The Correlation Between Early Net Fluid Balance and The Clinical Outcomes of Patients Receiving Extracorporeal Cardiopulmonary Resuscitation

Wei Li

The first affiliated hospital of Nanjing Medical University

Jinru Lv

The first affiliated hospital of Nanjing Medical University

Deliang Hu

The first affiliated hospital of Nanjing Medical University

Feng Sun

The first affiliated hospital of Nanjing Medical University

Fengpu He

The first affiliated hospital of Zhejiang University

Xufeng Chen

The first affiliated hospital of Nanjing Medical University

Yong Mei (✉ meiyong@jsph.org.cn)

The first affiliated hospital of Nanjing Medical University

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Abstract

Background: Large amounts of fluid administration are often needed during the extracorporeal cardiopulmonary resuscitation (ECPR) course. Finally, fluid overload is often present.

Methods: Adult patients on ECPR admitted to our center from May 2015 to December 2020 were included. Net fluid balance for consecutive 4 days after ECPR was recorded. The primary outcome was to intensive care unit(ICU) survival . We used multivariable logistic regression to assess the association between fluid status and clinical outcome.

Results: A total of 72 patients were enrolled and divided into two groups: the survivor group and the non-survivor group. The overall rate of ICU survival was 44.4%. Daily fluid balance(DFB) in the survivor group was lower than that in the non-survivor group at day 4 (-11.47[-19.74,8.7] vs -5.08[-12.94,13.9]ml/kg, $P=0.046$), as was CFB over the first 4 days (-36.03[-51.45,19.03] vs -7.22[-32.79,21.02] ml/kg, $P=0.009$). Both continuous renal replacement therapy(CRRT) and CFB from days 1-4 were significantly correlated with ICU survival(OR=14.617[95%CI:1.344,48.847], $P=0.028$; OR=1.261[95%CI1.091,1.375], $P=0.003$, respectively). CFB from day 1-4 was determined to have a roughly linear association with the log odds of ICU survival.

Conclusions: Early negative fluid balance maybe associated with ICU survival in patients receiving ECPR.

Background

The standard therapy for cardiac arrest (CA) is cardiopulmonary resuscitation (CPR). Recent studies have reported 20% survival to hospital discharge in patients after in-hospital CA (IHCA) and 10% after out-hospital CA (OHCA)[1-3]. To improve the neurological outcome and survival rate in patients with CA, extracorporeal cardiopulmonary resuscitation (ECPR) has been proposed in some selected cases of refractory CA. Once ECPR has been initiated, frequent blood and fluid transfusion may be required to maintain the targeted mean arterial pressure (MAP) and blood flow of extracorporeal membrane oxygenation (ECMO). Excessive positive fluid administration may, in turn, result in cardiogenic/non-cardiogenic pulmonary edema, acute kidney injury (AKI), systemic capillary leakage and so on. In light of this, the restrictive fluid balance strategy has been advocated in patients with septic shock, ARDS and AKI[3-5]. In terms of fluid management in patients receiving ECMO treatment, there are few studies reporting the association between fluid balance and clinical outcomes[6-7].

To date, no consensus on fluid administration strategies has been achieved in patients on ECPR. Given the high incidence of positive fluid administration and potential adverse effects caused by inappropriate fluid management, it is important to understand the association of fluid balance status with clinical outcomes.

Our objective was to determine the prevalence of positive fluid balance in patients receiving ECPR and to evaluate the association between fluid balance status and survival to intensive care unit (ICU) discharge.

Methods

Study design, setting, and subjects

Our retrospective study was conducted in a 17-bed ICU of an inner city, university-affiliated teaching hospital. Our ICU ECMO database was accessed to identify all patients from May 2015 to December 2020 who received ECPR. The need for written consent was waived because of the retrospective design of the study.

Study participants and inclusion criteria

A patient's eligibility for ECPR was assessed by the physician on duty who was leading the ECMO team, and this eligibility was based on the following factors: age < 70 years, witnessed CA, shockable rhythm, < 5 min of estimated no-flow time, < 30 min of low-flow time, and no malignant tumor.

The inclusion criteria in our study were as follows: adult patients on ECPR, duration of ECMO $\geq$ 96 hours. The exclusion criteria were patients under 18 years of age, pregnancy, duration of ECMO < 96 hours, ECMO modality switching and intracranial hemorrhage.

Data collection and outcomes measures

The patients' demographic and laboratory data were retrieved from electronic medical records. The data included age, sex, weight, comorbidities, location of CA, ECMO parameter settings, continuous renal replacement therapy (CRRT) and intra-aortic balloon pump (IABP) initiation, duration of mechanical ventilation (MV), ICU length of stay (LOS), and vasoactive inotropic score (VIS). VIS was calculated as $[(\text{epinephrine} + \text{noepinephrine}) \text{ ug/kg/min}] \times 100 + [(\text{dobutamine} + \text{dopamine}) \text{ ug/kg/min}] \times 100 + [\text{milrinone} \text{ ug/kg/min}] \times 15 + [\text{vasopressin} \text{ IU/kg/min}] \times 10000$ [8]. The amount of input fluid and output fluid were continuously recorded within 4 days of ECMO initiation. The daily fluid balance (DFB) was calculated by the difference between fluid inputs and outputs and was divided by the patient's actual body weight. Weight was measured using the automated-weighing bed system upon admission and daily at 8 am. The cumulative fluid balance (CFB) was defined as the cumulative total input fluid minus the cumulative total output fluid and obtained by the addition of each daily fluid balance from ECMO commencing until the day of evaluation. Survival was observed at ICU discharge, and patients were classified into the survivor group or non-survivor group according to their clinical outcome.

Statistical analysis

Continuous variables not normally distributed were expressed as median and IQR and compared with Mann-Whitney U test. Normally distributed continuous variables were expressed as mean $\pm$ SD and compared with Student's t-test. Categorical variables were expressed as percentages and compared with the chi-square test. Kendall's tau-b correlation was used to quantify the relationship between continuous

variables and categorical variables. Univariable and multivariable analyses were performed to identify factors associated with mortality at ICU discharge. Associations between clinical outcomes and net fluid balance were evaluated with the Cochran-Armitage trend test for binary variables. Statistical significance was set at a two-sided P value of less than 0.05. All data were analyzed using GraphPad Prism v8.0 and SPSS software v24.0.

Results

Characteristics of Study Subjects

A total of 84 patients admitted to the ICU for ECPR between May 2015 and December 2020 were enrolled. Eight patients were excluded due to a duration of ECMO support less than 96 hours, three patients were excluded because of ages under 18 years, and one patient was excluded due to ECMO modality switching. Finally, 72 patients were eligible for further analysis (Fig. 1).

The baseline characteristics of the patients are presented in Table 1. The mean age was 42.6 ± 16.3 years, and 66.67% (48/72) were males. The average time on V-AECMO was 164.8(98.1,212.3) hours in all patients, while the duration of MV was 173.5(93,233) hours. To investigate the factors associated with survival to ICU discharge, we categorized the enrolled patients into survivor and non-survivor groups according to clinical outcome at ICU discharge. Compared with the non-survivor group, those in the survivor group were more likely to have a lower APACHE II score and to be predisposed to receive CRRT (25[95%CI:17-45] versus 39[95%CI: 24-64], $P=0.033$; 37.5% versus 90%; [95%CI:1.3%-39.4%], $P=0.001$, respectively). In addition, the duration of MV was significantly shorter in the survivor group (100.5[95%CI:57.4-196.1] versus 200[95%CI:165.3-308.1], $P=0.003$). In contrast, the survivor group had a longer ICU LOS (17.5[95%CI:16.3-26.1] versus 9[95%CI:8.1-15.2], $P=0.001$). All other patient characteristics, including age, gender, body weight, location of CA, preexisting cardiovascular disease, ECMO therapy duration and VIS, were not different between the two groups($P>0.05$).

Daily and cumulative fluid status

Table 2 shows the details of DFB and CFB during the first 4 days of ECMO commencement. A positive DFB was only noted in the non-survivor group at day 1 (0.15[IQR -2.68 to 11.75]). At all other investigated time points, a negative DFB was achieved. DFB at day 4 was significantly higher in non-survivors (-5.08[95%CI: -8.5 to 11.6] versus -11.47[95%CI: -18.4 to -7.9], $P=0.046$). No difference was observed between the two groups from day 1 to day 3. CFB increased progressively over time. Further analysis demonstrated a strong statistically significant difference in day 1-4 CFB between the two groups (-36.03[95%CI: -51.2 to -3.9] versus -7.22[95%CI: -18.1 to 28.1], $P=0.009$).

Relationships between fluid status and ICU survival

The overall rate of ICU survival was 44.4%. Univariate logistic regression analysis showed a significant association between ICU survival and APACHE II on admission, ICU LOS, CRRT received, duration of MV, DFB at day 4 and CFB from day 1-4. Multivariate logistic regression analysis identified that both CRRT received and CFB from days 1-4 were significantly correlated with ICU survival (OR: 14.617[95%CI:1.344 to 48.847], $P=0.028$; OR: 1.261[95%CI:1.091 to 1.375], $P=0.003$) (Table 3).

The unadjusted association of CFB from day 1-4 with ICU survival was assessed with univariable logistic regression and natural cubic splines. CFB from day 1-4 was determined to have a roughly linear association with the log odds of ICU survival (Fig. 2).

Discussion

There is robust evidence in papers that discourages excessive fluid accumulation in critically ill patients with sepsis/septic shock[9-12]. Similar results were also reported in patients on V-VECMO or V-AECMO[6-7,13-14]. However, it is unclear whether patients on ECPR should also receive restrictive fluid administration. Patients receiving ECPR often require large-volume fluid infusion during and after ECPR initiation to guarantee appropriate ECMO blood flow and perfusion pressure[15-16]. Therefore, positive fluid balance or excessive fluid accumulation is sometimes inevitable. To date, there are scarce data that investigate the relationship between early net fluid balance status and clinical outcomes in patients on ECPR.

In clinical practice, fluid resuscitation is often the cornerstone of early management to stabilize hemodynamics in critically ill patients. Vincent has proposed four distinct phases of fluid resuscitation: rescue, optimization, stabilization and de-escalation in patients with sepsis.¹⁷ Strategies of fluid management emphasizes not only fluid resuscitation but also “reversed fluid resuscitation”, which equals de-escalation. Undoubtedly, intensivists around the world have attached great importance to the first two phases when critically ill patients manifest macrocirculation and/or microcirculation dysfunction. However, the last phase is not always given priority to by physicians after patients achieve hemodynamic improvement. Therefore, a positive fluid balance commonly occurs in patients, especially during the early phase. Brotfain reported that patients with sepsis/septic shock who had less positive cumulative fluid balance had lower ICU and in-hospital mortality ($P<0.001$ for both ICU and in-hospital mortality, OR:1.04[95%CI:1.02 to 10.6]; OR:1.06[95%CI:1.03 to 1.08])[11]. Chao WC also found that a positive CFB from days 1-4 was independently associated with a higher 30-day mortality in critically ill patients with influenza (HR:1.088[95%CI:1.007,1.074])[18].

Similar conclusions have been drawn by several authors regarding V-AECMO patients with refractory cardiac shock. In a retrospective analysis, Besnier et al. demonstrated that patients with more positive fluid balance at day 1 had higher mortality (OR:14.34[95%CI:1.58 to 129.79]). A threshold of 38.8 ml/kg fluid balance predicted mortality with a sensitivity of 60% and a specificity of 83%[19]. Another retrospective multicenter study enrolling 723 patients on V-AECMO revealed a significantly increased risk of 90-day mortality in patients with higher CFB during the first 3 days after ECMO initiation

(HR:1.76[95%CI:1.37 to 2.27], $P<0.001$). Further analysis found that the relative HR of mortality started to increase significantly when CFB exceeded 82.3 ml/kg[20]. Therefore, higher fluid balance was consistently linked to poor outcomes.

Similarly, CA is frequently considered as a sepsis-like syndrome[21]. Patients with CA typically encounter circulatory collapse and subsequently undergo a systemic inflammatory response, including pathologic vasodilation, increased capillary leakage, and low albumin levels. Large-volume fluid and other drugs are often administered to maintain intravascular volume and improve cardiac output, especially during the early stage during and after ECPR[22-23]. As mentioned above, liberal fluid resuscitation is actually not recommended in critically ill patients with sepsis. Thus, it is still unknown which fluid administration strategy is preferred in patients receiving ECPR. In this study, excessive CFB from day 1-4 was found to be independently associated with ICU survival. To date, few studies have evaluated the impact of fluid balance in patients receiving ECPR. A study conducted by Staudacher admitted 195 patients on V-AECMO due to refractory cardiogenic shock and found no evidence to support a liberal fluid strategy[7]. Of note, 149 of recruited patients developed IHCA or OHCA, which implied that the study might have comprised several patients receiving ECPR. However, further subgroup analysis was not available.

In our center, as long as macrocirculation and microcirculation got improvement, “reversed fluid resuscitation” was always put on the agenda during the ECMO course. Therefore, except for the daily fluid balance of non-survivors at day 1, a negative net fluid balance was acquired at all other investigated points within 4 days of ECMO commencement. Moreover, the difference in CFB between the two groups became more statistically significant over time. In addition, the application of CRRT was more common in the non-survivor group, which we thought accounted for more fluid administration in the non-survivor group. Strict fluid control has several advantages, including effective preload reduction, decreased cardiac-wall stress, avoidance of fluid congestion and high hydrostatic pressure, tissue edema alleviation, and so on. Actually, the conception of “less is more” should be recommended by intensivists during the management process of critically ill patients[24-26]. The core value of the conception is that physiological indexes and medical interventions matching the patient’s current pathophysiological state are strongly suggested. In other words, overtreatment should be avoided. Taking fluid resuscitation for instance, as long as both macrocirculation and microcirculation perfusion are sufficient, restrictive fluid management should be considered. Furthermore, if permitted, “reversed fluid resuscitation” should also be taken into consideration[27], which implies that it is strongly recommended to initiate the phases of stabilization and de-escalation as early as possible[19].

Limitations

Our study had a number of limitations. First, the definition of fluid inputs only included intravenous fluids, and enteral-nutritional-solution intake was not taken into account. On the other hand, fluid outputs included urine, adding the net fluid balance via CRRT. Drainage of serosal effusions was ignored. Second, all patients in our study had colloid fluid administration in conjunction with crystalloid fluid. Given the different effects of volume expansion between colloid and crystalloid fluids[28-29], the same amount of

fluid inputs with different crystal-colloid ratios may finally lead to different volume changes. Third, this was a single-center retrospective observational trial. Therefore, our findings cannot indicate causality. Further studies are warranted to confirm these findings.

Conclusion

We found a significant association between CFB during the first 4 days after ECMO treatment and survival to ICU discharge in this observational cohort study. Restrictive fluid administration may be an appropriate alternative for guiding the management of patients on ECPR.

Declarations

Acknowledges

Not applicable.

Authors' contributions

WL and JRL shared co-first authorship on this work. YM and XFC conceived the study, brought together the collaboration, and drafted the manuscript. DLH oversaw the assay development and contributed to troubleshooting the assay. FPH provided proofread and statistic analysis. All patients revised and approved the final version of the manuscript.

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Avability of data and materials

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

Ethics approval and consent to participate

The retrospective data in the study was extracted with the purpose of quality improvement. Visit data did not include personal identifiers or sensitive information regarding patient health status. Therefore ethical approval was not required.

Consent for publication

Not applicable.

Conflict of Interest Disclosure

None

References

1. Kim SJ, Kim HJ, Lee HY, et al. Comparing extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: a meta-analysis. *Resuscitation*. 2016;103:106-16.
2. Abrams D, Garan AR, Abdelbary A, et al. Position paper for the organization of the ECMO programs for cardiac failure in adults. *Intensive Care Med*. 2018;44 (6):717-29.
3. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. *Critical care*. 2015;19:251. doi:10.1186/s13054-015-0970-1.
4. Brotfain E, Koyfman L, Toledano R, et al. Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. *The American journal of emergency medicine*. 2016;34(11):2122-6.
5. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care*. 2008;12(3):R74.doi:10.1186/cc6916.
6. Schmidt M, Bailey M, Kelly J, et al. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. *Intensive Care Med*. 2014;40:1256-66.
7. Staudacher DL, Gold W, Biever PM, et al. Early fluid resuscitation and volume therapy in venoarterial extracorporeal membrane oxygenation. *J Crit Care*. 2016;37:130-5.
8. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-Inotropic Score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010;11:234–8.
9. Brotfain E, Koyfman L, Toledano R, et al. Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. *Am J Emerg Med*. 2016;34(11):2122-6.
10. Neyra JA, Li X, Canepa-Escaro F, et al. Cumulative Fluid Balance and Mortality in Septic Patients With or Without Acute Kidney Injury and Chronic Kidney Disease. *Crit Care Med*. 2016;44(10):1891-900.
11. de Oliveira FS, Freitas FG, Ferreira EM, et al. Positive fluid balance as a prognostic factor for mortality and acute kidney injury in severe sepsis and septic shock. *J Crit Care*. 2015;30(1):97-101.
12. Huang AC, Lee TY, Ko MC, et al. Fluid balance correlates with clinical course of multiple organ dysfunction syndrome and mortality in patients with septic shock. *Plos One*. 2019;14(12):e0225423.doi:10.1371/journal.pone.0225423.
13. McCanny P, Smith MW, O'Brien SG, et al. Fluid Balance and Recovery of Native Lung Function in Adult Patients Supported by Venovenous Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy. *ASAIO J*. 2019;65(6):614-9.
14. Besnier E, Boubèche S, Clavier T, et al. Early Positive Fluid Balance is Associated with Mortality in Patients Treated with Veno-Arterial Extra Corporeal Membrane Oxygenation for Cardiogenic Shock: a

- Retrospective Cohort Study. *Shock*. 2020;53(4):426-33.
15. Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: part 2-technical considerations. *J Cardiothorac Vasc Anesth*. 2010;24:164–72.
 16. Sidebotham D. Troubleshooting adult ECMO. *J Extra Corpor Technol*. 2011;43:27–32.
 17. Vincent JL, De Backer D. Circulatory shock. *The New England journal of medicine*. 2013;369(18):1726–34.
 18. Wen-Cheng Chao, Ching-Hua Tseng, Ying-Chun Chien, et al. Association of day 4 cumulative fluid balance mortality in critically ill patients with influenza: a multicenter retrospective cohort study in Taiwan. *Plos One*. 2018;13(1):e0190952.doi:10.1371/journal.pone.0190952.
 19. Emmanuel Besnier, Samia Boubèche, Thomas Clavier, et al. Early positive fluid balance is associated with mortality in patients treated with Veno-Arterial Extra Corporeal Membrane Oxygenation for cardiogenic shock: a retrospective cohort study. *Shock*. 2020;53(4):426-33.
 20. Hyoungnae Kim, Jin Hyuk Paek, Joo Han Song, et al. Permissive fluid volume in adult patients undergoing extracorporeal membrane oxygenation treatment. *Critical Care*. 2018;22(1):270.
 21. Bro-Jeppesen J, Kjaergaard J, Wanscher M, et al. Systemic Inflammatory Response and Potential Prognostic Implications After Out-of-Hospital Cardiac Arrest: A Substudy of the Target Temperature Management Trial. *Critical Care Med*. 2015;43(6):1223–32.
 22. Hou G, Yu K, Yin X, et al. Safety research of extracorporeal membrane oxygenation treatment on cardiogenic shock: a multicenter clinical study. *Minerva Cardioangiol*. 2016;64:121–6.
 23. Heradstveit BE, Guttormsen AB, Langorgen J, et al. Capillary leakage in post-cardiac arrest survivors during therapeutic hypothermia-a prospective, randomised study. *Scand J Trauma Resusc Emerg Med*. 2010;18:29.
 24. Dries D. Fluid resuscitation: less is more. *Crit Care Med*. 2014;42(4):1005-6.
 25. Seeley EJ. Fluid therapy during acute respiratory distress syndrome: less is more, simplified. *Crit Care Med*. 2015;43(2):477-8.
 26. Auriemma CL, Van den Berghe G, Halpern SD. Less is more in critical care is supported by evidence-based medicine. *Intensive Care Med*. 2019;45(12):1806-9.
 27. Self WH, Semler MW, Bellomo R, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. *Ann Emerg Med*. 2018;72(4):457-66.
 28. Gondos T, Marjanek Z, Ulakcsai Z, et al. Short-term effectiveness of different volume replacement therapies in postoperative hypovolaemic patients. *Eur J Anaesthesiol*. 2010;27(9):794-800.
 29. Marx G, obas Meyer M, Schuerholz T, et al. Hydroxyethyl starch and modified fluid gelatin maintain plasma volume in a porcine model of septic shock with capillary leakage. *Intensive Care Med*. 2002;28(5):629-35.

Tables

Table 1. Baseline data analysis: univariate comparisons of demographic factors and outcomes

Variables	Survivor(n=32)	Non-survivor(n=40)	P value
Characteristics			
Age(years)(mean±SD)	41.2±16.3	43.7±16.7	0.646
Male(%)	18/32(56.3%)	30/40(75%)	0.236
IHCA(%)	22/32(68.8%)	16/40(40%)	0.086
Preexisting CVD(%)	16/32(50%)	30/40(75%)	0.121
APACHEII on admission	25(18,38)	39(29,55)	0.033
ICU LOS(days),median(IQR)	17.5(13-44)	9(4-27)	0.001
CRRT received(%)	12/32(37.5%)	36/40(90%)	0.001
IABP received(%)	8/32(25%)	6/40(15%)	0.451
Duration of MV(hours),median(IQR)	100.5(17-174)	200(168.8-263)	0.003
Duration of ECMO(hours),median(IQR)	144.4(100.5-173.9)	176.6(98-227.5)	0.126
Blood flow of ECMO(lpm), mean(SD)	3.8±0.3	4.1±0.6	0.37
VIS score at day 1,median(IQR)	17.2(6.3-39.4)	31.5(0-92.8)	0.421
VIS score at day 2,median(IQR)	8.8(0-12.9)	16(0-77.8)	0.113
VIS score at day 3,median(IQR)	2.5(0-6.7)	9.6(0-75)	0.128
VIS score at day 4,median(IQR)	1.6(0-24,1)	10.7(0-33.8)	0.24

Continuous variables are presented as means±standard deviation or medians with quartiles

IQR: Interquartile range, SD:Standard deviation

CVD: Cardiovascular disease, LOS: Length of stay, MV: Mechanical ventilation

CRRT: Continuous renal replacement therapy; VIS: Vasoactive inotropic score

IABP: Intra-aortic balloon pump, OHCA: Out-hospital of cardiac arrest

IHCA: In-hospital of cardiac arrest

Table 2. Details of daily and cumulative fluid balance

Variables	Survivor(n=32)	Non-survivor(n=40)	P value(95%CI)
DFB(ml/kg)			
Day 1	-0.99(-7.24,6.22)	0.15(-2.68,11.75)	0.352(0.341,0.360)
Day 2	-7.67(-16.66,5.36)	-5.89(-8.63,8.12)	0.262(0.251,0.268)
Day 3	-10.69(-13.21,-4.28)	-5.93(-12.43,9.47)	0.095(0.088,0.099)
Day 4	-11.47(-19.74,-8.7)	-5.08(-12.94,13.92)	0.046(0.040,0.048)
CFB(ml/kg)			
Day 1-2	-13.98(-20.22,1.38)	-6.12(-15.72,15.07)	0.168(0.157,0.171)
Day 1-3	-25.02(-35.54,-6.51)	-8.35(-21.61,19.3)	0.053(0.047,0.056)
Day 1-4	-36.03(-51.45,-19.03)	-7.22(-32.79,21.02)	0.009(0.001,0.04)

Continuous variables expressed as median[quartile1 - quartile 3]

DFB: Daily fluid balance, CFB: Cumulative fluid balance, CI: Confidence interval

Table 3. Univariate and multivariate logistic regression analysis for ICU survival

Variables	Univariate	Multivariate	
	OR(95% CI)	P value	OR(95%CI) P value
APACHEII on admission	1.466(0.517,4.355)	0.033	
ICU LOS	0.858(0.764,0.963)	0.001	
CRRT received	15(2.537,88.701)	0.003	14.617(1.344,148.847) 0.028
Duration of MV	1.018(1,1.116)	0.003	
DFB at day 4	1.071(1.004,1.142)	0.046	
CFB from days 1-4	1.018(1.007,1.037)	0.009	1.261(1.091,1.375) 0.003

Continuous variables expressed as median[quartile1 - quartile 3]

DFB: Daily fluid balance, CFB: Cumulative fluid balance, CI: Confidence interval

OR: odds ratio

Figures

Figure 1

Flowchart of participant enrollment

Figure 2

Cubic spline curve for the association between CFB and ICU survival