# Critical Care Ultrasound Oriented Shock Treatment in Intensive Care Unit: A Randomized Controlled Trial

**Wanhong Yin**
West China Hospital of Sichuan University
**Yao Qin**
Sichuan University
**Tongjuan Zou**
West China Hospital of Sichuan University
**Xueying Zeng**
Sichuan University
**Yi Li**
West China Hospital of Sichuan University
**Chengyong Ma**
West China Hospital of Sichuan University
**Dong Wang**
University of Central Florida
**Jing Yang**
West China Hospital of Sichuan University
**Hui Kang**
West China Hospital of Sichuan University
**Bingyang Liu**
Nanchong Central Hospital
**Yan Kang** ( kangyan@scu.edu.cn )
West China Hospital of Sichuan University
**Xiaoting Wang**
Chinese Academy of Medical Sciences & Peking Union Medical College
**Yangong Chao**
Tsinghua University
**Lina Zhang**
Xiangya Hospital Central South University

**Research Article**

**Keywords:** Critical care ultrasound, shock, outcome, Intensive Care Unit

**DOI:** https://doi.org/10.21203/rs.3.rs-141725/v1

# Abstract

**Objective:** To determine whether our established Pathophysiology and etiology treatment for shock based on critical ultrasonography (PESCUS) workflow is superior to standard care in the setting of Intensive Care Unit (ICU).

**Materials and Methods:** This is a prospective randomized controlled study. Critically ill adult shock patients were assigned to critical care ultrasound oriented treatment (CUOT) group who received treatment designed for different phases of shock guided by PESCUS workflow or standard care (SC) group who received standard care without treatment guided by PESCUS workflow.

**Results:** Of the 147 enrolled patients, 77 were assigned to the CUOT group and 70 to the SC group. There were no significant difference between the two groups at baseline. The ICU mortality in CUOT group was significantly lower (29.9% vs. 45.7%, P=0.047). The CUOT group received significantly less fluid than SC group in the stabilization and de-escalation phases. The median duration of stabilization and de-escalation phase of shock in CUOT group was 35.0 [IQR 19.3-59.8] hours compared with 60.0[IQR 24.0-78.0] hours in SC group, p=0.024).

**Conclusions:** Our study suggests utilization of PESCUS workflow can potentially improve ICU outcome in shock patient and avoid unnecessary fluid overload during shock recovery phase.

**Trial registration:** Critical Care Ultrasound Oriented Shock Treatment in ICU, (28/03/2017) NCT03093987 Registered, Retrospectively registered .


# Introduction

Shock is a common condition in critical care, affecting about one third of patients in the intensive care unit (ICU) (1, 2) and resulting from four potential but not necessarily exclusive pathophysiological mechanisms: hypovolemia, cardiogenic factors, obstruction, or distributive factors. The treatment of shock requires accurately monitoring the above pathophysiological changes (2, 3).

Critical care ultrasound (CCUS) has been used widely in critically ill to monitor organ function, diagnose etiology or guide procedures (4–9). Usage of transthoracic ultrasound has been reported to improve ICU survival (10). Supported by echocardiography and lung ultrasound, CCUS was used in monitoring hemodynamics (11–13). Even more important, CCUS is an efficient and reliable way when incorporated into protocolized examinations to visualize the pathophysiological changes and to rule in or out the etiologies, which then can further guide a more appropriate and accurate treatment strategy (13, 14, 15). Now many protocols focused on the diagnosis and to guide treatment were established for shock patients (16–18). These protocols were proved to be helpful in early diagnosis, to differentiate the type of shock (19, 20), and to guide further shock treatment (21–24). However, despite the encouraging situation, there was no well-designed randomized control study to prove that by adhering to protocolized CCUS application in shock patients can actually improve patient outcomes. We conducted this randomized

controlled trial in ICU to evaluate whether our established Pathophysiology and etiology treatment for shock based on critical ultrasono -graphy (PESCUS) workflow can improve shock patients' outcomes.

# Methods And Materials

### Study design

This was a prospective, randomized, controlled study which enrolled shock patients in medical intensive care unit (MICU), neurology intensive care unit (NICU) and surgical intensive care unit (SICU) in West China Hospital from March 2017 to October 2017.

Patients were randomly assigned into the study group (CUOT group) and the control group (SC group). The patients assigned to the study group received shock treatment guided by PESCUS workflow(described in detail in the following part of method section), and patients in the control group received standard ICU care without the use of PESCUS workflow. The physicians (medical team) who participated in the study were those certified for critical care medicine and had over 5 years' experience in critical care practice. Besides, they were also certified for bedside CCUS practice. The members of the CCUS team who assigned to perform the ultrasound examination according to the protocol were certified by the Chinese Critical Ultrasound Study Group (CCUSG) and had at least one-year practice experience. The measurements were recorded using the CX50 diagnostic ultrasound system (Philips, CX50, Bothell, WA, USA) and M-Turbo ultrasound system (FUJIFILM Sonosite, Bothell, WA, USA).

The protocol of the study was approved by the human ethics committees at Sichuan University (No. 2017(35)) and was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association.

### Patients

Patients admitted in MICU, SICU and NICU during the study period were screened for entry into this trial.

The study inclusion criteria are: (1) systolic blood pressure (SBP) < 90mmHg or mean blood pressure < 65mmHg or SBP decrease >40mmHg; (2) the onset of shock was less than 6 hours before ICU admission; (3) positive with at least one of the conditions below: Lactate level >2mmol/L; Capillary Refill Time >4.5s; Urine output per hour<0.5ml/kg; Clammy skin, limbs cold, unconsciousness. The patient who met all three above mentioned criteria was eligible for entry into the study. Patients were excluded from the study if they were: (1) age of <18 years; (2) pregnant; (3) refused to participate the study.

The patients were followed once enrolled and the data were recorded till death or end of ICU stay by dedicated investigators. Primary and secondary outcomes were analyzed after the trial was completed.

The study team discussed the trial's risks, benefits and other aspects with the patients and, if required, the participants' legal representatives, before the trial began. The study team gave the potential participant ample time and opportunity to ask questions about the trial and discuss it with relatives and family

members. Informed written consent was obtained from a legal representative of the family under the circumstance that the patient was unconsciousness or sedated upon the enrollment. They were informed they have the right to withdraw consent at any time without penalty, repercussions or reason. In condition that the patient in salvage phase, the verbal consent was obtained immediately, and the informed written consent was signed after the rescue by the patient or the patient's legal representative.

### Interventions

Once enrolled, patients in the study group were immediately screened by PESCUS workflow. The results of the CCUS exams were double checked by two different qualified CCUS team members and reported to the leading physician of the medical team right after the examination. Then, the PESCUS workflow based treatment in different shock phases were enforced by the medical team under the lead of the responsible physician. The protocol compliance was monitored consistently by a dedicated study coordinator, who also was responsible to provide timed prompts.

Patients in the control group received standard ICU care which including standard but not protocolized ultrasound exam if it was decided to be necessary by the team attending.

### Pathophysiology and etiology treatment for shock based on critical ultrasonography(PESCUS) workflow

The PESCUS workflow was created by the Critical Care Medicine Department at West China Hospital based on the guidelines recommended shock diagnosis and treatment strategy (2, 25, 26) and the 3-year cumulative CCUS experience of the team. The protocol was not only an examination protocol to facilitate diagnosis but also to guide the treatment plan based on the established workflow (Figure 1).

If a patient was in shock salvage phase upon enrollment, a cardiorespiratory focused assessment performed by CCUS team will be initiated first (27), which included five standard views of heart (12) and ten views of lung. This bedside assessment was finished within 5 minutes and the results were then applied immediately to the patient to initiate "Pivotal treatment" or "Rapidly launching target treatment", or both. The "Pivotal treatment" focused on finding whether there were ultrasonic signs of massive pulmonary embolism, cardiac tamponade and pneumothorax that could be the culprit to the life threatening shock, and the bedside interventions were then applied immediately to "salvage" the conditions such as guided thrombolysis, needle aspiration, and tube drainage. As those interventions were the key to save shock patients in such conditions, they were defined as "Pivotal treatment". The "Rapidly launching target treatment" was then launched after "Pivotal treatment" or in the case patient did not require "Pivotal treatment" to shorten duration of salvage phase of shock, which included fluid challenge, inotrope and vasoactive drugs to treat the severe hypovolemia, pump failure and vasoparalysis, respectively.

For patients in optimization phase upon enrollment, hemodynamic detailed assessment with CCUS was performed. The examination which were performed within 20 minutes and the results were interpreted to guide treatment plan. The ECHO included the assessment of IVC, the right heart, the diastolic and systolic

function of LV, the cardiac output, the left atrium pressure, and the deduced systemic resistance; the lung ultrasound included the eight-area exam focused on the lung water. The detailed ultrasonic assessment has two aims: the first is to diagnose the type of shock to guide etiological treatment, which has been shown leading to a better outcome in previous publications(28, 29), such as searching and treating massive hemorrhage in hypovolemic shock; screening infection sources for drainage or surgery in patients who have distributive shock pattern; and finding the regional wall motion abnormalities which may indicate acute coronary syndrome in patients undergoing cardiogenic shock. The second aim is to initiate goal directed titration therapy, which is through searching the abnormally pathophysiological changes of circulation to provide precise treatments (2,13,15,30) to improve the tissue perfusion. The treatments, such as fluid resuscitation and vasopressin administration, were titrated to an improvement of more than 10% lactate clearance every two hours (31,32). The medical team repeated the examination every four hours thereafter and adjusted the treatments accordingly until the end of the optimization phase, which is indicated by no increasing of the vasopressors, the lactate level reached less than 2.0 mmol/L or Capillary refill time <2s, and hour urine volume>0.5 ml/kg.h.(25,33,34).

The patients in de-escalation phase were performed with volume focused ultrasonic assessment which mainly focused on the IVC, the left atrium pressure and the lung water to evaluate whether there was fluid overload (35-37). If there were signs of fluid overload, diuresis was administrated without compromise the hemodynamics.

Details regarding the PESCUS workflow are provided in the Methods section in the Supplementary Appendix (S1).

## Data collection

Data were collected at baseline in both groups including age, sex, APACHE II, SOFA, diagnosis at admission, mean blood pressure, use of vasoactive agents, urine output per hour, lactate level, tidal volume and PEEP and $PaO_2/FiO_2$. Reports of CCUS exam, hemodynamics, fluid and drugs usage in both groups were recorded. The ICU mortality was our primary outcome. We also recorded the volume of fluid balance, source control, length of shock, duration of ventilation, length of ICU and hospitalization as secondary outcomes.

## Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. The results were illustrated as continuous variables as means ±SD or medians and interquartile ranges depending on the normality of data. Categorical data were presented as proportions or percentages. Student's t-test or the Wilcoxon rank-sum test was used to analyze differences between groups as needed. Fisher's exact test was used to analyze categorical variables including the primary outcome. The Kaplan–Meier method was used to demonstrate patient risk of death from the start of the trial to the $28^{th}$ day of treatment. The SPSS for mac (version 22.0; IBM Corp., Armonk, NY) was used for data statistical analysis. $P < 0.05$ was considered as statistically significant.

# Results

A total of 296 patients were screened, of whom 146 were excluded due to onset of shock > 6h, declined or unable to give consent. The remaining 150 patients were randomly assigned to CUOT group or SC group. After randomization, 2 patients failed to provide delayed consent in the CUOT group and 1 patient in the SC group lost follow up, eventually 147 patients completed the study (Fig. 2).

Demographic and clinical characteristics at baseline were similar in the two groups, as listed in Table 1. There were no significant differences between CUOT group and SC group in terms of APACHE II score, SOFA score, norepinephrine dose, mean blood pressure, lactate, urine output, $PaO_2/FiO_2$, mechanical ventilation and types of shock on admission. Only one patient suffered obstructive shock secondary to pulmonary embolism which was confirmed by computed tomographic pulmonary angiography (CTPA). The control group received standard non-protocolized ultrasound exam for 28 cases of cardiac structural examination, 32 cases of thrombosis screening, and 30 cases of hemodynamic examination.

### Primary outcomes

23 out of 77 patients in the CUOT group died during ICU stay, while 32 out of 70 patients died in the SC group. The ICU mortality in CUOT group was lower than SC group (29.9% vs. 45.7%, p=0.047). The 28-day risk of death after ICU admission was also higher in the SC group (p=0.036) (Figure 3).

### Secondary outcomes

There was no significant difference between CUOT group and SC group regarding the total fluid intake and output, and shock duration during the salvage and optimization phase. However, the CUOT group received significantly less fluid intake and output than the SC group in the stabilization and de-escalation phases (7475.0 [IQR 4704.0-10465.7] vs.10000.0 [IQR 5864.0-14916.4], p=0.016; 6857.0 [IQR 4415.0-11384.0] vs. 8810.5 [IQR 6316.3-12901.3], p=0.046, respectively).

Also, there was a significantly shorter shock duration time in the stabilization and de-escalation phase in CUOT group compare with SC group (35.0 hours [IQR 19.3-59.8] vs. 60.0 hours [IQR 24.0-78.0], p=0.024) (Table 2). Infection sources were successfully detected at bedside by PESCUS workflow in 3 patients in the CUOT group, who were subsequently transferred to the operation room and had the source removed without delaying in the optimization phase of shock.

# Discussion

In this randomized trial conducted in a tertiary hospital in China, we showed that critical care ultrasound oriented shock treatment significantly reduced ICU mortality in shock patients. By utilization the PESCUS workflow, the source of infection is more likely to be detected at the early phase of septic shock, and less fluid is needed to maintain hemodynamic stability.

This is the first randomized controlled study to show that protocolized CCUS utilization improves the mortality in shock patients. It is different from the other published randomized controlled trial on shock patients, such as ARISE, ProCESS, PROMISE, ALBIOS and SEPSISPAM (1, 38–42), Since those studies were mainly focused on septic shock patients, especially early phase of septic shock to investigate whether an appropriate goal or the type of fluid used for resuscitation could improve the outcomes of shock. The negative results indicate to expect achieving a single target or administrating a special type of fluid to reverse shock is unrealistic at current stage (43). Thus, a protocol to continuously guide and integrate individual therapy into different phases of shock is required to improve outcomes in all types of shock in the setting of ICU. This PESCUS workflow we presented in this study was designed to fulfill this need.

There are several advantages by utilizing PESCUS workflow in shock patient. First, PESCUS workflow is not a protocol that aiming to achieve certain goals, instead, it is a workflow to guide the best clinical practice and improve efficiency during all phases of shock. This protocol was designed to facilitate shock etiology treatment as well as the standard critical care supportive treatment simultaneously, and this combined etiology and support treatment strategy has been proved more effective in previous publications (29). Furthermore, by utilizing protocolized CCUS at bedside, the types of shock can be identified in minutes and the etiology treatment can be initiated and completed significantly quicker after shock onset. To a patient presented with distributive shock on US with accompanied clinical signs of infection, septic shock would be highly suspected and the source of infection potentially can be searched immediately by using the same equipment and personnel at the same time without any delay, as presented by PESCUS workflow (44). On the other hand, without protocolized bedside US, the control group may cost more time identifying the type of shock and then search the source of infection with other tools, such as CT, MRI that needs transferring or may miss the diagnosis with non-protocolized ultrasound examination. In our study, infection sources were successfully identified in 3 patients at bedside in the CUOT group, who were then sent to the operation room and had the source controlled in timely manner. This is the most important factor which have contributed to the observed survival benefit in this group.

Second, PESCUS workflow guides the individual treatment regarding the pathophysiological changes in different courses of shock. Depending on the phase of shock, the main treatment focus are different. In the situation of acute severe shock, salvage treatment is usually the only option left (2); detailed monitoring of the hemodynamics should be initiated right after salvage to optimize the treatment; when the circulation is stable, try to remove the overloaded fluid and de-escalation should be always considered. The PESCUS workflow is designed to guide treatment at all phases of shock. By visualization of the heart and lung, CCUS makes it more efficient to search the cause of life threatening shock, as well as to facilitate the life-saving procedures. In the optimization phase the CCUS not only provides numbers but also pathophysiological changes in detail including the ventricular interaction which are essential to carry out optimized individual treatment.

Third, by following PESCUS workflow, we had demonstrated less fluid administration during de-escalation and stabilization phases of shock. In many cases, the fluid resuscitation is double-edged sword to patients; many studies had proved that fluid overload lead to bad outcome (45–47). The volume focused ultrasonic assessment in de-escalation phase operated as one of the daily routine can potentially limit the fluid intake without insult the circulation. The CUOT group in our study received significantly less fluid in the stabilization and de-escalation phases, which could contribute to the significantly shorter shock duration.

Therefore, PESCUS workflow application in shock treatment can not only monitor the hemodynamics to guide therapy, but also help to diagnose the type of shock to decide the key measurements, guide the etiologies searching and improve the outcome. Furthermore, in our protocol, the treatments for different phase of shock are covered and integrated into a bundle, which makes the therapy to shock patients more informative and effective.

There are several drawbacks of our study. First, though the mortality rate we reported in control group is comparable to several literatures reported (48, 49). The overall mortality rate reported in our study is higher than most of the other similar studies (49, 50). The reason behind may be the patients we recruited were usually more severe with overall condition since we are the end point of referral center for whole west part of China. This might affect the representativeness of the study to generally healthier patient population. Second, the patients and physicians were not blinded in this study which can potentially cause bias. We had set up regulations to minimize CCUS team's participation into the patients' management, however, with more eyes on the study group than the control group, this could potentially increase the attention to the patient and contribute to better outcome. Third, as a single center research, although the differences highlighted seem clinically substantial, the data are actually fragile. We have planned to expand the sample size with a multicenter study design to confirm those results.

# Conclusion

Our study suggests that CCUSOST is an effective and promising tool which can lead to more accurate and precise evaluation and treatment for the shock patients. The utilization of protocolized CCUS can potentially improve ICU outcome in shock patients.

# List Of Abbreviations

PESCUS, Pathophysiology and etiology treatment for shock based on critical ultrasonography;

CCUS, critical care ultrasound;

CCUE, critical care chest ultrasonic examination for emergency;

US, ultrasound;

PE, pulmonary embolism;

SVR, systemic vascular resistance;

PCI, Percutaneous Transluminal Coronary Intervention;

ACS, acute coronary syndrome;

RV, right ventricle;

Lac, lactate;

UOH, urine output per hour;

HR, heart rate;

CUOT, critical care ultrasound oriented treatment;

SC = standard care.

# Declarations

### Ethics approval and consent to participate

Our study was endorsed by the ethics committee of West China Hospital, Sichuan university, the committee's reference number is 2017 (No.35).All participants in the trial were agreed by the subjects or their family members and signed a consent form.

### Consent for publication

Written informed consents were obtained from all the patients for publication of this review and accompanying images.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

### Funding

No funding.

### Authors' contributions

WH wrote the manuscript and revised the manuscript. YQ organized and analyzed data, wrote the manuscript. DW and YK revised the manuscript. TZ, XZ, YL, CM, JY, HK and BL participated in trials and data collection. XW, YC and LZ participated in experimental design. All authors read and approved the final manuscript.

**Acknowledgment**

Not applicable

# References

1. Sakr Y, Reinhart K, Vincent JL, Sprung CL, Moreno R, Ranieri VM, et al. Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med* 2006; 34:589-597.
2. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med* 2013; 369:1726-1734 .
3. Weil MH, Shubin H. Proposed reclassification of shock states with special reference to distributive defects. *Adv Exp Med Biol* 1971; 23:13-23.
4. Mayo PH, Beaulieu Y, Doelken P, Feller-Kopman D, Harrod C, Kaplan A, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française Statement on Competence in Critical Care Ultrasonography. *Chest* 2009; 135:1050-1060.
5. Narasimhan M, Koenig SJ, Mayo PH. A Whole-Body Approach to Point of Care Ultrasound. *Chest* 2016; 150:772-776.
6. Beaulieu Y. Bedside echocardiography in the assessment of the critically ill. *Crit Care Med* 2007; 35[Suppl.]: S235–S249.
7. Moran DE, Gibney RG. Point-of-care ultrasonography. *New England Journal of Medicine* 2011; 104:749.
8. Frankel HL, Kirkpatrick AW, Elbarbary M, Blaivas M, Desai H, Evans D, et al. Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonography in the Evaluation of Critically Ill Patients-Part I: General Ultrasonography. *Crit Care Med* 2015; 43:2479-2502.
9. Volpicelli G, Elbarbary M, Blaivas M, Lichtensteinda DA, Mathis G, Kirkpatrick AW, et al. International Liaison Committee on Lung Ultra-sound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICLUS). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* 2012; 38:577–591.
10. Feng M, McSparron JI, Kien DT, Stone DJ, Roberts DH, Schwartzstein RM, et al. Transthoracic echocardiography and mortality in sepsis: analysis of the MIMIC-III database. *Intensive Care Med* 2018; 44:884-892LA.
11. Salem R, Vallee F, Rusca M, Mebazaa A. Hemodynamic monitoring by echocardiography in the ICU: the role of the new echo techniques. *Current Opinion in Critical Car* 2008; 14:561–568.

12. Via G , Hussain A , Wells M , Reardon R , ElBarbary M , Noble VE, et al. International Liaison Committee on Focused Cardiac UltraSound (ILC-FoCUS); International Conference on Focused Cardiac UltraSound (IC-FoCUS). International Evidence-Based Recommendations for Focused Cardiac Ultrasound. *J Am Soc Echocardiogr* 27:683.e1-e33 , 2014.
13. Levitov A, Frankel HL, Blaivas M, Kirkpatrick AW, Su E, Evans D, et al. Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonogra-phy in the Evaluation of Critically Ill Patients-Part II: Cardiac Ultrasonography. *Crit Care Med* 2016; 44:1206-1227.
14. Wang XT, Liu DW, Zhang HM, Chai WZ. Integrated cardiopulmonary sonography: a useful tool for assessment of acute pulmonary edema in the intensive care unit. *J Ultrasound Med* 32014; 3:1231-1239.
15. Yin WH, Li Y, Zeng XY, Qin Y,Wang D, Zou TJ, et al. The utilization of critical care ultrasound to assess hemodynamics and lung pathology on ICU admission and the potential for predicting outcome. *PLoS One* 2017; 12:e0182881.
16. Perera P, Mailhot T, Diley D. The RUSH Exam: rapid ultrasound in shock in the evaluation of the critically ill. *Emerg Med Clin N Am* 2010*;* 28:29–56.
17. Lichtenstein D. FALLS-protocol: lung ultrasound in hemodynamic assessment of shock. *Heart Lung and Vessels 2013;* 5:142–147.
18. Mok KL. Make it SIMPLE: enhanced shock management by focused cardiac ultrasound. *J Intensive Care* 2016; 4:51.
19. Manno E, Navarra M, Faccio L,Motevallian M, Bertolaccini L, Mfochivè A, et al. Deep impact of ultrasound in the intensive care unit: the "ICU-sound" protocol. *Anesthesiology* 2012; 117: 801-809.
20. Heiberg J, Elansary D, Canty DJ, et al. Focused echocardiography: a systematic review of diagnostic and clinical decision-making in anaesthesia and critical care. *Anaesthesia* 2016; 71:1091-1100.
21. Zhang Z, Xu X, Ye S, Xu L. Ultrasonographic measurement of the respiratory variation in the inferior vena cava diameter is predictive of fluid responsiveness in critically ill patients: systematic review and meta-analysis. *Ultrasound Med Biol* 2014; 40:845-853.
22. Long E , Oakley E, Duke T, Babl FE. Paediatric Research in Emergency Departments International Collaborative (PREDICT). Does respiratory variation in Inferior Vena Cava diameter predict fluid responsiveness: a systematic review and meta-analysis. *SHOCK* 2017; 550–559.
23. Cameli M, Mondillo S, Solari M, Righini FM, Andrei V, Contaldi C, et al. Echocardiographic assessment of left ventricular systolic func-tion: from ejection fraction to torsion. *Heart Fail Rev* 2016; 21:77-94.
24. Porter TR, Shillcutt SK, Adams MS, Desjardins G, Glas KE, Olson JJ, et al. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2015; 28:40-56.
25. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580-637.

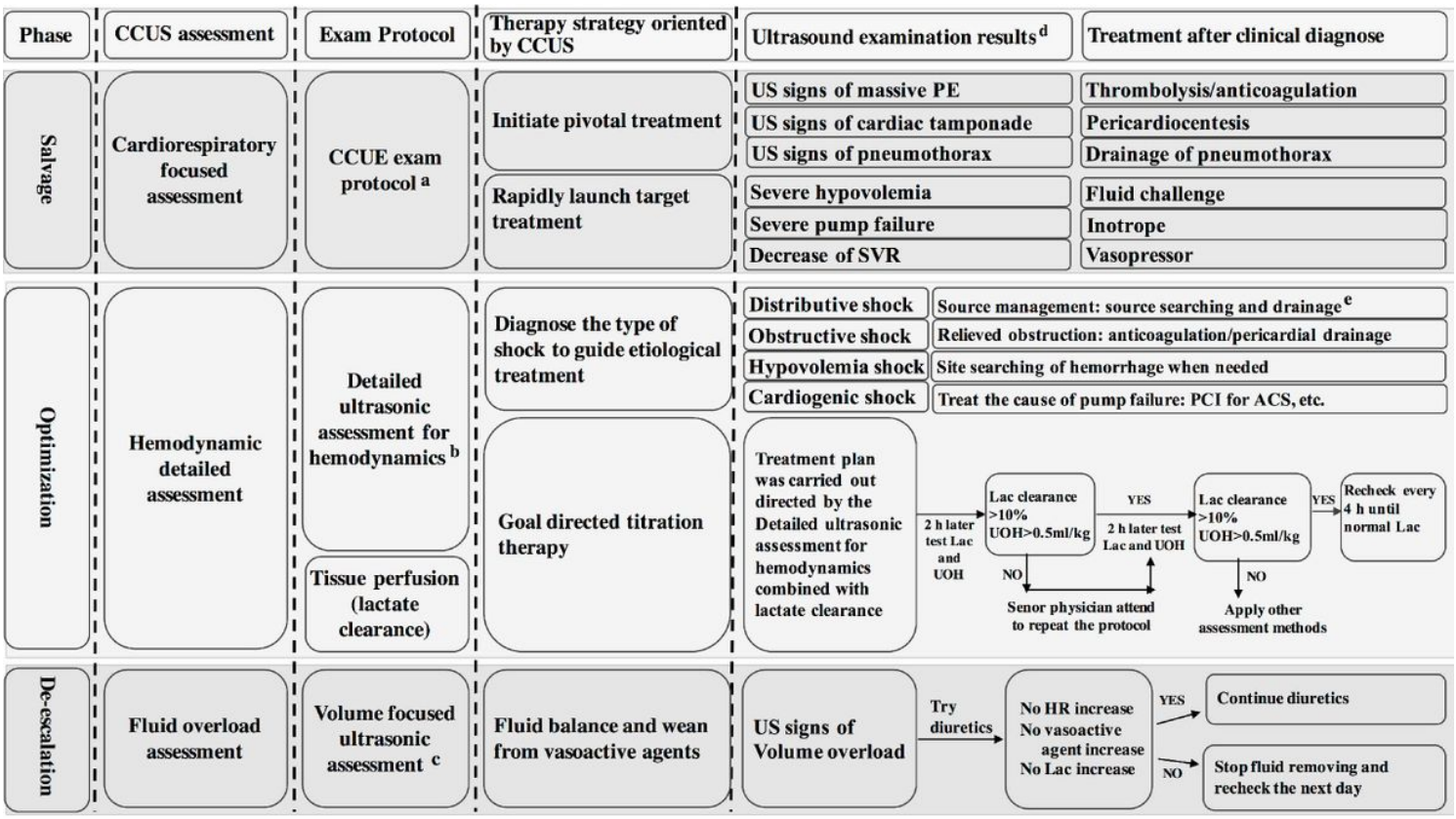
26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal* 2016; 37,2129–2200.
27. Wang XT, Liu DW, He HW, Du W, Zhang HM, Liu Y, et al. Using critical care chest ultrasonic examination in emergency consultation: a pilot study. *Ultrasound Med Biol* 2015; 41: 401-406.
28. Breitkreutz R, Walcher F, Seeger FH. Focused echocardiographic evaluation in resuscitation management: concept of an advanced life support-conformed algorithm. *Critical care medicine* 2007; 35:S150-161.
29. Leligdowicz A, Dodek PM, Norena M, Leligdowicz A1, Dodek PM, Norena M, et al. Cooperative Antimicrobial Therapy of Septic Shock Database Research Group : Association between source of infection and hospital mortality in patients who have septic shock. *American Journal of Respiratory & Critical Care medicine* 2014; 189:1204.
30. Shokoohi H, Boniface KS, Pourmand A, Davison DL, Hawkins KD, Buhumaid RE, et al. Bedside ultrasound reduces diagnostic uncertainty and guides resuscitation in patients with undifferentiated hypotension. *Crit Care Med* 2015; 43: 2562–2569.
31. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Critical Care Medicine* 2004; 32:1637.
32. Gu WJ, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. *Intensive Care Med* 2015; 41: 1862.
33. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996; 171:221–226.
34. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; 37:1670-1677.
35. Via G, Storti E, Gulati G, Neri L, Mojoli F, Braschi A. Lung ultrasound in the ICU: from diagnostic instrument to respirato-ry monitoring tool. *Minerva Anestesiol* 2012; 78:1282-1296.
36. Allyn J, Allou N, Dib M, Tashk P, Desmard M, Dufour G, et al. Echocardiography to predict tolerance to negative fluid balance in acute respiratory distress syndrome/acute lung injury. *J Crit Care* 2013; 28:1006-1010.
37. Boyd JH, Sirounis D, Maizel J, Slama M. Echocardiography as a guide for fluid management. *Crit Care* 2016; 20:274.
38. ARISE Investigators, Anzics Clinical Trials Group, Peake SL, Delaney A, Bailey M, CameronPA, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371:1496–1506.
39. Process Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; 370:1683–1693.

40. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311.
41. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; 370:1412-1421.
42. Asfar P, Meziani F, Hamel JF, SEPSISPAM Investigators. High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; 370:1583-1593.
43. Osborn TM. Severe Sepsis and Septic Shock Trials (ProCESS, ARISE, ProMISe): What is Optimal Resuscitation? *Crit Care Clin* 2017; 33:323-344.
44. Miyague AH, Mauad FM, Martins WP, Benedetti AC, Ferreira AE, Mauad-Filho F : Ultrasound scan as a potential source of nosocomial and crossinfection: a literature review. *Radiol Bras* 2015; 48:319-23.
45. Kuzkov VV, Kirov MY, Sovershaev MA, Kuklin VN, Suborov EV, Waerhaug K, et al. Extravascular lung water determined with single transpulmonary thermodilution correlates with the severity of sepsis-induced acute lung injury. *Critical Care Medicine* 2006; 34:1647-1653.
46. O'Connor ME, Prowle JR. Fluid Overload. *Crit Care Clin* 2015; 31:803-821.
47. Benes J, Kirov M, Kuzkov V, Lainscak M, Molnar Z, Voga G, et al. Fluid Therapy: Double-Edged Sword during Critical Care? *Biomed Res Int*2015; 2015:729075.
48. Cecconi M, De Backer A, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European society of Intensive Care Medicine. *Intensive Care Med* 2014; 40:1795-1815.
49. Puymirat E, Fagon JY, Aegerter P, Diehl JL, Monnier A, Hauw-Berlemont C, et al. Cardiogenic shock in intensive care units: evolution of prevalence, patient profile, management and outcomes, 1997-2012. *Eur J Heart Fail* 2017 ; 19:192-200.
50. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock:2016. *Intensive Care Med* 2017 ; 45: 486-

# Tables

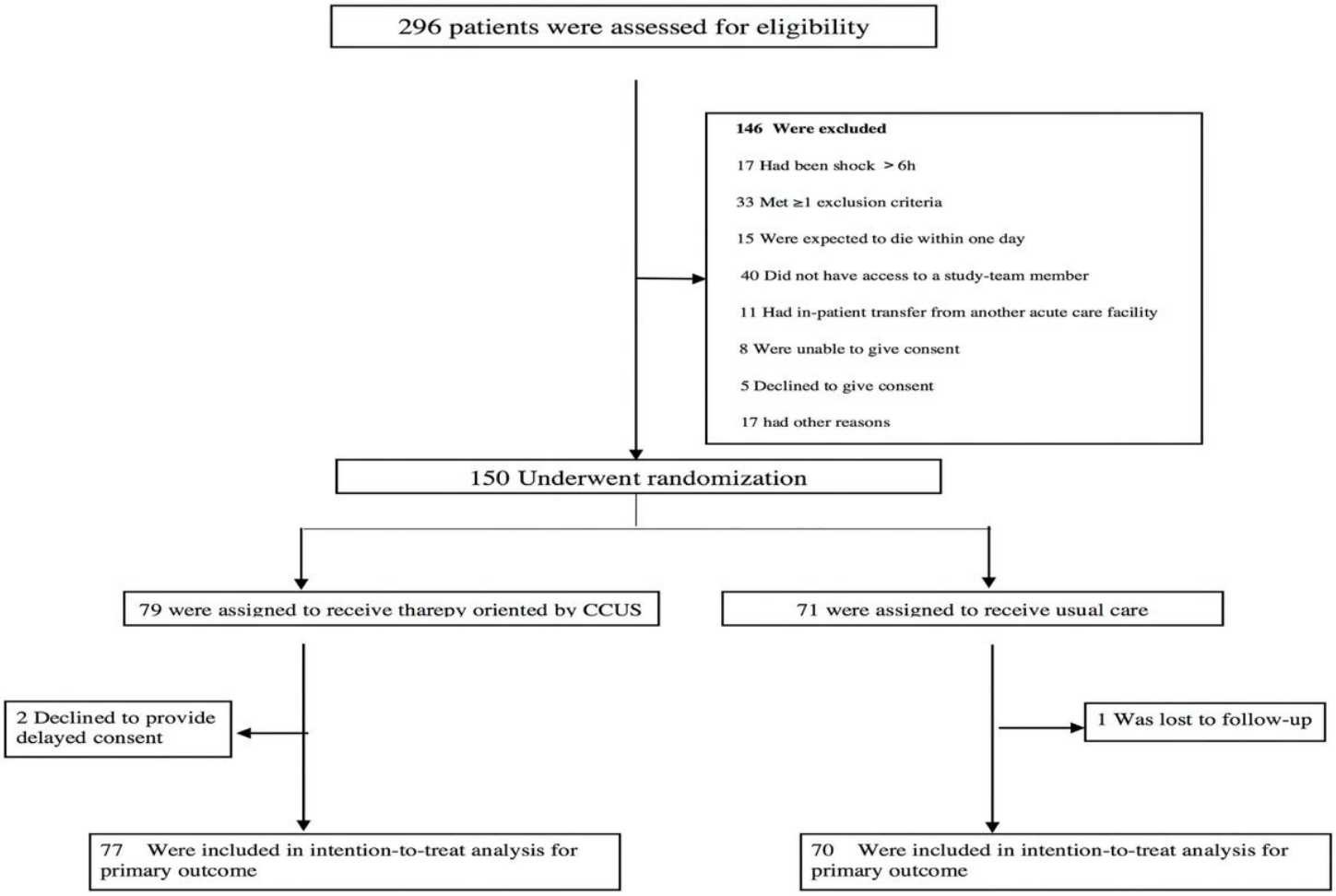
Due to technical limitations, table 1 & 2 PDFs are only available as a download in the Supplemental Files section.

# Figures



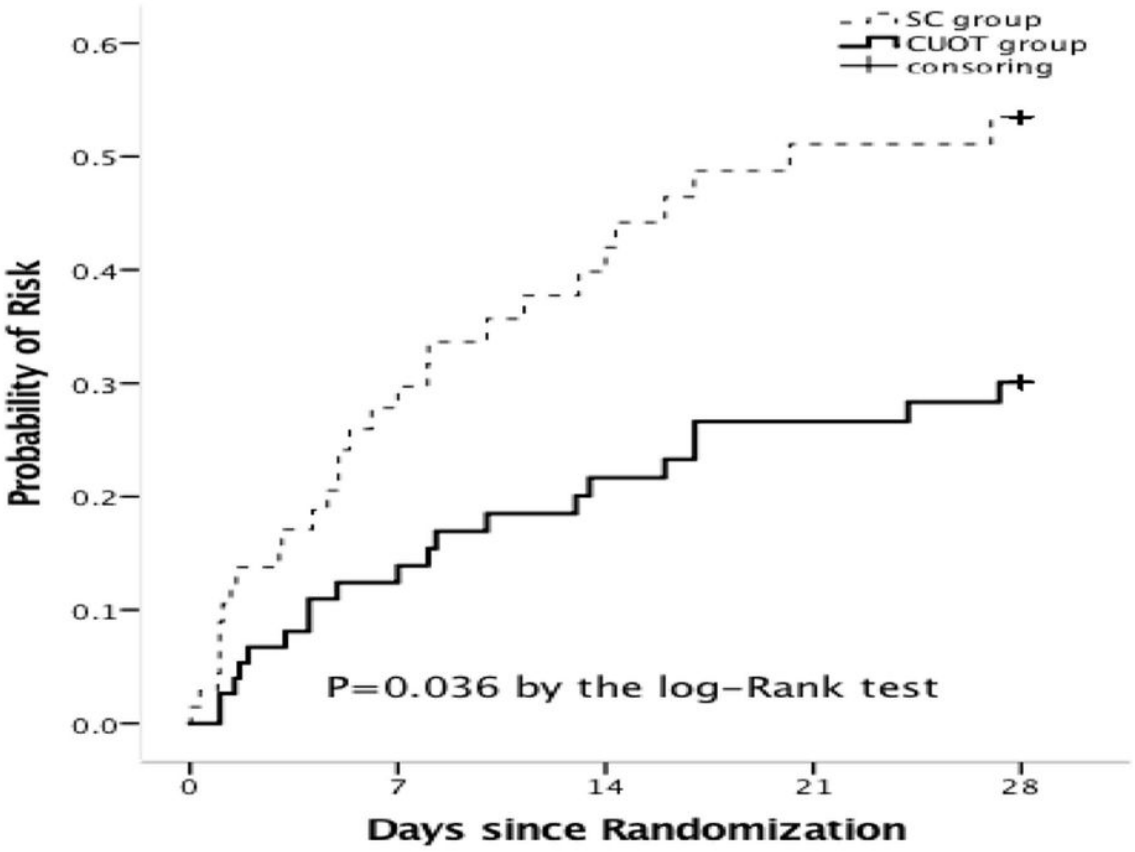

## Figure 1

The PESCUS workflow. CCUS = critical care ultrasound, CCUE = critical care chest ultrasonic examination for emergency, US = ultrasound, PE = pulmonary embolism, SVR = systemic vascular resistance, PCI = Percutaneous Transluminal Coronary Intervention, ACS = acute coronary syndrome, RV = right ventricle, Lac = lactate, UOH = urine output per hour, HR = heart rate. a CCUE exam protocol was a simplified combination of the eFATE and BLUE-plus protocols. The details were listed in Table S1. e The ultrasonic findings were the clues for estimating the sources of infection: consolidation with shred sign in lung ultrasound indicates pneumonia; hypoechoic yet heterogeneous at plural cavity indicates hemothorax or pyothorax; echogenic dots in free fluid indicates abscesses; echogenic dots in physiology cavity indicates infection etc.. With the clues above, we can clearly know what to do next and the diagnosis procedure can be efficient.




## Figure 2

Enrollment and outcomes.




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| SC group | 70 | 52 | 46 | 42 | 41 |
| CUOT group | 77 | 67 | 62 | 58 | 57 |

**Figure 3**

Probability of death from randomization through day 28. The graph shows the Kaplan–Meier estimates for the probability of death among patients receiving critical care ultrasound oriented treatment and standard care. The P value was calculated with the use of the log-rank test. CUOT= critical care ultrasound oriented treatment, SC = standard care.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S1DetailsregardingthePESCUSworkflow.pdf

- TABLE1.CharacteristicsofthePatientsatBaseline.pdf
- TABLE2.Studyoutcomes.pdf