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

Qi-hong Chen
Jiangdu People's Hospital of Yangzhou

Wei-li Liu
Affiliated hospital of Yangzhou University

Fei Wu
Affiliated hospital of Yangzhou University

Han-bing Chen
Subei People's Hospital

Jun Shao
Northern Jiangsu People's Hospital

Rui-qiang Zheng (✉️ 18051063567@163.com)
Northern Jiangsu People's Hospital

Hua-ling Wang
Subei People's Hospital

Research

Keywords: septic shock, initial fluid resuscitation, mortality

DOI: https://doi.org/10.21203/rs.3.rs-79455/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

OBJECTIVES

The 2018 Surviving Sepsis Campaign (SSC) recommends rapid administration of 30 ml/kg crystalloid for hypotension or lactate $\geq$ 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
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 $\geq$ 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 ∆SOFA**

In addition, we examined the relationship between initial fluid resuscitation dose and ∆SOFA 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 ∆SOFA was detected. The ∆SOFA 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 ∆SOFA 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 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.

Funding

Contract grant sponsor: Social Development Funds of Jiangsu Province; Contract grant number: BE2017691;

National Natural Science Foundations of China; Contract grant number: 81670065; Social Development Funds of Yangzhou City; Contract grant number: YZ2017086

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.

Acknowledgements

Not applicable

Author information

1. Qihong Chen

Department of Critical Care Medicine, Jiangdu People's Hospital of Yangzhou, Jiangdu People's Hospital Affiliated to Medical College of Yangzhou University, Yangzhou, Jiangsu 225200, China

2. Weili Liu and Fei Wu

Department of Intensive Care Unit, Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, Jiangsu, 225001, China

3. Hanbing Chen, Ruiqiang Zheng and Jun Shao

Department of Critical Care Medicine, Northern Jiangsu People's Hospital, Clinical Medical College, Yangzhou University, Yangzhou, Jiangsu 225001, China

4. Hualing Wang

Department of Cardiology, Northern Jiangsu People's Hospital, Clinical Medical College of Yangzhou University, Yangzhou, Jiangsu, 225001, China.

References

1. Hotchkiss RS, Moldawer LL, Opal SM, et al. Sepsis and septic shock. Nat Rev Dis Primers. 2016 Jun 30;2:16045.

2. 10.1001/jama.2017.0131

   Howell MD, Davis AM. Management of Sepsis and Septic Shock. JAMA. 2017 Jan 19. doi: 10.1001/jama.2017.0131. [Epub ahead of print].
3. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA. 2017 Jan 17;317(3):301–308.

4. Kellum JA, Pike F, Yealy DM, et al. Relationship Between Alternative Resuscitation Strategies, Host Response and Injury Biomarkers, and Outcome in Septic Shock: Analysis of the Protocol-Based Care for Early Septic Shock Study. Crit Care Med. 2017 Mar;45(3):438–45.

5. Rivers EP, Jaehne AK, Eichhorn-Wharry L, et al. Fluid therapy in septic shock. Curr Opin Crit Care. 2010;16:297–308.

6. Gupta RG, Hartigan SM, Kashiouris MG, et al. Early goal-directed resuscitation of patients with septic shock: current evidence and future directions. Crit Care. 2015;19:286.

7. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;43:304–77.

8. Loflin R, Winters ME. Fluid resuscitation in severe sepsis. Emerg Med Clin North Am. 2017;35:59–74.

9. Lee SJ, Ramar K, Park JG, et al. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: a retrospective cohort study. Chest. 2014;146:908–15.

10. Bo Hu, Joy CY, Chen Y, Dong, et al. Effect of initial infusion rates of fluid resuscitation on outcomes in patients with septic shock: a historical cohort study. Crit Care 2020 Apr 7;24(1):137.

11. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364:2483–95.

12. Andrews B, Semler MW, Muchemwa L, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. JAMA. 2017;318:1233–40.

13. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med. 2018 Jun;44(6):925–8.

14. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):775–87.

15. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):762–74.

16. Bo Hu, Joy CY, Yue D, et al. Effect of initial infusion rates of fluid resuscitation on outcomes in patients with septic shock: a historical cohort study. Crit Care 2020 Apr 7;24(1):137.

17. Paul EM, Liam B, Frank vH. Fluid resuscitation in sepsis: the great 30 mL per kg hoax. J Thorac Dis 2020 Feb;12(Suppl 1):S37-S47.

18. Ciornei CD, Egesten A, Engström M, et al. Bactericidal/permeability-increasing protein inhibits endotoxin-induced vascular nitric oxide synthesis. Acta Anaesthesiol Scand. 2002 Oct;46(9):1111–8.
19. Wesley H, Matthew W, Rinaldo B, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Ann Emerg Med. 2018 Oct;72(4):457–66.

20. Leisman DE, Doerfler ME, Schneider SM, Masick KD, D’Amore JA, D’Angelo JK. Predictors, prevalence, and outcomes of early crystalloid responsiveness among initially hypotensive patients with Sepsis and septic shock. Crit Care Med. 2018;46:189–98.

21. Gunnar G, Christof H, Jasmin A, et al. Vasopressors for hypotensive shock. Cochrane Database Syst Rev 2016 Feb 15;2(2):CD003709.

22. Thomas WL, Jan B, Daniel DB, et al. Current use of vasopressors in septic shock. Ann Intensive Care 2019 Jan 30;9(1):20.

23. Stephanie PT, Colleen HK, Megan AT, et al. Initial fluid resuscitation following adjusted body weight dosing is associated with improved mortality in obese patients with suspected septic shock. J Crit Care. 2018 Feb;43:7–12.

24. Philippe Guerci B, Ergin, Zuhre U, et al. Glycocalyx Degradation Is Independent of Vascular Barrier Permeability Increase in Nontraumatic Hemorrhagic Shock in Rats. Anesth Analg. 2019 Aug;129(2):598–607.

25. Suvi TV, Anna-Maija K, Kirsi-Maija K, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Crit Care 2012 Oct 17;16(5):R197.

26. Olivier L, Eugénie D, Pierre A, et al. Hemodynamic support in the early phase of septic shock: a review of challenges and unanswered questions. Ann Intensive Care 2018 Oct 29;8(1):102.

27. Bram R, Waleed A, Anees S, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med 2014 Sep 2;161(5):347–55.

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/m²                | 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% Cl 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
This is a list of supplementary files associated with this preprint. Click to download.

- renamed64dbe.jpg