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*Original Article*

# The effects of early restrictive fluid resuscitation on the clinical outcomes in sepsis patients

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**Abstract:** Objective: To investigate the effects of early restrictive fluid resuscitation (RFR) on the clinical outcomes in sepsis patients. Methods: A total of 122 sepsis patients admitted to our hospital were recruited for this study and divided into a study group (the SG, n=56) and a control group (the CG, n=66) according to the treatment method each patient was administered. The SG was administered early RFR, and the CG was administered adequate fluid resuscitation. The clinical data were analyzed retrospectively in both groups. The total infusion volumes, the hemorrhage amounts, the urine outputs, and the Acute Physiology and Chronic Health Evaluation (APACHE II) scores were compared between the two groups. In addition, the heart rates, the mean arterial pressure levels, the central venous pressure levels, and the cardiac function indices were compared between the two groups at 1-7 days after the procedures. The survival and the complication incidence rates were followed up. Results: The SG showed significantly lower heart rates and mean arterial pressure levels and higher central venous pressure levels than the CG at 1-7 days after the procedures ($P$<0.05). The cardiac troponin, N-terminal brain pro-natriuretic peptide, and C-reactive protein levels at 3-7 days after the procedures in the SG were significantly lower than the levels in the CG ($P$<0.05). The cardiac output, stroke volume, and left ventricular ejection fraction scores in the SG were significantly higher than they were in the CG ($P$<0.05). The survival rate in the SG was significantly higher than it was in the CG at 16, 32, and 64 days after the procedures ($P$<0.05). The incidence of complications in the SG was lower than it was in the CG ($P$<0.05). Conclusion: Early RFR can remarkably improve the clinical outcomes, the myocardial injury and survival rates, and the multiple complications incidence rate in sepsis patients.

**Keywords:** Sepsis, restrictive fluid, resuscitation therapy, clinical outcomes, influence investigation

## Introduction

Sepsis is a systemic response caused by the presence of pathogenic microorganisms and/or their toxins (superantigens) in the blood [1]. Sepsis is a leading cause of neonatal death and is common in the neonatal period. A study has indicated that the high incidence of neonatal sepsis may be related to the immature neonatal immune system, the fragile skin and mucous membrane barrier, long-term mechanical ventilation, and the improper operation of indwelling needles [2]. One epidemiological study indicated that sepsis is the third leading cause of neonatal death. Early-onset sepsis (EOS) has a high mortality rate of 10%-17%, while late-onset sepsis (LOS) has a low mortality rate of about 9% [3]. The clinical findings show that even if some patients with neonatal sepsis can survive after treatment, their motor skills, memory, and attention are still greatly affected. Therefore, aggressive interventions are recommended for sepsis patients to improve their prognoses and mortality rate [4].

Fluid resuscitation is the basic technique of the clinical treatment in the intensive care unit (ICU) and is also an effective option for the treatment of sepsis. Fluid resuscitation can quickly restore the effective circulating blood volume (ECBV), improve the microcirculation and organ perfusion state of individuals, and help alleviate systemic inflammatory responses and shock symptoms [5]. At present, fluid resuscitation can be divided into adequate fluid resuscitation (AFR) and restrictive fluid resuscitation (RFR). AFR is

commonly used for the treatment of hemorrhagic and septic shocks in traditional clinical settings. A previous study suggested that AFR can quickly restore patients' blood volumes and blood pressure levels, ensure the perfusion of organs and tissues, and prevent further shock progression [6]. However, some recent studies have found that large volume fluid resuscitation may lead to blood loss, induce diluted coagulation dysfunction, and aggravate the symptoms of tissue hypoxia, and thus increase the possibility of metabolic acidosis. In addition, an investigation has shown that excessive fluid supplementation may change the microcirculation state of the body, promote plasma extravasation, cause capillary dilation, induce edema of tissues and organs, and further aggravate metabolic injury and hypoxia [7]. RFR is used to conduct fluid replacement through a reasonable control of the fluid volume and infusion speed to find the balance point of resuscitation and ensure the effective recovery of tissue perfusion without affecting the compensatory mechanism of the body [8]. Clinical practice has proved that restrictive fluid therapy can effectively improve the clinical symptoms and mortality rates of sepsis patients [8]. The purpose of this study was to investigate the efficacy of early RFR in the treatment of sepsis patients, so as to provide clinical references for improving the prognosis of sepsis patients.

## Materials and methods

### *General data*

A total of 122 sepsis patients admitted to our hospital from January 2019 to January 2020 were recruited as the study cohort and divided into a study group (the SG, n=56) and a control group (the CG, n=66) according to the treatment method each patient was administered. The clinical data of the patients were analyzed retrospectively. This study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine [No. 2020 (120)].

Inclusion criteria: (1) patients with a clinical diagnosis of sepsis [9]; (2) patients with complete clinical medical records; (3) investigations submitted to Hospital Ethics Committee for approval and implementation; (4) patients or their families who voluntarily signed the informed consent form.

Exclusion criteria: (1) patients comorbid with mental illness; (2) patients with poor compliance; (3) patients comorbid with severe hepatic and renal dysfunctions; (4) patients comorbid with malignant tumors; (5) patients also suffering from systemic inflammatory responses; (6) drug or alcohol addicts; (7) patients also suffering from abnormal blood potassium levels or metabolic acidosis.

### *Intervention methods*

All the patients had deep venous pathways after admission, mainly responsible for the infusion of antibiotics and vasoactive drugs [Hydroxyethyl starch 130/0.4 sodium chloride injection (Approval No. H20103246, Beijing Fresenius Kabi Pharmaceutical Company Limited) and Ringer's Solution (approval No. H20055488, Sichuan Kelun Pharmaceutical Co., Ltd.)]. Meanwhile, the patients' vital signs were continuously monitored. The CG was administered AFR, namely, the patients were administered fast and adequate fluid replacement at the early stage, and 1000-1500 mL of hydroxyethyl starch 130/0.4 sodium chloride injection (approval No. H20103246, Beijing Fresenius Kabi Pharmaceutical Company Limited) within 1 h after resuscitation. Their mean arterial pressure (MAP) was maintained at about 70 mmHg and their urine output was maintained at 1-1.5 mL/(kg·h). The SG was administered RFR, namely, the patients were administered 500-1000 mL of hydroxyethyl starch 130/0.4 sodium chloride injections (approval No. H20103246, Beijing Fresenius Kabi Pharmaceutical Company Limited) within 1 h after resuscitation. When the patients' MAP levels increased to 50-60 mmHg, the infusion speed was slowed down, and the volume of fluid replacement was restricted kept below 3000 mL/d.

### *Observational indices and assessment criteria*

#### *Primary observation indices*

*Comparison of the hemodynamic and laboratory indices between the two groups after the procedures:* An electrocardiogram (ECG) monitor was used to record the hemodynamic indices, including the heart rate (HR), MAP, and

central venous pressure (CVP) after the procedures, and the differences between the two groups were compared. Meanwhile, fasting venous blood samples were collected from both groups. After centrifugation, the serum cardiac troponin (cTnI), N-terminal brain pronatriuretic peptide (NT-proBNP), and C-reactive protein (CRP) levels were measured in both groups using a Synchion fully automatic biochemical analyzer, and the differences between the two groups were compared.

*Assessment of the cardiac function indices in the two groups after the procedures:* A ZXG-F detector for cardiac function indices was used to determine the cardiac function, such as the cardiac output (CO), the stroke volumes (SV), and the left ventricular ejection fractions (LVEF) in the two groups after the procedures. Each index was tested three consecutive times, and the average values were taken as the final result to compare the differences between the two groups.

*Comparison of the two groups' clinical therapeutic outcomes:* The prognoses of both groups were followed up, the two groups' clinical therapeutic outcomes were recorded, and the differences in the mortality rates were compared between the two groups.

Secondary observation indices

*Comparison of the general clinical indices:* The total infusion volumes, the hemorrhage amounts, the urine outputs, and the Acute Physiology and Chronic Health Evaluation (APACHE II) scores were recorded in both groups, and the differences were compared between the two groups, among which the infusion volumes, the hemorrhage amounts, and the urine outputs were recorded by the nursing staff, and the APACHE II scale was used by the physicians based on the patients' conditions. The APACHE II scale is commonly used for the assessment of clinical symptoms, including the acute physiological score, the age score, and the chronic health score. The theoretical maximum score of the scale is 71 points, with higher scores indicating more serious clinical symptoms.

*Comparison of the complication incidence rates between the two groups:* The multiple complication incidence rates (e.g., acute renal failure, acute respiratory distress syndrome, multiple organ failure, and disseminated intravascular coagulation) were measured in both groups, and the differences were compared between the two groups.

*Statistical analysis*

The collected data were input into an EXCEL table, and SPSS 22.0 was used for the statistical analysis. The collected data were analyzed using a normal distribution. The data conforming to a normal distribution were represented by [n (%)]. The differences between groups were compared using *Chi*-square tests. The measurement data were expressed as the means ± standard deviations (means ± SD). The differences between groups were analyzed using *t* tests. The graphics software GraphPad Prism 8 was used to plot the figures. $P<0.05$ indicated a statistically significant difference.

## Results

*Comparison of the general data between the two groups*

There were no significant differences in terms of gender, age, mean weight, mean course of the disease, the APACHE II scale scores before the procedures, or the causes of the injuries between the two groups ($P>0.05$), which were comparable (**Table 1**).

*Comparison of the general clinical indices between the two groups*

After the procedures, the total infusion volumes, the hemorrhage amounts, the urine outputs, and the APACHE II scores in the SG were significantly lower than they were in the CG ($P<0.05$) (**Figure 1**).

*Analysis of the changes in the hemodynamic indices in the two groups after the intervention*

Before the intervention, there was no significant difference in the hemodynamic indices between the two groups ($P>0.05$). The HR and MAP levels in the SG were markedly lower than they were in the CG at 1-7 days after the procedures, but the CVP level in the SG was significantly higher than it was in the CG ($P<0.05$) (**Figure 2**).

*Analysis of the changes in the laboratory indices in the two groups after the intervention*

There was no marked difference in the serum cTnI, NT-proBNP, or CRP levels between the two

**Table 1.** Comparison of the general data between the two groups ($\bar{x} \pm s$)/[n (%)]

| General data | | Study group (n=56) | Control group (n=66) | $t/X^2$ | *P* |
|---|---|---|---|---|---|
| Gender | M | 30 | 40 | 0.613 | 0.434 |
| | F | 26 | 26 | | |
| Mean age (year) | | 40.19±3.22 | 39.98±3.35 | 0.351 | 0.726 |
| Mean weight (kg) | | 60.19±2.39 | 60.28±2.31 | 0.211 | 0.833 |
| APACHE II scores | | 20.19±2.22 | 19.98±2.41 | 0.497 | 0.62 |
| Cause of injury | Post-traumatic infection | 12 | 16 | 0.891 | 0.431 |
| | Severe pneumonia | 20 | 23 | | |
| | Burn infection | 14 | 13 | | |
| | Others | 10 | 14 | | |

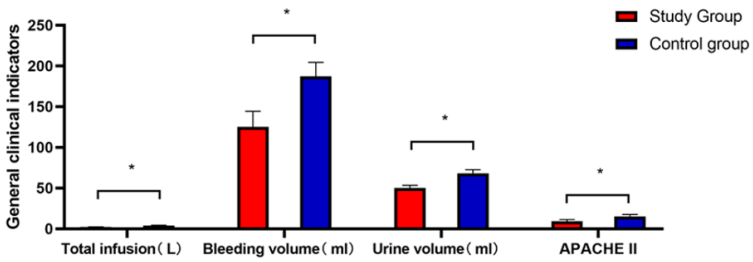


**Figure 1.** Comparison of the general clinical indices between the two groups after the procedures. The total infusion volumes, the hemorrhage amounts, the urine outputs, and the APACHE II scores in the study group were lower than they were in the control group (*P*<0.05). *indicates a statistically significant difference in the same index between the two groups.

groups before the intervention (*P*>0.05). After the intervention, the levels of the above-mentioned serum factors were significantly reduced in both groups, and there were significant differences between the two groups before and after the intervention (*P*<0.05). At 3-7 days after the intervention, the cTnI, NT-proBNP, and CRP levels in the SG were remarkably lower than the corresponding levels in the CG (*P*<0.05) (**Figure 3**).

*Analysis of the changes in cardiac function between the two groups after the procedures*

There were no significant differences in the cardiac function indices, including CO, SV, and LVEF between the two groups before the intervention (*P*>0.05). At 7 days after the intervention, the CO, SV and LVEF levels in the SG were significantly higher than they were in the CG (*P*<0.05). After the intervention, the aforementioned indices in both groups were significantly higher than they were before the procedures (*P*<0.05) (**Figure 4**).

*Comparison of the clinical outcomes between the two groups*

The patients in both groups were followed up for 64 days, and the survival rates of both groups were recorded. The longitudinal observation showed that the survival rates of the patients in both groups showed a downward trend with time, and the late mortality rate decreased significantly. The horizontal comparison between the groups suggested that the survival rate of patients in the SG was basically higher than the rate in the CG during the observation period (only slightly lower than it was in the CG at 40-60 days). The differences in the survival rates between the two groups were statistically significant at 16, 32, and 64 days of follow-up (**Figure 5**).

*Comparison of the complication incidence rates between the two groups*

According to our data, there was 1 case of acute renal failure in the SG, for a total complication incidence rate of 1.79%, and there were 2 cases of acute renal failure, 3 cases of acute distress syndrome, 2 cases of multiple organ failure, and 1 case of disseminated intravascular coagulation in the CG, for a total complication incidence rate of 12.12%. The differences in the complication rates between the two groups were significant (*P*<0.05) (**Table 2**).

## Discussion

Clinically, sepsis is a common and critical disease. Patients with sepsis are prone to organ

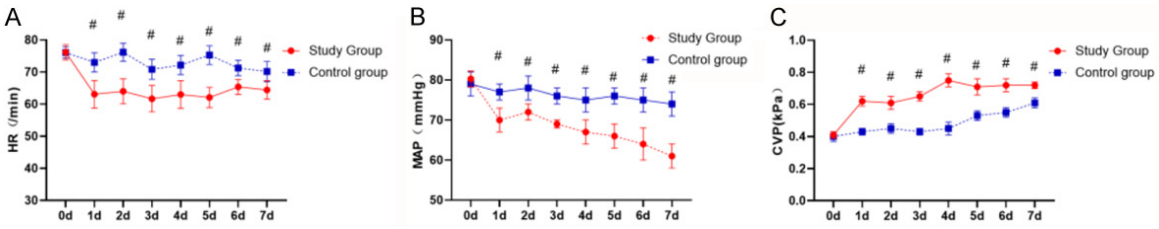


**Figure 2.** Comparison of the changes in the hemodynamic indices in the two groups after the procedures. There was no marked difference in HR (A), MAP (B), or CVP (C) between the two groups at 0 days after the procedures ($P>0.05$). After the procedures, the HR and MAP in study group were higher than they were in the control group, while the CVP in the study group was lower than it was in the control group at 1-7 days after the intervention ($P<0.05$). #indicates a statistically significant difference in the same index between the two groups.

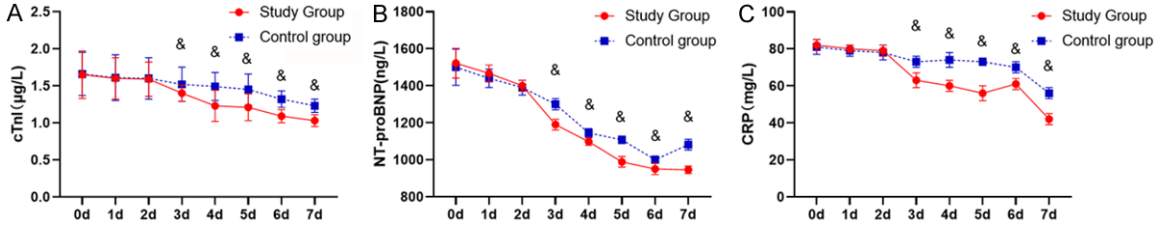


**Figure 3.** Comparison of the changes in the laboratory indices in the two groups after the intervention. There was no significant difference in the cTnI (A), NT-proBNP (B), or CRP (C) levels between the two groups before the intervention and at 1-2 days after the intervention ($P>0.05$). At 3-7 days after the intervention, the levels of the above-mentioned factors in the study group were markedly lower than they were in the control group ($P<0.05$). &indicates a statistically significant difference in the same index between the two groups at the same time point.

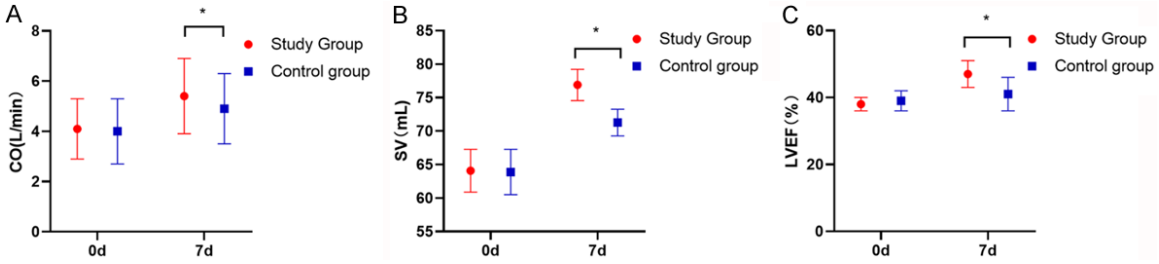


**Figure 4.** Analysis of the changes in the cardiac function in the two groups before and after the intervention. There was no significant difference in CO (A), SV (B), or LVEF (C) between the two groups before the intervention ($P>0.05$). After the intervention, the above-mentioned indices in the study group were significantly higher than they were in the control group ($P<0.05$). *indicates a statistically significant difference in the same index between the two groups.

failure, shock, and other symptoms [10]. Late and ineffective interventions in sepsis patients can lead to very high mortality rates [11]. The European Society of Intensive Care Medicine (ESICM) recommends that all patients with septic shock should be rapidly injected with at least 30 mL/kg of crystal liquid to improve the decreased blood volume and the insufficient perfusion of the visceral organs induced by shock. However, clinical findings prove that there are some issues regarding this recommendation [12]. On the one hand, a strict implementation of the above-mentioned procedures may lead to a sudden increase in blood volume, increasing the burden on the heart and kidneys, and further aggravating organ damage in sepsis patients with cardiac or renal failure. On the other hand, physicians rarely have time to assess and calculate the amount of liquid for sepsis patients experiencing acute septic shock. As a result, it is difficult to get an accurate amount of liquid [13]. Previous clinical studies have indicated that the causes of sepsis-induced organ hypoperfusion include ele-

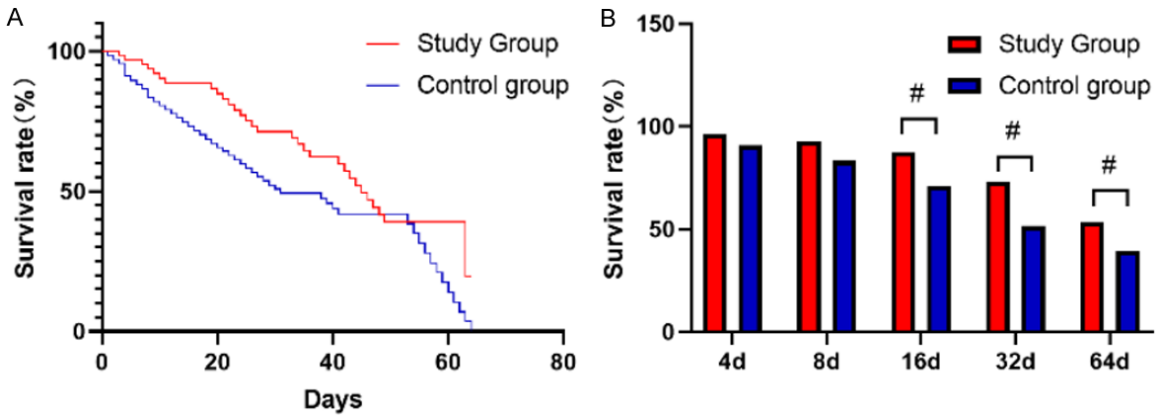


**Figure 5.** Comparison of the survival rates at the follow-ups between the two groups. The survival rates were significantly decreased in both groups during the 64-day follow-up (A), and the survival rate in the study group was markedly higher than it was in the control group at 16, 32, and 64 days of follow-up ($P<0.05$) (B). #indicates marked differences in the same index between the two groups.

**Table 2.** Comparison of the complication incidence rates between the two groups [n (%)]

| Group | Number of cases | Acute renal failure | Acute distress syndrome | Multiple organ failure | Disseminated intravascular coagulation | Total incidence rate |
|---|---|---|---|---|---|---|
| Study group | 56 | 1 (1.79) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 1 (1.79) |
| Control group | 66 | 2 (3.03) | 3 (4.55) | 2 (3.03) | 1 (1.52) | 8 (12.12) |
| $X^2$ | - | - | - | - | - | 4.736 |
| $P$ | - | - | - | - | - | 0.03 |

vated blood lactic acid levels, a decreased urine output, hepatic dysfunction, and mental state changes. Fluid resuscitation can increase the cardiac output and improve the aforementioned symptoms. However, recent studies have suggested that the dysfunctions of the brain, heart, kidneys, and liver are caused by a bioenergy failure rather than by a microcirculation dysfunction and organ perfusion injury. Meanwhile, the hearts of sepsis patients are less responsive to fluid load, and excessive fluid resuscitation may further impair cardiac function [14, 15]. An investigation has shown that overload of fluid will damage the central, respiratory, renal and gastrointestinal systems and lead to several complications, such as cognitive impairment, pulmonary edema, uremia and indigestion [16]. Therefore, exceptional caution should be exercised when AFR is intended for clinical use.

In recent years, RFR has been extensively implemented in clinical studies as an early resuscitation treatment. Investigations have shown that although the volume of fluid replacement is relatively reduced when RFR is implemented, RFR can significantly affect such indices as MAP and CVP, greatly improve insufficient organ perfusion in patients with septic shock, save organs or tissues on the verge of necrosis as much as possible, and improve the prognosis of sepsis patients [17, 18]. In addition, comparative investigations have revealed that restrictive fluid therapy can markedly alleviate the myocardial injury, and the mechanism may be related to the increased blood supply to the coronary arteries by RFR [19, 20]. Finally, statistics show that RFR can effectively reduce the complication incidence rate including renal failure and disseminated blood coagulation. Hence, RFR has a positive significance in improving the prognoses of sepsis patients [21].

The aforementioned investigations provide theoretical references for this study. Our retrospective study was conducted to analyze the feasibility of early RFR in the treatment of sepsis patients. The results show that there are certain differences in the total infusion volumes, the hemorrhage amounts, the urine outputs, and the APACHE II scores between the

two groups. The SG was superior to the CG regarding the total infusion volume, the urine output, and the APACHE II scores, indicating that the clinical symptoms in the SG improve more significantly after the procedures. After a further comparison of the hemodynamic and laboratory indices between the two groups, the HR, MAP, cTnI, NT-proBNP, and CRP in the SG were significantly decreased after the procedures, and there were marked differences between the two groups. A retrospective analysis of 90 sepsis patients grouped according to the adequacy of the early fluid resuscitation found that the mortality rate was significantly lower in the patients with fluid restrictions after resuscitation than in the other group [22]. In a large study, sepsis patients were randomized to an RFR group and a liberal fluid group, and the intervention results showed that the durations of the treatment in the ICU and mechanical ventilation times were shorter in the RFR group than in the liberal fluid group, although there was no difference in the mortality rate at 60 days [23]. The authors of this study believe that AFR can maintain appropriate preload and organ perfusion, and it is a convenient and effective option for the treatment of sepsis. However, when a large volume of fluid resuscitation is carried out in sepsis patients, it will cause excessive fluid accumulation in the interstitial spaces, resulting in fluid overload and edema of the tissues and organs, an increase in oxygen diffusion distance, and microcirculation disorder. These are also specifically reflected in the hemodynamic and laboratory indices, i.e., increased HR and blood pressure, and significant inflammatory responses. The comparison of the cardiac function indices (e.g., CO, SV and LVEF) between the two groups also confirmed this view, revealing that excessive fluid infusion can increase the cardiac load instead of improving the cardiac function, and leading to a decrease in cardiac output power [24].

The clinical outcomes and complication incidence rates were compared between the two groups. The results showed that the survival rate in the SG was remarkably higher than it was in the CG at 16, 32, and 64 days of follow-up. European scholars conducted a multi-center prospective study on sepsis patients in the ICU to explore the prognoses of the patients with fluid balance, sepsis and critical sepsis, and the results showed that the 60-day mortality rate of sepsis patients was 36%, while that of patients with fluid balance was 16%; in addition to advanced age, capacity overload is also an independent risk factor for mortality outcome prediction, so the scholars proposed that the mortality rate of sepsis patients could be effectively reduced by restricting fluid, which is similar to the results of this study [25]. Finally, the incidence of complications was compared between the two groups. The results suggested that the incidence of complications (e.g., acute renal failure and multiple organ dysfunctions) in the SG were lower than those in CG. This may be due to the reason that the restrictive fluid therapy can elevate the intravascular pressure and reduce acidosis from a microscopic perspective, and thus avoid further damages to important tissues and organs (e.g., heart and kidney), resulting in relatively lower incidence rates of multiple complications.

The innovation of this study is its exploration of the feasibility of RFR in the treatment of sepsis patients through a comparative study, and to illustrate the effectiveness of RFR from multiple perspectives through a follow-up comparison of cardiac functions, the inflammatory indices, and the hemodynamic indices, thereby providing detailed data references for the scholars conducting subsequent studies. The shortcomings of this study are its lack of assessment of the survival and quality of life of patients, and the lack of a detailed analysis of the adverse reactions of treatment. Therefore, improved studies should be performed in the future.

In summary, early RFR can remarkably ameliorate the clinical outcomes, the myocardial injury rate, the survival rate, and the incidence rate of multiple complications of sepsis patients.

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## Disclosure of conflict of interest

None.

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## References

[1] Brovkovych V, Gao XP, Ong E, Brovkovych S, Brennan ML, Su X, Hazen SL, Malik AB and Skidgel RA. Augmented inducible nitric oxide synthase expression and increased NO production reduce sepsis-induced lung injury and mortality in myeloperoxidase-null mice. Am J Physiol Lung Cell Mol Physiol 2008; 295: L96-103.

[2] Lai D, Tang J, Chen L, Fan EK, Scott MJ, Li Y, Billiar TR, Wilson MA, Fang X, Shu Q and Fan J. Group 2 innate lymphoid cells protect lung endothelial cells from pyroptosis in sepsis. Cell Death Dis 2018; 9: 369.

[3] Sweeney TE, Perumal TM, Henao R, Nichols M, Howrylak JA, Choi AM, Bermejo-Martin JF, Almansa R, Tamayo E, Davenport EE, Burnham KL, Hinds CJ, Knight JC, Woods CW, Kingsmore SF, Ginsburg GS, Wong HR, Parnell GP, Tang B, Moldawer LL, Moore FE, Omberg L, Khatri P, Tsalik EL, Mangravite LM and Langley RJ. A community approach to mortality prediction in sepsis via gene expression analysis. Nat Commun 2018; 9: 694.

[4] Prescott HC and Angus DC. Enhancing recovery from sepsis: a review. JAMA 2018; 319: 62-75.

[5] Brown RG, Marchesi JR, Lee YS, Smith A, Lehne B, Kindinger LM, Terzidou V, Holmes E, Nicholson JK, Bennett PR and MacIntyre DA. Vaginal dysbiosis increases risk of preterm fetal membrane rupture, neonatal sepsis and is exacerbated by erythromycin. BMC Med 2018; 16: 9.

[6] Brenner T, Decker SO, Grumaz S, Stevens P, Bruckner T, Schmoch T, Pletz MW, Bracht H, Hofer S, Marx G, Weigand MA and Sohn K. Next-generation sequencing diagnostics of bacteremia in sepsis (Next GeneSiS-Trial): study protocol of a prospective, observational, noninterventional, multicenter, clinical trial. Medicine (Baltimore) 2018; 97: e9868.

[7] Meyer N, Harhay MO, Small DS, Prescott HC, Bowles KH, Gaieski DF and Mikkelsen ME. Temporal trends in incidence, sepsis-related mortality, and hospital-based acute care after sepsis. Crit Care Med 2018; 46: 354-360.

[8] Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, Machado FR, Martin GS, Martin-Loeches I, Nunnally ME, Antonelli M, Evans LE, Hellman J, Jog S, Kesecioglu J, Levy MM and Rhodes A. Surviving sepsis campaign: research priorities for sepsis and septic shock. Crit Care Med 2018; 46: 1334-1356.

[9] Sunahara S, Watanabe E, Hatano M, Swanson PE, Oami T, Fujimura L, Teratake Y, Shimazui T, Lee C and Oda S. Influence of autophagy on acute kidney injury in a murine cecal ligation and puncture sepsis model. Sci Rep 2018; 8: 1050.

[10] van Engelen TSR, Wiersinga WJ, Scicluna BP and van der Poll T. Biomarkers in sepsis. Crit Care Clin 2018; 34: 139-152.

[11] Jensen IJ, Sjaastad FV, Griffith TS and Badovinac VP. Sepsis-induced t cell immunoparalysis: the ins and outs of impaired t cell immunity. J Immunol 2018; 200: 1543-1553.

[12] Cockrell RC and An G. Examining the controllability of sepsis using genetic algorithms on an agent-based model of systemic inflammation. PLoS Comput Biol 2018; 14: e1005876.

[13] Álvaro-Meca A, Jiménez-Sousa MA, Micheloud D, Sánchez-Lopez A, Heredia-Rodríguez M, Tamayo E and Resino S. Epidemiological trends of sepsis in the twenty-first century (2000-2013): an analysis of incidence, mortality, and associated costs in Spain. Popul Health Metr 2018; 16: 4.

[14] Olijve L, Jennings L and Walls T. Human parechovirus: an increasingly recognized cause of sepsis-like illness in young infants. Clin Microbiol Rev 2018; 31: e00047-17.

[15] Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM and Fraley SI. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev 2018; 31: e00089-17.

[16] Elke G, Bloos F, Wilson DC, Brunkhorst FM, Briegel J, Reinhart K, Loeffler M, Kluge S, Nierhaus A, Jaschinski U, Moerer O, Weyland A and Meybohm P. The use of mid-regional proadrenomedullin to identify disease severity and treatment response to sepsis - a secondary analysis of a large randomised controlled trial. Crit Care 2018; 22: 79.

[17] Prescott HC and Costa DK. Improving long-term outcomes after sepsis. Crit Care Clin 2018; 34: 175-188.

[18] Fujii T, Ganeko R, Kataoka Y, Furukawa TA, Featherstone R, Doi K, Vincent JL, Pasero D, Robert R, Ronco C and Bagshaw SM. Correction to: polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2018; 44: 279-280.

[19] Min J, Nothing M, Coble B, Zheng H, Park J, Im H, Weber GF, Castro CM, Swirski FK, Weissleder R and Lee H. Integrated biosensor for rapid and point-of-care sepsis diagnosis. ACS Nano 2018; 12: 3378-3384.

[20] Tai LH, Ananth AA, Seth R, Alkayyal A, Zhang J, de Souza CT, Staibano P, Kennedy MA and Auer RC. Sepsis increases perioperative metastases in a murine model. BMC Cancer 2018; 18: 277.
[21] Vallabhajosyula S, Pruthi S, Shah S, Wiley BM, Mankad SV and Jentzer JC. Basic and advanced echocardiographic evaluation of myocardial dysfunction in sepsis and septic shock. Anaesth Intensive Care 2018; 46: 13-24.
[22] Rello J, van Engelen TSR, Alp E, Calandra T, Cattoir V, Kern WV, Netea MG, Nseir S, Opal SM, van de Veerdonk FL, Wilcox MH and Wiersinga WJ. Towards precision medicine in sepsis: a position paper from the European society of clinical Microbiology and infectious diseases. Clin Microbiol Infect 2018; 24: 1264-1272.
[23] Liverani E, Mondrinos MJ, Sun S, Kunapuli SP and Kilpatrick LE. Role of protein kinase C-delta in regulating platelet activation and platelet-leukocyte interaction during sepsis. PLoS One 2018; 13: e0195379.
[24] Geven C, Peters E, Schroedter M, Struck J, Bergmann A, McCook O, Radermacher P, Kox M and Pickkers P. Effects of the humanized anti-adrenomedullin antibody adrecizumab (HAM8101) on vascular barrier function and survival in rodent models of systemic inflammation and sepsis. Shock 2018; 50: 648-654.
[25] Kell DB and Pretorius E. To what extent are the terminal stages of sepsis, septic shock, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome actually driven by a prion/amyloid form of fibrin? Semin Thromb Hemost 2018; 44: 224-238.