Association between Early Fluid Overload and Mortality in Critically-ill Mechanically Ventilated Children: A Single Center Prospective Cohort Study

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Research

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Abstract

Background: This study retrospectively analyzed the relationship between early fluid overload(FO) and in-hospital mortality in Children with mechanical ventilation in pediatric intensive care unit.

Methods: Patients who were on mechanical ventilation (MV) for≧48 h and aged over 28 days and less than 18 years from March 2014 to March 2019 in department of PICU, Xinhua hospital. Daily FO was calculated as {(daily fluid intake-daily fluid output)/weight at ICU admission * 100%}.We defined the early FO as the FO in the first three days of mechanical ventilation, and divided it into four bands: %FO ≤ 0%, 0%＜%FO≤ 10%, 10%＜%FO≤ 20%, and %FO > 20%. We compared the mortality in discharge between groups with different FO. We also compared the early FO between survivors and non-survivors. Multivariate stepwise logistic regression analysis was used to analyze the prognostic factors of mortality in hospital.

Results: 309 patients were included. There were 202 cases in non-operative and 107 cases in operative. The mean early FO was 8.83 ± 8.81%, and the mortality in hospital was 26.2% (81/309). The percentage of % FO＞10% was in present 41.4%(131/309) and %FO＞20% was in present 8.7% (27/309). There was no significant difference in discharge-mortality between different FO groups(p=0.053) and in FO between survivors and non-survivors(p=0.992). Regression analysis demonstrated that the more vasoactive drugs, the presence of MODS, the longer duration of MV, and the non-operation reason for PICU admission were related to the increase of mortality(p＜0.05); although early FO and %FO>10% were not associated with in-hospital mortality(β=0.030, p=0.090, 95% C.I.=0.995~1.067; β=0.479, p=0.153, 95% C.I.= 0.837~3.117), %FO>20% was related to the increase of mortality (β=1.057, OR=2.878, p=0.029, 95% C.I.=1.116~7.418). There was positive correlation between early FO and LOS in PICU (r=0.148, p=0.009), but the relation is weak.

Conclusions: Affected by interventions and the severity of the disease, the correlation between the early FO and %FO>10% with mortality was not clear, but %FO>20% was related to the increase of mortality in critically-ill mechanically ventilated Children.

Trial registration: Not applicable

Background

Proper fluid management is always one of the important treatment methods for critically illness to maintain a good circulation capacity and tissue perfusion. The adverse effects of high levels of fluid accumulation have been confirmed in most studies, including deterioration of lung function, prolonged duration of mechanical ventilation(MV), and length of stay (LOS) in hospital, pediatric intensive care unit (PICU), focusing on pediatric acute respiratory distress syndrome(ARDS)/acute lung injury(ALI), septic shock and CRRT and so on[1–8]. However, there are few studies on the treatment of severe diseases with PICU as a whole[9–11]. Although the relationship between fluid overload (FO) and mortality is controversial in those studies, fluid overload may be a predictor of death in critically ill children.

With the researches on the fluid accumulation, the early FO has been paid more and more attention. At present, most studies evaluate the early fluid overload as a percentage of the cumulative amount of fluid in and out and the weight at admission or admission to PICU. Based on a retrospective study of 638 hospitalized patients with mechanical ventilation in PICU[11], fluid overload within 48 hours of admission was not related to mortality, but related to deterioration of oxygenation index and prolongation of mechanical ventilation time in survival patients, especially when %FO ≥ 15%. Sutherland et al. [7]divided %FO into□20% and ≥ 20% for correlation analysis in their study. The results showed that the mortality of children with ≥ 20% was about 8.5 times of the former. Some studies directly defined the existence of early fluid overload as %FO ≥ 10%, and is also confirmed that when %FO ≥ 10%, often has adverse clinical consequences[6, 9, 12].

In this study, we will compare the mortality between groups with different FO, and the early FO between survivors and non-survivors in PICU. At the same time, we will study the prognostic factors of mortality, so as to explore the association about early fluid overload, %FO > 10% and %FO > 20% with mortality.

Methods

Study design

This study was a retrospective analysis of children with invasive mechanical ventilation admitted to the PICU of Xinhua Hospital Affiliated to Shanghai Jiao tong University School of Medicine. The PICU is a national key treatment center for critical patients, and covers a wide range of diseases. It is composed of two disease treatment units: one is mainly for the treatment of internal medicine related critically illness, and the other is for the treatment of surgical perioperative care patients. The age range of the patients was more than 28 days and less than 16 years old. Local research ethics approval for study was obtained from ethics committee of Xinhua Hospital Affiliated to Shanghai Jiao tong University School of Medicine.

Patient Population And Date Collection

The subjects were the Children with invasive mechanical ventilation admitted by PICU of Xinhua Hospital from March 2014 to March 2019. The age range was more than 28 days and less than 16 years old, and the duration of invasive mechanical ventilation was at least 48 hours. Children with MV time less than 48 hours were not included in this collection.

Basic demographic information mainly included: age, gender, weight when entering PICU, presence of basic diseases, duration of mechanical ventilation, length of stay(LOS) in hospital, length of stay(LOS) in ICU, presence of multiple organ dysfunction syndrome(MODS), main intervention measures (receipt of continuous renal replacement therapy(CRRT), use of vasoactive drugs), daily access, etc. The main reasons for PICU admission were groups into surgical patients and medical patients. The third generation of admission pediatric risk of mortality score (PRISM-□) was used as the measure of illness severity and

was performed for all patients during the first 24 hours following admission to PICU. Vasoactive medications were defined as any continuous vasoactive infusion used for cardiovascular support. Based on clinical diagnosis, basic diseases refered to congenital malformation, immune deficiency, genetic and metabolic diseases, benign and malignant tumors, and severe malnutrition that existed and clearly diagnosed before admission. MODS was defined as the presence of at least 2 failed organs at any time during PICU admission, according to recently published criteria[13]. Mortality was defined as mortality in hospital.

The first duration of MV in days was measured as the time from first mechanical ventilator support to the first extubation attempt or the time of PICU in discharge without extubation. Extubation failure was defined as the reinstitution of MV within 48 hours of extubation. If the weaning failed, MV is considered as the one time. Duration of MV was similarly defined as the time from the initial intubation to the time of the last extubation or the time of PICU in discharge without extubation. Duration of MV longer than 7 days was concerned based on the effect of prolonged MV on prognosis[14, 15].

The daily fluid intake included all intravenous fluid and oral rehydration; the daily fluid output included urine volume, feces, all kinds of drainage volume, CRRT dehydration, etc. The ratio of the difference of daily fluid in and out and the weight at the time of occupancy in PICU was expressed as percentage {i.e. %FO= (daily fluid intake in liters - daily fluid output in liters) / admission weight in kilograms * 100%}. We defined the early FO as the fluid overload in the first three days of mechanical ventilation, and divided it into four groups: %FO ≤ 0%, 0%<%FO ≤ 10%, 10%<%FO ≤ 20%, and %FO > 20%. We had focused on %FO > 10% and %FO > 20%.The study duration of FO was defined as the LOS in MV if it was<7 days and as the initial 7days of the MV stay if it was ≥ 7 days.

The main purpose of this study was to investigate the relationship between early fluid overload and mortality in hospital. The secondary objective to study the relationship between early FO and LOS in hospital, LOS in PICU.

Statistical Analysis

SPSS Statistics version 22.0(IBM, Armonk, NY) was used in this study. Kruskal-Wallis test was used to analyze continuous variables in different groups for research, and Mann-Whitney U test was used for continuous variables between survivors and non-survivors. Pearson chi-square test were used for categorical variables. For continuous variables, data was reported as medians with interquartile ranges (IQRs) or means ± standard deviation (SD); percentage was used for categorical variables. The relationship between early FO and LOS in PICU, LOS in hospital was assessed by Spearman rank correlation coefficient. The binary multivariate logistic(log) regressions were used to evaluate the association between early FO, %FO > 10% and %FO > 20% with mortality in hospital. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs) for logistic regression. P values < 0.05 were considered significant.

Results

Demographics in all subjects

We collected and analyzed the cases in the past 5 years, 309 cases were eligible for inclusion. There were 107 cases in the non-operative patients and 202 cases in the operative patients. The in-hospital mortality was 26.2% (81/309), the median age was 13.4 months (month, m), the male was 187 cases (60.5%), more than half of the subjects (69.3%) had basic diseases, the median mechanical ventilation time was 6.0 days, the median LOS in PICU was 18.0 days, and the in-hospital LOS was 27.0 days. The mean early FO was 8.83 ± 8.81%, 59 patients(19.1%) received CRRT, 91 patients(29.4%) diagnosed MODS, the median PRISM-Ⅲ was 5.0 (Table 1).The median value of daily FO was gradually stabilized (Fig. 1). The cumulative FO was gradually increased and positive in the study (Fig. 2)

Different Early Fo And Mortality

Different groups of early FO were correlated with age, weight, presence of basic diseases, reason for PICU admission, use of vasoactive drugs and CRRT, presence of MODS, and PRSIM-III. There was no statistical difference in the in-hospital mortality, duration of MV, LOS in hospital, LOS in PICU.

Compared with the other groups, the %FO ≤ 0% group was older and had more CRRT treatment; it used more vasoactive drugs, had MODS, and higher score of PRSIM-III than 0%<%FO ≤ 10% and 10%<FO ≤ 20% group, and was heavier than10%<%FO ≤ 20% and %FO > 20% group. Compared with the 10%<%FO ≤ 20% group, the 0%<%FO ≤ 10% was older and received more CRRT treatment; it was heavier than 10% <FO ≤ 20% and %FO > 20% group. Compared with the other groups, the 10%<%FO ≤ 20% group had less medical patients and more surgical patients. Compared with the %FO ≤ 0% and 0%<%FO ≤ 10% group, the 10%<%FO ≤ 20% and %FO > 20% group had more basic diseases. The %FO > 20% group had more use of vasoactive drugs than the 10%<FO ≤ 20% group (all $p < 0.05$)(Table 2).

Table 1. Characteristics of all patients

Variable	N = 309
Age(months,m),median (IQR)	13.4(4.7–52.6)
Weight(kg)	8.8(6.0–15.0)
Gender, N(%)	
Male	187(60.5%)
Female	122(39.5%)
Basic disease, N(%)	214(69.3%)
Reason for PICU admission, N(%)	
Medical, N(%)	202(65.4%)
Surgical, N(%)	107(34.6%)
Receipt of CRRT, N(%)	59(19.1%)
Receipt of vasoactive drugs, N(%)	158(51.1%)
Num of vasoactive drugs,median (IQR)	1.0(0.0–2.0)
Diagnosis of MODS, N(%)	91(29.4%)
PRSIM-III,median (IQR)	5.0(2.0–9.0)
Mortality in hospital, N(%)	81(26.2%)
Times from hospital admission to PICU(day), median (IQR)	0.0(0.0–5.0)
LOS in PICU(day),median (IQR)	18.0(9.0-27.5)
LOS in hospital(day),median (IQR)	27.0(17.0–43.0)
Times of MV,median (IQR)	1(1–1)
Duration of MV(day),median (IQR)	6.0(4.0–12.0)
The first duration of MV(day),median (IQR)	6.0(4.0–11.0)
Proportion of MV over 7 days N(%)	124(40.1%)
Early FO,mean ± SD	8.38 ± 8.81
Percentage of %FO>10%, N(%)	131(42.4%)
Percentage of %FO>20%, N(%)	27(8.7%)

LOS: length of stay; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; PICU: pediatric intensive care unit; FO: fluid overload; Continuous variables was reported as medians or means ± standard deviation;

Table 2
Comparison of all patients by FO percent groups

Variable	%FO ≤ 0%	0%<%FO ≤ 10%	10%<%FO ≤ 20%	%FO >20%	P value
Number, N(%)	53(17.2%)	125(40.5%)	104(33.6%)	27(8.7%)	
Age(months,m),median (IQR)	42.4(14.9–88.3)	18.5(4.2–60.4)[a,c]	7.5(4.4–19.9)[a]	5.8(3.5–14.8)[a]	<0.001
Weight(kg)	15.0(9.5–25.0)	11.0(6.6–19.5)	7.0(5.4–11.0)[a,b]	5.8(4.9–8.2)[a,b]	<0.001
Gender, N(%)					0.747
Male	29(54.7%)	77(61.6%)	63(60.6%)	18(66.7%)	
Female	24(45.3%)	48(39.4%)	41(39.4%)	9(33.3%)	
Basic disease, N(%)	26(49.1%)	81(64.8%)	84(80.8%)[a,b]	23(85.2%)[a,b]	<0.001
Reason for PICU admission, N(%)					0.030
Medical, N(%)	39(73.6%)	85(68.0%)	57(54.8%)[a,b,d]	21(77.8%)	
Surgical, N(%)	14(26.4%)	40(32.0%)	47(45.2%)[a,b,d]	6(22.2%)	
Receipt of CRRT, N(%)	22(41.5%)	25(20.0%)[a]	7(6.7%)[a,b]	5(18.5%)[a]	<0.001
Receipt of vasoactive drugs, N(%)	38(71.7%)	62(49.6%)[a]	41(39.4%)[a,d]	17(63.0%)	0.001
Num of vasoactive drugs,median (IQR)	2.0(0.0–3.0)[b,c]	1.0(0.0–2.0)	0.0(0.0–1.0)	1.0(0.0–2.0)	<0.001
Diagnosis of MODS, N(%)	28(52.8%)[b,c]	35(28.0%)	19(18.3%)	9(33.3%)	0.001
PRSIM-III,median (IQR)	8.0(5.5–12.5)[b,c]	4.0(2.5-8.0)	4.0(1.0–8.0)	5.0(2.0–10.0)	0.001
Mortality in hospital, N(%)	17(32.1%)	31(24.8%)	21(20.2%)	12(44.4%)	0.053
Time from hospital admission to PICU(day), median (IQR)	0.0(0.0–5.0)	0.0(0.0-4.5)	1.0(0.0–5.0)	0.0(0.0–4.0)	0.356

LOS: length of stay; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; PICU: pediatric intensive care unit; FO: fluid overload. a: VS %FO ≤ 0%; b: VS 0%<%FO ≤ 10%; c:10%<%FO ≤ 20%;d: VS %FO > 20%.Continuous variables: p value obtained with Kruskal-Wallis test; Categorical variables: p value obtained with Pearson chi-square test.

Variable	%FO ≤ 0%	0%<%FO ≤ 10%	10%<%FO ≤ 20%	%FO >20%	P value
LOS in PICU(day),median (IQR)	16.0(9.0–22.0)	16.0(9.0–27.0)	18.5(10.0–31.0)	21.0(9.0–32.0)	0.240
LOS in hospital(day),median (IQR)	27.0(18.5–42.0)	25.0(16.0–42.0)	30.0(18.0-46.8)	27.0(15.0–44.0)	0.240
Times of MV,median (IQR)	1(1–1)	1(1–1)	1(1–1)	1(1–1)	0.780
Duration of MV(day),median (IQR)	5.0(4.0–14.0)	6.0(4.0–11.0)	7.0(4.0-13.8)	7.0(5.0–14.0)	0.733
The first duration of MV(day),median (IQR)	5.0(4.0–13.0)	6.0(4.0–10.0)	7.0(4.0–12.0)	7.0(5.0–14.0)	0.625
Proportion of MV over 7 days N(%)	20(37.7%)	46(36.8%)	47(45.2%)	11(10.8%)	0.616
Early FO,median (IQR)	-3.7(-6.9–1.2)	5.8(3.0-7.7)	14.2(12.0-16.9)	23.1(21.0-24.3)	

LOS: length of stay; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; PICU: pediatric intensive care unit; FO: fluid overload. a: VS %FO ≤ 0%; b: VS 0%<%FO ≤ 10%; c:10%<%FO ≤ 20%;d: VS %FO > 20%.Continuous variables: p value obtained with Kruskal-Wallis test; Categorical variables: p value obtained with Pearson chi-square test.

Univariate Analysis For Mortality

There were 228 cases in the survivors and 81 cases in the non-survivors. There was no statistical difference in early FO(p = 0.992). But the duration of MV, LOS in hospital, use of vasoactive drugs and CRRT, presence of MODS, PRISM-III and operation had statistical difference (all p<0.05). Compared with the survivors, the non-survivors had more medical patients, use more vasoactive drugs and CRRT, longer duration of MV, less days of stay in hospital and more percentage of %FO>20%.(Table 3)

Table 3
Comparison of survivors with non-survivors

Variable	Survivors	Non-survivors	P value
Number, N(%)	228(73.8%)	81(26.2%)	
Age(months,m),median (IQR)	11.5(4.4–48.6)	16.4(5.1–56.6)	0.264
Weight(kg)	8.6(5.8–15.0)	10.0(6.0–15.0)	0.440
Gender, N(%)			0.692
Male	136(59.6%)	51(63.0%)	
Female	92(40.4%)	30(37.0%)	
Basic disease, N(%)	155(68.0%)	59(72.8%)	0.484
Reason for PICU admission, N(%)			<0.001
Medical, N(%)	135(59.2%)	67(82.7%)	
Surgical, N(%)	93(40.8%)	14(17.3%)	
Receipt of CRRT, N(%)	33(14.5%)	26(32.1%)	0.001
Receipt of vasoactive drugs, N(%)	96(42.1%)	62(76.5%)	<0.001
Num of vasoactive drugs, median (IQR)	0.0(0.0–1.0)	2.0(1.0–3.0)	<0.001
Diagnosis of MODS, N(%)	37(16.2%)	54(66.7%)	<0.001
PRSIM-III, median (IQR)	5.0(2.3-9.0)	6.0(2.0-12.5)	0.098
Time from hospital admission to PICU(day), median (IQR)	0.0(0.0–5.0)	0.0(0.0-3.5)	0.153
LOS in PICU(day),median (IQR)	18.0(11.0-27.8)	16.0(6.5–28.0)	0.088
LOS in hospital(day),median (IQR)	30.0(20.0-46.8)	17.0(8.0-31.5)	<0.001
Times of MV, median (IQR)	1.0(1.0–1.0)	1.0(1.0–1.0)	0.064
Duration of MV(day),median (IQR)	6.0(4.0–11.0)	9.0(5.0–22.0)	0.001
The first duration of MV(day),median (IQR)	6.0(4.0–10.0)	9.0(5.0–19.0)	0.001

LOS: length of stay; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; PICU: pediatric intensive care unit; FO: fluid overload; Continuous variables: p value obtained with Mann-Whitney U test; Categorical variables: p value obtained with Pearson chi-square test.

Variable	Survivors	Non-survivors	P value
Proportion of MV over 7 days N(%)	77(33.8%)	47(58.0%)	<0.001
Early FO, median (IQR)	8.1(1.5–13.9)	7.6(1.7–16.1)	0.992
Percentage of %FO>10%, N(%)	98(43.0%)	33(40.7%)	0.794
Percentage of %FO>20%, N(%)	15(6.6%)	12(14.8%)	0.037

LOS: length of stay; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; PICU: pediatric intensive care unit; FO: fluid overload; Continuous variables: p value obtained with Mann-Whitney U test; Categorical variables: p value obtained with Pearson chi-square test.

Multivariate Logistic Regressions Analysis For Mortality

The binary multivariate logistic regressions model was used to analyze the effect of mortality in hospital. Other outcome measures with a $p<0.1$ were introduced in the multivariate logistic regressions model. The duration of MV overlapped with the duration of the first mv and LOS in PICU, so we choose the duration of MV as the interference factor. We adjusted for the prespecified variables (number of vasoactive drugs, times of MV, duration of mechanical ventilation, and CRRT, diagnosis of MODS, reason for PICU admission, PRISM-Ⅲ) to evaluate the association between early FO, %FO > 10% and %FO > 20% with mortality in hospital (Table 4.1,4.2,4.3).

In the logistic regressions model between early FO with mortality, the results showed that the more vasoactive drugs, the presence of MODS, the longer duration of mechanical ventilation, and the non-operation reason for PICU admission were related to the increase of mortality(all $p<0.05$). Although there was no statistical correlation between early FO and mortality, it was a positive correlation between early FO and mortality ($\beta = 0.030$, $p = 0.090$, 95% C.I. = 0.995 ~ 1.067) (Table 4.1). Similar results were shown by the logistic regressions model between %FO > 10% with mortality. There was no statistical correlation between %FO > 10% and mortality ($\beta = 0.479$, $p = 0.153$, 95% C.I. = 0.837 ~ 3.117) (Table 4.2). But in the logistic regressions model between %FO > 20% with mortality, %FO > 20% was related to the increase of mortality ($\beta = 1.057$, OR = 2.878, $p = 0.029$, 95% C.I. = 1.116 ~ 7.418) (Table 4.3).

Table 4.1
Multivariate log regression analysis for early FO associated with Mortality

Outcome measure	β	OR	95% C.I.	P value
Num of vasoactive drugs	0.413	1.511	1.107–2.063	0.009
Times of MV	-0.080	0.923	0.428–1.991	0.838
Duration of MV	0.045	1.046	1.017–1.075	0.001
Receipt of CRRT	-0.329	0.720	0.316–1.638	0.433
Diagnosis of MODS	1.724	5.609	2.570-12.239	<0.001
Surgery	-0.869	0.419	0.190–0.924	0.031
early FO	0.030	1.031	0.995–1.067	0.090
PRISM-Ⅲ	0.016	1.016	0.964–1.071	0.561

Hosmer-lemeshow: p = 0.805, the predicted percentage was 80.3%; OR: odds ratio; 95%C.I.: 95% confidence interval; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; FO: fluid overload.

Table 4.2
Multivariate log regression analysis for %FO>10% associated with Mortality

Outcome measure	β	OR	95% C.I.	P value
Num of vasoactive drugs	0.412	1.510	1.106–2.063	0.010
Times of MV	-0.043	0.958	0.444–2.065	0.913
Duration of MV	0.044	1.045	1.017–1.074	0.002
Receipt of CRRT	-0.343	0.710	0.314–1.603	0.409
Diagnosis of MODS	1.718	5.572	2.563–12.115	<0.001
Surgery	-0.886	0.412	0.188–0.904	0.027
%FO>10%	0.479	1.615	0.837–3.117	0.153
PRISM-Ⅲ	0.011	1.011	0.960–1.065	0.684

Hosmer-lemeshow: p = 0.894, the predicted percentage was 79.6%; OR: odds ratio; 95%C.I.: 95% confidence interval; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; FO: fluid overload.

Table 4.3
Multivariate log regression analysis for %FO>20% associated with Mortality

Outcome measure	β	OR	95% C.I.	P value
Num of vasoactive drugs	0.385	1.469	1.079-2.000	0.014
Times of MV	-0.039	0.962	0.442–2.091	0.922
Duration of MV	0.046	1.047	1.018–1.076	0.001
Receipt of CRRT	-0.431	0.650	0.287–1.470	0.301
Diagnosis of MODS	1.733	5.656	2.591–12.345	<0.001
Surgery	-0.886	0.412	0.185–0.916	0.030
%FO>20%	1.057	2.878	1.116–7.418	0.029
PRISM-Ⅲ	0.012	1.012	0.961–1.066	0.652

Hosmer-lemeshow: p = 0.625, the predicted percentage was 80.9%; OR: odds ratio; 95%C.I.: 95% confidence interval; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; FO: fluid overload.

Early Fo And Los In Picu, Los In Hospital

The relationship was analyzed by Spearman's method. There was no significant correlation between early FO and LOS in hospital (r = 0.056, p = 0.329). There was positive correlation between early FO and LOS in PICU (r = 0.148, p = 0.009), but the relation is weak.

Discussion

Our study was a retrospective study on the relationship between early FO and mortality in discharge during mechanical ventilation in children with critical illness. We tried to compare the related factors in different FO groups, in particularly mortality. We have focused on %FO > 10% and %FO > 20%, to evaluate the association between early FO, %FO > 10% and %FO > 20% with mortality in discharge adjusted for the prespecified variables. At present, the adverse effects of positive fluid accumulation have been confirmed in adult related research[1–4]. The research of ARDS fluid management strategy directly confirmed that: compared with the positive fluid management strategy, the conservative fluid treatment strategy better realizes the negative balance of fluid management, improves lung function, shortens the duration of mechanical ventilation and LOS in ICU. Although there are differences in humoral homeostasis and disease types between adults and children, similar negative effects of early FO have also been confirmed in the studies of children's critical illness, especially in ARDS/ALI, sepsis, shock, acute kidney injury (AKI), CRRT treatment, perioperative FO of congenital heart disease[5, 9, 16–19].Of course, there were also studies on multisystem diseases about FO. However, in these studies, the adverse effects of positive FO

always excluded children with hemodynamic instability or CRRT[20]. We did not select a single disease, but included all the related critically-ill patients with MV in PICU, including the diseases with hemodynamic instability and treated by CRRT and so on.

The main reasons for PICU admission were groups into surgical patients and medical in our study. The results showed different groups of early FO were correlated with main reason for PICU admission, and the main reasons was statistical related to mortality and had statistical difference between the survivors and the non-survivors. It was a risk factor for death. Therefore, we must pay attention to effect of the main reasons for PICU admission with outcomes. Some studies have found similar conclusion. Sinitsky et al. [11]found that diagnostic category was an independent prognostic factor in the study of the correlation between FO at 48 hours and respiratory morbidity. Vidal et al. [14]reported that respiratory and septic shock were related with prolonged MV in the study of the correlation between fluid balance and length of MV in children. Moreover, this study included all the related critically-ill patients in PICU, and the complexity of disease spectrum may be an important factor affecting prognosis. We also reported for the first time that the 10%≤%FO ≤ 20% group had less medical patients and more surgical patients.

In our study, 69.3% of patients had basic diseases before they were admitted to PICU, 19.1% of patients received CRRT, 29.4% of patients diagnosed MODS, which reflected the complexity and severity of patients admitted to PICU in our hospital. We also needed to pay attention to the fact that there were statistical differences in CRRT treatment, basic diseases, presence of MODS, use of vasoactive drugs, and PRSIM-III in different groups of early FO. In this study, the use of vasoactive drugs and the treatment of CRRT were considered as the intervention measures for serious diseases, and the PRISM-Ⅲ was considered as the main marker to evaluate the severity of diseases. In children with severe diseases, positive fluid balance may be related to more early fluid resuscitation and capillary leakage. Some studies have found that: during hospitalization in ICU, early active FO is easy to form; and the more serious the disease, the more likely it is to cause the increase of fluid overload[20]. The study confirmed that the severity of the disease is related to the increase of FO. In most studies, pediatric logistic organ dysfunction(PELOD) score and PRISM are the main factors to evaluate the disease severity, while the evaluation value of PRISM-Ⅲ to the disease severity has been confirmed[10, 19–25]. Although some studies have also confirmed that the increase of FO is an independent predictor of adverse effects such as the prolongation of duration of MV and LOS in ICU, the correlation still exists after excluding the influence of disease severity[20]. What we need to pay attention to is that the adverse effects in these studies were mostly concentrated in the dead patients, and the single disease spectrum was the main research, while the survival patients as the research object may not be confirmed and the related research was less. We thought in this study PRISM-Ⅲ may not indicate severity of the whole course of hospitalization, which was assessed within 24 hours of admission. There are many similar situations in previous reports by referring to relevant literature[21, 22].

In this study, we conducted the univariate and multivariate analysis on the factors that may affect the mortality. We paid attention to the effect of vasoactive drugs on mortality, so we also analyzed the number of vasoactive drugs. We found that that use of vasoactive drugs and CRRT, presence of MODS

had statistical difference between the survivors and non-survivors; the more vasoactive drugs, longer duration of MV and the presence of MODS were an independent risk factor for mortality; but PRISM-Ⅲ was not a risk factor for mortality. A study of mortality related factors in CRRT treatment of AKI confirmed that mechanical ventilation, the use of vasoactive drugs and other factors were related to the increase of mortality[26]. Another related study also found that: the potential etiology and disease severity are independent factors of mortality, and the side effects of FO only occur in the treatment of mild diseases by CRRT[23]. However, it is worth noting that in a study on FO and mortality in 118 children with mechanical ventilation[27]. Although there was no significant correlation between FO and mortality, there is a significant correlation between FO and organ dysfunction in children with mechanical ventilation. So, it is very important to evaluate the severity of the disease correctly and accurately, and they may have a greater impact on the outcomes.

In this study, the early FO refers to the accumulated FO in the first three days since the first day of mechanical ventilation. Flori et al. [16]and Valentine et al. [28]also found that the increase of FO mainly occurred in the first three days. Related studies on septic shock confirmed the increase of FO in the first 72 hours and its possible negative effects[6]; a study on early fluid accumulation in children with shock also showed that the peak of fluid accumulation occurred within 3 days after admission to ICU[5]. For severe children with respiratory failure, who need extracorporeal life support and CRRT treatment, it has been reported that FO occurs more in the first 24 hours of fluid treatment[29]. Therefore, it is more important to choose the appropriate time of early FO assessment according to the time of the peak of fluid accumulation for accurately exploring the correlation between FO and prognostic factors. In our study, the mean early FO was 8.83 ± 8.81%, in which 42.4% of patients had an early FO of more than 10% and 8.7% of patients had an early FO of more than 20%. This was also consistent with the results of Arikan et al. in which 75% of the FO in the first two days was 11%[20], and Vanlentine et al. in which the average FO in the three days was 8.5 ± 10.5%[28]. With the study of prognostic factors of FO, the fluid management has become one of the most important treatment measures for critically ill children, but FO was still very common. A previous study in North America and European countries showed that only 29% of acute lung injury(ALI) patients achieved restrictive fluid management in clinical treatment.[30] Even some studies have found that the actual amount of FO in children's ALI was similar to that in adults' studies, even though restrictive fluid therapy strategy was used[28].

In this study, although surgical patients received mechanical ventilation on the first day after receiving PICU, the perioperative or intraoperative fluid accumulation was not evaluated in this study; similarly, for non-surgical patients, the level of FO before mechanical ventilation was not clear, and the peak time of FO accumulation may have deviation. Non dominant water loss was a very important part of fluid loss, and the evaluation of endogenous water was also lacking. Although we analyzed the time from hospital admission to PICU in days to further eliminate the effect of FO before MV, it was no statistical difference in different groups of FO or survival and non- survival patients. In our study, the %FO ≤ 0% group was older and had more CRRT treatment than other groups; it used more vasoactive drugs, had MODS, and higher score of PRSIM-III than 0%□%FO ≤ 10% and 10%□FO ≤ 20% group, but there was no statistical difference in the in-hospital mortality, duration of MV, LOS in hospital, LOS in PICU. According to the

complexity and severity of patients, clinicians may gave intervention therapy, and choose a more appropriate fluid management strategy, which also had a corresponding impact on the FO. These factors may have an impact on the results of this study.

The relationship between FO and mortality has also been a research hotspot. In this study, the in-discharge mortality was 26.2% (81/309). This was basically consistent with the case fatality rate of 25%-28% reported in the past. Adult related studies have confirmed that %FO≥10% is often accompanied by poor clinical prognosis, and it is recommended to use it as an indicator of CRRT intervention[31]. In the field of children's research, most of them are mainly observational studies, and the adverse effects of %FO≥10%,≥15% and≥20% can be seen in the relevant reports. The guidelines for children's septic shock also suggest that %FO≥10% in fluid management can be considered to give diuretic or RRT treatment and other interventions. According to previous studies, we have noticed that 10% or 20% of FO may be an important threshold for prognosis. Therefore, in this study, we divided the subjects into four groups according to the early FO. But there was no significant statistical relationship between early FO with mortality in our study. There are also studies confirmed that there was no significant correlation between FO and mortality[11, 22]. However, the related studies on CRRT, ARDS/ALI, severe sepsis and other single disease spectrum have also confirmed that the increase of early FO was related to the increase of mortality, and even FO was considered as an independent predictor of death[6, 16, 19, 32, 33]. Although the correlation between early FO with mortality was not confirmed in this study, there was a positive correlation between the two; This may be due to the complexity and severity of the disease spectrum involved in this study. Compared with the single disease study, it may require a larger sample size and a more accurate assessment of the disease degree. Of course, there are also some reports about the multisystem diseases in PICU[9, 10, 34]. A study on the relationship between mortality and FO in children with severe diseases confirmed that FO was a risk factor of death in children with severe diseases. What we need to pay attention to is that in this study, the correlation analysis between FO and mortality is a single factor analysis. Another study in PICU, South Africa, focusing on fluid overload in children with all severe diseases showed that high levels of FO were associated with increased mortality. However, it should be noted that the study site was in Africa, and the disease spectrum is different from that of our study subjects, of which %FO > 10% only accounted for 3% in the study, and the fluid accumulation of most patients was not high. Although there was no significant statistical relationship between %FO > 10% with mortality in our study, the results showed %FO > 20% was related to the increase of mortality.

Of course, there were some shortcomings in this study: 1) this was a retrospective analysis study, information bias was not negligible; the number of research objects was still small; although we also used the concept of %FO in fluid evaluation, the fluid management including invasive and non-invasive monitoring results were not recorded or applied in time, which may affect the assessment of the body's changes in FO; 2) many patients may have a certain degree of FO before entering the ICU or before mechanical ventilation in the ICU, and we did not complete the relevant assessment or eliminate the interference in this study; 3) the disease spectrum included was complex, and there were obvious defects in the assessment of disease severity and organ function in this study; 4) there was a lack of evaluation on the factors related to mechanical ventilation. Although we have evaluated the relationship between

early FO and the duration of MV, the evaluation of ventilator parameters or oxygenation index that reflect lung function cannot be completed due to the lack of retrospective analysis of data. These factors may interfere with the correlation between FO and the duration of mechanical ventilation.

Conclusions

In critically-ill mechanically ventilated children, influenced by the severity of the disease and the intervention measures, the correlation between the early FO and %FO > 10% with mortality was not clear in this study, but %FO > 20% was related to the increase of mortality. We think the positive FO may cause adverse effect. Therefore, we believe that our study further provides a foundation for the development and evaluation of interventional strategies to mitigate the potential hazards associated with FO.

Abbreviations

FO: fluid overload; LOS: length of stay; MV: mechanical ventilation; MODS: multiple organ dysfunction syndrome; CRRT: continuous renal replacement therapy; PRISM-Ⅲ: the third generation of admission pediatric risk of mortality score; PICU: pediatric intensive care unit; ARDS: adult respiratory distress syndrome; ALI: acute lung injury; AKI: acute kidney injury; PELOD: pediatric logistic organ dysfunction

Declarations

Ethics approval and consent to participate

Local research ethics approval for study was obtained from ethics committee of Xinhua Hospital Affiliated to Shanghai Jiao tong University School of Medicine.(Approval No.XHEC-D-2020-163)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

XZ participated in the design of the study and performed the statistical analysis. YZ conceived of the study and performed the statistical analysis. XK participated in its design, data collection and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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Figures

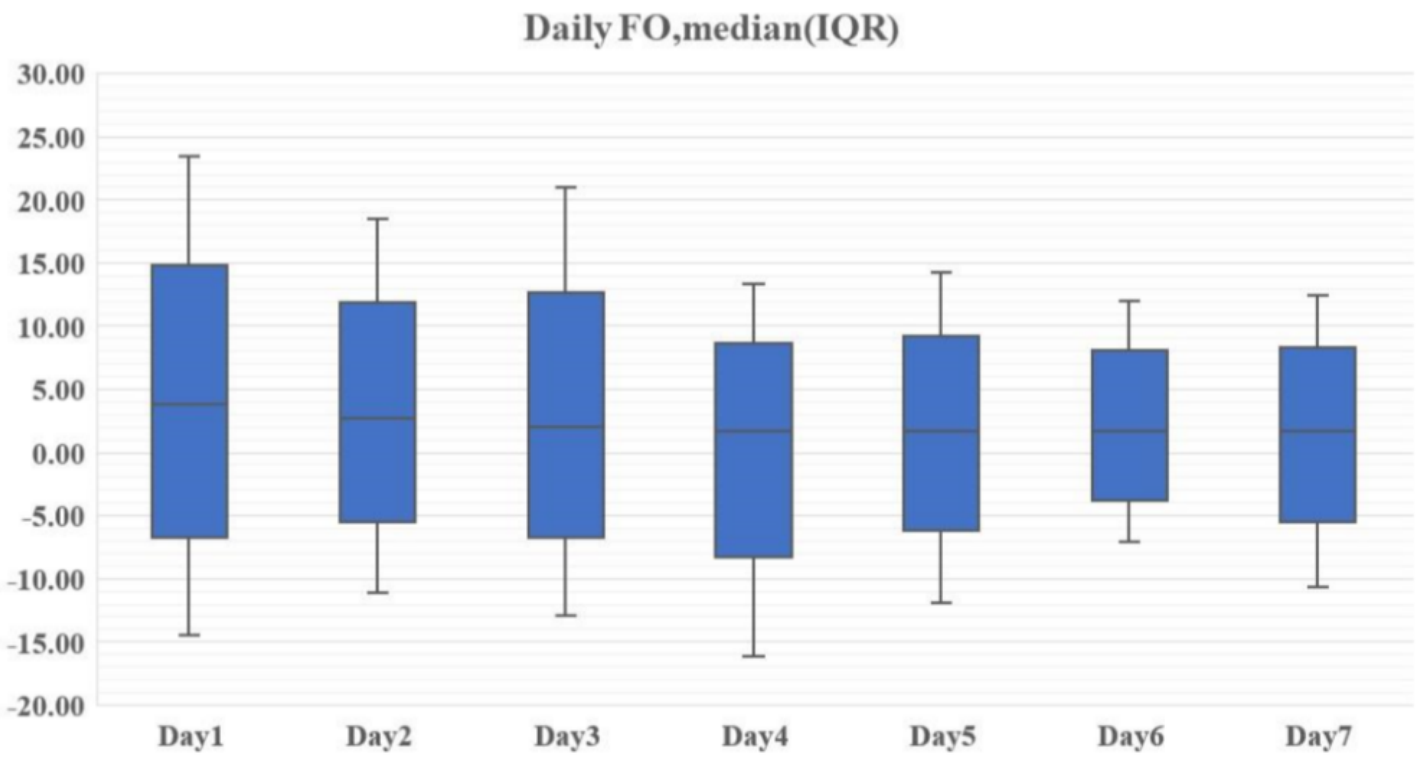

Figure 1

The median (IQR) of daily FO in the first 7 days. The median value of daily FO was gradually stabilized.

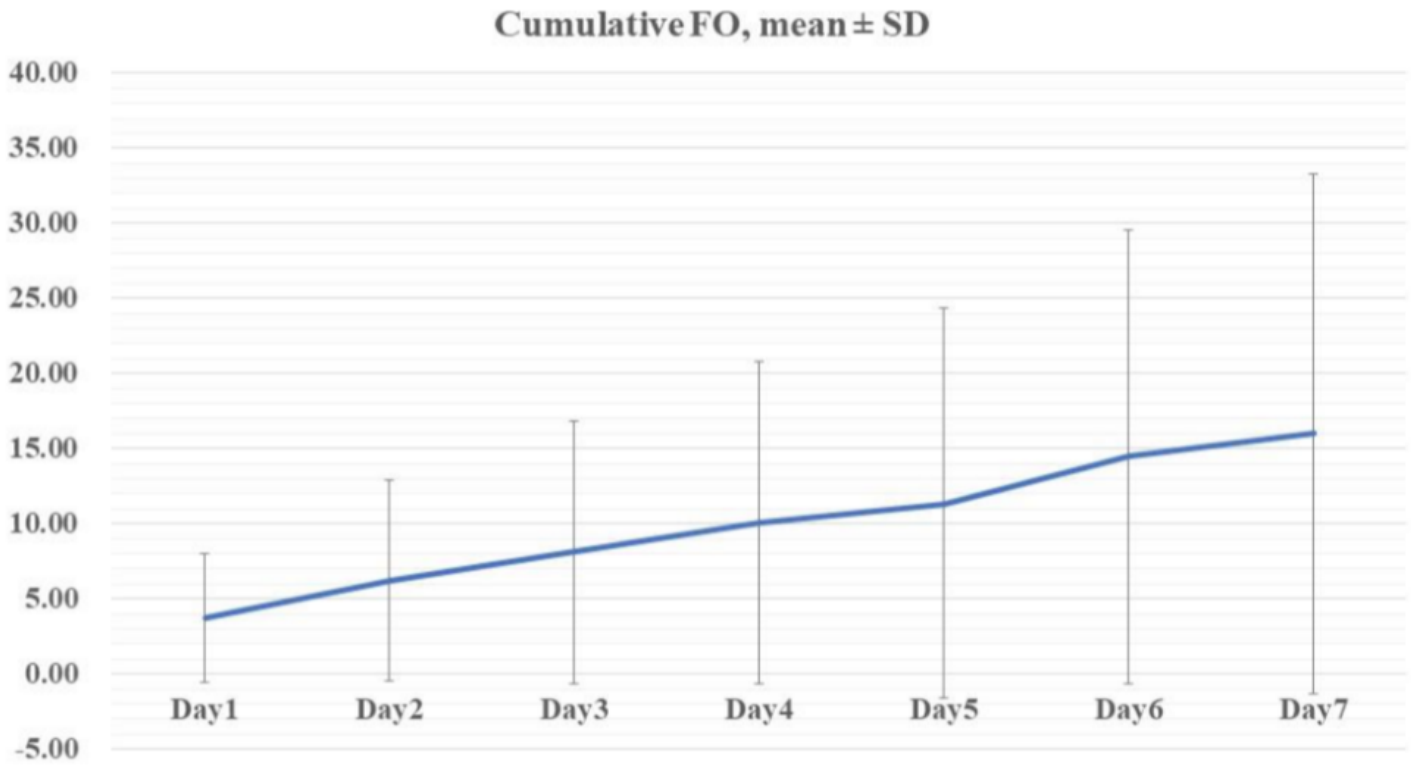

Figure 2

The cumulative FO in the first 7 days. The cumulative FO was gradually increased and positive in the study.