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ExtraCorporeal Membrane Oxygenation in the therapy for REfractory Septic shock with Cardiac function Under Estimated (ECMO-RESCUE): a prospective, multicenter, non-randomised cohort study

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ABSTRACT

Introduction: Severe septic cardiomyopathy (SCM) is one of the main causes of refractory septic shock (RSS), with a high mortality. The application of VA-ECMO to support the impairment cardiac function in patients with septic shock remains controversial. Moreover, no prospective studies have been taken to address whether VA-ECMO treatment could improve the outcome of patients with sepsis-induced cardiogenic shock. The objective of this study is to assessed whether VA-ECMO treatment can improve the 30-day survival rate of patients with sepsis-induced refractory cardiogenic shock.

Methods and analysis: ECMO-RESCUE is a prospective, multicenter, non-randomized, cohort study on the application of ECMO in SCM. At least 64 patients with SCM and RSS will be enrolled in an estimated ratio of 1:1.5. Participants taking VA-ECMO during the period of study are referred to as cohort 1, and patients receiving only conventional therapy without ECMO belong to cohort 2. The primary outcome is survival in a 30-day follow-up period. Other end points include survival to ICU discharge, hospital survival, 6-month survival, quality of life for long-term survival (EQ-5D score), successful rate of ECMO weaning, long-term survivors' cardiac function, the number of days alive without CRRT, mechanical ventilation and vasopressor, ICU and hospital length of stay, the rate of complications potentially related to ECMO treatment.

Ethics and dissemination: The trial has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (2020-hs-51). Participants will be screened and enrolled from ICU patients with septic shock by clinicians, with no public advertisement for recruitment. Results will be disseminated in research journals and through conference presentations.

Trial registration: NCT05184296

ARTICLE SUMMARY

Strengths and limitations of this study

- The use of ECMO in adult patients with refractory septic shock (RSS) is still controversial and prospective trials of using ECMO in the adult patients with sepsis-induced cardiogenic shock have not yet been reported.
- ECMO-RESCUE is a prospective, multicenter, non-randomized, cohort study on the application of ECMO in sepsis-induced refractory cardiogenic shock, positive outcome will help to promote the application of VA-ECMO in patients with septic shock due to cardiac depression
- This prospective cohort study was designed with reference to indications of ECMO initiation in refractory cardiogenic shock due to no clear indications for determining which patients with sepsis-induced cardiogenic shock should be treated with ECMO.
- A limitation of the study is its non-randomized design, which would yield bias.

INTRODUCTION

Sepsis, a life-threatening syndrome with organ dysfunction caused by infection, is a leading cause of death in ICU[1]. The global burden of disease arising from sepsis was estimated at 30 million episodes and 6 million deaths per year in 2017 [2-3]. The mortality is as high as 50% when septic shock is present[4]. Septic cardiomyopathy (SCM) is one of the main causes of septic shock, affecting 20-65% of patients with sepsis[5]. Severe SCM leads to refractory septic shock (RSS), with a mortality up to 70%[6-7]. However, there are no evidence-based recommendations for the management of SCM.

In addition to aggressive treatment with antibiotics for infection control, adequate fluid resuscitation and vasoactive drugs administration according to the SCCM guidelines, a variety of drugs to improve cardiac function have also been attempted for the treatment of SCM. However, the results were not satisfactory. A single center crossover study done in 20 patients with septic shock shown that dobutamine failed to improve microcirculatory perfusion and metabolic despite an increasing cardiac index, heart rate and LVEF compared to placebo[8]. Another multi-center RCT found a combination of dobutamine and norepinephrine showed no effect on 28-day-mortality compared to epinephrine[9]. It may be related to the increase of myocardial oxygen consumption by dobutamine. In recent years, some positive inotropic drugs, such as levosimendan, have been tried to applied in the treatment of SCM[10-11]. However, the therapeutic effect is still controversial. A recent RCT showed that levosimendan did not reduce mortality in patients with septic shock[12]. Therefore, there is few recognized effective treatments for sepsis-induced cardiogenic shock at present.

SCM is consider as a sepsis-associated acute syndrome of cardiac dysfunction unrelated to ischemia[13]. Most studies have suggested that recovery from SCM is prompt. A retrospective study showed that although left ventricular dysfunction may persist in approximately one-third of patients with severe sepsis and septic shock in long-term follow-up, the survival rates did not differ[14]. Therefore, trying new, innovative therapeutic approaches in SCM are valuable and urgently needed.

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a circulatory

support technology, which can increase cardiac output as well as improving hypoxemia by increasing oxygen delivery. Therefore, the application of VA-ECMO in the treatment of RSS has theoretical feasibility. However, sepsis has been considered as a contraindication for ECMO in the past decades due to the presence of foreign membranes in the circuitry and the need for anticoagulation, which can easily lead to perpetuated bacteremia, enhance the risk of bleeding, and a persistence of inflammation[15-16]. Of course, the immaturity of ECMO technology and backward equipment may also be one of the reasons. Based on the improvement of the technology and equipment of ECMO, its application in neonatal and pediatric patients with sepsis has achieved great success. It is reported that in neonatal and children with septic shock, the survival rate of ECMO treatment was nearly 80% and 50%, respectively[17-18]. ECMO treatment of septic shock in neonatal and children has been in guidelines and consensus since 2008[19-20]. More and more clinical investigators suggested that sepsis should not be contraindicated for ECMO use. However, there is no RCT to provide evidence for this so far. The outcomes varied from different retrospective studies. Park et al reported a hospital survival rate of 21.9% in 32 patients with RSS received ECMO. Similarly, Huang et al. described 52 patients in RSS and requiring VA-ECMO for circulatory support in Taiwan also with much lower (15%) survival to hospital discharge. On the contrary, single-centre retrospective study found that VA-ECMO rescued more than 70% of the patients who developed refractory cardiovascular dysfunction during severe bacterial septic shock. Another multicentre cohort study found that survival at 90 days for patients with severe sepsis-induced cardiomyopathy who received VA-ECMO was significantly higher than for controls (60% *vs* 25%)[21].

In summary, the use of ECMO in adult patients with RSS is still controversial. To date, prospective trials of using ECMO in the adult patients with sepsis-induced cardiogenic shock have not yet been reported nor have clear indications been proposed to help determine which patients with sepsis-induced cardiogenic shock should be treated with ECMO. Therefore, prospective clinical studies would face many problems. For example, before ECMO is initiated how long does RSS last and

what dose of vasoactive drug is needed? This prospective cohort study was designed with reference to indications of ECMO initiation in refractory cardiogenic shock. In this study, we aimed to assessed whether VA-ECMO treatment can improve the 30-day survival rate of patients with sepsis-induced refractory cardiogenic shock.

METHODS AND ANALYSIS

Study design, setting and patient population

The ECMO-RESCUE study is a prospective, multicenter, non-randomized, cohort study. All patients admitted to the ICUs of participating centers will be considered as potential candidates for the study. Once the patient is diagnosed of septic shock, he/she should be screened for eligibility by the physicians. When the patient fulfills the criterion of recruitment, the researcher provides details on the purpose, specific content and instructions on how to complete the trial. After we obtain written informed consent (online supplementary file 1) from the patient or a responsible surrogate, patients are enrolled in the study.

During the period of study, the participants can decide whether to accept ECMO based on their personal conditions. If a patient is willing to accept ECMO treatment, we initiate VA-ECMO within 6 hours. Participants taking VA-ECMO during the period of study are referred to as cohort 1, and patients receiving only conventional therapy without ECMO belong to cohort 2. ECMO is established and managed by a professional team. The teams of each center have more than 5-year experience.

The study will be conducted in 6 ICUS in Guangdong, China. The study is expected to last for 3 years. Recruitment of participants has been started in May 2022.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Inclusion criteria

1. Age between 18 and 75 years.

2. Patients admitted into ICU and diagnosed as septic shock (sepsis-3.0)[1], after adequate fluid resuscitation, high-dose vasoactive drug application [vasoactive inotropic score (VIS) > 120] and conventional therapy together with at least one of the following criteria: (1) sustained hypotension [mean arterial pressure (MAP) < 65 mmHg]; (2) persistent lactacemia (two consecutive values > 5 mmol/L with at least 30 min interval between samples), with non-decreasing trend on steady doses of inotropes and/or vasopressors; (3) persistent low mixed venous blood oxygen saturation (SvO_2) (two consecutive values < 55% with at least 30 min interval between samples), with non-increasing trend on steady doses of inotropes and/or vasopressors. The above condition lasts more than 5 hours.
3. Rapidly deteriorating sepsis-induced myocardial impairment is defined by at least one of the following criteria: (1) rapidly deteriorating ventricular function (LVEF < 35%); (2) cardiac index (CI) < 2.0 L/min/m^2 (> 3 hr); (3) emerging refractory arrhythmia.
4. Informed consent provided by the patient or person with decisional responsibility.

Exclusion criteria

1. Cardiac dysfunction caused by other causes is excluded, such as acute myocardial infarction, chronic heart failure, congenital cardiac disease, myocardial effusion, moderate to severe aortic regurgitation, severe aortic coarctation and so on.
2. High suspicion of pulmonary embolism, tension pneumothorax or cardiac tamponade as a cause of shock.
3. Prolonged cardiac arrest (> 30 min) before ECMO, or CPR survivors remaining comatose.
4. Irreversible condition or meet the inclusion criteria for more than 12 hr.
5. Presence of active bleeding or anticoagulant contraindications.
6. Peripheral artery disease disabling insertion of outflow cannula to femoral artery.
7. Irreversible neurological pathology
8. Severe underlying condition with lift expectancy less than 1 year.
9. Special population, such as pregnancy, acquired immune deficiency syndrome

(AIDS).

10. Patient included in another interventional clinical trial.

Study definitions

Septic shock

Septic shock, a subset of sepsis, can be identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate greater than 2 mmol/L despite of resuscitation.

Vasoactive inotropic score

VIS was calculated as [(epinephrine + norepinephrine) μg/kg/min] × 100 + [(dobutamine + dopamine) μg/kg/min] + [milrinone μg/kg/min] × 15 + [vasopressin IU/kg/min] × 10,000.

Successful weaning off ECMO

Successful weaning was defined as maintaining stable condition within 24 hours of ECMO weaning.

Study intervention

The study flow chart is detailed in Figure 1.

All patients received fluid resuscitation, antibiotic, vasoactive drugs and control of the focus of infection according to the international guidelines of Surviving Sepsis Campaign 2016 and 2018[122]. The gold of MAP is ≥ 65 mmHg. For multiple organ dysfunction, life support technologies such as mechanical ventilation and continuous renal replacement therapy (CRRT) are provided as needed. The patient's primary physicians will determine the management of other comorbidities.

ECMO implantation and management

All patients in cohort 1 will initiate ECMO as fast as possible. A maximum of 6 hours is allowed between enrollment and the actual initiation of ECMO. ECMO catheterization and management will be operated by an experienced ECMO team and carried out at the bedside. The initiation and weaning or cessation time, the data of ECMO will be recorded by nurses.

- Therapy mode

VA or VAV mode will be chosen according to the patient's condition. Intra-aortic balloon pump (IABP) will be performed simultaneously when necessary to relieve the afterload of left ventricle.

- Canulation

All patients will undergo peripheral cannulation. The arterial catheter is placed into the femoral artery, and the venous catheter is placed into the femoral vein. Ultrasound examination will be performed bedside to select vessels with better conditions and suitable diameter canula before catheterization. After the arterial cannulation, the distal branch is inserted to perform lower limb perfusion.

- The blood flow and the goal

The initial flow rate is 80~100 ml/kg of ideal body weight/min. The ECMO blood flow is adjusted to: (1) maintain a MAP > 65 mmHg; (2) reach a preoxygenator oxygen saturation > 65%; (3) restore blood lactate to normal level; (4) revert the MODS.

- Management[1523]

(1) Inotropes are discontinued or reduced to minimal dosed within a few hours of achieving goal-directed flows (norepinephrine or epinephrine < 0.05 μg/kg/min, and dopamine or dobutamine < 5 μg/kg/min are suggested).

(2) During the period of ECMO, maintain a hemoglobin of > 100 g/L, a platelet count of ≥ 50×10^9/L, antithrombin III (AT3) of > 80%, and fibrinogen > 2 g/L.

(3) Echocardiography is performed at least daily to monitor cardiac function.

- Anticoagulation

Unfractionated heparin (UFH) is recommended for anticoagulation. A bolus dose of UFH is administered at cannulation followed by continuous infusion. Activated partial thrombin time (APTT) is targeted between 1.5 and 2 times of normal, or active clotting time (ACT) is targeted between 180 and 220 s. if the patient is at high risk of bleeding, the target ACT value is lowered to 160 s. UFH may be stopped for severe bleeding or coagulation disorders.

- Wean off ECMO

ECMO weaning should be considered when patients exhibit stable hemodynamics and sufficient cardiac recovery[24].

Indications for ECMO weaning: (1) adequate upper limb PaO_2 and saturation with FiO_2 < 50%, PIP < 30 cmH_2O, PEEP <8 cmH_2O from ventilator when ECMO gas flow at 21%; (2) ECMO flow is reduced to 10% ~ 25% of normal blood flow (150ml/kg/min, ideal body weight) or 1.5 L/min; (3) patients exhibit stable hemodynamic (MAP > 65 mmHg, pulse pressure > 20 mmHg), SvO_2 >70%, LVEF > 40%, blood lactate < 2.0 mmol/L and without malignant arrhythmia on no/low doses vasoactive, inotropic support (norepinephrine or epinephrine < 0.02 μ g/kg/min, and dopamine or dobutamine < 5 μ g/kg/min) for more than 2 hours.

The ECMO weaning test is gradually performed according to the patient's systemic hemodynamics and tissue perfusion improvement[24-25]. During weaning, ECMO flow is decreased progressively by 500 ml every 5-10 minutes. Patients are evaluated after 3-5 minutes of no support (circuit clamped) or alternatively at minimum of 1 L/min of support. Successful weaning is defined as maintaining stable condition within 48 hours of ECMO weaning.

- Cessation of ECMO

ECMO will be discontinued with one of the following conditions: (1) irreversible brain damage; (2) other vital organ dysfunction is difficult to reverse; (3) refractory bleeding; (4) there is no signs of cardiac function recovery and no better therapeutic regimen after 7 to 10 days of ECMO treatment; (5) an uncontrollable infection.

Primary outcome

The primary outcome is 30-day survival measured from the date of enrolled (D0) until death or day 30. For patients who were discharged alive from ICU, information on the primary endpoint will be acquired by a telephone call.

Secondary outcomes

The secondary outcomes include: (1) survival to ICU discharge, hospital survival, 6-

month survival and quality of life for long-term survival (EQ-5D score); (2) successful rate of ECMO weaning; (3) long-term survivors' cardiac function was evaluated according to Doppler echocardiography; (4) the number of days alive without CRRT, mechanical ventilation and vasopressor (the numbers of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, between D0 and up to D30); (5) ICU and hospital length of stay (LOS).

Other endpoints include: establish a decision tree model to decide whether sepsis-induced cardiogenic shock patients need ECMO treatment.

Safety assessments

In addition to the focus on prognosis of patients with septic cardiomyopathy treated with VA-ECMO, the safety of the VA-ECMO treatment is also a major focus. The complications potentially related to ECMO treatment include: (1) major bleeding associated with anticoagulants (defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells)[26]; (2) thrombosis (ischemic stroke, pulmonary embolism, deep venous thrombosis or catheter-associated thrombosis during study confirmed by ultrasound or CT scan); (3) leg ischemia; (4) cannulation-related injuries (such as arterial laceration, arterial aneurysm and peripheral nerve defect).

Sample size

The primary outcome in this study is to compare the survival rate at day 30 between VA-ECMO treatment and conventional treatment on patients with sepsis-induced refractory cardiogenic shock. Our primary hypothesis is that VA-ECMO treatment might beneficial to patients with sepsis-induced refractory cardiogenic shock. According to a retrospective study from Bréchot et al.[21], the survival rate of patients with severe sepsis-induced cardiomyopathy was 60% in VA-ECMO group and 25%

in control group, elevation in survival of 35% in VA-ECMO group can be expected. Considering the high cost and uncertain therapeutic effect of ECMO treatment, fewer participants may choose ECMO treatment than conventional treatment, with an estimated ratio of 1:1.5. The sample size for differences between two independent proportions was calculated by the PASS 14.0 software to ensure 80% power using a two-sided test with a significance level of $\alpha = 0.05$. We need 23 participants in VA-ECMO treatment cohort and 35 participants in conventional treatment cohort. Considering a projected dropout rate of 10%, the sample size of VA-ECMO treatment cohort and conventional treatment cohort should be 25 and 39, respectively. The total sample size should be 64.

Data collection and follow-up

Each investigator from the 6 participating ICUs was trained to the protocol and data collection in the Case Record Form (CRF) before trial initiation. The data is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China).

Flowchart of patient follow-up is shown in table 2. Demographic data and medical history will be collected. Details data including reasons for ICU admission, cause of septic shock, focus of infection, acute physiology and chronic health evaluation II (APACHEII) score, dates of hospital and ICU admission will be recorded. Details of mechanical ventilation, vasopressor, CRRT and PiCCO will be documented daily. Sequential organ failure assessment score (SOFA) will be calculated at baseline, D1, D3 and D7. Cardiac function will be assessed by echocardiography and recorded at baseline, D1, D3, D5, D7, D10, D14, D30. Blood will be collected at baseline, D1, D3, D5, D7. The following laboratory results will be recorded: white blood cell count and differentials in peripheral circulation, serum electrolyte levels, liver and myocardial enzyme concentrations, arterial blood gas analysis, C-reactive protein (CRP), procalcitonin and lactate. EQ-5D assessment will be acquired through phone call at 6 months.

During ECMO intervention, details of initiation, mode, setting parameters, weaning or

cessation, complications will be noted.

All enrolled participants will be followed to determine adverse events, cardiac function recovery and mortality until death or at ICU/hospital discharge, 30 days and 6 months.

Table 2 Flow chart of patient follow-up

	screening	Inclusion D0	Study period	Death/30d	Follow-up 6 months
Baseline information					
Demographic data and history	√	√			
Inclusion and exclusion criteria	√				
Written informed consent	√				
Diagnosis and focus of infection	√	√	√		
Vital signs		√			
APACHEII/SOFA		√	√D1, 3, 7		
Efficacy observation					
Cardiac function assessment (CI, LVEF)	√	√	√D1, 3, 5, 7, 10, 14	√	√
ECMO intervention			√		
Treatment with vesopressor	√	√	√		
Mechanical ventilation		√	√		
CRRT implication		√	√		
Laboratory tests	√	√	√D1, 3, 5, 7		
Safety observation					
Complications of ECMO			√		
Adverse event			√		
Additional observation					
ICU and hospital LOS				√	
Alive or dead status				√	√
Life quality (EQ-5D score)					√

APACHEII, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CI, cardiac index; LVEF, left ventricular ejection fraction; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; LOS, length of stay.

Statistical analysis

Data will be double checked by the clinical research team, and the data base is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China).

For each cohort, quantitative variables with normal distribution will be described as mean and standard deviation. Quantitative variables with skewed distribution will be described as median (M) and inter-quartile range (IQR, 25th percentile to 75th percentile). Qualitative variables will be described as frequency and percentage.

The effect of VA-ECMO treatment versus conventional treatment on 30 days survival will be performed using chi-squared (χ^2) test or Fisher's exact test, with secondary analysis by Kaplan-Meier survival analyses, comparison using a log rank test. A propensity score-weighted analysis was done for treatment-effect estimation. Covariate balance between the two groups was assessed after weighting, and we considered an absolute standardized difference of less than 0.1 as evidence of balance. The effect of ECMO on survival at 30 days will be estimated within the weighted pseudopopulation. Adjusted Kaplan-Meier estimator and log-rank test (considering the weighting scheme) will be used. Decision tree analysis will be used to establish a decision tree model to decide whether sepsis-induced cardiogenic shock patients need ECMO treatment.

Safety will be analyzed by the frequency of complications in both cohorts and comparing rates using χ^2 or Fisher's exact test, with an alpha risk set at 0.05.

Statistical analyses of the pre-specified secondary endpoints will be performed with descriptive and inductive statistical methods. Categorical variables will be compared using the χ^2 or Fisher's exact test, as appropriate. Continuous variables will be compared using Student's t test or the Mann-Whitney test, as appropriate.

Therapeutic efficiency will be analyzed using the data of the full analysis set (FAS) and per protocol set (PPS); safety evaluation will be based on the data of the safety analysis set (SS) for statistical analysis.

All analyses were performed with commercially available statistical software SPSS 22.0 and R software version 4.1.0 or later.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (version 2.0, registration number: 2020-hs-51; date of approval: 17 November 2020). Participants will be screened and enrolled from ICU patients with sepsis-induced cardiogenic shock by clinicians, with no public advertisement for recruitment. When the patient fulfills the criterion of recruitment, written informed consent (online supplementary file 1) should be obtained from the patient or a responsible surrogate before enrolled. After enrolled, the participants can decide whether to accept ECMO based on their personal conditions. All information from the participants will be kept private and will not be provided to any company or institution. Results will be disseminated in research journals and through conference presentations.

DISCUSSION

VA-ECMO is an effective and supportive means for patients with acute cardiogenic shock. However, due to the complex condition of sepsis, septic shock was considered as a contraindication for the application of VA-ECMO. Based on the great success of VA-ECMO in the treatment of pediatric with RSS, it is supposed that VA-ECMO may also benefit to improve survival of adult patients with RSS.

Unfortunately, the hypothesis is supported by only a few retrospective studies. More prospective studies are needed to clarify this issue. According to the previous studies, patient selection seems to be a key issue affecting prognosis. In Park et al's study, a total of 32 patients received ECMO support for RSS, 14 of whom had undergone cardiopulmonary resuscitation (CPR). At last, only 7 patients (21.9%) survived to hospital discharge. CPR was considered as an independent predictor of in-hospital mortality after ECMO in patients with RSS. Park et al. suggested that implantation of ECMO during RSS could be considered in patients with severe myocardial injury but should be avoided in patients who have received CPR[27]. In Huang et al.'s study,

hospital survival rate was much lower (15%). They found that the non-survivors were significantly older than the survivors, and all 20 patients (38%) ages 60 years or older died. It suggested that age might be a contraindication[28]. Therefore, our study excluded patients older than 75 years, prolonged cardiac rest (>30 min) and CPR survivors remaining comatose.

Besides this, the difference in the therapeutic effect of ECMO on RSS may be attributed to the complex pathophysiological mechanisms of RSS. Circulatory failure is a main characteristic of RSS. Cardiac depression, vasoplegia and capillary leakage all lead to circulatory failure in septic shock [29]. Falk et al. reported a 90% hospital survival rate in septic shock patients with left ventricular failure and 64.7% in patients with distributive shock[29]. It suggested that the patients with sepsis-induced refractory cardiogenic shock may be received high survival benefit from VA-ECMO, and superior to distributed shock. Two other studies also demonstrated that a significant survival benefit from VA-ECMO treatment in patients with failing heart. Moreover, all survivors restored their cardiac function and had good long-term quality of life[2130]. It also implied that perhaps RSS is not an absolute contraindication to ECMO, but rather that the ideal candidates for this treatment should be identified.

Therefore, we hypothesize that VA-ECMO treatment may attenuate mortality in septic shock patients with cardiac function impairment through increasing additional CO and improving tissue hypoxia. If this study confirms our hypothesis, it will help to promote the application of VA-ECMO in patients with septic shock due to cardiac depression. Negative result will also encourage us to pay a deeper attention to identified the ideal candidates for this treatment: should the inclusion criteria be stricter? Is the timing for ECMO initiation too late? Are there subtypes of SCM that differ in their responsiveness to ECMO treatment?

Supplementary file

Online supplement file 1: consent form.

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Contributors

De-liang Wen and Wei-yan Chen designed the trial and draft the manuscript. Zhen-hui Zhang provided critical revision of the manuscript. De-liang Wen and Wei-yan Chen obtained funding for the trial. All authors discussed and helped to improve the protocol, and read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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References

1 M Singer, CS Deutschman, CW Seymour, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):801.

2 K Reinhart, R Daniels, N Kissoon, et al. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med* 2017;377(5):414-17.

3 KE Rudd, SC Johnson, KM Agesa, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet (British edition)* 2020;395(10219):200-11.

4 P Asfar, JL Teboul, P Radermacher. High versus low blood-pressure target in septic shock. *N Engl J Med* 2014;371(3):283-84.

5 SJ Beesley, G Weber, T Sarge, et al. Septic Cardiomyopathy. *Crit Care Med* 2018;46(4):625-34.

6 I Narváez, A Canabal, C Martín, et al. Incidence and evolution of sepsis-induced cardiomyopathy in a cohort of patients with sepsis and septic shock. *Med Intensiva* 2018;42(5):283-91.

7 R Sato, A Kuriyama, T Takada, M Nasu, SK Luthe. Prevalence and risk factors of sepsis-induced cardiomyopathy: A retrospective cohort study. *Medicine* 2016;95(39):e5031.

8 G Hernandez, A Bruhn, C Luengo, et al. Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study. *Intens Care Med* 2013;39(8):1435-43.

9 D Annane, P Vignon, A Renault, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. In, 2007:676-84.

10 J Meng, M Hu, Z Lai, et al. Levosimendan Versus Dobutamine in Myocardial Injury Patients with Septic Shock: A Randomized Controlled Trial. In, 2016:1486-96.

11 BB Pinto, S Rehberg, C Ertmer, M Westphal. Role of levosimendan in sepsis and septic shock. *Current opinion in anaesthesiology* 2008;21(2):168-77.

12 AC Gordon, GD Perkins, M Singer, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. *The New England journal of medicine* 2016;375(17):1638-48.

13 L Martin, M Derwall, ZS Al, et al. The Septic Heart: Current Understanding of Molecular Mechanisms and Clinical Implications. *Chest* 2019;155(2):427-37.

14 S Vallabhajosyula, JC Jentzer, JB Geske, et al. New-Onset Heart Failure and Mortality in Hospital Survivors of Sepsis-Related Left Ventricular Dysfunction. *Shock* 2018;49(2):144-49.

15 J Riera, E Argudo, JC Ruiz-Rodríguez, R Ferrer. Extracorporeal Membrane Oxygenation for Adults With Refractory Septic Shock. *Asaio J* 2019;65(8):760-68.

16 BV Kirkpatrick, TM Krummel, DG Mueller, et al. Use of extracorporeal membrane oxygenation for respiratory failure in term infants. *Pediatrics* 1983;72(6):872-76.

17 M Tembo, C Harvey, M Duthie, et al. Extracorporeal membrane oxygenation for refractory septic shock in children: One institution's experience. In, 2009:534-35, 535.

18 S McCune, BL Short, MK Miller, A Lotze, KD Anderson. Extracorporeal membrane oxygenation therapy in neonates with septic shock. In, 1990:479-82.

19 AL Davis, JA Carcillo, RK Aneja, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med* 2017;45(6):1061-93.

20 J Brierley, JA Carcillo, K Choong, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009;37(2):666-88.

21 N Bréchot, D Hajage, A Kimmoun, et al. Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study. *The Lancet (British edition)* 2020;396(10250):545-52.

22 A Rhodes, LE Evans, W Alhazzani, et al. Surviving Sepsis Campaign. *Crit Care Med* 2017;45(3):486-552.

23 N Aissaoui, CE Luyt, P Leprince, et al. Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. *Intensive Care Med* 2011;37(11):1738-45.

24 R Lorusso, K Shekar, G MacLaren, et al. ELSO Interim Guidelines for Venoarterial Extracorporeal Membrane Oxygenation in Adult Cardiac Patients. *Asaio J* 2021;67(8):827-44.

25 JB Zwischenberger, HT Pitcher. Extracorporeal Membrane Oxygenation Management: Techniques

to Liberate from Extracorporeal Membrane Oxygenation and Manage Post-Intensive Care Unit Issues. *Crit Care Clin* 2017;33(4):843-53.

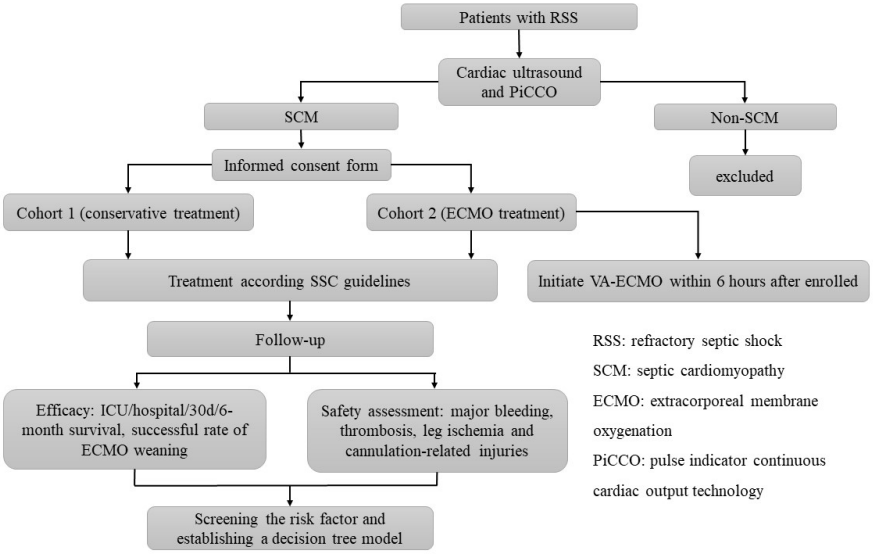
26 S Schulman, C Kearon. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-94.

27 TK Park, JH Yang, K Jeon, et al. Extracorporeal membrane oxygenation for refractory septic shock in adults. *Eur J Cardio-Thorac* 2015;47(2):e68-74.

28 C Huang, Y Tsai, P Tsai, W Ko. Extracorporeal membrane oxygenation resuscitation in adult patients with refractory septic shock. *The Journal of Thoracic and Cardiovascular Surgery* 2013;146(5):1041-46.

29 L Falk, J Hultman, LM Broman. Extracorporeal Membrane Oxygenation for Septic Shock. *Crit Care Med* 2019;47(8):1097-105.

30 N Bréchot, C Luyt, M Schmidt, et al. Venoarterial Extracorporeal Membrane Oxygenation Support for Refractory Cardiovascular Dysfunction During Severe Bacterial Septic Shock*. *Crit Care Med* 2013;41(7):1616-26.



study flow chart

338x190mm (96 x 96 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	12-13
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	14
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

ExtraCorporeal Membrane Oxygenation in the therapy for REfractory Septic shock with Cardiac function Under Estimated (ECMO-RESCUE): study protocol for a prospective, multicenter, non-randomized cohort study

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ExtraCorporeal Membrane Oxygenation in the therapy for REfractory Septic shock with Cardiac function Under Estimated (ECMO-RESCUE): study protocol for a prospective, multicenter, non-randomized cohort study

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ABSTRACT

Introduction: Severe septic cardiomyopathy (SCM) is one of the main causes of refractory septic shock (RSS), with a high mortality. The application of venoarterial extracorporeal membrane oxygenation (ECMO) to support the impairment cardiac function in patients with septic shock remains controversial. Moreover, no prospective studies have been taken to address whether venoarterial ECMO treatment could improve the outcome of patients with sepsis-induced cardiogenic shock. The objective of this study is to assessed whether venoarterial ECMO treatment can improve the 30-day survival rate of patients with sepsis-induced refractory cardiogenic shock.

Methods and analysis: ECMO-RESCUE is a prospective, multicenter, non-randomized, cohort study on the application of ECMO in SCM. At least 64 patients with SCM and RSS will be enrolled in an estimated ratio of 1:1.5. Participants taking venoarterial ECMO during the period of study are referred to as cohort 1, and patients receiving only conventional therapy without ECMO belong to cohort 2. The primary outcome is survival in a 30-day follow-up period. Other end points include survival to intensive care unit (ICU) discharge, hospital survival, 6-month survival, quality of life for long-term survival (EQ-5D score), successful rate of ECMO weaning, long-term survivors' cardiac function, the number of days alive without continuous renal replacement therapy (CRRT), mechanical ventilation and vasopressor, ICU and hospital length of stay, the rate of complications potentially related to ECMO treatment.

Ethics and dissemination: The trial has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (2020-hs-51). Participants will be screened and enrolled from ICU patients with septic shock by clinicians, with no public advertisement for recruitment. Results will be disseminated in research journals and through conference presentations.

Trial registration: NCT05184296

ARTICLE SUMMARY

Strengths and limitations of this study

- ECMO-RESCUE is a prospective, multicenter, non-randomized, cohort study on the application of ECMO in sepsis-induced refractory cardiogenic shock.
- Patients admitted to ICU and meet diagnostic criteria for cardiogenic shock induced by sepsis will be enrolled in the study and subsequently assigned to one of two cohorts based on their willingness to undergo ECMO.
- All patients willing to undergo ECMO treatment will initiate venoarterial ECMO within 6 hours of enrollment.
- Risks of bleeding, thrombosis, leg ischemia and cannulation-related injuries may be elevated in patients undergoing ECMO treatment; however, this intervention may offer a potential benefit to improve survival.
- A limitation of the study is its non-randomized design, which would yield bias.

INTRODUCTION

Sepsis, a life-threatening syndrome with organ dysfunction caused by infection, is a leading cause of death in ICU[1]. The global burden of disease arising from sepsis was estimated at 30 million episodes and 6 million deaths per year in 2017[2]. The mortality is as high as 50% when septic shock is present[3, 4]. Septic cardiomyopathy (SCM) is one of the main causes of septic shock, affecting 20-65% of patients with sepsis. Severe cardiac function impairment leads to refractory septic shock (RSS), with a mortality up to 70%[5-7]. However, there are no evidence-based recommendations for the management of SCM[8].

In addition to aggressive treatment with antibiotics for infection control, adequate fluid resuscitation and vasoactive drugs administration according to the International Guidelines for Management of Sepsis and Septic Shock[9], a variety of drugs to improve cardiac function have also been attempted for the treatment of SCM. However, the results were not satisfactory. Studies on dobutamine have demonstrated that the administration of either dobutamine alone or a combination of norepinephrine failed to improve survival rate, microcirculatory perfusion and metabolic despite an increasing cardiac index, heart rate and left ventricular ejection fractions (LVEF)[10, 11]. Another positive inotropic drug, levosimendan, also has been tried to applied in the treatment of SCM. However, the therapeutic effect is still controversial[12-14]. Therefore, there is few recognized effective treatments for sepsis-induced cardiogenic shock at present.

SCM is consider as a sepsis-associated acute syndrome of cardiac dysfunction unrelated to ischemia[15]. Most studies have suggested that recovery from SCM is prompt. A retrospective study showed that although left ventricular dysfunction may persist in approximately one-third of patients with severe sepsis and septic shock in long-term follow-up, the survival rates did not differ[16]. Therefore, trying new, innovative therapeutic approaches in SCM are valuable and urgently needed.

Venoarterial extracorporeal membrane oxygenation (ECMO) is a circulatory support technology, which can increase cardiac output as well as improving hypoxemia by

increasing oxygen delivery. Therefore, the application of venoarterial ECMO in the treatment of RSS has theoretical feasibility. However, sepsis has been considered as a contraindication for ECMO due to its complexity and the unsatisfactory outcomes of earlier studies. As an extracorporeal circulation device, ECMO may be susceptible to pathogen attachment, leading to refractory infections that exacerbate the underlying condition[17]. Furthermore, patients with sepsis often present with thrombocytopenia and abnormal coagulation function, while ECMO necessitates anticoagulation therapy which can potentially worsen bleeding[18, 19]. In Park et al.'s study, a total of 32 patients received ECMO support for RSS, only 7 patients (21.9%) survived to hospital discharge[20]. In Huang et al.'s study, hospital survival rate was much lower (15%)[21]. However, as the advancement of ECMO technology, improvements in materials of ECMO[22], and the emergence of new research findings, there is a growing reconsideration regarding the utilization of ECMO in sepsis. It is reported that in neonatal and children with septic shock, the survival rate of ECMO treatment was nearly 80% and 50%, respectively[23, 24]. ECMO treatment of septic shock in neonatal and children has been in guidelines and consensus since 2008[25, 26]. Besides this, a single-center retrospective study found that venoarterial ECMO rescued more than 70% of the patients who developed refractory cardiovascular dysfunction during severe bacterial septic shock[27]. Another multicenter cohort study found that survival at 90 days for patients with severe sepsis-induced cardiomyopathy who received venoarterial ECMO was significantly higher than for controls (60% *vs* 25%)[28]. Falk et al. reported a 90% hospital survival rate in septic shock patients with left ventricular failure and 64.7% in patients with distributive shock[29]. Cardiac depression, vasoplegia and capillary leakage all lead to circulatory failure in septic shock. Falk et al.'s study suggested that the patients with sepsis-induced refractory cardiogenic shock may be received high survival benefit from venoarterial ECMO, and superior to distributed shock. Moreover, all survivors restored their cardiac function and had good long-term quality of life[30]. It also implied that perhaps RSS is not an absolute contraindication to ECMO, but rather that the ideal candidates for this treatment should be identified.

In summary, the use of ECMO in adult patients with RSS is still controversial. More

studies are still needed to determine whether the benefit of ECMO outweighs the risk. To date, prospective trials of using ECMO in the adult patients with sepsis-induced cardiogenic shock have not yet been reported. Therefore, prospective clinical studies would face many problems. For example, before ECMO is initiated how long does RSS last and what dose of vasoactive drug is needed? This prospective cohort study was designed with reference to indications of ECMO initiation in refractory cardiogenic shock. In this study, we aimed to assessed whether venoarterial ECMO treatment can improve the 30-day survival rate of patients with sepsis-induced refractory cardiogenic shock.

METHODS AND ANALYSIS

Study design, setting and patient population

The ECMO-RESCUE study is a prospective, multicenter, non-randomized, cohort study. All patients admitted to the ICUs of participating centers will be considered as potential candidates for the study. Once the patient is diagnosed of septic shock, he/she should be screened for eligibility by the physicians. When the patient fulfills the criterion of recruitment, the researcher provides details on the purpose, specific content and instructions on how to complete the trial. After we obtain written informed consent (online supplementary file 1) from the patient or a responsible surrogate, patients are enrolled in the study.

During the period of study, the participants' legal representative can decide whether to accept ECMO based on their personal conditions. If the participant is confirmed to receive ECMO treatment, we initiate ECMO within 6 hours. Participants taking ECMO during the period of study are referred to as cohort 1, and patients receiving only conventional therapy without ECMO belong to cohort 2. ECMO is established and managed by a professional team. The teams of each center have more than 5-year experience.

The study will be conducted in six ICUs located in Guangdong, China. It is anticipated that the study will span a duration of 3 years. Participants recruitment commenced in May 2023, with an anticipated completion date for enrollment set for December 2025.

The anticipated completion time for followed-up is projected to be in May 2026.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Inclusion criteria

1. Age between 18 and 75 years.
2. Patients admitted into ICU and diagnosed as septic shock (sepsis-3.0), after adequate fluid resuscitation, high-dose vasoactive drug application [vasoactive inotropic score (VIS) > 120] and conventional therapy together with at least one of the following criteria: (1) sustained hypotension [mean arterial pressure (MAP) < 65 mmHg]; (2) persistent lactacemia (two consecutive values > 5 mmol/L with at least 30 min interval between samples), with non-decreasing trend on steady doses of inotropes and/or vasopressors; (3) persistent low central venous blood oxygen saturation ($ScvO_2$) (two consecutive values < 55% with at least 30 min interval between samples), with non-increasing trend on steady doses of inotropes and/or vasopressors. The above condition lasts more than 5 hours.
3. Rapidly deteriorating sepsis-induced myocardial impairment is defined by at least one of the following criteria: (1) rapidly deteriorating ventricular function (LVEF < 35%); (2) cardiac index (CI) < 2.0 L/min/m^2 (> 3 hours); (3) emerging refractory arrhythmia.
4. Informed consent provided by the patient or person with decisional responsibility.

Exclusion criteria

1. Cardiac dysfunction caused by other causes is excluded, such as acute myocardial infarction, chronic heart failure, congenital cardiac disease, myocardial effusion, moderate to severe aortic regurgitation, severe aortic coarctation and so on.
2. High suspicion of pulmonary embolism, tension pneumothorax or cardiac tamponade as a cause of shock.

3. Prolonged cardiac arrest (> 30 min) before ECMO, or cardiopulmonary resuscitation (CPR) survivors remaining comatose.
4. Irreversible condition or meet the inclusion criteria for more than 12 hours.
5. Presence of active bleeding or anticoagulant contraindications.
6. Peripheral artery disease disabling insertion of outflow cannula to femoral artery.
7. Irreversible neurological pathology
8. Severe underlying condition with lift expectancy less than 1 year.
9. Special population, such as pregnancy, acquired immune deficiency syndrome (AIDS).
10. Patient included in another interventional clinical trial.

Study definitions

Septic shock

Septic shock, a subset of sepsis, can be identified by a vasopressor requirement to maintain a MAP of 65 mm Hg or greater and serum lactate greater than 2 mmol/L despite of resuscitation.

Vasoactive inotropic score

VIS was calculated as [(epinephrine + norepinephrine) μg/kg/min] × 100 + [(dobutamine + dopamine) μg/kg/min] + [milrinone μg/kg/min] × 10 + levosimendan μg/kg/min × 50 + [vasopressin units/kg/min] × 10,000[31].

Successful weaning off ECMO

Successful weaning was defined as maintaining stable condition within 24 hours of ECMO weaning.

Study intervention

The study flow chart is detailed in Figure 1.

All patients received fluid resuscitation, antibiotic, vasoactive drugs and control of the focus of infection according to the international guidelines of Surviving Sepsis Campaign 2021[9]. The gold of MAP is ≥ 65 mmHg. For multiple organ dysfunction, life support technologies such as mechanical ventilation and continuous renal

replacement therapy (CRRT) are provided as needed. The patient's primary physicians will determine the management of other comorbidities.

ECMO implantation and management

All patients in cohort 1 will initiate ECMO as fast as possible. A maximum of 6 hours is allowed between enrollment and the actual initiation of ECMO. ECMO catheterization and management will be operated by an experienced ECMO team and carried out at the bedside. The initiation and weaning or cessation time, the data of ECMO will be recorded by nurses.

- Therapy mode

Venoarterial or venovenoarterial mode will be chosen according to the patient's condition. Intra-aortic balloon pump (IABP) will be performed simultaneously when necessary to relieve the afterload of left ventricle.

- Canulation

All patients will undergo peripheral cannulation. The arterial catheter is placed into the femoral artery, and the venous catheter is placed into the femoral vein. Ultrasound examination will be performed bedside to select vessels with better conditions and suitable diameter canula before catheterization. After the arterial cannulation, the distal perfusion catheter is inserted to perform lower limb perfusion.

- The blood flow and the goal

The initial flow rate is 80~100 ml/kg of ideal body weight/min. The ECMO blood flow is adjusted to: (1) maintain a MAP > 65 mmHg; (2) reach a preoxygenator oxygen saturation > 65%; (3) restore blood lactate to normal level; (4) revert the MODS.

- Management

(1) Inotropes are discontinued or reduced to minimal dosed within a few hours of achieving goal-directed flows (norepinephrine or epinephrine < 0.05 μg/kg/min, and dopamine or dobutamine < 5 μg/kg/min are suggested).

(2) During the period of ECMO, maintain a hemoglobin of > 100 g/L, a platelet count of ≥ 50×10^9/L, antithrombin III (AT3) of > 80%, and fibrinogen > 2 g/L.

(3) Echocardiography is performed at least daily to monitor cardiac function.

- Anticoagulation

Unfractionated heparin (UFH) is recommended for anticoagulation. A bolus dose of UFH is administered at cannulation followed by continuous infusion. Activated partial thrombin time (APTT) is targeted between 1.5 and 2 times of normal, or active clotting time (ACT) is targeted between 180 and 220 s. if the patient is at high risk of bleeding, the target ACT value is lowered to 160 s. UFH may be stopped for severe bleeding or coagulation disorders.

- Wean off ECMO

ECMO weaning should be considered when patients exhibit stable hemodynamics and sufficient cardiac recovery[32].

Indications for ECMO weaning: (1) adequate upper limb partial pressure of oxygen in arterial blood (PaO_2) and saturation with fraction of inspire oxygen (FiO_2) < 50%, peak inspiratory pressure (PIP) < 30 cmH_2O, positive end expiratory pressure (PEEP) <8 cmH_2O from ventilator when ECMO gas flow at 21%; (2) ECMO flow is reduced to 10% ~ 25% of normal blood flow or 1.5 L/min; (3) patients exhibit stable hemodynamic (MAP > 65 mmHg, pulse pressure > 20 mmHg), $ScvO_2$ >70%, LVEF > 40%, blood lactate < 2.0 mmol/L and without malignant arrhythmia on no/low doses vasoactive, inotropic support (norepinephrine or epinephrine < 0.02 μg/kg/min, and dopamine or dobutamine < 5 μg/kg/min) for more than 2 hours.

The ECMO weaning test is gradually performed according to the patient's systemic hemodynamics and tissue perfusion improvement[32, 33]. During weaning, ECMO flow is decreased progressively by 500 ml every 5-10 minutes. Patients are evaluated after 3-5 minutes of no support (circuit clamped) or alternatively at minimum of 1 l/min of support. Successful weaning is defined as maintaining stable condition within 48 hours of ECMO weaning.

- Cessation of ECMO

ECMO will be discontinued with one of the following conditions: (1) brain death; (2) other vital organ dysfunction is difficult to reverse; (3) major bleeding (defined as fatal bleeding, and/or symptomatic bleeding, does ≥1 of the following factors apply: (1) Bleeding at a critical site, such as intracranial, intraspinal, intraocular, retroperitoneal,

intra-articular or pericardial, or intramuscular with compartment syndrome; (2) Hemodynamic instability; (3) Clinically overt bleeding with hemoglobin decrease ≥2 g/dL or administration of ≥2 units red blood cells)[34]; (4) there is no signs of cardiac function recovery and no better therapeutic regimen after 7 to 10 days of ECMO treatment; (5) an uncontrollable infection.

Primary outcome

The primary outcome is 30-day survival measured from the date of enrolled (D0) until death or day 30. For patients who were discharged alive from ICU, information on the primary endpoint will be acquired by a telephone call.

Secondary outcomes

The secondary outcomes include: (1) survival to ICU discharge, hospital survival, 6-month survival and quality of life for long-term survival (EQ-5D score); (2) successful rate of ECMO weaning; (3) long-term survivors' cardiac function was evaluated according to Doppler echocardiography; (4) the number of days alive without CRRT, mechanical ventilation and vasopressor (the numbers of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, between D0 and up to D30); (5) ICU and hospital length of stay (LOS).

Safety assessments

In addition to the focus on prognosis of patients with septic cardiomyopathy treated with venoarterial ECMO, the safety of the venoarterial ECMO treatment is also a major focus. The complications potentially related to ECMO treatment include: (1) major bleeding associated with anticoagulants; (2) thrombosis (ischemic stroke, pulmonary embolism, deep venous thrombosis or catheter-associated thrombosis during study confirmed by ultrasound or CT scan); (3) leg ischemia; (4) cannulation-related injuries (such as arterial laceration, arterial aneurysm and peripheral nerve defect).

Sample size

According to a retrospective study from Bréchot et al., the survival rate of patients with severe sepsis-induced cardiomyopathy was 60% in venoarterial ECMO group and 25% in control group, elevation in survival of 35% in venoarterial ECMO group can be expected. Considering the high cost and uncertain therapeutic effect of ECMO treatment, fewer participants may choose ECMO treatment than conventional treatment, with an estimated ratio of 1:1.5. The sample size for differences between two independent proportions was calculated by the PASS 14.0 software to ensure 80% power using a two-sided test with a significance level of $\alpha = 0.05$. We need 23 participants in venoarterial ECMO treatment cohort and 35 participants in conventional treatment cohort. Considering a projected dropout rate of 10%, the sample size of venoarterial ECMO treatment cohort and conventional treatment cohort should be 25 and 39, respectively. The total sample size should be 64.

Data collection and follow-up

Each investigator from the 6 participating ICUs was trained to the protocol and data collection in the Case Record Form (CRF) before trial initiation. The data is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China).

Flowchart of patient follow-up is shown in table 1. Demographic data and medical history will be collected. Details data including reasons for ICU admission, cause of septic shock, focus of infection, acute physiology and chronic health evaluation II (APACHEII) score, dates of hospital and ICU admission will be recorded. Details of mechanical ventilation, vasopressor and CRRT will be documented daily. Sequential organ failure assessment score (SOFA) will be calculated at baseline, Day 1 (D1), D3 and D7. Cardiac function will be assessed by echocardiography and recorded at baseline, D1, D3, D5, D7, D10, D14, D30. Blood will be collected at baseline, D1, D3, D5, D7. The following laboratory results will be recorded: white blood cell count and differentials in peripheral circulation, serum electrolyte levels, liver and myocardial enzyme concentrations, arterial blood gas analysis, C-reactive protein (CRP), procalcitonin and lactate. EQ-5D assessment will be acquired through phone call at 6

months.

During ECMO intervention, details of initiation, mode, setting parameters, weaning or cessation, complications will be noted.

All enrolled participants will be followed to determine adverse events, cardiac function recovery and mortality until death or at ICU/hospital discharge, 30 days and 6 months. If the participants survive beyond 30 days and 6 months, they will be requested to revisit the hospital for a cardiac ultrasound examination or provide a cardiac ultrasound report from a local hospital.

Table 1 Flow chart of patient follow-up

	screening	Inclusion D0	Study period	Death/30d	Follow-up 6 months
Baseline information					
Demographic data and history	√	√			
Inclusion and exclusion criteria	√				
Written informed consent	√				
Diagnosis and focus of infection	√	√	√		
Vital signs		√			
APACHEII/SOFA		√	√D1, 3, 7		
Efficacy observation					
Cardiac function assessment (CI, LVEF)	√	√	√D1, 3, 5, 7, 10, 14	√	√
ECMO intervention			√		
Treatment with vesopressor	√	√	√		
Mechanical ventilation		√	√		
CRRT implication		√	√		
Laboratory tests	√	√	√D1, 3, 5, 7		
Safety observation					
Complications of ECMO			√		
Adverse event			√		
Additional observation					
ICU and hospital LOS				√	
Alive or dead status				√	√
Life quality (EQ-5D score)					√

APACHEII, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CI, cardiac index; LVEF, left ventricular ejection fraction; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; LOS, length of stay.

Statistical analysis

Data will be double checked by the clinical research team, and the data base is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China).

For each cohort, quantitative variables with normal distribution will be described as mean and standard deviation. Quantitative variables with skewed distribution will be described as median (M) and inter-quartile range (IQR, 25th percentile to 75th percentile). Qualitative variables will be described as frequency and percentage.

The effect of venoarterial ECMO treatment versus conventional treatment on 30 days survival will be performed using Fisher's exact test, with secondary analysis by Kaplan-Meier survival analyses, comparison using a log rank test. A propensity score-weighted analysis was done for treatment-effect estimation. Covariate balance between the two groups was assessed after weighting, and we considered an absolute standardized difference of less than 0.1 as evidence of balance. The effect of ECMO on survival at 30 days will be estimated within the weighted pseudopopulation. Adjusted Kaplan-Meier estimator and log-rank test (considering the weighting scheme) will be used. Decision tree analysis will be used to establish a decision tree model to decide whether sepsis-induced cardiogenic shock patients need ECMO treatment.

Safety will be analyzed by the frequency of complications in both cohorts and comparing rates using χ^2 or Fisher's exact test, with an alpha risk set at 0.05.

Statistical analyses of the pre-specified secondary endpoints will be performed with descriptive and inductive statistical methods. Categorical variables will be compared using the χ^2 or Fisher's exact test, as appropriate. Continuous variables will be compared using Student's t test or the Mann-Whitney test, as appropriate.

Therapeutic efficiency will be analyzed using the data of the full analysis set (FAS) and

per protocol set (PPS); safety evaluation will be based on the data of the safety analysis set (SS) for statistical analysis.

All analyses were performed with commercially available statistical software SPSS 22.0 and R software version 4.1.0 or later.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (version 2.0, registration number: 2020-hs-51; date of approval: 17 November 2020). Participants will be screened and enrolled from ICU patients with sepsis-induced cardiogenic shock by clinicians, with no public advertisement for recruitment. When the patient fulfills the criterion of recruitment, written informed consent (online supplementary file 1) should be obtained from the patient or a responsible surrogate before enrolled. After enrolled, the participants can decide whether to accept ECMO based on their personal conditions. All information from the participants will be kept private and will not be provided to any company or institution. Results will be disseminated in research journals and through conference presentations.

Abbreviations

SCM	Septic cardiomyopathy
RSS	Refractory septic shock
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
CRRT	Continuous renal replacement therapy
LVEF	Left ventricular ejection fractions
VIS	Vasoactive inotropic score
MAP	Mean arterial pressure
$ScvO_2$	Central venous blood oxygen saturation
CI	Cardiac index
CPR	Cardiopulmonary resuscitation
AIDS	Acquired immune deficiency syndrome
IABP	Intra-aortic balloon pump
UFH	Unfractionated heparin
APTT	Activated partial thrombin time
ACT	Active clotting time
PaO_2	Partial pressure of oxygen in arterial blood
FiO_2	Fraction of inspire oxygen
PIP	Peak inspiratory pressure

PEEP	Positive end expiratory pressure
LOS	Length of stay
CRF	Case record form
APACHEII	Acute physiology and chronic health evaluation II
SOFA	Sequential organ failure assessment score
CRP	C-reactive protein
M	median
IQR	Inter-quartile range
FAS	Full analysis set
PPS	Per protocol set
SS	Safety analysis set

Supplementary file

Online supplement file 1: consent form.

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Contributors

Wei-yan Chen and Ze-bin Guo designed the trial. Tian-yu Kong, Qi-lin Yang, Yi-chao Wen and Xu-ming Xiong participated in the discussion of the plan, De-liang Wen and Zhen-hui Zhang made a decision to revise the plan. Ze-bin Guo, Tian-yu Kong, Wei-xiao Chen, Xiao-hua Chen, Qi-lin Yang, Yi-chao Wen, Qi-rui Wen and Feng Zhou conduct the plan. Wei-yan Chen draft the manuscript. De-liang Wen and Zhen-hui Zhang provided critical revision of the manuscript. De-liang Wen and Wei-yan Chen obtained funding for the trial. All authors discussed and helped to improve the protocol, and read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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References:

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *JAMA* 2016, **315**(8):801.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S *et al*: **Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study**. *The Lancet (British edition)* 2020, **395**(10219):200-211.
3. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K: **Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations**. *AM J RESP CRIT CARE* 2016, **193**(3):259-272.
4. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S: **Recognizing Sepsis as a Global Health Priority - A WHO Resolution**. *N Engl J Med* 2017, **377**(5):414-417.
5. Narváez I, Canabal A, Martín C, Sánchez M, Moron A, Alcalá J, Giacoman S, Magro M: **Incidence and evolution of sepsis-induced cardiomyopathy in a cohort of patients with sepsis and septic shock.** *MED INTENSIVA* 2018, **42**(5):283-291.
6. Sato R, Kuriyama A, Takada T, Nasu M, Luthe SK: **Prevalence and risk factors of sepsis-induced cardiomyopathy: A retrospective cohort study.** *MEDICINE* 2016, **95**(39):e5031.
7. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, Shahul S, Brown SM: **Septic Cardiomyopathy**. *CRIT CARE MED* 2018, **46**(4):625-634.
8. Ravikumar N, Sayed MA, Poonsuph CJ, Sehgal R, Shirke MM, Harky A: **Septic Cardiomyopathy: From Basics to Management Choices**. *Curr Probl Cardiol* 2021, **46**(4):100767.
9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC *et al*: **Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021**. *Intensive Care Med* 2021, **47**(11):1181-1247.
10. Hernandez G, Bruhn A, Luengo C, Regueira T, Kattan E, Fuentealba A, Florez J, Castro R, Aquevedo A, Pairumani R *et al*: **Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study.** *INTENS CARE MED* 2013, **39**(8):1435-1443.
11. Annane D, Vignon P, Renault A, Bollaert P, Charpentier C, Martin C, Troché G, Ricard J, Nitenberg

G, Papazian L *et al*: **Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial.** In., vol. 370; 2007: 676-684.

12. Meng J, Hu M, Lai Z, Ji C, Xu X, Zhang G, Tian S: **Levosimendan Versus Dobutamine in Myocardial Injury Patients with Septic Shock: A Randomized Controlled Trial.** In., vol. 22; 2016: 1486-1496.

13. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RML, Santhakumaran S, Mason AJ, Cross M, Al-Beidh F, Best-Lane J *et al*: **Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis.** *The New England journal of medicine* 2016, **375**(17):1638-1648.

14. Pinto BB, Rehberg S, Ertmer C, Westphal M: **Role of levosimendan in sepsis and septic shock.** *Current opinion in anaesthesiology* 2008, **21**(2):168-177.

15. Martin L, Derwall M, Al ZS, Zechendorf E, Reuter DA, Thiemermann C, Schuerholz T: **The Septic Heart: Current Understanding of Molecular Mechanisms and Clinical Implications**. *CHEST* 2019, **155**(2):427-437.

16. Vallabhajosyula S, Jentzer JC, Geske JB, Kumar M, Sakhuja A, Singhal A, Poterucha JT, Kashani K, Murphy JG, Gajic O *et al*: **New-Onset Heart Failure and Mortality in Hospital Survivors of Sepsis-Related Left Ventricular Dysfunction**. *SHOCK* 2018, **49**(2):144-149.

17. Han L, Zhang Y, Zhang Y, Wu W, He P: **Risk factors for refractory septic shock treated with VA ECMO**. *Annals of Translational Medicine* 2019, **7**(18):476.

18. Kirkpatrick BV, Krummel TM, Mueller DG, Ormazabal MA, Greenfield LJ, Salzberg AM: **Use of extracorporeal membrane oxygenation for respiratory failure in term infants**. *PEDIATRICS* 1983, **72**(6):872-876.

19. Riera J, Argudo E, Ruiz-Rodríguez JC, Ferrer R: **Extracorporeal Membrane Oxygenation for Adults With Refractory Septic Shock**. *ASAIO J* 2019, **65**(8):760-768.

20. Park TK, Yang JH, Jeon K, Choi S, Choi J, Gwon H, Chung CR, Park CM, Cho YH, Sung K *et al*: **Extracorporeal membrane oxygenation for refractory septic shock in adults**. *EUR J CARDIO-THORAC* 2015, **47**(2):e68-e74.

21. Huang C, Tsai Y, Tsai P, Ko W: **Extracorporeal membrane oxygenation resuscitation in adult patients with refractory septic shock**. *The Journal of Thoracic and Cardiovascular Surgery* 2013, **146**(5):1041-1046.

22. Formica F, Avalli L, Martino A, Maggioni E, Muratore M, Ferro O, Pesenti A, Paolini G: **Extracorporeal Membrane Oxygenation With a Poly-Methylpentene Oxygenator (Quadrox D). The Experience of a Single Italian Centre in Adult Patients With Refractory Cardiogenic Shock**. *ASAIO J* 2008, **54**(1):89-94.

23. Tembo M, Harvey C, Duthie M, Pooboni S, Whitelaw J, Pandya H, Barry P, Peek G, Fermin R: **Extracorporeal membrane oxygenation for refractory septic shock in children: One institution's experience.** In., vol. 10; 2009: 534-535, 535.

24. McCune S, Short BL, Miller MK, Lotze A, Anderson KD: **Extracorporeal membrane oxygenation therapy in neonates with septic shock.** In., vol. 25; 1990: 479-482.

25. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA *et al*: **Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine**. *CRIT CARE MED* 2009, **37**(2):666-688.

26. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, Okhuysen-Cawley RS, Relvas MS, Rozenfeld RA, Skippen PW *et al*: **American College of Critical Care Medicine Clinical Practice**

Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *CRIT CARE MED* 2017, **45**(6):1061-1093.

27. Bréchot N, Luyt C, Schmidt M, Leprince P, Trouillet J, Léger P, Pavie A, Chastre J, Combes A: **Venoarterial Extracorporeal Membrane Oxygenation Support for Refractory Cardiovascular Dysfunction During Severe Bacterial Septic Shock***. *CRIT CARE MED* 2013, **41**(7):1616-1626.

28. Bréchot N, Hajage D, Kimmoun A, Demiselle J, Agerstrand C, Montero S, Schmidt M, Luyt C, Lebreton G, Hékimian G *et al*: **Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study**. *The Lancet (British edition)* 2020, **396**(10250):545-552.

29. Falk L, Hultman J, Broman LM: **Extracorporeal Membrane Oxygenation for Septic Shock**. *CRIT CARE MED* 2019, **47**(8):1097-1105.

30. Barreto BB, Gusmao-Flores D: **Long-Term Mortality in Extracorporeal Membrane Oxygenation**. *CRIT CARE MED* 2018, **46**(4):e348.

31. Koponen T, Karttunen J, Musialowicz T, Pietiläinen L, Uusaro A, Lahtinen P: **Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery.** In., vol. 122; 2019: 428-436.

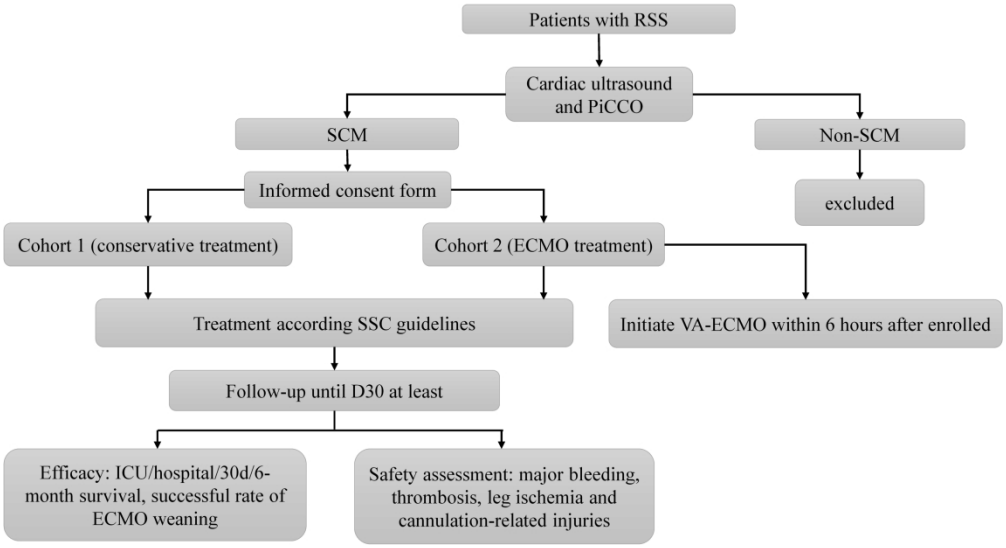
32. Lorusso R, Shekar K, MacLaren G, Schmidt M, Pellegrino V, Meyns B, Haft J, Vercaemst L, Pappalardo F, Bermudez C *et al*: **ELSO Interim Guidelines for Venoarterial Extracorporeal Membrane Oxygenation in Adult Cardiac Patients**. *ASAIO J* 2021, **67**(8):827-844.

33. Zwischenberger JB, Pitcher HT: **Extracorporeal Membrane Oxygenation Management: Techniques to Liberate from Extracorporeal Membrane Oxygenation and Manage Post-Intensive Care Unit Issues**. *CRIT CARE CLIN* 2017, **33**(4):843-853.

34. Schulman S, Kearon C: **Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients**. *J THROMB HAEMOST* 2005, **3**(4):692-694.

Figure legend:

Figure 1. Study flow chart. RSS, refractory septic shock; SCM, septic cardiomyopathy; ECMO, extracorporeal membrane oxygenation; PiCCO, pulse indicator continuous cardiac output techonology.



Study flow chart. RSS, refractory septic shock; SCM, septic cardiomyopathy; ECMO, extracorporeal membrane oxygenation; PiCCO, pulse indicator continuous cardiac output techonology.

293x159mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No.	Description	Page No.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,16
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

ExtraCorporeal Membrane Oxygenation in the therapy for REfractory Septic shock with Cardiac function Under Estimated (ECMO-RESCUE): study protocol for a prospective, multicenter, non-randomized cohort study

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Primary Subject Heading:	Intensive care
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Keywords:	Patients, Cardiomyopathy < CARDIOLOGY, INFECTIOUS DISEASES, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

ExtraCorporeal Membrane Oxygenation in the therapy for REfractory Septic shock with Cardiac function Under Estimated (ECMO-RESCUE): study protocol for a prospective, multicenter, non-randomized cohort study

Wei-yan Chen[#], Ze-bin Guo[#], Tian-yu Kong, Wei-xiao Chen, Xiao-hua Chen, Qi-lin Yang, Yi-chao Wen, Qi-rui Wen, Feng Zhou, Xu-ming Xiong, De-liang Wen[*], Zhen-hui Zhang[*]

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ABSTRACT

Introduction: Severe septic cardiomyopathy (SCM) is one of the main causes of refractory septic shock (RSS), with a high mortality. The application of venoarterial extracorporeal membrane oxygenation (ECMO) to support the impairment cardiac function in patients with septic shock remains controversial. Moreover, no prospective studies have been taken to address whether venoarterial ECMO treatment could improve the outcome of patients with sepsis-induced cardiogenic shock. The objective of this study is to assessed whether venoarterial ECMO treatment can improve the 30-day survival rate of patients with sepsis-induced refractory cardiogenic shock.

Methods and analysis: ECMO-RESCUE is a prospective, multicenter, non-randomized, cohort study on the application of ECMO in SCM. At least 64 patients with SCM and RSS will be enrolled in an estimated ratio of 1:1.5. Participants taking venoarterial ECMO during the period of study are referred to as cohort 1, and patients receiving only conventional therapy without ECMO belong to cohort 2. The primary outcome is survival in a 30-day follow-up period. Other end points include survival to intensive care unit (ICU) discharge, hospital survival, 6-month survival, quality of life for long-term survival (EQ-5D score), successful rate of ECMO weaning, long-term survivors' cardiac function, the number of days alive without continuous renal replacement therapy (CRRT), mechanical ventilation and vasopressor, ICU and hospital length of stay, the rate of complications potentially related to ECMO treatment.

Ethics and dissemination: The trial has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (2020-hs-51). Participants will be screened and enrolled from ICU patients with septic shock by clinicians, with no public advertisement for recruitment. Results will be disseminated in research journals and through conference presentations.

Trial registration: NCT05184296

ARTICLE SUMMARY

Strengths and limitations of this study

- ECMO-RESCUE is a prospective, multicenter, non-randomized, cohort study on the application of ECMO in sepsis-induced refractory cardiogenic shock.
- Patients admitted to ICU and meet diagnostic criteria for cardiogenic shock induced by sepsis will be enrolled in the study and subsequently assigned to one of two cohorts based on their willingness to undergo ECMO.
- All patients willing to undergo ECMO treatment will initiate venoarterial ECMO within 6 hours of enrollment.
- Risks of bleeding, thrombosis, leg ischemia and cannulation-related injuries may be elevated in patients undergoing ECMO treatment; however, this intervention may offer a potential benefit to improve survival.
- A limitation of the study is its non-randomized design, which would yield bias.

INTRODUCTION

Sepsis, a life-threatening syndrome with organ dysfunction caused by infection, is a leading cause of death in ICU[1]. The global burden of disease arising from sepsis was estimated at 30 million episodes and 6 million deaths per year in 2017[2]. The mortality is as high as 50% when septic shock is present[3, 4]. Septic cardiomyopathy (SCM) is one of the main causes of septic shock, affecting 20-65% of patients with sepsis. Severe cardiac function impairment leads to refractory septic shock (RSS), with a mortality up to 70%[5-7]. However, there are no evidence-based recommendations for the management of SCM[8].

In addition to aggressive treatment with antibiotics for infection control, adequate fluid resuscitation and vasoactive drugs administration according to the International Guidelines for Management of Sepsis and Septic Shock[9], a variety of drugs to improve cardiac function have also been attempted for the treatment of SCM. However, the results were not satisfactory. Studies on dobutamine have demonstrated that the administration of either dobutamine alone or a combination of norepinephrine failed to improve survival rate, microcirculatory perfusion and metabolic despite an increasing cardiac index, heart rate and left ventricular ejection fractions (LVEF)[10, 11]. Another positive inotropic drug, levosimendan, also has been tried to applied in the treatment of SCM. However, the therapeutic effect is still controversial[12-14]. Therefore, there is few recognized effective treatments for sepsis-induced cardiogenic shock at present.

SCM is consider as a sepsis-associated acute syndrome of cardiac dysfunction unrelated to ischemia[15]. Most studies have suggested that recovery from SCM is prompt. A retrospective study showed that although left ventricular dysfunction may persist in approximately one-third of patients with severe sepsis and septic shock in long-term follow-up, the survival rates did not differ[16]. Therefore, trying new, innovative therapeutic approaches in SCM are valuable and urgently needed.

Venoarterial extracorporeal membrane oxygenation (ECMO) is a circulatory support technology, which can increase cardiac output as well as improving hypoxemia by

increasing oxygen delivery. Therefore, the application of venoarterial ECMO in the treatment of RSS has theoretical feasibility. However, sepsis has been considered as a contraindication for ECMO due to its complexity and the unsatisfactory outcomes of earlier studies. As an extracorporeal circulation device, ECMO may be susceptible to pathogen attachment, leading to refractory infections that exacerbate the underlying condition[17]. Furthermore, patients with sepsis often present with thrombocytopenia and abnormal coagulation function, while ECMO necessitates anticoagulation therapy which can potentially worsen bleeding[18, 19]. In Park et al.'s study, a total of 32 patients received ECMO support for RSS, only 7 patients (21.9%) survived to hospital discharge[20]. In Huang et al.'s study, hospital survival rate was much lower (15%)[21]. However, as the advancement of ECMO technology, improvements in materials of ECMO[22], and the emergence of new research findings, there is a growing reconsideration regarding the utilization of ECMO in sepsis. It is reported that in neonatal and children with septic shock, the survival rate of ECMO treatment was nearly 80% and 50%, respectively[23, 24]. ECMO treatment of septic shock in neonatal and children has been in guidelines and consensus since 2008[25, 26]. Besides this, a single-center retrospective study found that venoarterial ECMO rescued more than 70% of the patients who developed refractory cardiovascular dysfunction during severe bacterial septic shock[27]. Another multicenter cohort study found that survival at 90 days for patients with severe sepsis-induced cardiomyopathy who received venoarterial ECMO was significantly higher than for controls (60% *vs* 25%)[28]. Falk et al. reported a 90% hospital survival rate in septic shock patients with left ventricular failure and 64.7% in patients with distributive shock[29]. Cardiac depression, vasoplegia and capillary leakage all lead to circulatory failure in septic shock. Falk et al.'s study suggested that the patients with sepsis-induced refractory cardiogenic shock may be received high survival benefit from venoarterial ECMO, and superior to distributed shock. Moreover, all survivors restored their cardiac function and had good long-term quality of life[30]. A meta-analysis reported by Ling et al. found that survival among patients with LVEF < 20% was significantly higher than those with LVEF > 35% (62.0% *vs*. 32.1%), and patients with LVEF between 20% to 35% had intermediate survival

(42.3%)[31]. These also implied that perhaps RSS is not an absolute contraindication to ECMO, but rather that the ideal candidates for this treatment should be identified.

In summary, the use of ECMO in adult patients with RSS is still controversial. More studies are still needed to determine whether the benefit of ECMO outweighs the risk. To date, prospective trials of using ECMO in the adult patients with sepsis-induced cardiogenic shock have not yet been reported. Therefore, prospective clinical studies would face many problems. For example, before ECMO is initiated what dose of vasoactive drug is needed? Are there any other indicators of cardiac function that help to determine the initiation of ECMO in addition to the level of LVEF? This prospective cohort study was designed with reference to indications of ECMO initiation in refractory cardiogenic shock. In this study, we aimed to assessed whether venoarterial ECMO treatment can improve the 30-day survival rate of patients with sepsis-induced refractory cardiogenic shock.

METHODS AND ANALYSIS

Study design, setting and patient population

The ECMO-RESCUE study is a prospective, multicenter, non-randomized, cohort study. All patients admitted to the ICUs of participating centers will be considered as potential candidates for the study. Once the patient is diagnosed of septic shock, he/she should be screened for eligibility by the physicians. When the patient fulfills the criterion of recruitment, the researcher provides details on the purpose, specific content and instructions on how to complete the trial. After we obtain written informed consent (online supplementary file 1) from the patient or a responsible surrogate, patients are enrolled in the study.

During the period of study, the participants' legal representative can decide whether to accept ECMO based on their personal conditions. If the participant is confirmed to receive ECMO treatment, we initiate ECMO within 6 hours. Participants taking ECMO during the period of study are referred to as cohort 1, and patients receiving only conventional therapy without ECMO belong to cohort 2. ECMO is established and managed by a professional team. The teams of each center have more than 5-year

experience.

The study will be conducted in six ICUs located in Guangdong, China. It is anticipated that the study will span a duration of 3 years. Participants recruitment commenced in May 2023, with an anticipated completion date for enrollment set for December 2025. The anticipated completion time for followed-up is projected to be in May 2026.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Inclusion criteria

1. Age between 18 and 75 years.
2. Patients admitted into ICU and diagnosed as septic shock (sepsis-3.0), after adequate fluid resuscitation, high-dose vasoactive drug application [vasoactive inotropic score (VIS) > 120] and conventional therapy together with at least one of the following criteria: (1) sustained hypotension [mean arterial pressure (MAP) < 65 mmHg]; (2) persistent lactacemia (two consecutive values > 5 mmol/L with at least 30 min interval between samples), with non-decreasing trend on steady doses of inotropes and/or vasopressors; (3) persistent low central venous blood oxygen saturation ($ScvO_2$) (two consecutive values < 55% with at least 30 min interval between samples), with non-increasing trend on steady doses of inotropes and/or vasopressors. The above condition lasts more than 5 hours.
3. Rapidly deteriorating sepsis-induced myocardial impairment is defined by at least one of the following criteria: (1) rapidly deteriorating ventricular function (LVEF < 35%); (2) cardiac index (CI) < 2.0 L/min/m^2 (> 3 hours); (3) emerging refractory arrhythmia.
4. Informed consent provided by the patient or person with decisional responsibility.

Exclusion criteria

1. Cardiac dysfunction caused by other causes is excluded, such as acute myocardial

infarction, chronic heart failure, congenital cardiac disease, myocardial effusion, moderate to severe aortic regurgitation, severe aortic coarctation and so on.

2. High suspicion of pulmonary embolism, tension pneumothorax or cardiac tamponade as a cause of shock.
3. Prolonged cardiac arrest (> 30 min) before ECMO, or cardiopulmonary resuscitation (CPR) survivors remaining comatose.
4. Irreversible condition or meet the inclusion criteria for more than 12 hours.
5. Presence of active bleeding or anticoagulant contraindications.
6. Peripheral artery disease disabling insertion of outflow cannula to femoral artery.
7. Irreversible neurological pathology
8. Severe underlying condition with lift expectancy less than 1 year.
9. Special population, such as pregnancy, acquired immune deficiency syndrome (AIDS).
10. Patient included in another interventional clinical trial.

Study definitions

Septic shock

Septic shock, a subset of sepsis, can be identified by a vasopressor requirement to maintain a MAP of 65 mm Hg or greater and serum lactate greater than 2 mmol/L despite of resuscitation.

Vasoactive inotropic score

VIS was calculated as [(epinephrine + norepinephrine) μg/kg/min] × 100 + [(dobutamine + dopamine) μg/kg/min] + [milrinone μg/kg/min] × 10 + levosimendan μg/kg/min × 50 + [vasopressin units/kg/min] × 10,000[32].

Successful weaning off ECMO

Successful weaning was defined as maintaining stable condition within 24 hours of ECMO weaning.

Study intervention

The study flow chart is detailed in Figure 1.

All patients received fluid resuscitation, antibiotic, vasoactive drugs and control of the focus of infection according to the international guidelines of Surviving Sepsis Campaign 2021[9]. The gold of MAP is ≥ 65 mmHg. For multiple organ dysfunction, life support technologies such as mechanical ventilation and continuous renal replacement therapy (CRRT) are provided as needed. The patient's primary physicians will determine the management of other comorbidities.

ECMO implantation and management

All patients in cohort 1 will initiate ECMO as fast as possible. A maximum of 6 hours is allowed between enrollment and the actual initiation of ECMO. ECMO catheterization and management will be operated by an experienced ECMO team and carried out at the bedside. The initiation and weaning or cessation time, the data of ECMO will be recorded by nurses.

- Therapy mode

Venoarterial or venovenoarterial mode will be chosen according to the patient's condition. Intra-aortic balloon pump (IABP) will be performed simultaneously when necessary to relieve the afterload of left ventricle.

- Canulation

All patients will undergo peripheral cannulation. The arterial catheter is placed into the femoral artery, and the venous catheter is placed into the femoral vein. Ultrasound examination will be performed bedside to select vessels with better conditions and suitable diameter canula before catheterization. After the arterial cannulation, the distal perfusion catheter is inserted to perform lower limb perfusion.

- The blood flow and the goal

The initial flow rate is 80~100 ml/kg of ideal body weight/min. The ECMO blood flow is adjusted to: (1) maintain a MAP > 65 mmHg; (2) reach a preoxygenator oxygen saturation > 65%; (3) restore blood lactate to normal level; (4) revert the MODS.

- Management

(1) Inotropes are discontinued or reduced to minimal dosed within a few hours of achieving goal-directed flows (norepinephrine or epinephrine < 0.05 μg/kg/min,

and dopamine or dobutamine < 5 μg/kg/min are suggested).

(2) During the period of ECMO, maintain a hemoglobin of > 70 g/L, a platelet count of ≥ 50 × 10^9/L, antithrombin III (AT3) of > 80%, and fibrinogen > 2 g/L.

(3) Echocardiography is performed at least daily to monitor cardiac function.

- Anticoagulation

Unfractionated heparin (UFH) is recommended for anticoagulation. A bolus dose of UFH is administered at cannulation followed by continuous infusion. Activated partial thrombin time (APTT) is targeted between 1.5 and 2 times of normal, or active clotting time (ACT) is targeted between 180 and 220 s. if the patient is at high risk of bleeding, the target ACT value is lowered to 160 s. UFH may be stopped for severe bleeding or coagulation disorders.

- Wean off ECMO

ECMO weaning should be considered when patients exhibit stable hemodynamics and sufficient cardiac recovery[33].

Indications for ECMO weaning: (1) adequate upper limb partial pressure of oxygen in arterial blood (PaO_2) and saturation with fraction of inspire oxygen (FiO_2) < 50%, peak inspiratory pressure (PIP) < 30 cmH_2O, positive end expiratory pressure (PEEP) <8 cmH_2O from ventilator when ECMO gas flow at 21%; (2) ECMO flow is reduced to 10% ~ 25% of normal blood flow or 1.5 L/min; (3) patients exhibit stable hemodynamic (MAP > 65 mmHg, pulse pressure > 20 mmHg), $ScvO_2$ >70%, LVEF > 40%, blood lactate < 2.0 mmol/L and without malignant arrhythmia on no/low doses vasoactive, inotropic support (norepinephrine or epinephrine < 0.02 μ g/kg/min, and dopamine or dobutamine < 5 μ g/kg/min) for more than 2 hours.

The ECMO weaning test is gradually performed according to the patient's systemic hemodynamics and tissue perfusion improvement[33, 34]. During weaning, ECMO flow is decreased progressively by 500 ml every 5-10 minutes. Patients are evaluated after 3-5 minutes of no support (circuit clamped) or alternatively at minimum of 1 l/min of support. Successful weaning is defined as maintaining stable condition within 48 hours of ECMO weaning.

- Cessation of ECMO

ECMO will be discontinued with one of the following conditions: (1) brain death; (2) other vital organ dysfunction is difficult to reverse; (3) major bleeding (defined as fatal bleeding, and/or symptomatic bleeding, does ≥1 of the following factors apply: ① Bleeding at a critical site, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; ② Hemodynamic instability; ③ Clinically overt bleeding with hemoglobin decrease ≥2 g/dL or administration of ≥2 units red blood cells)[35]; (4) there is no signs of cardiac function recovery and no better therapeutic regimen after 7 to 10 days of ECMO treatment; (5) an uncontrollable infection.

Primary outcome

The primary outcome is 30-day survival measured from the date of enrolled (D0) until death or day 30. For patients who were discharged alive from ICU, information on the primary endpoint will be acquired by a telephone call.

Secondary outcomes

The secondary outcomes include: (1) survival to ICU discharge, hospital survival, 6-month survival and quality of life for long-term survival (EQ-5D score); (2) successful rate of ECMO weaning; (3) long-term survivors' cardiac function was evaluated according to Doppler echocardiography; (4) the number of days alive without CRRT, mechanical ventilation and vasopressor (the numbers of CRRT-free days, mechanical ventilation-free days and vasopressor-free days, between D0 and up to D30); (5) ICU and hospital length of stay (LOS).

Safety assessments

In addition to the focus on prognosis of patients with septic cardiomyopathy treated with venoarterial ECMO, the safety of the venoarterial ECMO treatment is also a major focus. The complications potentially related to ECMO treatment include: (1) major bleeding associated with anticoagulants; (2) thrombosis (ischemic stroke, pulmonary

embolism, deep venous thrombosis or catheter-associated thrombosis during study confirmed by ultrasound or CT scan); (3) leg ischemia; (4) cannulation-related injuries (such as arterial laceration, arterial aneurysm and peripheral nerve defect).

Sample size

According to a retrospective study from Bréchot et al., the survival rate of patients with severe sepsis-induced cardiomyopathy was 60% in venoarterial ECMO group and 25% in control group, elevation in survival of 35% in venoarterial ECMO group can be expected. Considering the high cost and uncertain therapeutic effect of ECMO treatment, fewer participants may choose ECMO treatment than conventional treatment, with an estimated ratio of 1:1.5. The sample size for differences between two independent proportions was calculated by the PASS 14.0 software to ensure 80% power using a two-sided test with a significance level of $\alpha = 0.05$. We need 23 participants in venoarterial ECMO treatment cohort and 35 participants in conventional treatment cohort. Considering a projected dropout rate of 10%, the sample size of venoarterial ECMO treatment cohort and conventional treatment cohort should be 25 and 39, respectively. The total sample size should be 64.

Data collection and follow-up

Each investigator from the 6 participating ICUs was trained to the protocol and data collection in the Case Record Form (CRF) before trial initiation. The data is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China).

Flowchart of patient follow-up is shown in table 1. Demographic data and medical history will be collected. Details data including reasons for ICU admission, cause of septic shock, focus of infection, acute physiology and chronic health evaluation II (APACHEII) score, dates of hospital and ICU admission will be recorded. Details of mechanical ventilation, vasopressor and CRRT will be documented daily. Sequential organ failure assessment score (SOFA) will be calculated at baseline, Day 1 (D1), D3 and D7. Cardiac function will be assessed by echocardiography and recorded at baseline,

D1, D3, D5, D7, D10, D14, D30. Blood will be collected at baseline, D1, D3, D5, D7. The following laboratory results will be recorded: white blood cell count and differentials in peripheral circulation, serum electrolyte levels, liver and myocardial enzyme concentrations, arterial blood gas analysis, C-reactive protein (CRP), procalcitonin and lactate. EQ-5D assessment will be acquired through phone call at 6 months.

During ECMO intervention, details of initiation, mode, setting parameters, weaning or cessation, complications will be noted.

All enrolled participants will be followed to determine adverse events, cardiac function recovery and mortality until death or at ICU/hospital discharge, 30 days and 6 months. If the participants survive beyond 30 days and 6 months, they will be requested to revisit the hospital for a cardiac ultrasound examination or provide a cardiac ultrasound report from a local hospital.

Table 1 Flow chart of patient follow-up

	screening	Inclusion D0	Study period	Death/30d	Follow-up 6 months
Baseline information					
Demographic data and history	√	√			
Inclusion and exclusion criteria	√				
Written informed consent	√				
Diagnosis and focus of infection	√	√	√		
Vital signs		√			
APACHEII/SOFA		√	√D1, 3, 7		
Efficacy observation					
Cardiac function assessment (CI, LVEF)	√	√	√D1, 3, 5, 7, 10, 14	√	√
ECMO intervention			√		
Treatment with vesopressor	√	√	√		
Mechanical ventilation		√	√		
CRRT implication		√	√		
Laboratory tests	√	√	√D1, 3, 5, 7		
Safety observation					
Complications of ECMO			√		

Adverse event			√		
Additional observation					
ICU and hospital LOS				√	
Alive or dead status				√	√
Life quality (EQ-5D score)					√

APACHEII, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CI, cardiac index; LVEF, left ventricular ejection fraction; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; LOS, length of stay.

Statistical analysis

Data will be double checked by the clinical research team, and the data base is managed and closed by the Clinical Research center of the Second Affiliated of Guangzhou Medical University (China).

For each cohort, quantitative variables with normal distribution will be described as mean and standard deviation. Quantitative variables with skewed distribution will be described as median (M) and inter-quartile range (IQR, 25th percentile to 75th percentile). Qualitative variables will be described as frequency and percentage.

The effect of venoarterial ECMO treatment versus conventional treatment on 30 days survival will be performed using Fisher's exact test, with secondary analysis by Kaplan-Meier survival analyses, comparison using a log rank test. A propensity score-weighted analysis was done for treatment-effect estimation. Covariate balance between the two groups was assessed after weighting, and we considered an absolute standardized difference of less than 0.1 as evidence of balance. The effect of ECMO on survival at 30 days will be estimated within the weighted pseudopopulation. Adjusted Kaplan-Meier estimator and log-rank test (considering the weighting scheme) will be used. Decision tree analysis will be used to establish a decision tree model to decide whether sepsis-induced cardiogenic shock patients need ECMO treatment.

Safety will be analyzed by the frequency of complications in both cohorts and comparing rates using χ^2 or Fisher's exact test, with an alpha risk set at 0.05.

Statistical analyses of the pre-specified secondary endpoints will be performed with descriptive and inductive statistical methods. Categorical variables will be compared using the χ^2 or Fisher's exact test, as appropriate. Continuous variables will be compared using Student's t test or the Mann-Whitney test, as appropriate.

Therapeutic efficiency will be analyzed using the data of the full analysis set (FAS) and per protocol set (PPS); safety evaluation will be based on the data of the safety analysis set (SS) for statistical analysis.

All analyses were performed with commercially available statistical software SPSS 22.0 and R software version 4.1.0 or later.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Clinical Research and Application Institutional Review Board of the Second Affiliated Hospital of Guangzhou Medical University (version 2.0, registration number: 2020-hs-51; date of approval: 17 November 2020). Participants will be screened and enrolled from ICU patients with sepsis-induced cardiogenic shock by clinicians, with no public advertisement for recruitment. When the patient fulfills the criterion of recruitment, written informed consent (online supplementary file 1) should be obtained from the patient or a responsible surrogate before enrolled. After enrolled, the participants can decide whether to accept ECMO based on their personal conditions. All information from the participants will be kept private and will not be provided to any company or institution. Results will be disseminated in research journals and through conference presentations.

Abbreviations

SCM	Septic cardiomyopathy
RSS	Refractory septic shock
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
CRRT	Continuous renal replacement therapy
LVEF	Left ventricular ejection fractions
VIS	Vasoactive inotropic score
MAP	Mean arterial pressure
$ScvO_2$	Central venous blood oxygen saturation
CI	Cardiac index

CPR	Cardiopulmonary resuscitation
AIDS	Acquired immune deficiency syndrome
IABP	Intra-aortic balloon pump
UFH	Unfractionated heparin
APTT	Activated partial thrombin time
ACT	Active clotting time
PaO_2	Partial pressure of oxygen in arterial blood
FiO_2	Fraction of inspire oxygen
PIP	Peak inspiratory pressure
PEEP	Positive end expiratory pressure
LOS	Length of stay
CRF	Case record form
APACHEII	Acute physiology and chronic health evaluation II
SOFA	Sequential organ failure assessment score
CRP	C-reactive protein
M	median
IQR	Inter-quartile range
FAS	Full analysis set
PPS	Per protocol set
SS	Safety analysis set

Supplementary file

Online supplement file 1: consent form.

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Contributors

Wei-yan Chen and Ze-bin Guo designed the trial. Tian-yu Kong, Qi-lin Yang, Yi-chao Wen and Xu-ming Xiong participated in the discussion of the plan, De-liang Wen and Zhen-hui Zhang made a decision to revise the plan. Ze-bin Guo, Tian-yu Kong, Wei-xiao Chen, Xiao-hua Chen, Qi-lin Yang, Yi-chao Wen, Qi-rui Wen and Feng Zhou conduct the plan. Wei-yan Chen draft the manuscript. De-liang Wen and Zhen-hui Zhang provided critical revision of the manuscript. De-liang Wen and Wei-yan Chen obtained funding for the trial. All authors discussed and helped to improve the protocol, and read and approved the final manuscript.

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References:

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**. *JAMA* 2016, **315**(8):801.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S *et al*: **Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study**. *The Lancet (British edition)* 2020, **395**(10219):200-211.
3. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K: **Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations**. *AM J RESP CRIT CARE* 2016, **193**(3):259-272.
4. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S: **Recognizing Sepsis as a Global Health Priority - A WHO Resolution**. *N Engl J Med* 2017, **377**(5):414-417.
5. Narváez I, Canabal A, Martín C, Sánchez M, Moron A, Alcalá J, Giacoman S, Magro M: **Incidence and evolution of sepsis-induced cardiomyopathy in a cohort of patients with sepsis and septic shock.** *MED INTENSIVA* 2018, **42**(5):283-291.
6. Sato R, Kuriyama A, Takada T, Nasu M, Luthe SK: **Prevalence and risk factors of sepsis-induced cardiomyopathy: A retrospective cohort study.** *MEDICINE* 2016, **95**(39):e5031.
7. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, Shahul S, Brown SM: **Septic Cardiomyopathy**. *CRIT CARE MED* 2018, **46**(4):625-634.
8. Ravikumar N, Sayed MA, Poonsuph CJ, Sehgal R, Shirke MM, Harky A: **Septic Cardiomyopathy: From Basics to Management Choices**. *Curr Probl Cardiol* 2021, **46**(4):100767.

9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC *et al*: **Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021**. *Intensive Care Med* 2021, **47**(11):1181-1247.

10. Hernandez G, Bruhn A, Luengo C, Regueira T, Kattan E, Fuentealba A, Florez J, Castro R, Aquevedo A, Pairumani R *et al*: **Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study.** *INTENS CARE MED* 2013, **39**(8):1435-1443.

11. Annane D, Vignon P, Renault A, Bollaert P, Charpentier C, Martin C, Troché G, Ricard J, Nitenberg G, Papazian L *et al*: **Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial.** In., vol. 370; 2007: 676-684.

12. Meng J, Hu M, Lai Z, Ji C, Xu X, Zhang G, Tian S: **Levosimendan Versus Dobutamine in Myocardial Injury Patients with Septic Shock: A Randomized Controlled Trial.** In., vol. 22; 2016: 1486-1496.

13. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RML, Santhakumaran S, Mason AJ, Cross M, Al-Beidh F, Best-Lane J *et al*: **Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis.** *The New England journal of medicine* 2016, **375**(17):1638-1648.

14. Pinto BB, Rehberg S, Ertmer C, Westphal M: **Role of levosimendan in sepsis and septic shock.** *Current opinion in anaesthesiology* 2008, **21**(2):168-177.

15. Martin L, Derwall M, Al ZS, Zechendorf E, Reuter DA, Thiemermann C, Schuerholz T: **The Septic Heart: Current Understanding of Molecular Mechanisms and Clinical Implications**. *CHEST* 2019, **155**(2):427-437.

16. Vallabhajosyula S, Jentzer JC, Geske JB, Kumar M, Sakhuja A, Singhal A, Poterucha JT, Kashani K, Murphy JG, Gajic O *et al*: **New-Onset Heart Failure and Mortality in Hospital Survivors of Sepsis-Related Left Ventricular Dysfunction**. *SHOCK* 2018, **49**(2):144-149.

17. Han L, Zhang Y, Zhang Y, Wu W, He P: **Risk factors for refractory septic shock treated with VA ECMO**. *Annals of Translational Medicine* 2019, **7**(18):476.

18. Kirkpatrick BV, Krummel TM, Mueller DG, Ormazabal MA, Greenfield LJ, Salzberg AM: **Use of extracorporeal membrane oxygenation for respiratory failure in term infants**. *PEDIATRICS* 1983, **72**(6):872-876.

19. Riera J, Argudo E, Ruiz-Rodríguez JC, Ferrer R: **Extracorporeal Membrane Oxygenation for Adults With Refractory Septic Shock**. *ASAIO J* 2019, **65**(8):760-768.

20. Park TK, Yang JH, Jeon K, Choi S, Choi J, Gwon H, Chung CR, Park CM, Cho YH, Sung K *et al*: **Extracorporeal membrane oxygenation for refractory septic shock in adults**. *EUR J CARDIO-THORAC* 2015, **47**(2):e68-e74.

21. Huang C, Tsai Y, Tsai P, Ko W: **Extracorporeal membrane oxygenation resuscitation in adult patients with refractory septic shock**. *The Journal of Thoracic and Cardiovascular Surgery* 2013, **146**(5):1041-1046.

22. Formica F, Avalli L, Martino A, Maggioni E, Muratore M, Ferro O, Pesenti A, Paolini G: **Extracorporeal Membrane Oxygenation With a Poly-Methylpentene Oxygenator (Quadrox D). The Experience of a Single Italian Centre in Adult Patients With Refractory Cardiogenic Shock**. *ASAIO J* 2008, **54**(1):89-94.

23. Tembo M, Harvey C, Duthie M, Pooboni S, Whitelaw J, Pandya H, Barry P, Peek G, Fermin R: **Extracorporeal membrane oxygenation for refractory septic shock in children: One institution's experience.** In., vol. 10; 2009: 534-535, 535.

24. McCune S, Short BL, Miller MK, Lotze A, Anderson KD: **Extracorporeal membrane oxygenation therapy in neonates with septic shock.** In., vol. 25; 1990: 479-482.

25. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA *et al*: **Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine**. *CRIT CARE MED* 2009, **37**(2):666-688.

26. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, Okhuysen-Cawley RS, Relvas MS, Rozenfeld RA, Skippen PW *et al*: **American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock.** *CRIT CARE MED* 2017, **45**(6):1061-1093.

27. Bréchot N, Luyt C, Schmidt M, Leprince P, Trouillet J, Léger P, Pavie A, Chastre J, Combes A: **Venoarterial Extracorporeal Membrane Oxygenation Support for Refractory Cardiovascular Dysfunction During Severe Bacterial Septic Shock***. *CRIT CARE MED* 2013, **41**(7):1616-1626.

28. Bréchot N, Hajage D, Kimmoun A, Demiselle J, Agerstrand C, Montero S, Schmidt M, Luyt C, Lebreton G, Hékimian G *et al*: **Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study**. *The Lancet (British edition)* 2020, **396**(10250):545-552.

29. Falk L, Hultman J, Broman LM: **Extracorporeal Membrane Oxygenation for Septic Shock**. *CRIT CARE MED* 2019, **47**(8):1097-1105.

30. Barreto BB, Gusmao-Flores D: **Long-Term Mortality in Extracorporeal Membrane Oxygenation**. *CRIT CARE MED* 2018, **46**(4):e348.

31. Ling RR, Ramanathan K, Poon WH, Tan CS, Brechot N, Brodie D, Combes A, MacLaren G: **Venoarterial extracorporeal membrane oxygenation as mechanical circulatory support in adult septic shock: a systematic review and meta-analysis with individual participant data meta-regression analysis**. *CRIT CARE* 2021, **25**(1):246.

32. Koponen T, Karttunen J, Musialowicz T, Pietiläinen L, Uusaro A, Lahtinen P: **Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery.** In., vol. 122; 2019: 428-436.

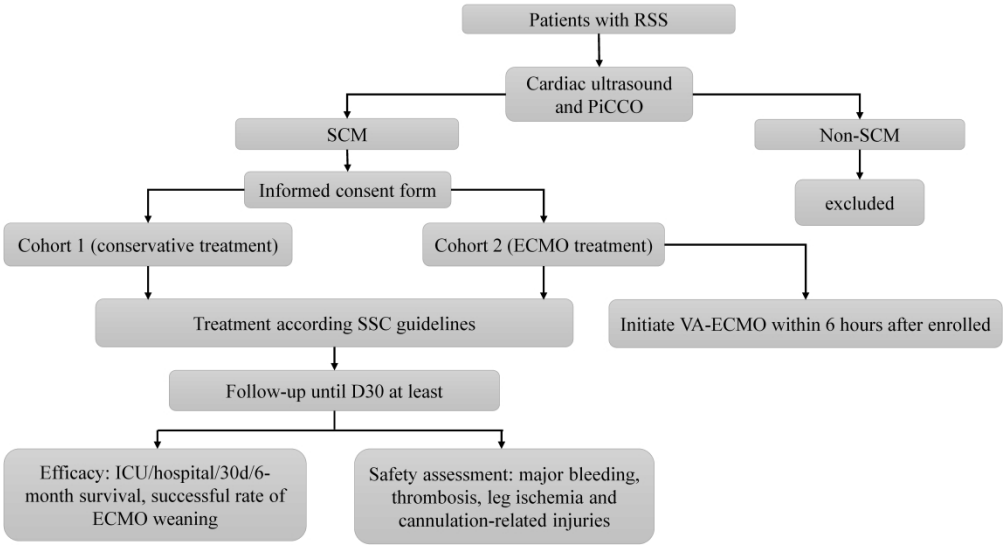
33. Lorusso R, Shekar K, MacLaren G, Schmidt M, Pellegrino V, Meyns B, Haft J, Vercaemst L, Pappalardo F, Bermudez C *et al*: **ELSO Interim Guidelines for Venoarterial Extracorporeal Membrane Oxygenation in Adult Cardiac Patients**. *ASAIO J* 2021, **67**(8):827-844.

34. Zwischenberger JB, Pitcher HT: **Extracorporeal Membrane Oxygenation Management: Techniques to Liberate from Extracorporeal Membrane Oxygenation and Manage Post-Intensive Care Unit Issues**. *CRIT CARE CLIN* 2017, **33**(4):843-853.

35. Schulman S, Kearon C: **Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients**. *J THROMB HAEMOST* 2005, **3**(4):692-694.

Figure legend:

Figure 1. Study flow chart. RSS, refractory septic shock; SCM, septic cardiomyopathy; ECMO, extracorporeal membrane oxygenation; PiCCO, pulse indicator continuous cardiac output techonology.



Study flow chart. RSS, refractory septic shock; SCM, septic cardiomyopathy; ECMO, extracorporeal membrane oxygenation; PiCCO, pulse indicator continuous cardiac output techonology.

293x159mm (600 x 600 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No.	Description	Page No.
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,16
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6,13
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.