PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Chen, Wei-yan; Guo, Ze-bin; Kong, Tian-yu; Chen, Wei-xiao; Chen, Xiao-hua; Yang, Qilin; Wen, Yi-chao; Wen, Qi-rui; Zhou, Feng; Xiong, Xu-ming; Wen, De-liang; Zhang, Zhen-hui

VERSION 1 – REVIEW

REVIEWER	Kollengode Ramanathan National University of Singapore
REVIEW RETURNED	01-Oct-2023

GENERAL COMMENTS	Introduction 1. What is severe septic cardiomyopathy ? 2. the SCCM guidelines needs citaton 3. Dobutamine failed to improve microcirculatory perfusion and metabolic despite an increasing cardiac index, heart rate and LVEF compared to placebo. 4. The paragraph highlighting the use of dobutamine and levosimendon can be summarised to one sentence to make the introduction shorter. 5. Resons for why sepsis is contraindication for ecmo is unclear from the paragraph. 6. What is backward equipment? 7. Which clinical investigators revealed that sepsis is not a contraindication? Can you cite them please? 8. Papers by PArk etal, Huang etal and Brechot etal needs to be cited. 9.nor have clear indications been proposed to help determine which patients with sepsis-induced cardiogenic shock should be treated with ECMO- I disagree with this statement. i refer the authors to the articles by Ling etal and Brechot etal which throw more light on when ECMO can be used in septic shock. Methods 10. How do the authors define SCM for the purpose of the study 11. Why should all patietns be considered as eligible candidates. Only patients with septic shock should be included. 12.Why do the authors insert a distal branch? It should be a distal perfusion catheter. 13. How is ECMO management standardised in the 6 ICUs. 14. If recruitment of patients has already started in May 2022, why is this paper submitted 18 months later. 15. How was the cut off VIS calculated as 120. Please provide evidence for this. Most centres provide VA ECMO if VIS > 30 16. The use of IABP in septic shock is controversial. Why do the

	authors include IABP in their therapy mode. 17. Please expalin the rationale for a Hb of 10 g/dL. Restrictive strategies are usually adopted for transfusion thresholds on ECMO. 18. How is irreversible brain damage and refractory bleeding diagnosed? 19, How can a decision tree become an endpoint?

REVIEWER	Lars Mikael Broman Karolinska University Hospital
REVIEW RETURNED	23-Jan-2024

GENERAL COMMENTS	bmjopen-2023-079212.r.0_review The authors have submitted a study protocol of a study that, according to the submitted text, has been ongoing for more than 1.5 years. I do not know if the study has started, hence, the format of some of my answers. The study aims to compare different outcome measures in refractory septic shock patients that have accepted extracorporeal life support, to patients that was offered conventional intensive care. The goal is to enroll 23-25 patients that will be subjects to ECMO and 35-39 patients that will serve as controls (conventional Intensive care). A power calculation has been performed. GENERAL VA ECMO (Please comply with the ELSO Maastricht Treaty Part 1 and Part 2 publications on terminology and nomenclature, Conrad et al. AJRCCM 2018; Broman et al. Crit Care 2019). English language needs editing Six (6) intensive care units will participate in this 3-year study. That means that each center will treat an average of 4 ECMOs (1 annual ECMO of 23-25 total in this study), and 6 controls (2 per year of the 35-39 “controls”). I seriously doubt both patient number and centers’ experience to be too low not to influence the outcome of this study. My worst worries are that there is no randomization and no control system reported in this protocol that prohibits the first 25 patient representatives to decide for ECMO, even in the same hospital, leaving all the later cases as controls treated at any of six hospitals. It is also unclear when, and who decides when it is time to back out (withdrawal of ECLS) in unclear cases, i.e. family financial situation may influence/bias this study (socio-economic bias). MAJOR On several spots references are not separated by comma, space. Page 5/23, Line 39-43: Reference missed/not stated Page 6/23, line 46/47: Did recruitment start in May 2022? Please check. Page 6/23, line 27-31: I would not expect any of these patients to be awake at all. All would need legal representative for consent. Then, ethically, I do not find it just for the representative to choose treatment arm, randomization at this stage would be better. Page 7/23: VIS >120 could be the cause for cardiac failure and patient failing due to afterload problem since vascular tone is not considered in any of the variables reported. Better go for Inotropic score, i.e. skip pure pressors - norepinephrine, vasopressin, angiotensin, and dopamine. How is “adequate fluid resuscitation” evaluated? Given a VIS of >120, I get the impression that, in everyday practice, a number of patients are still hypovolemic in this ICU culture. Page 8/23: VIS, reference since there are different algorithms. This far in the manuscript participants in this “multicenter” work has not been delineated. How about VIS also including levosimendan? Next question would be the value of separating inotropes/inodilators from

	pressors/inopressors and thus use an inotropic score and a vasopressor score to offer possibility for a mor detailed analysis of mosaic of distributive shock and cytotoxic cardiac failure in this prospective material. Page 9/23: Will cannulation configuration and cannula choice be standardized. An extremely important item excluded is cannula design and where the cannula tip will e placed. This is uttermost important for the drainage cannula in the perspective of development and severity of differential oxygenation. Sub-optimal VA ECMO cannulation, wrong cannulae, and bad ECMO management may be a killer, worse than the disease, refractory septic shock itself. Weaning criteria (page 10/23, line 9-16), A: Is “150 mL/kg per minute” normal Cardiac output or “Normal” ECMO blood flow? To me it is an ECMO flow in extremis, and it is certainly extremely high if you suggest Cardiac output at rest too B: Page 10/23, line 17: “SvO2” please define item correctly. Do you mean mixed venous saturations , albeit when ECMO is running a better term is “pulmonary” or “main pulmonary”, SpreO2 (preox sat?), SpaO2 (pulmonary artery?) [ELSO Maastricht]. On page 9, line 27 you use the correct “pre-oxygenator”. I suggest that you make a list of all physiologic abbreviations with explanation and definition to evade any misunderstandings. C: Cessation of ECMO (4). If, say, 20 days have passed and the pre-determined weaning criteria has not been reached (they are set ambitiously high), the patient is still recovering but patient reimbursement does not cover treatment any more will then ECLS be withdrawn? Who decides, healthcare or patient’s legal representative(s)? Separate funfing? Page 10/23: Primary outcome: Who will be called, and how many phone call attempts will be made? Other means to gather this information? How can this call response be validated? Page 11/23. Safety assessment: on (1), is the detailed investigational protocol for anatomical site of bleeding feasible in this multicentric study? Power/Sample size (P 12/23, top): “Fewer patients may choose ECMO …”. If it is the “patient”, i.e. legal representative that decides ECMO or conventional arm of study, a bias is introduced already from start, not the least from socio-economic standpoint; Paragraph partly repetitive (no need to tell “30-day again …” . P12/23, L 48-51: Blood samples only every second day? And only on four occasions? P13/23: How is the patient follow up at 30 days and 6 months? A phone call (method reported above for dead or alive at 30 days) will not do the Cardiac function assessment. P14/23, L 8: What do you men with database “… closed by the … “. Stats: How is “normality” checked? This section is to me repetitive and could be condensed. Since the 30-day outcome (dead or alive) is a 2 by 2 table, why not decide for Fisher’s Exact test from start? Describe how you will perform the propensity matching of the 23-25 ECMOs to the 35-39 “controls”. Are the control number large enough, will you have dropouts? P16/23, L27-29: “Two other studies also demonstrated … “ needs to be referenced or deleted. MINOR Number of abbreviations are not explained (ICU, RCT, PiCCO, etc.). Please check. “et al.” comes with a dot since it is a shortening of a Latin word (“alia”). Please check.

	Page 6/23, line 45: " … six Page 7/23, Line 55: (6), "return cannula" (ELSO Maastricht Treaty); Please check (7) and (9) fo conformity, no dots at end of sentence. Page 8/23, line 43: "The goal of MAP …" Page 8/2, line 56: (one dot too many after "s" (220 s) Page 10/23, row 29: " … by 500 mL/min every ..."; and check for other typos all through, for example spaces embedded in units, < 0.02 µ g/kg/min

VERSION 1 – AUTHOR RESPONSE

- **Reviewer 1** (Kollengode Ramanathan, National University of Singapore)

Introduction

1. What is severe septic cardiomyopathy?

- Thank you for your question. The statement "severe septic cardiomyopathy" is primarily base on the findings of our retrospective analysis, which we have published (Chen WY, Zhang ZH, Tao LL, Xu Q, Wei X, Chen MS: **Afterload-related cardiac performance identifies cardiac impairment and associates with outcome in patients with septic shock: a retrospective cohort study**. *J Intensive Care* 2021, **9**(1):33.). We utilized afterload-related cardiac performance (ACP, it is a ratio of measured to predicted cardiac output, which represents the cardiac ability to increase its output when systemic vascular resistance decreases in order to maintain a constant mean arterial pressure.) to stratify septic cardiomyopathy, defining ACP < 40% as indicative of severe impairment in cardiac function, and observed a significantly high mortality rate among patients. However, it should be noted that the definition and diagnostic criteria for septic cardiomyopathy remain unclear. Therefore, there are certain inaccuracies present in the assertion of severe septic cardiomyopathy. So we have changed "severe SCM" to "severe cardiac function impairment".

2. the SCCM guidelines needs citation

- thank you for your reminding. The citation has been added.

3. Dobutamine failed to improve microcirculatory perfusion and metabolic despite an increasing cardiac index, heart rate and LVEF compared to placebo. The paragraph highlighting the use of dobutamine and levosimendon can be summarized to one sentence to make the introduction shorter.

- Thank you for your suggestion. We have shortened the paragraph highlighting the use of dobutamine and levosimendon as follow: "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) Another positive inotropic drug, levosimendan, also has been tried to applied in the treatment of SCM."

4. Reasons for why sepsis is contraindication for ECMO is unclear from the paragraph.

- Thank you for your reminding. We have added reasons for why sepsis is contraindication for ECMO is unclear as follow: "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. Furthermore, patients with sepsis often present with thrombocytopenia and abnormal coagulation function, while ECMO necessitates anticoagulation therapy which can potentially worsen bleeding. 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. In Huang et al.'s study, hospital survival rate was much lower (15%)."

5. What is backward equipment?

- Thank you for your question. Here backward equipment means that the materials of ECMO at the early stage were not as good as it is now. "backward equipment" has been deleted for reason

of unclear expression and replaced with detailed reasons for why sepsis is contraindication for ECMO.

6. Which clinical investigators revealed that sepsis is not a contraindication? Can you cite them please?

- Thank you for your suggestions. The clinical researches supporting the use of ECMO in sepsis have been listed in the manuscript as follow" However, as the advancement of ECMO technology, improvements in materials of ECMO, 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. ECMO treatment of septic shock in neonatal and children has been in guidelines and consensus since 2008. Besides this, a single-center retrospective study found that V-A ECMO rescued more than 70% of the patients who developed refractory cardiovascular dysfunction during severe bacterial septic shock. Another multicenter cohort study found that survival at 90 days for patients with severe sepsis-induced cardiomyopathy who received V-A ECMO was significantly higher than for controls (60% vs 25%). Falk et al. reported a 90% hospital survival rate in septic shock patients with left ventricular failure and 64.7% in patients with distributive shock13. 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 V-A ECMO, and superior to distributed shock. Moreover, all survivors restored their cardiac function and had good long-term quality of life. 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."

7. Papers by Park et al, Huang et al and Brechot et al needs to be cited.

- Thank you for reminding. The citations have been added.

8. nor have clear indications been proposed to help determine which patients with sepsis-induced cardiogenic shock should be treated with ECMO- I disagree with this statement. I refer the authors to the articles by Ling etal and Brechot etal which throw more light on when ECMO can be used in septic shock.

- I am very sorry that I have searched Ling et al.'s and Brechot et al.'s literature on ECMO, but only found the discussion on the application of ECMO in sepsis and the indication of ECMO initiation in cardiogenic shock, but no specific indication of ECMO initiation in sepsis or in cardiac dysfunction caused by sepsis. Could you please provide specific literature for learning?

Methods

9. How do the authors define SCM for the purpose of the study

- To date, the definition and diagnostic criteria for septic cardiomyopathy remain unclear. In our study, SCM is the cardiac impairment associated with sepsis. Our study was designed with reference to indications of ECMO initiation in refractory cardiogenic shock.

10. Why should all patients be considered as eligible candidates. Only patients with septic shock should be included.

- 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.

11. Why do the authors insert a distal branch? It should be a distal perfusion catheter.

- Thank you for reminding. "a distal branch" has been changed to "a distal perfusion catheter".

12. How is ECMO management standardized in the 6 ICUs.

- First, the ECMO teams in the 6 centers were uniformly trained and qualified. Secondly, each center has more than 5 years of ECMO management experience with more than 200 cases. Third, operation indications contain therapy mode, canulation, the blood flow and the goal, management, anticoagulation, wean off ECMO and cessation of ECMO.

13. If recruitment of patients has already started in May 2022, why is this paper submitted 18 months later.
- I'm terribly sorry. I made a mistake. Participants recruitment commenced in May 2023.

14. How was the cut off VIS calculated as 120. Please provide evidence for this. Most centres provide VA ECMO if VIS > 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. "sustained hypotension despite infusion of very high-dose catecholamines (epinephrine > 1) μg/kg/min or dobutamine > 20) μg/kg/min with norepinephrine > 1 μg/kg/min)"
- 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. "despite adequate intravascular volume and the inability to maintain mean arterial pressure >65 mmHg despite infusion of very high-dose catecholamines (norepinephrine > 1 μg/kg/min, dopamine > 20 μg/kg/min or epinephrine > 1 μg/kg/min with dobutamine > 20 μg/kg/min)"
- According to the VIS formula, the VIS of the above studies was 100-120. In China, the number of sepsis patients with VIS > 30 in ICU is very large, and a majority of these cases can be effectively reversed. Consequently, researchers argue that the criteria of VIS > 30 is too low

15. The use of IABP in septic shock is controversial. Why do the authors include IABP in their therapy mode.
- From the perspective of the action principle of IABP, although IABP may not improve prognosis, researchers believe that IABP can reduce cardiac afterload and has a favorable effect on the heart.

16. Please explain the rationale for a Hb of 10 g/dL. Restrictive strategies are usually adopted for transfusion thresholds on ECMO.
- Thank you for your question. 2021 ELSO Adult and Pediatric Anticoagulation Guidelines recommend maintaining Hb > 70 g/L - 90 g/L. considering that patients with Refractory septic shock usually have abnormal coagulation function and impaired oxygen utilization, we have targeted Hb of 10 g/dL.

17. How is irreversible brain damage and refractory bleeding diagnosed?
- It may be more appropriate to use brain death instead of irreversible brain damage. The manuscript has been revised. The diagnostic criteria and protocol refer to World Brain Death Project-Determination of Brain Death/Death by Neurologic Criteria published in JAMA in 2020.
- Refractory bleeding here means major bleeding. The manuscript has been revised. Does ≥1 of the following factors apply: (1) Bleeding at a critical site; (2) Hemodynamic instability; (3) Clinically overt bleeding with hemoglobin decrease ≥2 g/dL or administration of ≥2 units RBCs.

18. How can a decision tree become an endpoint?
- Thank you for your suggestion. This endpoint has been deleted.
- **Reviewer 2** (Dr. Lars Mikael Broman, Karolinska University Hospital)

1. The authors have submitted a study protocol of a study that, according to the submitted text, has been ongoing for more than 1.5 years. I do not know if the study has started, hence, the format of some of my answers. The study aims to compare different outcome measures in refractory septic shock patients that have accepted extracorporeal life support, to patients that was offered conventional intensive care. The goal is to enroll 23-25 patients that will be subjects to ECMO

and 35-39 patients that will serve as controls (conventional Intensive care). A power calculation has been performed.

- Thank you for your question. I'm terribly sorry. I made a mistake. Participants recruitment commenced in May 2023.

GENERAL

2. VA ECMO (Please comply with the ELSO Maastricht Treaty Part 1 and Part 2 publications on terminology and nomenclature, Conrad et al. AJRCCM 2018; Broman et al. Crit Care 2019).

- Thank you for reminding. VA ECMO has been change to venoaterial ECMO

3. English language needs editing

- The English language has edited.

4. Six (6) intensive care units will participate in this 3-year study. That means that each center will treat an average of 4 ECMOs (1 annual ECMO of 23-25 total in this study), and 6 controls (2 per year of the 35-39 "controls"). I seriously doubt both patient number and centers' experience to be too low not to influence the outcome of this study.

- Firstly, each center has more than 50 ICU beds and treats approximately 2000 patients per year. each center has more than 5 years of ECMO management experience with more than 200 cases. Second, according to our review analysis, we have admitted many patients with septic shock, but after adequate fluid resuscitation and antibiotic utilization, few patients can meet the criteria of severe cardiac function impairment and refractory shock.

5. My worst worries are that there is no randomization and no control system reported in this protocol that prohibits the first 25 patient representatives to decide for ECMO, even in the same hospital, leaving all the later cases as controls treated at any of six hospitals. It is also unclear when, and who decides when it is time to back out (withdrawal of ECLS) in unclear cases, i.e. family financial situation may influence/bias this study (socio-economic bias).

- The current retrospective studies suggests that ECMO may significantly improve patient outcomes. Considering this, conducting randomized controlled studies may not be fair or ethical to patients in the conservative treatment group. Therefore, we only conducted cohort study.

MAJOR

6. On several spots references are not separated by comma, space.

- Thank you for reminding. References have been checked and revised.

7. Page 5/23, Line 39-43: Reference missed/not stated

- Reference has been added.

8. Page 6/23, line 46/47: Did recruitment start in May 2022? Please check.

- I'm terribly sorry. I made a mistake. Participants recruitment commenced in May 2023.

9. Page 6/23, line 27-31: I would not expect any of these patients to be awake at all. All would need legal representative for consent. Then, ethically, I do not find it just for the representative to choose treatment arm, randomization at this stage would be better.

- Thank you for your suggestions. Indeed, all participants should not awake during the enrollment phase, and the decision will be made by their legal representatives. The manuscript has been revised.
- As mentioned above, the current retrospective studies suggests that ECMO may significantly improve patient outcomes. Considering this, conducting randomized controlled studies may not

be fair or ethical to patients in the conservative treatment group. Therefore, we only conducted cohort study.

10. Page 7/23: VIS >120 could be the cause for cardiac failure and patient failing due to afterload problem since vascular tone is not considered in any of the variables reported. Better go for Inotropic score, i.e. skip pure pressors - norepinephrine, vasopressin, angiotensin, and dopamine.
How is “adequate fluid resuscitation” evaluated? Given a VIS of >120, I get the impression that, in everyday practice, a number of patients are still hypovolemic in this ICU culture.

- Thank you for your question. In the inclusion of this study, VIS>120 is only a diagnostic criterion for refractory shock, while meeting diagnostic criteria for cardiac failure is also required. Currently, there remains ambiguity in defining and establishing diagnostic criteria for sepsis-induced cardiac function impairment. Both LVEF and CI fail to account for the influence of afterload. SVRI from PICCO will be use as a reference for the afterload. Parameters such as afterload-related cardiac performance (ACP, it is a ratio of measured to predicted cardiac output, which represents the cardiac ability to increase its output when systemic vascular resistance decreases in order to maintain a constant mean arterial pressure.) could be consider for introduction, but were excluded from the criteria due to their lack of recognition.
- In fact, most patients with sepsis or septic shock require continued fluid administration following initial resuscitation. The fluid resuscitation strategy in our study follows the Surviving Sepsis Campaign Guidelines 2021, guided by dynamic measures, including stroke volume, stroke volume variation, pulse pressure variation, echocardiography, or serum lactate.

11. Page 8/23: VIS, reference since there are different algorithms. This far in the manuscript participants in this “multicenter” work has not been delineated. How about VIS also including levosimendan? Next question would be the value of separating inotropes/inodilators from pressors/inopressors and thus use an inotropic score and a vasopressor score to offer possibility for a more detailed analysis of mosaic of distributive shock and cytotoxic cardiac failure in this prospective material.

- The algorithm for VIS has been outlined in the section on Study Definitions. According to your suggestion, levosimendan has been added to the formula and the reference has been cited.
- Regarding separating inotropes/inodilators from pressors/inopressors, we have not come across any relevant literature reports at present. Therefore, further consideration is required to determine how to distinguish between distributive shock and impaired cardiac function.

12. Page 9/23: Will cannulation configuration and cannula choice be standardized. An extremely important item excluded is cannula design and where the cannula tip will e placed. This is uttermost important for the drainage cannula in the perspective of development and severity of differential oxygenation. Sub-optimal VA ECMO cannulation, wrong cannulae, and bad ECMO management may be a killer, worse than the disease, refractory septic shock itself.

- The ECMO teams in the 6 centers were uniformly trained and qualified. Each center has more than 5 years of ECMO management experience with more than 200 cases. The quality of ECMO’s operation and management is guaranteed.

13. Weaning criteria (page 10/23, line 9-16), A: Is “150 mL/kg per minute” normal Cardiac output or “Normal” ECMO blood flow? To me it is an ECMO flow in extremis, and it is certainly extremely high if you suggest Cardiac output at rest too.
B: Page 10/23, line 17: “SvO2” please define item correctly. Do you mean mixed venous saturations , albeit when ECMO is running a better term is “pulmonary” or “main pulmonary”, SpreO2 (preox sat?), SpaO2 (pulmonary artery?) [ELSO Maastricht]. On page 9, line 27 you use the correct “pre-oxygenator”. I suggest that you make a list of all physiologic abbreviations with explanation and definition to evade any misunderstandings.
C: Cessation of ECMO (4). If, say, 20 days have passed and the pre-determined weaning criteria has not been reached (they are set ambitiously high), the patient is still recovering but patient reimbursement does not cover treatment any more will then ECLS be withdrawn? Who decides, healthcare or patient’s legal representative(s)? Separate funding?

- Here “150 mL/kg per minute” refers to normal cardiac output.
- SvO_2 has been changed to $ScvO_2$, which refers to central venous blood oxygen saturation.
- Whether ECMO will be withdrawn will be decided by the patient’s legal representative.

14. Page 10/23: Primary outcome: Who will be called, and how many phone call attempts will be made? Other means to gather this information? How can this call response be validated?
- At the time of enrollment, we will leave more than 3 contact numbers and 1-2 contact addresses. The patient's legal representative is first contacted, followed by other immediate family members or those closest to the patient.

15. Page 11/23. Safety assessment: on (1), is the detailed investigational protocol for anatomical site of bleeding feasible in this multicentric study? Power/Sample size (P 12/23, top): “Fewer patients may choose ECMO …”. If it is the “patient”, i.e. legal representative that decides ECMO or conventional arm of study, a bias is introduced already from start, not the least from socio-economic standpoint; Paragraph partly repetitive (no need to tell “30-day again …”.
- Locating the bleeding site when major bleeding occurs is a routine procedure. Although venoarterial ECMO can affect the blood flow and increase the difficulty of operation, most bleeding sites can be identified by CT, endoscopy, contrast and ultrasound. And all centers have diagnostic capacity.

16. P12/23, L 48-51: Blood samples only every second day? And only on four occasions?
- The blood sample test conducted here is solely intended for data collection purposes, not the actual number of clinical tests.

17. P13/23: How is the patient follow up at 30 days and 6 months? A phone call (method reported above for dead or alive at 30 days) will not do the Cardiac function assessment.
- We will initially call to confirm the patient’s survival status. If the patient is still alive and has been discharged, then we will kindly request them to revisit the hospital for further follow-up. Alternatively, if the patient remains under care at another health care facility, we will kindly ask them to provide a cardiac function test report.

18. P14/23, L 8: What do you men with database “… closed by the … “. Stats: How is “normality” checked? This section is to me repetitive and could be condensed. Since the 30-day outcome (dead or alive) is a 2 by 2 table, why not decide for Fisher’s Exact test from start? Describe how you will perform the propensity matching of the 23-25 ECMOs to the 35-39 “controls”. Are the control number large enough, will you have dropouts?
- “… closed by the … “ means that the existence of a dedicated data management center, which ultimately secures the data upon group completion.
- Thank you for your suggestion. The effect of venoarterial ECMO treatment versus conventional treatment on 30 days survival has been changed to be performed using Fisher’s exact test.
- The initial objective is to achieve a 1:1 patient matching between the two groups based on age, SOFA score, VIS score or cardiac function, and other relevant parameters.

19. P16/23, L27-29: “Two other studies also demonstrated … “ needs to be referenced or deleted.
- In accordance with the editor's opinion, the discussion section has been deleted.

MINOR

20. Number of abbreviations are not explained (ICU, RCT, PiCCO, etc.). Please check.
- Thank you for reminding. All abbreviations have been checked.

21. “et al.” comes with a dot since it is a shortening of a Latin word (“alia”). Please check.
- Thank you for reminding. The manuscript has been checked.

22. Page 6/23, line 45: " … six Page 7/23, Line 55: (6), "return cannula" (ELSO Maastricht Treaty); Please check (7) and (9) fo conformity, no dots at end of sentence.
- Thank you for reminding. The manuscript has been checked.

23. Page 8/23, line 43: "The goal of MAP …"
- Thank you for reminding. The manuscript has been checked.

24. Page 8/2, line 56: (one dot too many after "s" (220 s)
- Thank you for reminding. The manuscript has been checked.

25. Page 10/23, row 29: " … by 500 mL/min every ..."; and check for other typos all through, for example spaces embedded in units, <0.02 µ g/kg/min
- Thank you for reminding. The manuscript has been checked.

VERSION 2 – REVIEW

REVIEWER	Kollengode Ramanathan National University of Singapore
REVIEW RETURNED	21-Apr-2024

GENERAL COMMENTS	Thank you for submitting the revised version. I still feel there are 3 important things to address 1. To answer author's question on the paper by Ling etal, I am sending the citation for their perusal. The papers of Ling etal and Brechot etal clearly outline which group of septic patients benefit most from VA ECMO and contradicts the author's statement. 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 Jul 14;25(1):246. doi: 10.1186/s13054-021-03668-5. PMID: 34261492; PMCID: PMC8278703. 2. If the termination of ECMO will be decided by the patient relative, I fear that the outcome measured will be biased. Imagine patients who are getting better but the next of kin request for termination of ECMO, the mortality in the intervention arm will definitely go up. This will affect the power calculation too. This needs to be addressed properly. 3. I also have my concerns about maintaining a supranormal Hb in this cohort. When ELSO guidelines are clear the authors explanation that a higher hemoglobin helps in oxygen utilisation in the tissues in refractory shock does not conform to logic. By increasing Hb you would increase oxygen delivery. Such a strategy is helpful if the patient is refractorily hypoxemic. In refractory septic shock the problem remains with the tissue extraction of oxygen and not with delivery. So aiming for Hb >10 would lead to unnecessary transfusions. I suggest the authors stick to ELSO guidelines and transfuse above recommended values only if patient is refractorily hypoxemic.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 (Kollengode Ramanathan , National University of Singapore)

1. To answer author's question on the paper by Ling etal, I am sending the citation for their perusal. The papers of Ling etal and Brechot etal clearly outline which group of septic patients benefit most from VA ECMO and contradicts the author's statement. (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 Jul 14;25(1):246. doi: 10.1186/s13054-021-03668-5. PMID: 34261492; PMCID: PMC8278703.)

 Thank you for sending us the paper by Ling etal. We have updated the introduction section of our manuscript based on the evidence from the study as follow: 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 addition, we have also revised part of our statement. For example, change “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?” to “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?”.

2. If the termination of ECMO will be decided by the patient relative, I fear that the outcome measured will be biased. Imagine patients who are getting better but the next of kin request for termination of ECMO, the mortality in the intervention arm will definitely go up. This will affect the power calculation too. This needs to be addressed properly.

 Thank you for your question. The decision to terminate ECMO treatment is normally made by the physician based on the cessation criteria during the study period. The decision to discontinue ECMO treatment will only be made by the legal representative of the patient in the event of a strong request for withdrawal from the study and cessation of treatment. Due to the limited funding of the study and the patient's legal representative’s right to withdraw from the study at any time, this situation is currently unavoidable. Given that the recovery period for septic cardiomyopathy is typically less than two weeks and the current limit of medical insurance coverage is high, coupled with the fact that families of ECMO patients are generally required to provide a deposit for treatment costs, the likelihood of this occurrence is reduced.

3. I also have my concerns about maintaining a supranormal Hb in this cohort. When ELSO guidelines are clear the authors explanation that a higher hemoglobin helps in oxygen utilisation in the tissues in refractory shock does not conform to logic. By increasing Hb you would increase oxygen delivery. Such a strategy is helpful if the patient is refractorily hypoxemic. In refractory septic shock the problem remains with the tissue extraction of oxygen and not with delivery. So aiming for Hb >10 would lead to unnecessary transfusions. I suggest the authors stick to ELSO guidelines and transfuse above recommended values only if patient is refractorily hypoxemic.

 Thank you for your suggestion. Based on your recommendation, following thorough discussion, we have made the decision to adhere to 2021 ELSO Adult and Pediatric Anticoagulation Guidelines and maintaining Hb > 70 g/L during ECMO treatment.