Effect of Initial Infusion Doses of Fluid Resuscitation on Prognosis in Patients with Septic Shock: A Prospective Multicentre Observational Study

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Abstract

OBJECTIVES

The 2018 Surviving Sepsis Campaign (SSC) recommends rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L in patients with septic shock; however, there is no credible evidence to support this recommendation. The purpose of this study was to examine the relationship between initial fluid resuscitation doses and prognosis in patients with septic shock.

METHODS

This was a multicentre prospective observational study of adult patients with septic shock admitted to four intensive care units (ICUs) in a total of three Jiangsu province teaching hospitals over a 1-year span from May 8, 2018, to June 31, 2020. All enrolled patients with septic shock were categorized as below 20 ml/kg fluid, 20-30 ml/kg fluid and above 30 ml/kg fluid groups according to initial infusion doses of fluid resuscitation. Various demographic and other variables were collected from medical records. Logistic regression analysis and curve fitting were used to determine the relationship between initial fluid resuscitation and patient outcome.

MEASUREMENTS AND MAIN RESULTS

A total of 153 patients who presented to the ICU were diagnosed with septic shock. The 28-day mortality was highest in the fluid above 30 ml/kg group (47.8%) and lowest in the fluid 20-30 ml/kg group (26.5%, $P<0.05$). Patients who completed 30 ml/kg initial fluid resuscitation between the first 1-2 h had the lowest 28-day mortality rate (25.9%, $P<0.05$). Logistic regression showed that an initial liquid dose of 20-30 ml/kg was an independent protective factor, with a significant Odds Ratio(OR) or decreased mortality (OR, 0.393; 95% CI, 0.178-0.866; $P<0.05$). According to the curve fit, the sequential organ failure assessment change value (ΔSOFA) was highest for initial fluid resuscitation with 25.7 ml/kg within 1 h, reaching 5.807; the ΔSOFA score reached the maximum value (5.56) when the initial fluid resuscitation of 30 ml/kg was completed in 2.18 hours.

CONCLUSION

In septic shock patients, an initial fluid resuscitation rate of 20-30 ml/kg within the first 1 h or completion of the initial 30 ml/kg fluid resuscitation between the first 1-2 h may be associated with faster organ function recovery and lower 28-day mortality.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-OOC-17013223. Registered 2 November 2017, http://www.chictr.org.cn/showproj.aspx?proj=22674

Background

Septic shock is the major cause of death in intensive care units (ICUs)[1]. The published rates of in-hospital mortality caused by septic shock are approximately 30–50%[2–3]. Similar to other severe diseases, early identification and appropriate management in the initial hours after the development of septic shock can improve patient outcomes[4]. Initial fluid resuscitation for septic shock can restore tissue perfusion before the onset of irreversible tissue damage and prevent organ failure and death [5–6]. Therefore, appropriate initial fluid resuscitation within the first 3 h of septic shock is strongly recommended by the Surviving Sepsis Campaign (SSC) guidelines [7] as the cornerstone of septic shock treatment [8].

The initial infusion dose for patients with septic shock is based on limited evidence. Lee et al showed that septic shock patients who received a larger volume of fluid in the first 3 h were more likely to survive[9]. Another study[10] on critical care published this year showed that an initial fluid resuscitation rate of 0.25–0.50 ml/kg/min may be associated with early shock reversal and lower 28-day mortality in septic shock patients. Nonetheless, a few trials have demonstrated increased mortality with fluid resuscitation[11–12].

The 2018 SSC guidelines proposed the hour-1 bundle and recommended rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L in patients with septic shock[13]. However, the guidelines did not specify the fluid resuscitation dose within the first hour or the completion time of the initial 30 ml/kg fluid resuscitation in these patients. The purpose of this study was to examine the relationship between initial fluid resuscitation doses and prognosis in patients with septic shock.

Methods

Ethical approval

The study was approved by the Institutional Review Board of Northern Jiangsu People's Hospital (2017KY-021) and was registered in the Chinese Clinical Trial Registry (Registration Number: ChiCTR-OOC-17013223). Informed consent was obtained from each participant prior to his or her enrolment in this study.

Population study and design

This was a multicentre prospective observational study of adult patients with septic shock admitted to four intensive care units (ICUs) with more than 100 beds in a total in three Jiangsu province teaching hospitals, including Northern Jiangsu People's Hospital, Jiangdu People's Hospital of Yangzhou, Affiliated Hospital of Yangzhou University and Affiliated Hospital of Yangzhou University, over a 1-year span from May 8, 2018, to June 31, 2020. The patients enrolled were categorized into the following groups according to the initial infusion dose of fluid resuscitation: below 20 ml/kg fluid, 20-30 ml/kg fluid and above 30 ml/kg fluid. Patients younger than 18 years of age or with any of the following primary conditions were excluded: pregnancy, trauma, epilepsy, cardiogenic pulmonary oedema, stroke, or active

bleeding. Furthermore, patients whose eventual outcome was unknown or ICU length of stay was less than 72 hours were excluded.

Definitions

According to the Sepsis-3 categories[14-15], sepsis and septic shock are defined as follows. Sepsis is identified as an acute change in the total sequential organ failure (SOFA) assessment score of more than 2 points caused by infection. The baseline SOFA score is assumed to be zero in patients not known to have pre-existing organ dysfunction. Septic shock is defined as a clinical construct of sepsis if the patient has persistent hypotension that requires vasopressors to maintain a mean arterial blood pressure (MAP) greater than 65 mmHg and if the serum lactate level is greater than 2 mmol/L despite initial fluid resuscitation.

The initial infusion dose of fluid resuscitation (ml/kg) was calculated as the total fluid resuscitation within the first hour divided by the actual body weight on admission. As mentioned above, the patients were categorized into three groups based on the initial infusion dose of fluid resuscitation: below 20 ml/kg fluid, 20-30 ml/kg fluid and above 30 ml/kg fluid. SSCs and the literature support of the use of 30 ml/kg of crystalloid for initial volume resuscitation among septic shock patients, though the time to complete the 30 m/kg fluid resuscitation is unclear. Therefore, we further performed subgroup analysis according to the time to complete 30 ml/kg of crystalloid fluid resuscitation. The difference in sequential organ failure assessment between the third day after admission and the first day of admission (ΔSOFA) was defined as the SOFA score change from day 1 to day 3.

Data collection

We provided the principals of each research centre with important study information through emails and online training, including the protocol and answers to questions. Two data collectors collected prospective data, including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, first day and third day total SOFA scores, principal diagnosis, infection source, and initial lactate level. The fluid infusion volume per hour was recorded within 12 hours. Laboratory examinations were obtained from the electronic health database. The primary outcome of the study was 28-d mortality. Secondary outcomes included ICU length of stay, incidence of acute respiratory distress syndrome (ARDS) or acute kidney injury (AKI), respiratory support treatment radio, ventilator-free days and renal replacement therapy (RRT)-free days.

Statistical analysis

Continuous data with a normal distribution are expressed as the mean and standard deviation (±SD), and differences between groups were analysed by one-way analysis of variance. Continuous

data with skewed distributions are expressed as the median and interquartile range (IQR), and differences between groups were analysed by the Kruskal-Wallis test. Dichotomous variables are

reported as n (%), and differences between groups were compared using the Chi-square test (or Fisher exact test when appropriate).

A binary logistic regression model was applied to adjust for potential confounding factors influencing a poor prognosis in patients with septic shock. In addition, curve fitting was adopted to compare the relationship between the initial fluid resuscitation dose and ΔSOFA score. Data analysis was performed using SPSS 22.0 statistical software; P<0.05 was considered statistically significant.

Results

Among 850 ICU patients with a suspected infection, 528 met the sepsis criteria according to the Sepsis-3 definitions. In total, 316 of these patients met the septic shock criteria; 163 were excluded. The remaining 153 septic shock patients were entered into the registry. Of these patients, 39 completed a fluid resuscitation dose below 20 ml/kg within the first hour, and 68 completed a fluid resuscitation dose between 20 ml/kg and 30 ml/kg; the remaining 46 patients had a fluid resuscitation dose above 30 ml/kg (Figure 1). Table 1 shows the demographic characteristics of patients with septic shock according to each classification. The values of actual weight (67.9±6.8 kg), height (17.1±0.3 dm) and BMI (23.2±2.0 kg/m2) were highest in the below 20 ml/kg fluid group and lowest in the above 30 ml/kg fluid group [(58.2±7.3 kg), (16.5±0.5 dm), (21.4±2.9 kg/m2), P<0.01]. The initial SOFA score was lowest in the below 20 ml/kg fluid group (10.6±2.7) and highest in the 20-30 ml/kg fluid group (12.3±2.8, P<0.05); however, the SOFA score on the third day was lowest in the 20-30 ml/kg fluid group (6.3±2.7) and highest in the above 30 ml/kg fluid group (9.2±4.4, P<0.01). There were no significant differences in other patient demographics among the groups (Table 1).

Patient outcomes

A total of 153 septic shock patients had a 28-day mortality of 37.3%. Among them, 28-day mortality was highest in the above 30 ml/kg fluid group (47.8%) and lowest in the 20-30 ml/kg fluid group (26.5%, P<0.05, Figure 2). The incidence of ARDS was highest in the 30 ml/kg fluid group (80.4%) and lowest in the below 20 ml/kg fluid group (40.6%). Patients in the above 30 ml/kg fluid group had the highest rate of invasive mechanical ventilation (67.4%) and the lowest number of mechanical ventilation-free days [24(1-28)], while patients in the 20-30 ml/kg fluid group had the lowest rate of invasive mechanical ventilation (35.3%, P<0.01) and the highest number of mechanical ventilation-free days [28(12-28), P<0.05] (Table 2).

Logistic regression analysis

Logistic regression showed that an initial liquid dose of 20-30 ml/kg was an independent protective factor with a significant OR for decreased mortality (OR, 0.393; 95% CI, 0.178-0.866; P<0.05, Table 3). Furthermore, an initial liquid dose of 10-20 ml/kg was also a protective factor for decreased mortality, but without a significant difference (OR, 0.843; 95% CI, 0.358-1.987; P=0.696) (Table 3).

Initial fluid resuscitation and mortality

First, we explored the relationship between the initial fluid resuscitation dose within 1 hour and the 28-day mortality rate in patients with septic shock. The 28-day mortality rate (100%) was highest in those who were given initial fluid resuscitation below 20 ml/kg within 1 hour; however, the 28-day mortality rate was lowest in septic shock patients with 20-30 ml/kg initial fluid resuscitation within 1 hour (26.5%, $P<0.05$) (Figure 2). We further investigated the relationship between the time to complete 30 ml/kg initial fluid resuscitation and the 28-day mortality rate. Our results showed that patients who completed 30 ml/kg initial fluid resuscitation within 1-2 hours had the lowest 28-day mortality rate (25.9%) and that those who completed more than 4 hours had the highest mortality rate (100%, $P<0.05$) (Figure 2).

Initial fluid resuscitation and ΔSOFA

In addition, we examined the relationship between initial fluid resuscitation dose and ΔSOFA score in patients with septic shock, and a parabolic relationship between liquid dose within 1 hour or time to complete 30 ml/kg liquid and ΔSOFA was detected. The ΔSOFA score was the highest for initial fluid resuscitation with 25.7 ml/kg within 1 hour, reaching 5.807. When the initial fluid resuscitation of 30 ml/kg was completed in 2.18 hours, the ΔSOFA score reached the maximum value of 5.56 (Figure 3).

Discussion

This study showed that an initial fluid resuscitation rate of 20-30 ml/kg within the first 1 h was associated with lower 28-day mortality and faster organ function recovery in patients with septic shock. Moreover, septic shock patients who completed 30 ml/kg initial fluid resuscitation between the first 1-2 h had a lower 28-day mortality rate and faster organ function recovery. This finding is consistent with a recent retrospective study, which found that an initial fluid resuscitation rate of 0.25-0.50 ml/kg/min may be associated with early shock reversal and lower 28-day mortality compared with slower rates of infusion[16]. In addition, this study showed that insufficient initial fluid resuscitation (below 20 ml/kg within the first 1 h) may increase 28-day mortality in these patients.

Fluid resuscitation is the cornerstone of septic shock treatment[17]. In septic shock, blood vessel dilation and vascular permeability increase, leading to relative and absolute blood volume deficiency[18]. The goal of initial fluid resuscitation in septic shock is to restore blood volume, thereby increasing cardiac output and oxygen delivery[19]. This finding is consistent with previous reports that insufficient initial fluid resuscitation is associated with higher 28-day mortality. Overall, a faster initial fluid resuscitation rate might improve the microcirculation and tissue perfusion, resulting in improved outcomes, including SOFA score, duration of hospital, and mortality rates[20]. Therefore, 30 ml/kg initial fluid resuscitation within the first 3 h of septic shock is strongly recommended by the SSC guidelines[7]. Furthermore, the 2018 SSC guidelines recommend faster start-up and completion of 30 ml/kg initial fluid resuscitation in patients with septic shock[13].

Although fluid resuscitation is very important in the early treatment of septic shock, there is often insufficient initial fluid resuscitation in clinical practice[21-22]. What factors may influence the clinician to start initial fluid resuscitation? First, it depends on the level of awareness and compliance of medical

staff with SSC treatment guidelines. The 2018 SSC guidelines recommend rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L in patients with septic shock[13], and awareness and compliance with these guidelines may affect the speed of early fluid resuscitation. In the present study, patients in the below 20 ml/kg fluid group had the longest time from diagnosis to ICU admission. The reason for the lack of initial fluid resuscitation in these patients may be the delay in entering the ICU. Medical staff outside the ICU have insufficient awareness of the importance of initial fluid resuscitation, which leads to insufficient initial fluid resuscitation. In addition, patients with a higher BMI or obesity receive relatively lower fluid volumes than patients without obesity[23]. This research also showed that the weight and BMI values in the low-dose liquid group were significantly higher than those in the high-dose liquid group. Thus, the initial fluid dosing strategy for septic shock should follow guidelines recommending weight-based fluid administration; however, the guidelines do not clearly specify whether actual, ideal, or adjusted body weight should be used to calculate total fluid volumes.

On the other hand, very fast initial fluid resuscitation may increase glycocalyx shedding and negatively impact its barrier function[24]. Fluid overload causes pulmonary oedema, pulmonary interstitial oedema, and oedema of other tissues and organs, which is not conducive to oxygen diffusion, aggravates hypoxia and is closely related to poor prognosis[25]. Our study showed that 28-day mortality was highest in patients with septic shock who received greater than 30 ml/kg initial fluid resuscitation within the first hour or completion the initial 30 ml/kg fluid resuscitation in less than 1 hour, which suggested that too much or too fast initial fluid resuscitation may lead to poor prognosis in patients with septic shock. The study further showed that an initial fluid resuscitation rate of 20-30 ml/kg within the first 1 h or completion of the initial 30 ml/kg fluid resuscitation between the first 1-2 h may be associated with faster organ function recovery and lower 28-day mortality in patients with septic shock. This finding is consistent with a recent retrospective study[10], which found that an initial fluid resuscitation rate of 0.25-0.50 ml/kg/min may be associated with early septic shock reversal and lower 28-day mortality compared with slower rates of infusion. Thus, using an appropriate initial fluid resuscitation rate may improve the prognosis of patients with septic shock.

This study has some limitations. First, this study had a prospective observational design with a small sample size. We were not able to detect any causal relationship, and a large sample randomized controlled trial study is needed to confirm the results. Second, Stephanie P T showed that using adjusted body weight to calculate initial fluid resuscitation volume for patients with obesity and suspected shock may improve outcomes compared to other weight-based dosing strategies[23]. This study followed actual weight-based fluid administration; however, it remains unclear whether it is possible to obtain different results if ideal or adjusted body weight is used to calculate initial total fluid volumes.

Conclusion

Initial fluid resuscitation is currently viewed as the cornerstone of the treatment of septic shock[26-27]. The 2018 SSC recommends rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L in patients with septic shock; however, there is no credible evidence to support this

recommendation. This study demonstrates that insufficient initial fluid resuscitation (below 20 ml/kg within the first 1 h) or too much resuscitation (above 30 ml/kg within the first 1 h) may increase 28-day mortality in patients with septic shock. The initial fluid resuscitation rate of 20-30 ml/kg within the first 1 h was associated with lower 28-day mortality and faster organ function recovery. Furthermore, septic shock patients who completed 30 ml/kg initial fluid resuscitation between the first 1-2 h had a lower 28-day mortality rate and faster organ function recovery.

Abbreviations

ICU, intensive care unit; SSC, Surviving Sepsis Campaign; SOFA, Sequential Organ Failure Assessment; ΔSOFA, Sequential Organ Failure Assessment change value; MAP, mean arterial blood pressure; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; RRT, renal replacement therapy; IQR, interquartile range; BMI, body mass index.

Declarations

Ethical Approval and Consent to participate

This study was approved by the Subei People's Hospital Institutional Review Board (2017KY-022). Informed consent was obtained from each participant prior to his or her enrolment in this study.

Consent for publication

All authors agree to publish the article.

Availability of supporting data

The data are available from the corresponding author upon reasonable request.

Competing interests

All authors declare no competing interests.

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Author contributions

QC: acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. **WL:** data analysis and interpretation and ensured that the accuracy and integrity of all work was appropriately maintained. **FW:** experimental conception and design, data acquisition, first drafting of the manuscript, and full access to all the data in the study. **HC:** data acquisition, analysis and interpretation; revision of the manuscript. **JS:** data acquisition and analysis of data; statistical analysis and revision of the manuscript. **RZ:** data acquisition and interpretation of data; administrative and technical aspects. **HW:** data acquisition and interpretation of data; study supervision; and critical revision of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

Baseline characteristics of the patients at inclusion in the study. Data are presented as the median and standard deviation or median and interquartile range. Abbreviations: COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment. BMI, body mass index.

	All(n = 153)	Below 20 ml/kg fluid(n = 39)	20–30 ml/kg fluid(n = 68)	Above 30 ml/kg fluid (n = 46)	P Value
Age-yr	68.7 ± 14.6	67.4 ± 16.5	68.9 ± 14.6	69.6 ± 13.2	0.484
Male sex-no.(%)	106(69.3)	29(74.3)	49(72.1)	28(60.8)	0.203
Actual weight-kg	64.2 ± 8.2	67.9 ± 6.8	65.8 ± 7.7	58.2 ± 7.3	0.001
Height-dm	16.8 ± 0.5	17.1 ± 0.3	16.9 ± 0.5	16.5 ± 0.5	0.001
BMI-Kg/m^2	22.6 ± 2.1	23.2 ± 2.0	22.9 ± 2.1	21.4 ± 2.9	0.001
Origin,no.(%)					
Emergency room	68(44.4)	20(51.3)	30(44.1)	18(11.8)	0.531
General ward	69(45.1)	16(41.0)	30(44.1)	23(50)	0.693
Intensive Care Unit	16(10.5)	3(7.7)	8(11.8)	5(3.3)	0.788
Time from diagnosis of septic shock to ICU-hour	0.61 ± 0.32	0.75 ± 0.38	0.55 ± 0.26	0.58 ± 0.31	0.014
Infection source,no.(%)					
Respiratory	105(68.6)	28(71.8)	47(69.1)	30(65.2)	0.804
Catheter-related	10(6.5)	2(5.1)	5(7.4)	3(6.5)	0.901
Abdominal	28(18.3)	7(17.9)	11(16.2)	10(21.7)	0.755
Urinary	5(3.3)	1(2.6)	3(4.4)	1(2.2)	0.772
Other	3(1.9)	1(2.6)	1(1.5)	1(2.2)	0.927
Infection of unknown source	2(1.3)	0(0)	1(1.5)	1(2.2)	0.532
Underlying disease-no. (%)					
Diabetes	30(19.6)	8(20.5)	12(17.6)	10(21.7)	852
Hypertension	41(26.8)	11(28.2)	16(23.5)	14(30.4)	0.697
Renal failure	11(7.2)	4(10.3)	5(7.4)	2(4.3)	0.567

	All(n = 153)	Below 20 ml/kg fluid(n = 39)	20–30 ml/kg fluid(n = 68)	Above 30 ml/kg fluid (n = 46)	P Value
Hepatic disease	4(2.6)	1(2.6)	2(2.9)	1(2.2)	0.968
COPD	21(13.7)	6(15.4)	9(13.2)	6(13.0)	0.942
Coronary artery disease	19(12.4)	6(15.4)	8(11.8)	5(10.9)	0.807
Stroke	10(6.5)	3(7.7)	5(7.4)	2(4.3)	0.771
Cancer	5(3.3)	1(2.6)	2(2.9)	2(4.3)	0.885
Other	5(3.3)	1(2.6)	3(4.4)	1(2.2)	0.772
APACHE II score	27.3 ± 7.9	25.7 ± 7.5	27.8 ± 7.1	28.1 ± 9.4	0.173
Initial SOFA score	11.8 ± 3.1	10.6 ± 2.7	12.3 ± 2.8	12.2 ± 3.7	0.018
SOFA score on the third day	7.3 ± 3.6	6.8 ± 3.1	6.3 ± 2.7	9.2 ± 4.4	0.002
Initial blood lactate(mmol/l)	4.9 ± 2.7	4.8 ± 2.6	4.8 ± 2.9	4.9 ± 2.5	0.889
Up to antibiotic use(hour)	1.2(0-1.5)	1.2(0.2–1.5)	1.1(0-1.4)	1.3(0-1.65)	0.36
Norepinephrine max. dose, μg/kg/min	0.9(0.6–1.5)	1.0(0.5–1.5)	0.85(0.6–1.5)	0.9(0.6–1.5)	0.796

Table 2

Association between initial fluid resuscitation rate and outcomes of septic shock patients. Abbreviations: ICU, intensive care unit, ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; RRT, renal replacement therapy.

	All(n = 153)	Below 20 ml/kg fluid(n = 39)	20–30 ml/kg fluid(n = 68)	Above 30 ml/kg fluid (n = 46)	P Value
Mortality of 28 days, n(%)	57(37.3)	17(43.6)	18(26.5)	22(47.8)	0.042
LOS-ICU,days	7.0(5.0–8.0)	7.0(6.0–8.0)	7.0(5.2-8.0)	6.0(4–8)	0.242
ARDS,n(%)	85(55.6)	17(40.6)	31(45.6)	37(80.4)	0.001
Respiratory support					
Noninvasive ventilation,n(%)	21(13.7)	7(17.9)	8(11.8)	6(13.0)	0.673
Invasive ventilation,n(%)	46(30.1)	15(38.5)	24(35.3)	31(67.4)	0.002
HFNC,n(%)	23(15.0)	4(10.3)	15(22.1)	4(8.7)	0.091
Mechanical ventilation-free days	24(3–28)	24(3–28)	28(12–28)	24(1–28)	0.026
AKI,n(%)	46(30.1)	15(38.5)	17(25.0)	14(30.4)	0.348
RRT-free days	6.0(5.0–8.0)	6.0(5.0–8.0)	6.5(5.0–7.0)	5.0(3.0–8.0)	0.493

Table 3

Logistic regression models using 28-day mortality among patients with septic shock as a dependent variable and definitions as independent variables.

	Wald	Sig.	Exp(B)	95.0% CI for Exp(B)	
				Lower	Upper
Liquid dose with 1 hour	6.121	0.047			
10–20 ml/kg	0.152	0.696	0.843	0.358	1.987
20–30 ml/kg	5.370	0.020	0.393	0.178	0.866
Constant	0.087	0.768	0.917		

Figures

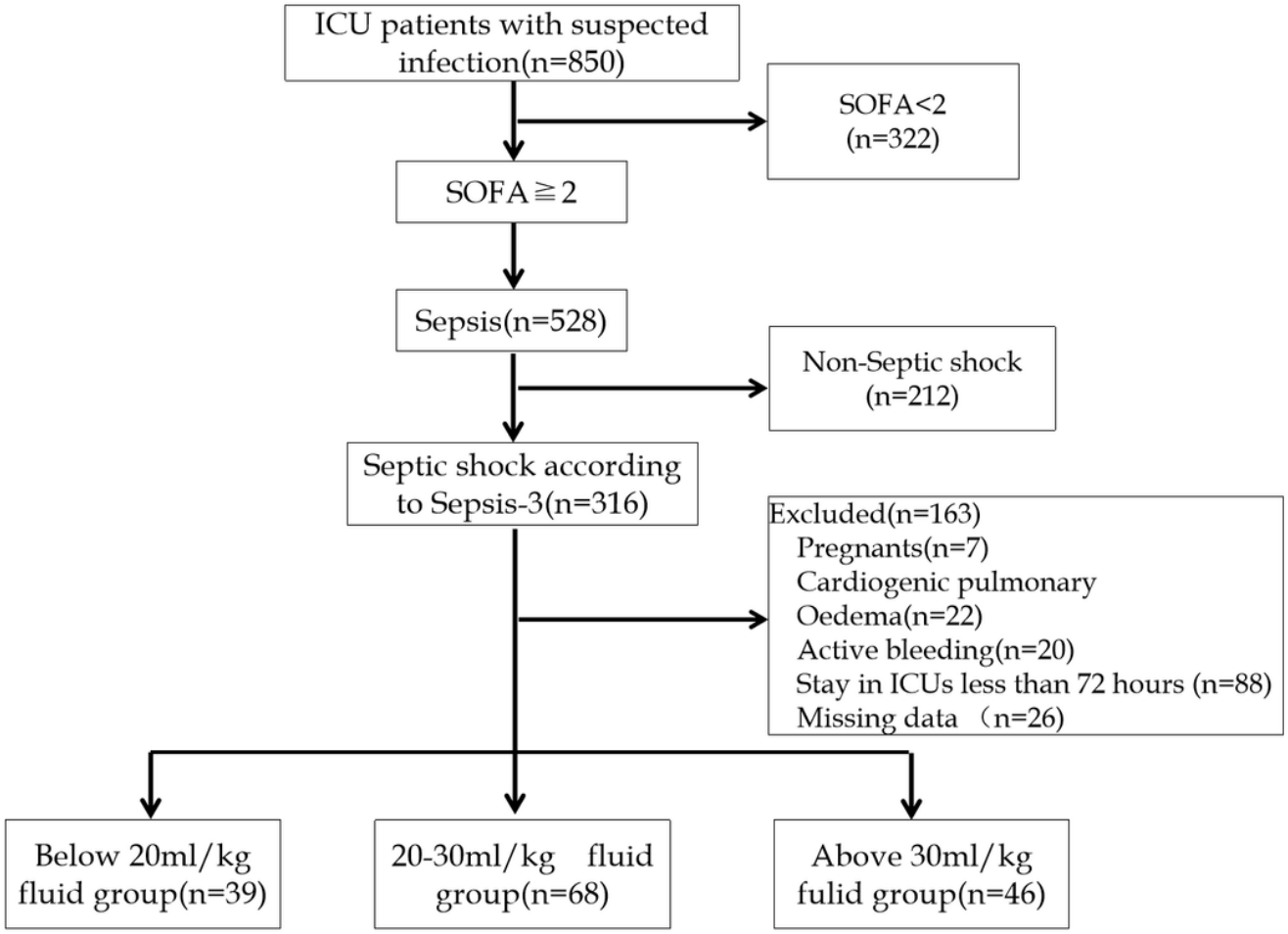

Figure 1

Flow diagram of the subjects by study period. Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

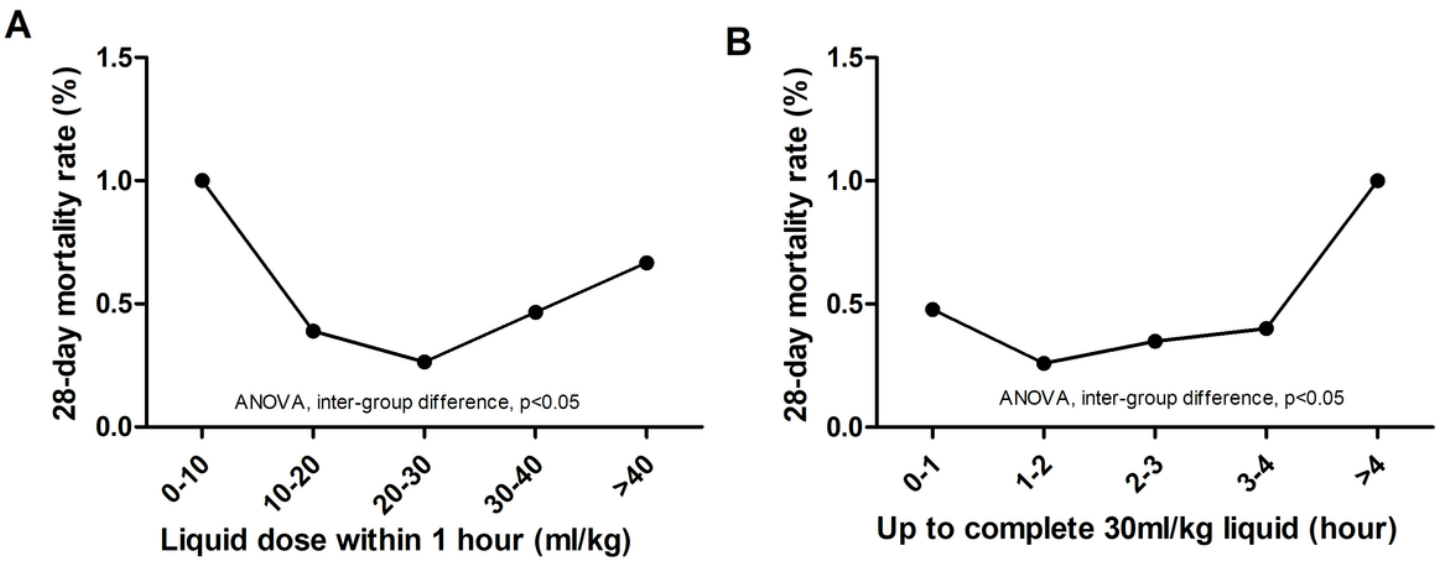

Figure 2

Effect of the initial fluid dose within the first hour and the completion of 30 ml/kg liquid on the 28-day mortality rate in patients with septic shock. Abbreviations: ANOVA, analysis of variance

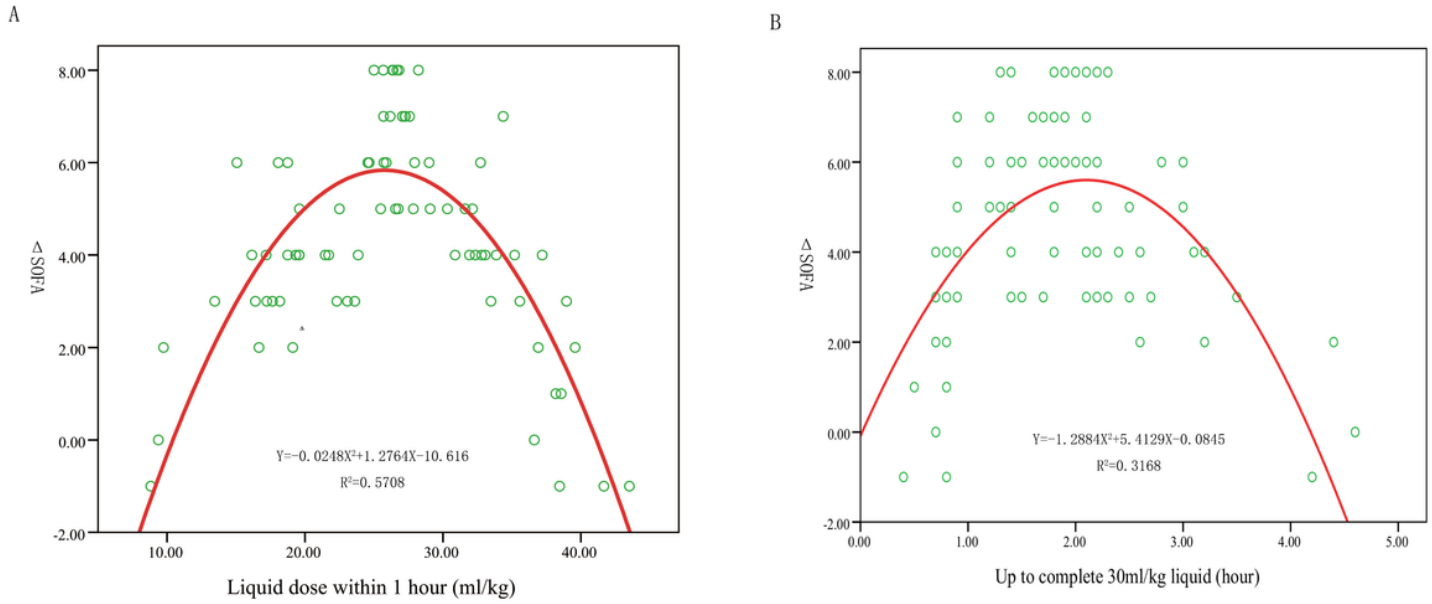

Figure 3

Effect of the initial fluid dose within the first hour and the completion of 30 ml/kg liquid on ΔSOFA in patients with septic shock. Abbreviations: ΔSOFA, the difference of Sequential Organ Failure Assessment between the third day of admission and the first day of admission.

Supplementary Files

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