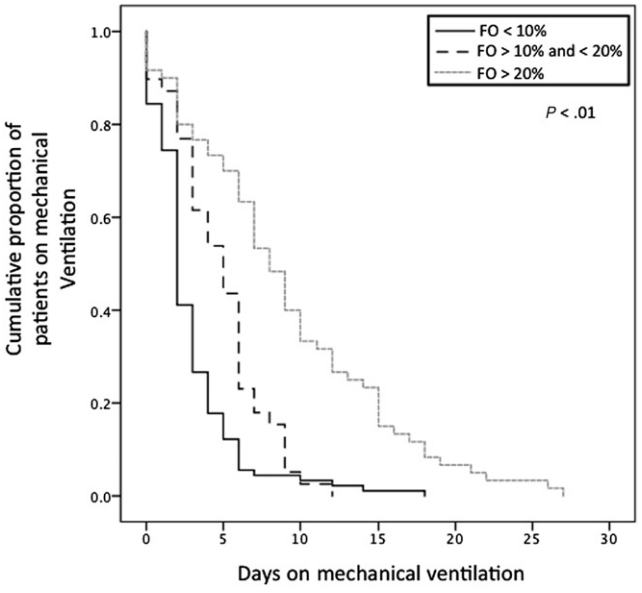

Fig. 2. Kaplan-Meier plots for cumulative proportion of patients on mechanical ventilation survival stratified by percentage of fluid Overload (FO).

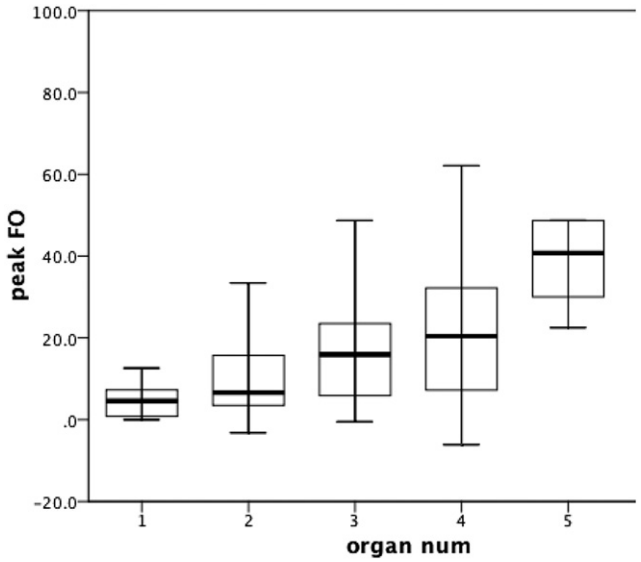

Fig. 3. A representative boxplot graph showing the median interquartile range and range of Peak FO (%) and number of organ failures (organ num). $p < 0.01$.

Peak FO was higher in patients with MODS and progressively increased with subsequent increases in the number of failed organs (Fig. 3).

3.2. Multivariate analysis for mortality

Multivariate analysis identified that the need for vasoactive support, >3 organ failures and AKI (according to pRIFLE criteria) but not peak FO were independent risk factors for mortality (Table 2).

4. Discussion

This is the first prospective study examining the potential negative effects of FO in the entire population of critically ill children in a tertiary care center PICU. The main finding of this study was that peak FO is not an independent risk factor for mortality, although our results show that FO is common in critically ill children and is correlated with PICU LOS and MV duration. Non-survivors had a higher peak FO, but multivariate analysis found that AKI, ≥3 failed organs and inotropic therapy requirements were independently correlated with mortality.

Our group and others have reported the association between FO and mortality in critically ill children with AKI who require renal replacement therapy [8-12,13-15], but the association between FO and mortality in other settings has been difficult to establish. Surrogate markers of morbidity, such as MV duration, LOS and MODS, have been reported in retrospective studies to demonstrate the detrimental effects of FO; however, whether these associations are causal or are the result of residual confounding from the severity of illness or the presence of AKI is not clear. Our data suggest that in a general population of critically ill children, FO is common and rates are higher in non-survivors, but FO is not an independent risk factor for death. Similar to previous reports, we found an association between peak FO and the number of organ failures in critically ill children, but a causative effect could not be determined. We think that these data show that FO is a marker of severity, but it does not have a central contributory role to MODS in a general PICU population.

The theory that FO has direct harmful effects is attractive, especially because FO is known to have some detrimental physiological effects, such as the initiation or exacerbation of intraabdominal hypertension, myocardial edema and stunning, and pulmonary edema, among others [32,33]. Some authors propose that FO itself can lead to organ dysfunction, causing inflammation, tissue hypoperfusion and the depletion of high-energetic phosphate compounds [24,34,35]. Organ edema may distort tissue architecture, obstructing capillary flow and lymphatic drainage, impairing oxygen and metabolite diffusion, and resulting in organ failure. These effects may be particularly pronounced in encapsulated organs, such as the kidney, but also may cause hemorrhage and fluid extravasation in highly capillarized tissue, such as the lung [18,19,28-32]. Overall, these mechanisms are not well characterized and are poorly understood in humans, especially in a clinical context, where in addition to FO, patients may present confounders such as systemic inflammation, infection or acute kidney injury.

In agreement with two recent retrospective studies [18,19], we found that FO was associated with the duration of MV. Many factors may influence the relationship between FO and respiratory system dysfunction, including increased extravascular lung fluid and intrapulmonary shunt, decreased chest wall compliance, and intraabdominal hypertension. In contrast, conservative fluid management strategies are associated with improved lung function [6,33]. We believe that our data increases awareness of the need for new tools to guide fluid therapy and protocols for limiting liberal fluid administration in critically ill children [31].

This study has some limitations. This is single-center study with a relatively small sample size, although it represents the largest prospective cohort assessing the effect of fluid overload on mortality in a general PICU population. In the same way, because of the low mortality in pediatrics, a type II error cannot be ruled out. Overall, the mortality rate may seem high, but almost 50% of the deaths were due to brain death. We believe that deaths by this cause may be overrepresented because our unit is the only pediatric trauma center in the area, increasing the mortality of the cohort. The definition of fluid overload that we used, which is based on fluid balance, is known to be inaccurate, and ideally, a weight-based determination of FO should have been performed. In critically ill patients, it is very difficult to assess weight because of instability and the supportive therapies being implemented. Although there is significant variability in FO depending on the method used for calculation, the association with clinical outcomes is very consistent. A fluid balance-based FO definition is accepted and is the main calculation used worldwide for critically ill patients [8-23].

In conclusion, this prospective study in a general PICU population shows that FO is common in critically ill patients. We found that non-survivors had higher peak FO, but this was not independently associated with mortality. In agreement with previous retrospective studies, we found an association between FO and significant morbidity and the duration of MV. Multicenter studies are needed to corroborate these findings and to address whether strategies to prevent or treat FO may improve clinical outcomes.

Table 2
Multivariate logistic regression model analysis for mortality adjusted for age and PRISM score. (OR, Odds Ratio; 95% CI, 95% confidence interval; FO, fluid overload.)

	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Vasoactive support	24.09 (7.09,81.86)	12.8 (3.56,46.19)
Peak FO	1.05 (1.02,1.06)	1.01 (0.98,1.02)
≥3 organ failures	7.67 (3.68,15.98)	4.55 (2.13,9.71)
AKI[a]	3.97 (1.83,8.61)	4.59 (1.84,11.48)

[a] No AKI and Risk v/s Injury and Failure on pRFILE score.

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Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

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