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RESEARCH PROTOCOL

Fluid bolus in suspected Sepsis patients with Hyperlactatemia (FISH): Study protocol for an open-labeled, randomized controlled trial

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ABSTRACT:

Background: The adequate preload was the goal of hemodynamic optimization for sepsis resuscitation. The fluid strategy in the early phase of sepsis is unclear.

Objectives: To investigate the efficacy of a fluid bolus to prevent new-onset hypotension in suspected sepsis patients with hyperlactatemia (Point-of-care serum lactate 2-4 mmol/L).

Methods: The Fluid Bolus in Suspected Sepsis Patients with Hyperlactatemia Trial (FISH) is a single-center, open-label randomized controlled trial. Participants will be patients suspected of having sepsis with hyperlactatemia (Point-of-care serum lactate 2-4 mmol/L) in the emergency department of Srinagarind Hospital, Thailand. Eligible patients will be randomized (1:1) to one of the study arms using block randomization. They will be placed in either the fluid bolus group (intervention, 30 mL/kg within 3 hours) or the standard care group (control). The primary outcome is new-onset hypotension within 24 hours after randomization. Secondary outcomes include lactate clearance, ΔSOFA at 72-hours, organ failure, and support 'free days' to day 28, 28-day mortality.

Hypothesis: We hypothesize that a fluid bolus will prevent new-onset hypotension in suspected sepsis patients with hyperlactatemia (point-of-care serum lactate 2-4 mmol/L).

Discussion: The optimal strategy for intravenous fluid therapy in a patient suspected of sepsis with hyperlactatemia is unknown. This is the first randomized trial examining fluid strategy in the early phase of sepsis with mild hyperlactatemia.

Ethics and dissemination: This study obtained approval from the Center for Ethics in Human Research at Khon Kaen University (Ethics Committee number: HE661012) and was registered at the Thai Clinical Trials Registry (TCTR20230502003).

Trial registration: TCTR20230502003

Keywords: Fluid therapy; Hyperlactatemia; Hypotension; Randomized controlled trial; Sepsis

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. [1] The global burden of sepsis is difficult to ascertain, although a recent scientific publication estimated that in 2017, there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths. [2] If not recognized early and managed promptly, it can lead to septic shock, multiple organ failure, and death. It is most frequently a serious complication of infection, particularly in low- and middle-income countries, where it represents a major cause of maternal and neonatal morbidity and mortality. [3] Early diagnosis and timely and appropriate clinical management of sepsis, such as optimal antimicrobial use and fluid resuscitation to achieve hemodynamic targets, are crucial to increasing the survival rate.

The Fluid Expansion As Supportive Therapy (FEAST) trial randomized 3400 children (median age 24 months.) with sepsis and evidence of hypoperfusion to receive bolus resuscitation with either crystalloid saline or albumin, and a control arm whose participants received only maintenance fluid without bolus. [4] The 48-hour mortality was 10.6%, 10.5%, and 7.3% in the albumin-bolus, saline-bolus, and control groups, respectively. There was no evidence of a difference in either primary or secondary end points between the albumin-bolus and saline-bolus groups.

The Restriction of Intravenous Fluid in ICU Patients with Septic Shock (REFRESH) assigned patients presenting to the emergency department with suspected sepsis and hypotension, a fluid-restricted and early vasopressor regimen resulted in a reduction in total fluid volume administered in the first 24 hours and was not associated with any signal of harm. [5]

An adequate preload was the goal of hemodynamic optimization for sepsis resuscitation. Meanwhile, the recent recommended protocol for fluid resuscitation was increasingly debated on hemodynamic stability vs. the risk of overloading.

OBJECTIVES

The primary objective of the FISH study is to investigate the efficacy of a fluid bolus to prevent new-onset hypotension in suspected sepsis patients with hyperlactatemia (Point-of-care serum lactate 2-4 mmol/L). We hypothesize that a fluid bolus of 30 mL/kg will prevent the new-onset hypotension.

MATERIALS AND METHODS

Participants

This is a single-center, open-label randomized controlled trial designed to evaluate the efficacy of fluid bolus compared to standard care in patients with suspected sepsis exhibiting hyperlactatemia. The methodology adheres to the Standard Protocol Items: Recommendations of Interventional Trials (SPIRIT) reporting guidelines. [6]

KEY MESSAGE:

- The aim of the study was to explore the efficacy of an early intravenous fluid bolus protocol for the initial resuscitation of patients presenting to the emergency department with suspected sepsis and hyperlactatemia, with the goal of preventing a new onset of hypotension.

Study setting

This trial is conducted at Srinagarind Hospital, affiliated with Khon Kaen University, Thailand. This hospital is an academic tertiary university hospital. Participant recruitment is primarily executed within the emergency department, with the initiation date being February 13, 2023.

Eligibility criteria

Eligibility for participation in this trial will be assessed by emergency physicians within the emergency department under the following criteria:

Inclusion criteria

1. Suspected sepsis, defined as systemic inflammatory response syndrome (SIRS) ≥ 2 points [7], is accompanied by either a suspected or confirmed source of infection.
2. Hyperlactatemia is characterized by a point-of-care serum lactate level ranging from 2 to 4 mmol/L, measured via arterial or venous blood gas analysis.
3. Age of 18 years or older.

Exclusion criteria

Patients will be excluded if they meet any of the following criteria:

1. Congestive heart failure, evident signs of volume overload, a history of low ejection fraction (EF < 40%), or functional class IV.
2. End-stage kidney disease, irrespective of whether they require renal replacement therapy.
3. Hypotension from any cause is defined as a SBP < 90 mmHg or a MAP < 65 mmHg.
4. Morbid obesity (BMI ≥ 40 kg/m^2)
5. Pregnancy
6. Patients transferred from another hospital.
7. Administration of intravenous fluid prior to arrival at the emergency department.
8. Refusal to participate in the study or presence of a Do-Not-resuscitate order.
9. Suspicion type B lactic acidosis such as toxin-induced (metformin, isoniazid, NRTIs), liver failure, or thiamine deficiency.

Trial definition

Sepsis [1] is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of ≥ 2 points or SIRS criteria of ≥ 2 points with a suspected or confirmed source of infection.

Systemic inflammatory response syndrome [7] represents a series of objective physical and laboratory findings indicative of an infectious or non-infectious insult provoking a systemic immune response. The criteria include (1) temperature > 38 °C or < 36 °C; (2) heart rate > 90 bpm; (3) respiratory rate > 20 or $PaCO_2$ < 32 mmHg; (4) WBC > 12000/mm^3 or < 4,000/mm^3 or > 10% bands.

The new onset of hypotension [8] is defined as changes in systolic blood pressure to less than 90 mm Hg, mean arterial pressure of less than 65 mm Hg, or a decrease in systolic blood pressure to less than 40 mm Hg from baseline.

Organ failure [5] is the failure of an essential system in the body. Renal failure is defined as a score of at least 1 on the Acute Kidney Injury Network (AKIN) score system at baseline and the number in each category of peak AKIN score during the 7 days after randomization and required renal replacement therapy. Respiratory failure is an impairment of oxygenation, carbon dioxide elimination, or both and a requirement for ventilation (NIV/IMV) during the 7 days after randomization.

Maintenance fluid [9] is fluid therapy that involves estimating normal maintenance requirements using the Holliday-Segar nomogram to approximate daily fluid loss.

Hyperlactatemia [10] is defined as higher than 2 mmol/L with or without acidosis.

Screening and randomization

Patients presenting clinical signs of infection will undergo screening for sepsis using standard clinical procedures, including the recording of vital signs and the collection of blood samples, including a full blood count, urea, and electrolytes, and arterial or venous blood gas analysis including, point-of-care serum lactate.

Patients who do not meet any exclusion criteria will be invited to participate in the trial. Those meeting the eligibility requirements and from whom consent has been obtained will be randomized and allocated in a 1:1 ratio to either of the study groups. This allocation will be conducted using block randomization, with block sizes of 8, 4, and 2, to ensure a balanced distribution.

The randomization sequence will be generated using the function 'allocationTable' in the 'REDCapAPI' package. This sequence will then be sealed within opaque envelopes by staff members not engaged in the conduct of the study.

Intervention group (Fluid bolus protocol)

Participants randomized into the intervention group will receive 30 mL/kg of actual body weight (ABW), an intravenous fluid bolus within the first 3 hours, followed by the rate of intravenous fluid as the maintenance rate by Holiday and Segar's laws at least 24 hours after randomization, and a fluid deficit according to the severity of dehydration. If the participants cannot measure their actual body weight, we will calculate the ideal body weight (IBW) using the 'Devine formula':

IBW of men = 50 kg + 0.91*(height in cm. – 152)

and

IBW of women = 45 kg + 0.91*(height in cm. – 152)

(Figure 1).

Control group (Conventional fluid protocol)

Participants in the control group will receive fluid as maintenance fluid that is calculated by Holiday and Segar's laws at least 24 hours after randomization and fluid deficit according to severity of dehydration

(Figure 1).

General management

Fluid management will be as per study protocol for the first 3 hours after randomization, regardless of whether the patient remains in the ED or is transferred to the ICU or to a ward. For patients with an unanticipated transfer during this time, the trial protocol will be suspended.

All participants will receive supplemental oxygen to maintain SpO_2 > 92%, will undergo routine blood sampling, and will receive antibiotics within 60 minutes of enrollment. The participants who develop respiratory failure will consider induction agents that minimize the risk of hypotension (such as ketamine) and manage mechanical ventilation using a lung protective strategy. [11] All fluids administered (bolus or maintenance) after enrollment must be balanced isotonic crystalloid during the first 3 hours. Hypotonic fluids, synthetic colloids, and 0.9% saline are to be avoided. Types of antibiotics, fluid administration, blood products, and albumin solutions may be the discretion of the treating clinician.

Clinical assessment of volume deficit and fluid overload will be assessed every hour for the first 6 hours, such as oral mucosal dryness, skin turgor, capillary refill, urine output, pulse oximetry, and lung auscultation.

Rescue therapy

If the participants develop hypotension, we will suggest fluid resuscitation with physical examination (such as lung auscultation) and the assessment of fluid-responsiveness (such as ultrasound guided fluid resuscitation, a fluid challenge test, or invasive monitoring). Vasopressor therapy will be initiated in participants who develop intractable hypotension. If a sign of volume overload is present, we will stop fluid replacement, provide oxygen support, and conduct a re-evaluation.

Criteria for withdrawal, stopping and study termination

The participants will be withdrawn from the study if they are transferred to another hospital or withdraw informed consent.

The fluid protocol will be stopped if participants develop volume overload after fluid replacement and need respiratory support (e.g., non-invasive or invasive mechanical ventilation).

The study will be deemed to have been terminated early if an unplanned serious adverse event (example: sudden cardiac arrest) presents more than 12 cases (10%).

OUTCOME MEASUREMENT

The primary outcome measure is the new onset of hypotension within 24 hours after randomization.

The secondary outcome measures include the following:

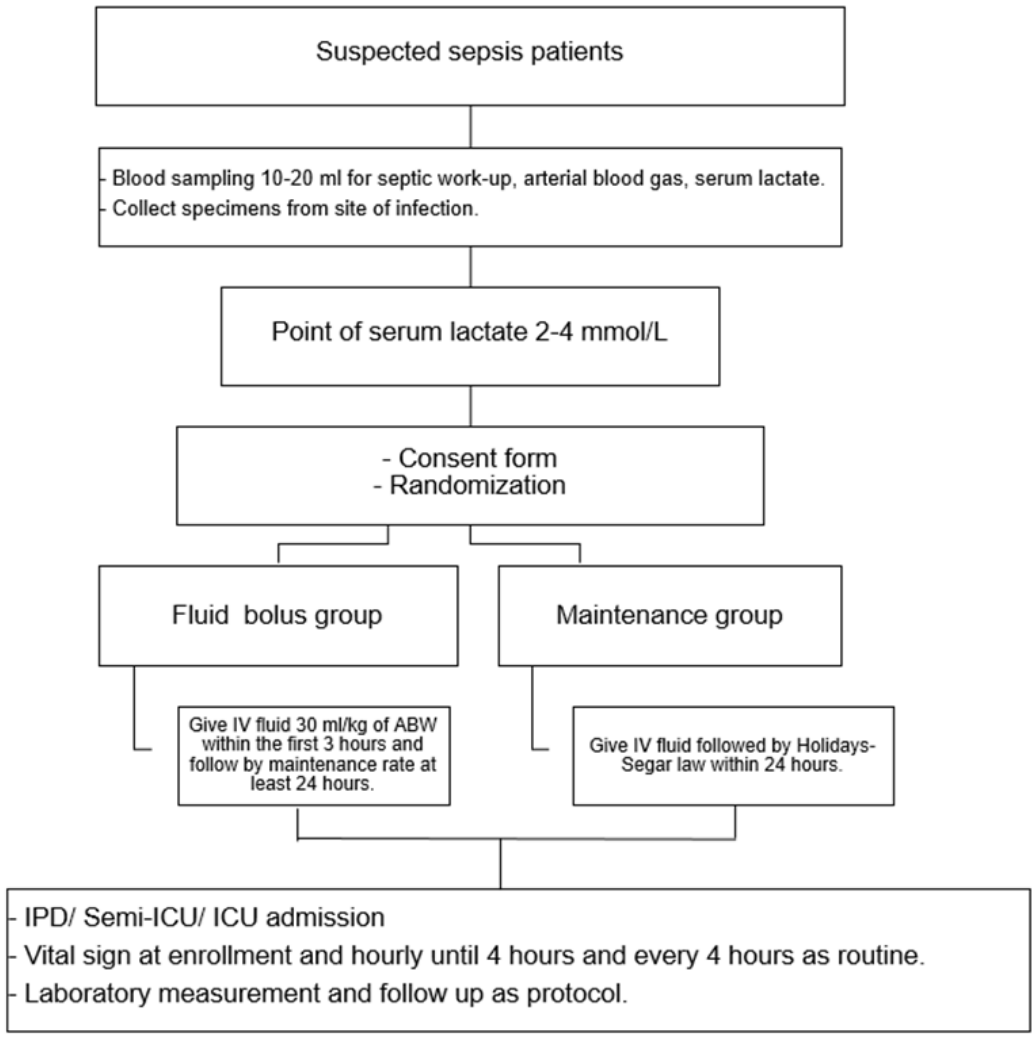

Figure 1. Flow of study.

Abbreviations: IPD: in-patient department; ICU: intensive care unit.

- Lactate clearance (6 hours after randomization)
- ΔSOFA at 72 hours after randomization
- Vasopressor use
- Vasopressor free day on day 28 after randomization
- A new organ failure in the first week
- Organ failure free day on day 28 after randomization
- Renal replacement therapy
- Renal replacement therapy free day on day 28 after randomization
- Mortality at day 28 after randomization

A safety outcome measure is the incidence of volume overload after fluid replacement and requiring respiratory support (e.g., non-invasive or invasive mechanical ventilation).

All primary and secondary outcomes were described in supplementary materials (Table 3).

DATA ANALYSIS PLAN

Sample size

To ascertain a statistically significant absolute difference of 20 percentage points in the incidence of new-onset hypotension between the treatment groups, we aim to enroll a total of 224 participants (112 per group). This sample size allows us to detect the specified between-group difference with a Type I error rate of 5% and a Type II error rate of 20%, corresponding to a statistical power of 80%. These calculations assume an anticipated incidence of new-onset hypotension of 70% in the control group.

The sample size was determined using the method described by Farrington and Manning (1990). [12] This methodology is specifically designed to test the differences between two binomial event rates. Furthermore, the calculated sample size incorporates an additional 20% to account for potential dropouts, ensuring that the study maintains adequate power to detect the specified effect size even in the case of participant attrition.

Data analysis

The analyses will be done in the intention-to-treat (ITT) population. We will perform the primary analyses adjusted for the important baseline risk factors (Charlson comorbidity index and systolic blood pressure). The continuous variables will be described by means and standard

deviation (S.D.) or median and interquartile range (IQR) as appropriate, depending on the normality of the data. The categorical variables will be described by number and percentage. The normality of the continuous variables is tested by the Shapiro-Wilk test.

For primary and secondary outcomes, adjusted absolute risk differences were reported with the use of point estimates and 95% confidence interval. The analysis will be made with the R program.

Interim analysis

There is one interim analysis assessing efficacy. After the first 112 patients reached their 28-day follow up; interim analysis was conducted in a timely manner. We use a symmetric two-sided group sequential design with a type I error rate of 5%. Bounds were derived using a Lan-DeMets O'Brien-Fleming approximation.

DATA MANAGEMENT AND DATA MONITORING

Data collection

Electronic case report forms will be completed by investigators and entered into a purpose-designed, secure Research Electronic Data Capture (REDCap) database hosted by Khon Kaen University. [13,14]

The data collection protocol includes the following baseline characteristics of each patient: age, sex, weight, height, BMI, Charlson comorbidity index, site of infection, lactate level, physiological variables, laboratory values, the Sequential Organ Failure Assessment (SOFA) score, the Acute Physiology and Chronic Health Evaluation (APACHE) III score, intubation with positive pressure ventilation, and time from ED registration to enrollment.

Clinical data collection will include type of intravenous fluid, timing and type of antibiotics, and vital signs enrollment and hourly until 4 hours and every 4 hours as routine.

Laboratory measurements will include arterial or venous blood gas, including point-of-care lactate, hemoglobin, and serum lactate at enrollment (T0), 6 hours (T6), and 12–24 hours (T24).

The schedule of enrollment, intervention, and assessment is shown in Table 1.

Ethical consideration

This study obtained approval from the Center for Ethics in Human Research at Khon Kaen University (Ethics Committee number: HE661012) and was registered at the Thai Clinical Trials Registry (TCTR20230502003).

Prospective, informed consent will be obtained wherever possible. Due to the time-critical nature of the condition, approval is in place for verbal consent to randomize and initiate care, followed by a formal written consent process. Some participants may lack capacity, so consent will be sought from their next of kin. If a next of kin is not immediately available, provisions are in place for enrollment under an initial waiver of consent (or procedural authorization), followed by delayed consent to continue in the trial.

Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient administered an investigational intervention, which does not necessarily have to have a causal relationship with this intervention.

The following will be considered AEs, regardless of study treatment allocation and subsequent intervention required: increased work of breathing or desaturation requiring respiratory support, signs of fluid overload, a

Table 1. Standard protocol items.

	Study period										
	Enrollment	Allocation	Post-allocation (hourly time points)								Follow up
Timepoint	**-T1**	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T24**	**T72**	**Day28**
Enrollment:											
Eligibility screen	x										
Informed consent	x										
Randomization		x									
Intervention:											
Fluid bolus			x	x	x						
Convention fluid			x	x	x						
Research blood sampling		x			x			x	x		
Assessments:											
Baseline Data		x									
New-onset of hypotension					x			x	x	x	
Cumulative fluid volume								x	x	x	
Organ failure free days											x
Vasopressor free days											x

decrease in urine output (less than < 0.5 ml/kg/hour) for 6 hours after randomization, and any other event that is considered to be of concern by the site investigator.

A serious adverse event (SAE) is defined as any untoward medical occurrence, including events that result in death, require inpatient hospitalization or the prolongation of hospitalization, are life-threatening, or result in a persistent or significant disability or incapacity. In this study, all SAEs will be reported regardless of suspected causality.

DISCUSSION

The optimal strategy for intravenous fluid therapy in patients with suspected sepsis and hyperlactatemia remains uncertain. Current evidence regarding fluid restriction and bolus volumes in this patient population is of low quality, with no definitive guidance for cases not presenting with sepsis-induced hypotension or septic shock.

The FISH study endeavors to address this knowledge gap by being the pioneering randomized trial investigating the role of fluid resuscitation in sepsis patients exhibiting mild hyperlactatemia (lactate levels of 2-4 mmol/L). Precious studies, such as the CLASSIC trial, have explored fluid restriction strategies in septic shock patients but failed to demonstrate a reduction in 90-day mortality. [15] Similarly, the CLOVERS trial, which focused on patients with sepsis-induced hypotension unresponsive to an initial 1-3 liters of intravenous fluid, found no mortality benefit from restrictive versus liberal fluid strategies. [16] Unlike these studies that centered on fluid restriction or late-phase sepsis management, our research uniquely examines fluid management strategies at the early phase of sepsis, prior to the onset of sepsis-induced hypotension or shock.

Although several studies have examined the role of fluid restriction, our study will examine the role of fluid management strategy in the early phase of sepsis before sepsis-induced hypotension or septic shock.

While the choice of intravenous crystalloid fluid for resuscitation may influence outcomes, our primary objective is to evaluate the benefits of fluid bolus administration. Nevertheless, we advocate for the use of balanced crystalloids over normal saline to potentially improve patient outcomes.

Strengths

This randomized controlled trial distinguishes itself by comparing fluid bolus therapy to standard care in patients with suspected sepsis and hyperlactatemia. It aims to validate the feasibility of implementing such a protocol within the emergency department setting, thereby offering a novel approach to early sepsis management.

Limitations

This trial is a single center randomized controlled trial involving unmasking for investigators, clinicians, and patients. Blinding different fluid strategies is not feasible, as it would increase the risk of bias. The study's applicability is contingent upon the availability of point-of-care lactate assessment facilities, restricting its generalizability to similarly equipped sites.

Trial status

At the time of submission, the FISH trial has enrolled 66 of its planned 224 participants.

CONFIDENTIALITY

None

ACKNOWLEDGEMENT

None

AUTHORS' CONTRIBUTIONS

(I) Conceptualization: All authors; (II) Formal analysis: Teeraporn Chayawuttipong, Anupol Panitchote; (III) Methodology: Teeraporn Chayawuttipong, Pariwat Phungoen, Anupol Panitchote; (IV) Project administration: Teeraporn Chayawuttipong, Anupol Panitchote; (V) Writing – original draft: Teeraporn Chayawuttipong; (VI) Writing – review & editing: Anupol Panitchote.

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SUPPLEMENTARY MATERIALS

Table 1. Baseline characteristics of the patients.

Baseline characteristic	Fluid bolus group (N=)	Conventional fluid group (N=)
Sex (n=%)		
• Male		
Age, Mean (SD), years		
Charlson co-morbidities score (n=%)		
Physiological variables, mean (SD)		
• Temperature, °C		
• Heart rate, beats/min		
• Systolic blood pressure, mmHg		
• Mean arterial pressure, mmHg		
• Respiratory rate, breaths/min		
• Glasgow Coma Scale score < 15		
Laboratory values, mean (SD)		
• Point-of-care serum lactate at ED, mmol/L		
• Serum lactate at ED, mmol/L		
• Serum creatinine, mg/dL		
• Hemoglobin, g/dL		
• Serum albumin, g/dL		
Source of sepsis (n=%)		
• Respiratory system		
• KUB system		
• Gastrointestinal system		
• Hepatobiliary system		
• Skin and soft tissue		
• Bone and joint infection		
Source of sepsis (n=%)		
• CNS infection		
• Primary bacteremia		
• Unknown site of infection		
• Other		
SOFA score, mean (SD)		
APACHE score, mean (SD)		
Intubation with positive pressure ventilation (n=%)		
• Yes		
Time from ED registration to enrollment, mean (SD), min		

Table 2. Elements of sepsis resuscitation.

Outcomes	Fluid bolus group (N=)	Conventional fluid group (N=)	p-value
Type of intravenous fluid: Balanced salt solution (n=%)			
• Yes			
Total Intravenous fluid administration, mean (SD), L			
• 6 hours			
• 24 hours			
• 72 hours Physiological variables, mean (SD)			
• Mean arterial pressure 3 hours after enrollment, mm Hg			
• Mean arterial pressure 6 hours after enrollment, mm Hg			
Laboratory values, mean (SD)			
• Change in serum lactate concentration from baseline to 6 hours after enrollment, mmol/L			
• Serum creatinine after 24 hours, mean (SD), mg/dL			
Time to antibiotics, mean (SD), hours			
Serious adverse events, (n=%)			
• Yes			

Table 3. Outcomes.

Outcomes	Fluid bolus group (N=)	Conventional fluid group (N=)	p-value
New-onset hypotension, (n=%)			
• Yes			
ΔSOFA at 72 hour after randomization Vasopressor used, mean (SD), day			
• During 6 hours after admitted			
• During Hospitalization			
Vasopressor free day, mean (SD), day			
New organ failure in the 1st week, (n=%)			
• Respiratory system			
• Cardiovascular system			
• Renal system			
• None			
Organ failure free day in 28 days, (n=%)			
Renal replacement therapy, (n=%)			
RRT free day in 28 days, (n=%)			
Length of stay in hospital, mean (SD), day			
Mortality at day 28th, (n=%)			
• Yes			