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ORIGINAL ARTICLE

Early fluid overload is associated with acute kidney injury and PICU mortality in critically ill children

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Abstract Fluid overload (FO) has been associated with an increased risk for adverse outcomes in critically ill patients. Information on the impact of FO on mortality in a general population of pediatric intensive care unit (PICU) is limited. We aimed to determine the association of early FO with the development of acute kidney injury (AKI) and mortality during PICU stay and evaluate whether early FO predicts mortality, even after adjustment for illness severity assessed by pediatric risk of mortality (PRISM) III. This prospective study enrolled 370 critically ill children. The early FO was calculated based on the first 24-h total of fluid intake and output after admission and defined as cumulative fluid accumulation ≥5 % of admission body weight. Of the patients, 64 (17.3 %) developed early FO during the first 24 h after admission. The PICU mortality rate of the whole cohort was 18 of 370 (4.9 %). The independent factors significantly associated with early FO were PRISM III, age, AKI, and blood bicarbonate level. The early FO was associated with AKI (odds ratio [OR]=1.34, $p<0.001$) and mortality (OR=1.36, $p<0.001$). The association of early FO with mortality remained significant after adjustment for potential confounders including AKI and illness severity. The area under the receiver operating characteristic curve (AUC) of early FO for predicting mortality was 0.78 ($p<0.001$). This result, however, was not better than PRISM III (AUC=0.85, $p<0.001$).

Conclusion: Early FO was associated with increased risk for AKI and mortality in critically ill children.

What is Known:
• *Fluid overload is associated with an increased risk for adverse outcomes in specific clinical settings of pediatric population.*

What is New:
• *Early fluid overload during the first 24 h after PICU admission is independently associated with increased risk for acute kidney injury and mortality in critically ill children.*

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Abbreviations

AKI	Acute kidney injury
AUC	Area under the receiver operating characteristic curve
CI	Confidence interval
CRRT	Continuous renal replacement therapy
FO	Fluid overload
MODS	Multi-organ dysfunction syndrome
MV	Mechanical ventilation
ROC	Receiver operating characteristic
IQR	Interquartile range
OR	Odds ratio
PICU	Pediatric intensive care unit
PRISM III	Pediatric Risk of Mortality III
VIF	Variance inflation factor

Introduction

Fluid administration is fundamental in critically ill patients; however, it often leads to the development of significant fluid overload (FO), which may promote tissue edema and contribute to organ dysfunction [4, 24]. There is growing evidence supporting the relationship between FO and adverse outcomes in critically ill adult patients admitted to the intensive care unit (ICU) [5, 29, 32, 35].

In pediatric population, the positive correlation between FO and adverse outcomes has been demonstrated in specific clinical settings [2, 12, 13, 16, 18, 21, 25, 26, 28, 30, 31], such as in children requiring continuous renal replacement therapy (CRRT) [26, 30] and in children undergoing cardiac surgery [18, 25]. Information on the impact of FO on mortality in a general pediatric ICU (PICU) population is limited. One study of 266 critically ill children admitted to the PICU found that FO ≥10 % was associated with increased morbidity and mortality [28].

Furthermore, in children undergoing cardiac surgery, children with early FO were more likely to develop acute kidney injury (AKI) and required prolonged mechanical ventilation (MV) than those without early FO, suggesting that early FO often precedes AKI and is associated with worse outcomes [18]. The predictive significance of early FO for mortality in general PICU patients remains unknown. In addition, very few studies have adjusted for illness severity in the analysis on FO and mortality [17, 28, 30].

AKI, which is well recognized as an independent risk factor for mortality, is commonly encountered in critically ill

patients [1, 10, 11, 27]. AKI patients are more likely to develop FO. AKI contributes to impaired free water and sodium excretion, resulting in fluid accumulation. In turn, FO results in tissue edema, contributing to progressive organ dysfunction. These effects are pronounced in the kidneys. Tissue edema may directly participate in the progression of AKI [8, 9, 15, 19, 24]. The previous studies conducted in children and infants suggest that both AKI and FO were associated with increased mortality [3, 28]. However, whether or not the association of FO with mortality is due to direct effects of FO itself or due to indirect associations between FO and other disease states, such as AKI, is unknown [9]. It remains unclear whether the effect of FO on mortality is independent of AKI.

The aims of the study were to evaluate the impact of early FO developed during the first 24 h after PICU admission on the development of AKI and PICU mortality, and to determine whether early FO predicts mortality, even after adjustment for potential risk factors associated with mortality, including AKI and illness severity assessed by the pediatric risk of mortality III (PRISM III) score, in the general population of PICU. In addition, given the potential importance of FO on clinical outcomes, it is worthwhile understanding risk factors associated with early FO.

Patients and methods

All patients admitted to the PICU from January to June 2011 and from May to August 2012 were eligible for the study. The criteria for PICU admission in the university-affiliated tertiary children hospital were as described previously [6]. The inclusion criteria were admission to the PICU, including both medical and surgical patients, for 24 h or more and age between 1 month and 16 years. The exclusion criteria were length of stay in the PICU less than 24 h, including patients who did not survive the first 24 h after admission and patients who did not require at least 24 h of PICU hospitalization judged by the chief physicians; transfer to another hospital; and unexpected discharge from the PICU due to economic reason. This study was approved by the Ethics Committees of the Children's Hospital of Soochow University and performed in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents of the critically ill children enrolled in the study.

Clinical and laboratory data collection

Demographic, clinical, and laboratory data collected on the first 24 h of PICU admission, including age, body weight, sex, admission diagnosis, arterial blood gas analysis, and routine biochemical profile, were analyzed to determine the independent contributors to the risk of early FO. The first available

laboratory results during the first 24 h after PICU admission were used for analysis.

Clinical status, medication, and therapies were recorded daily until PICU discharge or death. Multiple organ dysfunction syndrome (MODS) was diagnosed when three or more organ dysfunctions were detected during PICU stay, according to the criteria described previously [14, 33] .

Assessment of fluid overload

In order to quantify FO, 24-h total of fluid intakes and outputs were measured. Fluid intake included all enterally and parenterally administered fluids (maintenance fluids, medications, blood products, and all forms of nutritional support). Fluid output included urine, stool, blood loss, drain output, and nasogastric tube output. Fluid management was determined by the practicing physicians and not influenced by the study researchers. Urine output was calculated by weighing disposable diapers or measuring the volume of urine collected using an indwelling urethral catheter.

Fluid accumulation was calculated according to the following formula: [(total amount of fluid intake (L) − total amount of fluid output (L))/body weight at PICU admission (kg)]× 100 [17, 28]. FO was defined as ≥5 % of fluid accumulation [18]. The threshold of 5 % FO, which is equivalent to a positive fluid balance of 50 mL/kg, was recommended as a cutoff point for higher AKI risk in very high-risk patients who require mechanical ventilation and one or more vasoactive agents [7, 18]. Early FO was considered when FO occurred during the first 24 h after PICU admission.

Assessment of illness severity

The severity of illness was assessed by the PRISM III score, which was previously described in detail in the original studies [23]. Sixteen age-related physiological parameters required for calculation of the PRISM III score were collected during the first 24 h after PICU admission.

Definition of AKI and clinical outcomes

AKI was defined according to the AKI network (AKIN) criteria: a ≥50 % increase in the serum creatinine level from baseline and/or urine output <0.5 mL/kg per hour for 6 h [20]. The serum creatinine at the time of PICU admission was defined as baseline creatinine. For patients who presented to the PICU with an elevated serum creatinine (>106.1 μmol/L), the lowest creatinine value within 2 weeks in the PICU was considered as baseline creatinine adapted from a previous study [22]. Clinical outcomes measured included length of MV, length of PICU stay, and PICU mortality that was defined as a death occurring during PICU stay after admission.

Statistical analysis

Statistical analyses were conducted using SPSS 13.0. For continuous variables with normal or skewed distribution, descriptive results were expressed as mean±standard deviation (SD) or median and interquartile range (IQR), respectively. The student's t test for unpaired samples and the Mann-Whitney U test were used to determine the differences between two groups, depending on the distribution of the data. The chi-square test or Fisher's exact test were used to compare the differences of categorical variables between groups. Stepwise multivariate linear regression analysis was performed to investigate factors potentially associated with FO. To assess whether there was significant multicollinearity among variables, collinearity diagnostics were performed using variance inflation factor (VIF) and tolerance values. Continuous variables with skewed distribution were log-transformed for linear regression analysis. Univariate and multivariate binary logistic regression models were conducted to calculate odds ratio (OR) with 95 % confidence interval (CI) for PICU mortality. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was calculated to assess the predictive ability. The nonparametric method of Delong was performed to compare difference between AUCs, and sensitivity and specificity were calculated at the optimal cut-off values using the software of SigmaPlot 10.0. All probability values were two-sided. Differences with p values <0.05 indicated statistical significance.

Results

Patient characteristics

The study enrolled 370 critically ill children. During the study period, 407 children were admitted to PICU. Thirty-seven children were excluded: 4 died and 5 were discharged from PICU in the first 24 h after admission, 4 were transferred to another hospital or unexpectedly discharged due to economic reasons, and 24 had incomplete data on fluid balance. There were no significant differences between the included and excluded patients in age (median [IQR]: 11 [3–33] vs. 14 [7–26] months; p=0.300), gender (male/female 238:132 vs. 23/14; p=0.849), and PRISM III score (3 [0–6] vs. 2.5 [0–11.5]; p=0.621).

The PICU mortality rate of the whole cohort with or without early FO was 18 of 370 (4.9 %). Of the 370 patients, 64 (17.3 %) developed early FO defined as ≥5 % of fluid accumulation during the first 24 h after admission. Admission diagnoses in patients with and without early FO are listed in

Table 1. Early FO was associated with more severe illness as assessed by PRISM III score (6 [2–12.5] vs. 2 [0–6]; $p<0.001$), a larger proportion of AKI (18.8 vs. 4.2 %; $p<0.001$), and a higher mortality rate (15.6 vs. 2.6 %; $p<0.001$) when compared with patients without early FO. The comparison of demographic and clinical characteristics between patients with and without early FO is displayed in Table 2.

Determination of clinical and laboratory factors potentially associated with early fluid overload

Variables including age; gender; PRISM III scores; the first available laboratory results of PaO_2, $PaCO_2$, arterial pH, serum albumin, serum creatinine, blood urea nitrogen, blood glucose, serum sodium, serum potassium, and blood bicarbonate; and AKI and mechanical ventilation developed during PICU stay, were entered into a stepwise multivariate linear regression analysis. As displayed in Table 3, PRISM III score ($p<0.001$), age ($p<0.001$), AKI ($p=0.003$), and blood bicarbonate level at admission ($p=0.016$) were identified as independent factors significantly associated with early FO (total $R^2=0.20$). VIF and tolerance values of <2 and >0.5, respectively, indicate the absence of significant multicollinearity between variables in the final model of multivariate regression analysis.

Association of early fluid overload with AKI

AKI was diagnosed in 25 (6.8 %) patients, including 17 (68.0 %) classified as AKIN stage 1: 14 on the first, 2 on the third, and 1 on the fifth day after admission; 2 (8.0 %) classified as stage 2: 1 on the second and 1 on the third day; and 6 (24 %) classified as stage 3: 4 on the first, 1 on the fourth, and 1 on the seventh day after PICU admission. Diagnosis of AKI was based on serum creatinine change, except for four patients with AKIN stage 1 on the first day after admission, who were diagnosed based on urine output <0.5 mL/kg per hour for 6 h.

The early FO was associated with AKI developed during PICU stay (OR=1.31; 95 % CI, 1.17–1.46; $p<0.001$). The association, however, did not remain significant after adjustment for PRISM III score (OR=1.09; 95 % CI, 0.95–1.25; $p=0.231$). Fluid balance between patients with and without AKI is compared in Fig. 1a. The fluid balance during the first 24 h after admission was significantly higher in patients who developed AKI during PICU stay compared to those who did not (6.32 ± 1.17 vs. 1.94 ± 0.17 %; $p<0.001$).

Association of both early fluid overload and AKI with mortality

Both early FO (OR=1.36; 95 % CI, 1.20–1.55; $p<0.001$) and the presence of AKI (OR=15.77; 95 % CI, 5.52–45.03; $p<0.001$) were significantly associated with PICU mortality and independent of each other (FO: OR=1.28; 95 % CI, 1.11–1.48; $p=0.001$. AKI: OR=6.41; 95 % CI, 1.89–21.81; $p=0.003$).

In addition, the association of early FO with PICU mortality remained significant after adjustment for potential confounders including illness severity assessed by the PRISM III score and other risk factors for mortality such as the presence of AKI and the use of MV, as displayed in Table 4. However, the association between AKI and mortality did not remain significant after adjustment. The comparison of fluid balance between survival and non-survival critically ill children is shown in Fig. 1b. Non-survival children had significantly higher fluid balance during the first 24 h after admission compared to survivors (7.40 ± 1.52 vs. 1.97 ± 0.17 %; $p<0.001$).

Ability of early fluid overload to predict PICU mortality

The predictive ability of early FO calculated during the first 24 h after PICU admission for PICU mortality was assessed in Table 5. The level of early fluid accumulation achieved AUC of 0.78 (95 % CI, 0.65–0.91;

Table 1 Admission diagnosis in children with and without early fluid overload	Diagnosis on PICU admission, n (%)	Early FO <5 % (n=306)	Early FO ≥5 % (n=64)
	Respiratory diseases	117 (38.2)	18 (28.1)
	Neurologic diseases	72 (23.5)	9 (14.1)
	Sepsis	28 (9.2)	10 (15.6)
	Surgery/trauma	29 (9.5)	7 (10.9)
	Cardiovascular diseases	19 (6.2)	2 (3.1)
	Hematologic/oncologic diseases	13 (4.2)	8 (12.5)
	Gastrointestinal diseases	12 (3.9)	3 (4.7)
	Poisoning	6 (2.0)	1 (1.6)
	Others	10 (3.3)	6 (9.4)

FO fluid overload, *PICU* pediatric intensive care unit

Table 2 Comparison of clinical characteristics and laboratory findings between children with and without early fluid overload

Early fluid overload	<5 % (n=306)	≥5 % (n=64)	p value
Age, months	12 [3–36]	7.5 [3–24]	0.129
Body weight, kg	9.1 [6.5–15.0]	7.4 [5–11.0]	0.003
Male, n (%)	192 (62.7)	46 (65.6)	0.166
PRISM III score	2 [0–6]	6 [2–13.25]	<0.001
Dehydration[a], n (%)	2 (0.7)	3 (4.7)	0.038
Laboratory findings on the day of PICU admission[b]			
PaO$_2$, mmHg	122.1 [66.6–144.7]	106.4 [71.4–138.9]	0.350
PaCO$_2$, mmHg	30.2 [26.2–37.1]	29.4 [24.1–35.4]	0.097
Arterial pH	7.404 [7.351–7.455]	7.383 [7.304–7.457]	0.129
Blood bicarbonate, mmol/L	20.3 [18.3–22.7]	19.4 [14.2–22.0]	0.011
Serum albumin, g/L	42.0 [39.1–44.5]	38.7 [36.1–44.1]	0.001
Serum creatinine, μmol/L	25.9 [21.1–33.8]	29.6 [23.0–55.8]	0.008
Blood urea nitrogen, μmol/L	3.54 [2.60–4.93]	4.27 [2.69–7.72]	0.076
Blood glucose, mmol/L	6.69 [5.26–8.58]	7.04 [5.81–11.15]	0.011
Serum sodium, μmol/L	135.4 [133.1–137.3]	135.7 [132.6–137.3]	0.765
Serum potassium, μmol/L	4.18 [3.77–4.69]	4.26 [3.81–5.02]	0.218
Early fluid balance, during the first 24 h after PICU admission			
Total intake, mL	825 [588–1196]	1103 [795–1573]	<0.001
Total output, mL	667.5 [477.5–1041]	525.5 [382.5–809]	<0.001
Urine output, mL	630 [435–1015]	515 [362.5–730]	<0.001
Oliguria[c], n (%)	1 (0.3)	3 (4.7)	0.017
Acute kidney injury[d], n (%)	13 (4.2)	12 (18.8)	<0.001
Shock[d], n (%)	18 (5.9)	9 (14.1)	0.022
Septic shock[d], n (%)	7 (2.3)	3 (4.7)	0.387
MODS[d], n (%)	13 (4.2)	9 (14.1)	0.003
Diuretics[e], n (%)	136 (44.4)	28 (43.8)	0.902
MV[e], n (%)	80 (26.1)	26 (40.6)	0.020
Duration of MV, hours	0 [0–11.25]	0 [0–64.75]	0.041
Prolonged MV (>48 h), n (%)	52 (17.0)	17 (26.6)	0.074
Length of PICU stay[f], hours	49.0 [25.5–104.5]	80.0 [41.0–143.0]	0.010
PICU mortality, n (%)	8 (2.6)	10 (15.6)	<0.001

Values are median [interquartile range]

MODS multiple organ dysfunction syndrome, *MV* mechanical ventilation, *PICU* pediatric intensive care unit, *PRISM III* pediatric risk of mortality III

[a] On PICU admission

[b] The first available laboratory results during the first 24 h after PICU admission

[c] Developed during the first day of PICU stay

[d] Developed during PICU stay

[e] Administration during PICU stay

[f] Length of PICU stay of survivors

$p<0.001$), which was better than AKI (AUC=0.70; 95 % CI, 0.55–0.85; $p=0.005$), but not than PRISM III (AUC=0.85; 95 % CI, 0.74–0.96; $p<0.001$) for predicting mortality. The p value for comparison between the two AUCs of early FO and PRISM III was 0.422. In addition, when combining early FO and AKI, the predictive performance improved (AUC=0.83; 95 % CI, 0.72–0.95; $p<0.001$) over that of early FO alone, but not reaching statistical significance ($p=0.520$). The ROC curves of early FO and PRISM III for predicting the PICU mortality of critically ill children are displayed in Fig. 2.

The sensitivity and specificity of early FO and PRISM III score at the optimal cut-off value to predict PICU mortality are shown in Table 5. Early FO displayed a sensitivity of 78 % and a specificity of 74 % at the cut-off value of 3.8 %. At the

**Table 3** Clinical and laboratory factors potentially associated with early fluid overload

	Unstandardized coefficients		p value	Collinearity statistics	
	B	Coefficient (SE)		Tolerance	VIF
PRISM III score	0.163	0.041	<0.001	0.575	1.738
Age[a]	−1.093	0.304	<0.001	0.958	1.044
Acute kidney injury	2.584	0.878	0.003	0.648	1.543
Blood bicarbonate[a]	−3.668	1.519	0.016	0.824	1.214

Total R^2 =0.20. Variables including age, gender, PRISM III scores, the first available laboratory results of PaO_2, $PaCO_2$, arterial pH, serum albumin, serum creatinine, blood urea nitrogen, blood glucose, serum sodium, serum potassium and blood bicarbonate, and AKI and mechanical ventilation developed during PICU stay, were entered into the stepwise multivariate linear regression analysis. Early fluid overload was coded as a continuous variable. Continuous variables with skewed distribution were log-transformed for linear regression analysis

PRISM III pediatric risk of mortality III, *VIF* variance inflation factor

[a] Data were log-transformed for the regression analysis

optimal cut-off score of 5.5, the sensitivity and specificity were 83 and 72 %, respectively, for PRISM III score to predict PICU mortality.
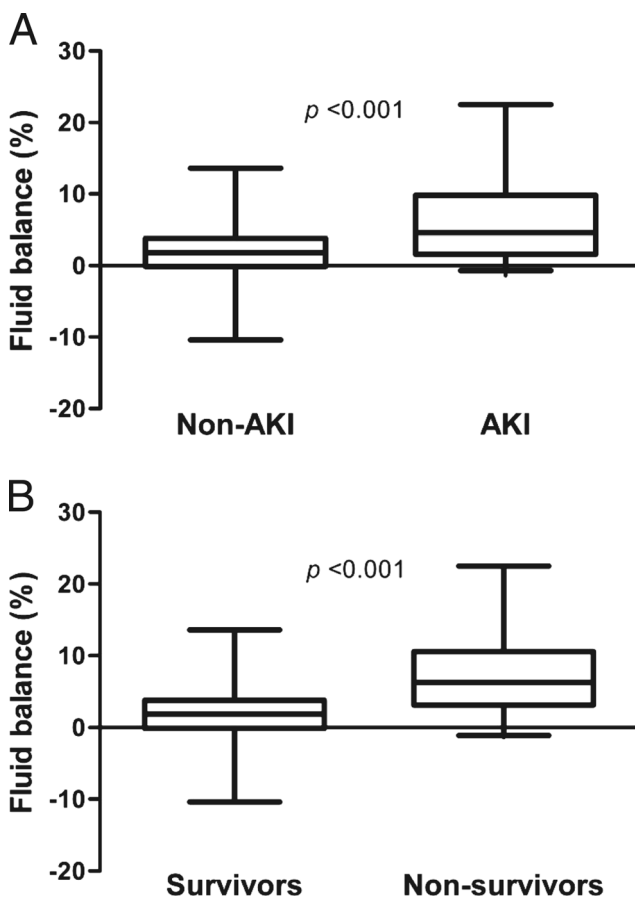
Fig. 1 Comparison of the fluid balance calculated during the first 24 h after admission between critically ill children who did or did not develop acute kidney injury (AKI) during PICU stay (**a**) and between survivors and non-survivors (**b**). *Boxes* represent medians and interquartile ranges and *whiskers* represent minimums and maximums. Probability values: Student's *t* test

Discussion

This study provides data on FO developed during the first 24 h after PICU admission in critically ill children and demonstrates that early FO is significantly associated with the development of AKI and mortality during PICU stay.

FO had been previously found to be associated with increased risk of mortality in pediatric patients [12, 13, 25, 26, 28, 30, 31]. To our knowledge, only one study verified the use of early FO as a predictive marker in the pediatric population. Early postoperative FO was independently associated with worse outcomes, including prolonged MV and extended length of hospital stay, in a subgroup of PICU patients after cardiopulmonary bypass [18]. We evaluated the impact of early FO on predicting mortality in a general PICU population, independent of the severity of illness.

It is reasonable to question the association of FO with clinical outcomes, because it may be a surrogate for illness severity. Indeed, the degree of FO was significantly affected by the severity of illness assessed by the PRISM III score in our study, and more severely ill patients had greater degrees of early FO. A limited number of pediatric studies have adjusted for illness severity in their analysis of FO and outcomes [17, 28, 30]. In critically ill children receiving CRRT, the effect of FO on the prediction of PICU mortality persisted after adjustment for disease severity measured by the PRISM II score [30]. In children admitted to the PICU, FO developed in the first 14 days of admission to the PICU was associated with increased mortality even when adjusted for age and PRISM II score [28]. These results are similar to our study. We further examined the confounding effects of illness severity and other clinical factors associated with mortality to account for differences between patients who are fluid overloaded and those who are not. Our data imply that early FO is not merely a marker of disease severity, but an independent factor associated with mortality.

The other major finding in this study was the association between FO in the first 24 h and AKI occurring within the first

Table 4 Association of both early fluid overload and AKI with PICU mortality

	OR	95 % CI	p value	Adjusted OR	95 % CI	p value
PRISM III	1.24[d]	1.15–1.33	<0.001			
Presence of AKI[a]	15.77	5.52–45.03	<0.001	2.51[g]	0.53–11.98	0.249
Early FO[b]	1.36[e]	1.20–1.55	<0.001	1.17[h]	1.01–1.37	0.035
Early FO × AKI[c]	28.83[f]	8.10–102.62	<0.001	5.46[i]	0.88–33.70	0.068

AKI acute kidney injury, *CI* confidence interval, *FO* fluid overload, *OR* odds ratio, *PICU* pediatric intensive care unit, *PRISM III* pediatric risk of mortality III

[a] AKI developed during PICU stay

[b] Early fluid overload was coded as a continuous variable

[c] Early FO was coded as a categorical variable with FO <5 % as the reference

[d] Odds ratio represents the increase in risk per 1-point increase in PRISM III score

[e] Odds ratio per 1 % increase in fluid accumulation

[f] Odds ratio represents increase in risk of mortality in patients with both early FO and AKI

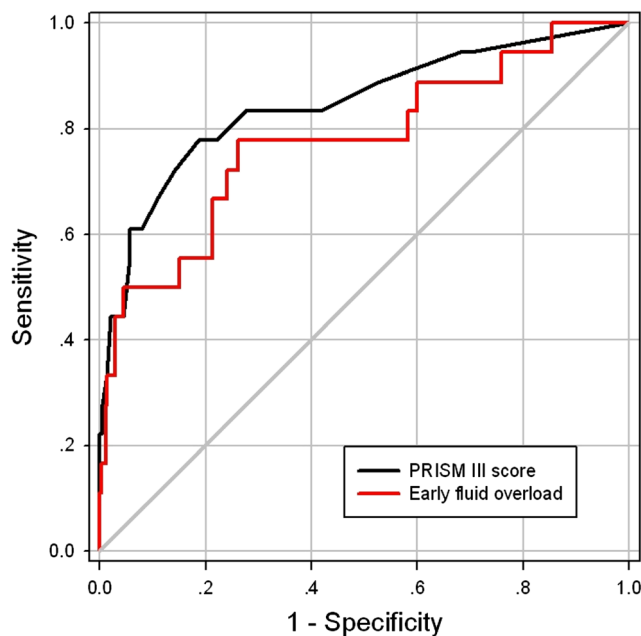[g] After adjustment for age, PRISM III, the use of mechanical ventilation, and early FO

[h] After adjustment for age, PRISM III, the use of mechanical ventilation, and the presence of AKI

[i] After adjustment for age, PRISM III, and the use of mechanical ventilation

week of PICU admission, suggesting that early FO relates to AKI as it is diagnosed by serum creatinine change and/or urine output. Previous studies suggest that significant FO may occur prior to the development of AKI, as defined by SCr rise [18, 25]. However, whether the fluid accumulation is a contributor to AKI is yet to be determined, because that AKI may have occurred before it was detected with current clinical diagnostics. Our study confirmed that both early FO

Fig. 2 Receiver operating characteristic (ROC) curves for the ability of early fluid overload and the score of pediatric risk of mortality III (PRISM III) to predict PICU mortality in critically ill children (*n*=370). The area under the ROC curve (AUC) for early fluid overload and PRISM III were 0.78 and 0.85, respectively. *p* value of comparison of the difference between AUCs=0.422

and AKI were associated with adverse outcomes. The bidirectional interaction between FO and AKI raises the question of whether it is possible that the association of FO with mortality could be at least partially attributed to the occurrence of AKI. Although the contiguity and possible overlapping of FO and AKI make it difficult to establish the exact border between these two clinical events in a study, we demonstrated that early FO was significantly associated with mortality, even accounting for its interaction with AKI. This implies that mortality might be impacted negatively by early FO regardless of the presence of AKI.

There are no specific criteria for defining fluid accumulation in critically ill children. This 5 % FO threshold was observed in the previous study performed in the subgroup of PICU patients with cardiopulmonary bypass [18]. The percentage threshold of FO may depend on what patient population is being studied [25]. One previous study demonstrated a dose-response relationship between FO and mortality, independent of the severity of illness [30]. In our data, for every 1 % increase in early fluid accumulation, the odds for PICU mortality increased by 36 %. Moreover, early FO achieved AUC of 0.78 for predicting mortality. However, the ROC curve analysis in the present study showed that PRISM III score (AUC=0.85) seemed to play a greater role than early FO in predicting the PICU mortality, although there was no significant difference between the two AUCs. This might be explained by the fact that the PRISM III score, which has been well validated as a measure of illness severity and predictor of mortality in children admitted to the PICU, is calculated using age-related physiological parameters measured precisely [23, 36]. However, documentation of the exact fluid intake and output may not be always accurate in critically ill children, especially in infants. These results suggested that accurate and precise measurements should be used to predict clinical

Table 5 Predictive characteristics of early fluid overload, AKI, and PRISM III for PICU mortality

	AUC	95 % CI	*p* value	Cut-off value	Sensitivity (%)	Specificity (%)
PRISM III	0.85	0.74–0.96	<0.001	5.5	83	72
Early fluid overload[a]	0.78	0.65–0.91	<0.001	3.8	78	74
Presence of AKI[b]	0.70	0.55–0.85	0.005	NA	NA	NA
Early fluid overload[a] combined with AKI	0.83	0.72–0.95	<0.001	NA	83	74

AKI acute kidney injury, *AUC* area under the receiver operating characteristic curve, *CI* confidence interval, *NA* not applicable, *PICU* pediatric intensive care unit, *PRISM III* pediatric risk of mortality III

[a] Early fluid overload was coded as a continuous variable

[b] Developed during PICU stay

outcomes in critically ill children. Moreover, the possibility of the low performance of AKI in predicting mortality might be due to the fact that 68 % of the patients with AKI in the study had AKIN stage 1. One previous study suggests a nearly linear increase in hospital mortality with increasing the severity of AKI [27, 34]. Less severity of AKI may have resulted in underestimation of the impact of AKI on mortality.

This study has some limitations. First, we were not able to ascertain the fluid balance before PICU admission. The information concerning initial fluid resuscitation, pressor administration, and diuretic therapy prior to PICU admission, which contributes significantly to the fluid balance, was not available [8, 20, 21]. Therefore, whether the general PICU patients with early 5 % FO truly had pathologic fluid accumulation has to be considered. Second, because of the observational nature of the study, we cannot determine if early FO has a precise pathogenesis in increasing mortality or is merely a valuable biomarker of critical illness [5]. Third, although definition and staging of AKI are based on serum creatinine and urine output [20], the use of urine output criteria for diagnosis has not been well validated. Four patients were diagnosed with AKI based on urine output in our study, which might increase the likelihood of observing an association between FO and AKI. Fourth, the PICU mortality found in this study was lower compared to our previous report [6], which might be explained by the fact that we excluded patients who died within 24 h after PICU admission. Nevertheless, we also excluded patients who did not require at least 24 h of PICU hospitalization. There was no significant difference between excluded and included patients in the illness severity assessed by the PRISM III score. Fifth, AKI occurred in the first week of PICU admission, with 72 % in the first day, implying that patients might be admitted later to the PICU in our unit. In addition, only 25 % of survivors are mechanically ventilated during PICU stay, suggesting that patients received less aggressive treatment. These may limit the generalizability of our findings to critically ill children admitted earlier in

their critical illness courses and receiving aggressive management in the PICU. The exclusion of children who were unexpectedly discharged from the PICU due to economic reasons may also make it difficult to generalize the results of this study. Further multicenter studies are necessary to improve the generalizability of our findings.

In conclusion, our study indicates that early FO was significantly associated with increased risk for AKI and mortality in critically ill children. These findings support increased attention to monitoring the fluid balance. Further randomized and controlled clinical trials are needed to explore whether early FO would be a treatment target to lower mortality in PICU patients.

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