

Effect of focused cardiopulmonary ultrasonography on clinical outcome of septic shock: a randomized study

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Abstract

Objective: To investigate the effect of focused ultrasonography on clinical outcomes of septic shock.

Methods: Patients with septic shock were randomized into an integrated cardiopulmonary ultrasonography (ICUS) group and conventional (CON) group. Within 1 hour of admission, the ICUS group underwent ICUS examination for hemodynamic decision-making, while the CON group received standard treatment. The primary endpoint was 28-day mortality after admission. The secondary endpoints were cumulative fluid administration in the first 6, 24, and 72 hours; use of vasoactive drugs; lactate clearance; duration of ventilation; and ICU stay.

Results: Ninety-four qualified patients were enrolled (ICUS group, 49; CON group, 45). ICUS showed no significant effect on 28-day mortality. Within the initial 6 hours, the ICUS group tended to have a higher fluid balance and fluid intake than the CON group. The duration of vasopressor support was shorter in the ICUS group. There were no differences in the cumulative fluid infusion within 24 or 72 hours, lactate clearance, ICU stay, or duration of ventilation.

Conclusions: The initially focused ICUS did not affect the clinical outcomes of septic shock, but it tended to be associated with a higher fluid balance within the initial 6 hours and shorter duration of vasopressor support.

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Introduction

Sepsis is the third most lethal disease in China, contributing to more than 1 million deaths in 2015.¹ Worldwide efforts have been made to standardize treatment and improve outcomes of sepsis. According to the latest Surviving Sepsis Campaign guidelines, the hour-1 bundle recommends the use of early fluid resuscitation and vasopressors for patients with hypotension.² However, the resuscitation strategy remains controversial.^{3–7} In fact, patients with sepsis may share similar clinical manifestations but different mechanisms of circulatory compromise, including overlapping factors of hypovolemia, hypokinesia, and vasoplegia. Therefore, it is necessary to identify the major factor that contributes to successful treatment.

With its advantage of providing visual estimates of patients' volume status and heart function, focused echocardiography has been regarded as the first-line modality for differentiating the causes of shock.⁸ When targeted at functional assessment rather than morphological abnormalities of the heart, focused echocardiography may influence clinical decisions based on the fluid requirement and inotropic or vasoactive choices. Multiple studies have focused on the prognostic value of specific echocardiographic measures in patients with sepsis or their influence on changes in the diagnostic and therapeutic plans; the incidences of such changes ranged from 17% to 67% in the intensive care unit (ICU) setting and even reached about

80% in anesthesia settings.^{9–11} However, randomized controlled trials are required to confirm whether these changes benefit patient outcomes. In a recent study, focused ultrasonography had little effect on the final outcomes among patients with undifferentiated shock.¹² No studies to date have revealed the effect of focused ultrasonography on septic shock. Considering that the circulatory failure of sepsis is multifactorial and the presence of extravascular lung water impacts the hemodynamic treatment, we considered that the focused ultrasonography used for hemodynamic management in sepsis should be an integrated cardiopulmonary ultrasonography (ICUS) technique rather than echocardiography alone. This study was performed to investigate the effect of focused cardiopulmonary ultrasonography within the first hour of ICU admission on the clinical outcomes of septic shock.

Methods**Setting**

This prospective randomized pilot study was conducted in a single center located in the division of critical care medicine at Xiangya Hospital, Central South University, Changsha City, Hunan Province, China.

The study protocol followed the requirements of the Declaration of Helsinki and was approved by the Ethics Committee of Xiangya Hospital (2017121158). This study was also registered in ClinicalTrials.gov

(NCT number: 01920776). Written informed consent was obtained from the enrolled patients or their authorized family members.

Patient enrollment and definition of sepsis onset

From September 2014 to January 2016, patients diagnosed with sepsis were preliminarily screened and were required to fulfill two or more conditions of systemic inflammatory response syndrome in the setting of suspected infection or organ dysfunction.¹³ The patients included in this study were required to meet at least one of the following inclusion criteria: (1) systolic blood pressure of ≤ 90 mmHg or a >40 mmHg decrease compared with baseline or mean arterial blood pressure of ≤ 65 mmHg after infusion of 20 mL/kg of crystalloid; (2) serum lactate concentration of ≥ 4 mmol/L; and (3) initiation of intravenous vasopressors. The exclusion criteria were (1) age of <18 years; (2) history of hospitalization due to chronic heart disease such as ischemic disease, valvular disease, dilated cardiomyopathy, or hypertrophic cardiomyopathy; (3) end-stage malignant tumor or irreversible terminal condition; and (4) pregnancy. Sepsis time 0 was defined as the time of admission to the ICU for sepsis treatment. For patients already in the ICU, sepsis time 0 was considered the earliest time at which the patients satisfied any of the inclusion criteria.

Study design

The patients were randomized in a 1:1 ratio into an ICUS group and conventional (CON) group using a random number table. Blood cultures and additional laboratory examinations were conducted in all patients. An attending physician was consulted to prescribe appropriate antibiotics

based on each patient's medication history, disease course, laboratory tests, imaging findings, and clinical severity. Analgesia and sedation were given to maintain a Critical-Care Pain Observation Tool score of 0 to 2 and a Richmond Agitation-Sedation Scale score of -2 to 0. Mechanical ventilation was set in standard mode.

The two groups differed in the initial 6 hours of hemodynamic management, including the indications for intravenous fluid and vasoactive and inotropic agents. These decisions were made by one of the two assigned physicians who were available within 10 minutes, 24 hours per day, for bedside ultrasonographic examinations. Both of the on-call physicians had been trained and certified by the World Interactive Network Focused On Critical Ultrasound (WINFOCUS) after >150 examinations of practice. With their knowledge and skill qualifications, the two physicians were also trainers for the Chinese Critical Ultrasound Study Group. In the CON group, fluid infusion was guided by the central venous pressure (CVP). The patients immediately underwent CVP monitoring until stabilization of vital signs without a vasopressor. Crystalloids were used for resuscitation until the CVP reached ≥ 10 mmHg. After the required pressure had been reached, fluid infusion was restricted and inotropes were initiated if the central venous oxygen saturation was $<70\%$ or cardiac dysfunction was suspected. In the ICUS group, the CVP was measured 6 hours later. Hemodynamic management was based on combined echocardiography with a 2- to 5-MHz phase probe (Vivid i; General Electric Company, Boston, MA, USA) and lung ultrasonography with a 2- to 5-MHz convex probe, which were performed within 1 hour after sepsis time 0 with no interruption of the life-saving therapy. The prerequisite of the ultrasonographic protocol was

identification of the subtype of septic shock based on the core components of Rapid Ultrasound for Shock and Hypotension protocol excluding the abdominal assessment.¹⁴ The hemodynamic decision-making procedures (Table 1) were based on the following four ultrasonographic views.

(1) Subcostal four-chamber and inferior vena cava (IVC) long-axis view: the IVC diameter was measured 2 cm from the right atrial junction at the end of expiration. Whether the respiratory variations were qualitatively defined was determined (no or yes). (2) Parasternal long- and short-axis views (at the level of the papillary muscles): the left ventricular (LV) contractility pattern was categorized as hyperdynamic [LV ejection fraction (LVEF) of $\geq 70\%$], normal (LVEF of $50\%–70\%$), moderately depressed (LVEF of $30\%–50\%$), or severely depressed (LVEF of $\leq 30\%$) by “eyeballing.” (3) Apical view: the right ventricular (RV)/LV telediastolic area was compared by eyeballing, and a ratio of ≥ 0.6 was considered to indicate RV dilation. (4) The bilateral lung ultrasound protocol was performed as described previously:¹⁵ Each of the 10 covered regions was assessed based on an A/B3/B7/C/P

pattern with detailed pleural sliding and morphology.¹⁶

Generally, the diagnoses based on lung artifacts varied according to the definition established by Lichtenstein and Meziere.¹⁷ For example, multiple anterior diffuse B lines with lung sliding indicated pulmonary edema. If the ultrasonographic examination was not completed within 10 minutes, the examination was stopped. If indeterminate results were obtained, such as heterogeneous contractility or an obvious valve or chamber abnormality, an advanced echocardiographer was required for an official report. All videos and images were validated in a timely manner by an experienced senior physician who was a certified trainer of WINFOCUS.

From sepsis time 0, the first-choice vasopressor was norepinephrine, which was then continuously infused to maintain a mean arterial blood pressure of >65 mmHg in both groups. After the initial 6 hours, all patients received usual care and both groups were able to undergo sonographic examinations if needed. Pulse index continuous cardiac output (PiCCO) was available for patients with refractory shock. In this randomized controlled trial, only the data analysts were blinded. The demographic

Table 1. Decision-making procedure directed by focused cardiopulmonary ultrasonography.

Ultrasonography Finding Question	Answer Choices
What is the IVC diameter?	<10 mm/ ≥ 20 mm*/other
What is the RV size?	Normal or dilated*
Is there evidence of diffuse interstitial syndrome?	Yes* or no
What is the LV systolic function?	Hyperdynamic/normal/ moderately impaired ^{##} / severely impaired ^{##}

*If none of these choices applied, fluid resuscitation was given at 30 mL/kg within 3 hours; if any of these choices applied, fluid resuscitation was cautiously performed; if two of these choices applied, fluid resuscitation was dispensed and vasopressor support was enhanced.

^{##}Inotropic support was initiated as needed.

IVC, inferior vena cava; RV, right ventricular; LV, left ventricular.

data, laboratory results, and related variables were collected at the time of admission. The primary endpoint was whether focused cardiopulmonary ultrasonography affected the 28-day mortality from sepsis 0. The secondary endpoints were the cumulative fluid intake and fluid balance in the first 6, 24, and 72 hours of mechanical ventilation and the ICU stay. The lactate clearance rate was calculated as the first measurement within 1 hour from sepsis time 0 minus the first measurement after the initial 6 hours of therapy, which was then divided by the former value. Any changes in the diagnostic and therapeutic plans were recorded.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). With the assumption of a 15% absolute reduction of 28-day mortality, a sample size of 94 patients was projected to have a power of 80% and an alpha error of 0.05 (two-tailed). Considering that 15% of patients might decline further treatment or be lost to follow-up, the projected sample size was 100. The 28-day mortality was compared with a log-rank test, and the survival curve was analyzed with the Kaplan–Meier method. All continuous variables were explored with the Kolmogorov–Smirnov test. Parametric variables are reported as mean \pm standard deviation, and group comparisons were performed with the independent-samples *t* test. Nonparametric variables are expressed as median (interquartile range), and group comparisons were performed using the Wilcoxon rank sum test. Categorical variables are reported as frequency (percentage), and group differences were compared using the chi-square test or Fisher's exact test (if any $n < 5$). All comparisons were two-tailed, and $p < 0.05$ was considered to exclude the null hypothesis.

Results

Baseline characteristics of study population

During the study period, 100 patients were screened and 97 were considered eligible. The participant flow chart is shown in Figure 1. Data of 94 patients were collected; of these, 2 patients voluntarily dropped out of the study and 1 patient was lost to follow-up. Finally, the ICUS group comprised 49 patients and the CON group comprised 45 patients. The demographic characteristics of the patients are presented in Table 2. Thirty-six (73.5%) patients in the ICUS group and 34 (75.6%) patients in the CON group received assisted mechanical ventilation. No patient received controlled ventilation or muscle relaxants. Twenty-four (49.0%) patients in the ICUS group and 30 (66.7%) patients in the CON group underwent surgery. Twelve patients in each group (ICUS vs. CON group: 24.5% vs. 26.7%) developed hospital-acquired infections. Negative culture was more frequent in the ICUS group than CON group [28 (57.1%) vs. 16 (35.6%), respectively; $p = 0.04$].

Primary and secondary endpoints

The 28-day mortality rate was not significantly different between the two groups (50.6% vs. 60.0%) (Figure 2). The fluid balance volume within the initial 6 hours in the ICUS group was almost 600 mL more than that in the CON group (2092.0 ± 1452.9 vs. 1508.9 ± 1211.8 mL, respectively; $p = 0.04$) (Figure 3), while the fluid intake volume was 450 mL more (2568.2 ± 1442.6 vs. 2111.1 ± 1115.5 mL, respectively) without a significant difference.

The lactate reduction rate, cumulative fluid intake, and fluid balance within 24 and 72 hours were not significantly different between the two groups. Although the

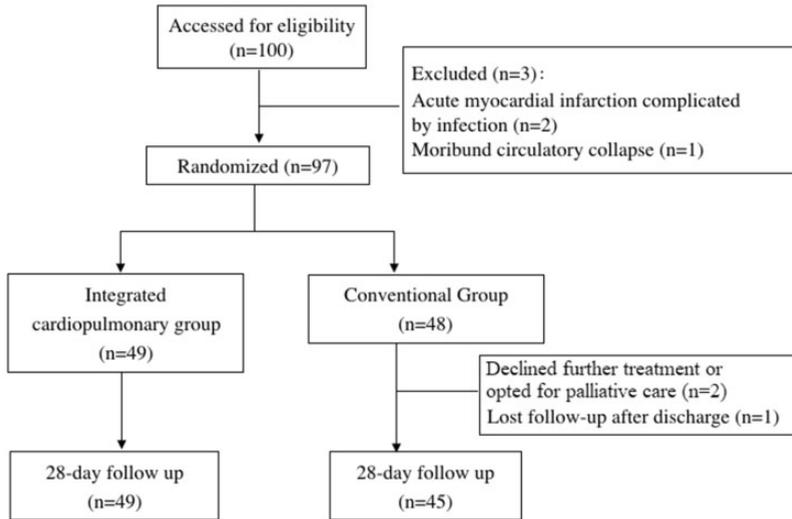


Figure 1. Flow diagram of study.

ICUS group tended to have a shorter duration of vasopressor support than the CON group [48 hours (interquartile range, 24.0–83.5 hours) vs. 69 hours (interquartile range, 34.0–97.9 hours)], the duration of mechanical ventilation and ICU stay showed no significant differences between the groups. The details regarding the secondary endpoints and hemodynamic interventions are shown in Table 3. All patients received norepinephrine to maintain perfusion. The administration of other vasoactive or inotropic drugs was similar between the two groups. Nine patients in each group (ICUS vs. CON group: 18.4% vs. 20.0%) showed cardiac dysfunction by echocardiography or PiCCO. Eleven patients in the ICUS group also had PiCCO measurements; however, the cardiac output as measured by ultrasonography was not totally consistent with that measured by PiCCO, which may have been due to the smaller sample size.

Ultrasonography findings

For four patients without adequate subcostal views, transhepatic views of the IVC

were used as alternate views. For all patients, standard images were obtained in both the parasternal and apical views. No obvious errors were observed through subsequent validation. The major findings are shown in Table 4. Five patients had moderate LV depression, two patients had an RV/LV ratio of >0.6 , and six patients had diffuse pulmonary edema. Two of these patients had LV depression combined with diffuse pulmonary edema. No patients had an LVEF of $\leq 30\%$, IVC of >20 mm, or absence of respiratory variation. As a result, 38 (77.6%) patients in the ICUS group and 28 (62.2%) patients in the CON group received >30 mL/kg crystalloid fluid for resuscitation within the initial 6 hours. Two patients with an obviously enlarged left atrium underwent consultation with an advanced echocardiographer, and both were diagnosed with mitral disease. In addition, five (10.2%) patients underwent bronchoscopy or thoracentesis because of ultrasonographic atelectasis or mass pleural effusion. Such pathologies were located in a unilateral lung; therefore, these patients were not considered to have diffuse pulmonary edema.

Table 2. Demographic and clinical characteristics of patients at time of admission to intensive care unit.

Items	ICUS group (n = 49)	CON group (n = 45)	p value
Sex, male/female	24/25	28/17	
Age, years	54.5 ± 15.2	56.7 ± 11.0	0.51
BMI, kg/m ²	23.1 ± 3.3	23.6 ± 4.6	0.51
Comorbidities			
Diabetes	4 (8.2)	5 (11.1)	0.73
Hypertension	8 (16.3)	9 (20.0)	0.79
Chronic pulmonary disease	4 (8.2)	1 (2.2)	0.36
History of operation	5 (10.2)	11 (24.4)	0.10
Coronary artery disease	5 (10.2)	1 (2.2)	0.21
Hepatology	4 (8.2)	6 (13.3)	0.51
Renal disease	3 (6.1)	9 (20.0)	0.06
Others	17 (34.7)	8 (17.8)	0.10
Mechanical ventilation	36 (73.5)	34 (75.6)	0.60
PaCO ₂	34.0 (28.0–42.5)	39.0 (31.3–47.5)	0.16
PaO ₂ /FiO ₂	190.0 (126.7–241.3)	170.0 (115.00–225.8)	0.24
WBCs, ×10 ⁹ /L	12.9 (6.9–21.2)	13.3 (5.8–18.2)	0.44
Platelets, ×10 ⁹ /L	92.0 (58.0–149.5)	122.00 (67.5–166.5)	0.22
Total bilirubin, mmol/L	24.7 (12.9–56.1)	24.0 (13.1–37.3)	0.67
Serum creatinine, mmol/L	147.6 (88.0–255.4)	179.3 (140.6–311.6)	0.05
APACHE II score	20.8 ± 8.2	21.8 ± 6.7	0.75
SOFA score	13.2 ± 4.8	13.2 ± 4.1	0.86
Etiology			
Urosepsis	4 (8.2)	10 (22.2)	0.08
Pneumonia	10 (20.4)	6 (13.3)	0.42
Bloodstream	23 (46.9)	20 (44.4)	0.84
Peritonitis	20 (40.8)	20 (44.4)	0.84
Meningitis	5 (10.2)	2 (4.4)	0.44
Cholangitis	2 (4.1)	2 (4.4)	1.0
Microorganisms			
Hospital-acquired infection	12 (24.5)	12 (26.7)	0.82
Gram-positive bacilli	11 (22.4)	14 (31.1)	0.36
Gram-negative bacilli	22 (44.9)	28 (62.2)	0.10
Fungi	5 (10.2)	2 (4.4)	0.44
No microorganisms found	28 (57.1)	16 (35.6)	0.04
Heart rate, beats/minute	129.0 (119.0–139.0)	126.5 (104.5–140.0)	0.30
Respiratory rate, breaths/minute	26.9 ± 7.0	24.7 ± 6.8	0.13
MAP, mmHg	69.8 ± 13.4	66.9 ± 15.1	0.36
Temperature, °C	40.0 ± 1.2	37.7 ± 1.3	0.30
Number of SIRS presentations			
2	11 (22.4)	12 (26.7)	0.81
3	24 (49.0)	18 (40.0)	0.41
4	14 (28.6)	15 (33.3)	0.66
Lactate, mmol/L	4.2 (2.3–6.9)	4.0 (2.6–5.6)	0.66
Procalcitonin, ng/mL	14.9 (2.9–80.9)	35.9 (6.7–103.3)	0.15
NT-proBNP, pg/mL	4746.5 (1207.3–7941.0)	5728.0 (1066.0–25000.0)	0.42

Values are reported as n (%), median (interquartile range), or mean ± standard deviation.

ICUS, integrated cardiopulmonary ultrasonography; CON, conventional; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; PaCO₂, partial pressure of carbon dioxide in arterial blood; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of oxygen in arterial blood; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; SIRS, systemic inflammatory response syndrome; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Discussion

In the present study, early focused sonography demonstrated little effect on 28-day mortality among patients with septic shock; however, it still tended to enhance fluid resuscitation within the initial 6 hours, and it shortened the duration of vasopressor support. To the best of our knowledge, this is the first randomized controlled study to investigate the effect of bedside focused cardiopulmonary sonography on patients with sepsis.

Our study results revealed that focused cardiopulmonary ultrasonography did not result in beneficial clinical outcomes in patients with septic shock. Several factors led to death, and the hemodynamic monitoring tool was not sufficient to influence the outcomes.¹⁸ Only 11 (22.4%) patients had abnormal ultrasound findings, and this percentage was less than expected, thus weakening the clinical effects. Another explanation is that our ultrasonographic protocol was too simple to guide delicate hemodynamic treatment. Notably, the 28-day mortality rate in our study was much higher than that in several other multicenter sepsis trials.³⁻⁵ This might be attributable to the relatively lower medical level in our department, which is located in an underdeveloped area in China. In previous studies, the mortality rate of hospitalized patients with septic shock varied from 31.1% to 75.9% in different countries.^{19,20} A recent international study demonstrated that when using the same focused ultrasonography technique among patients with undifferentiated shock, patients recruited from South Africa had a 20% higher mortality rate than those from North America.¹²

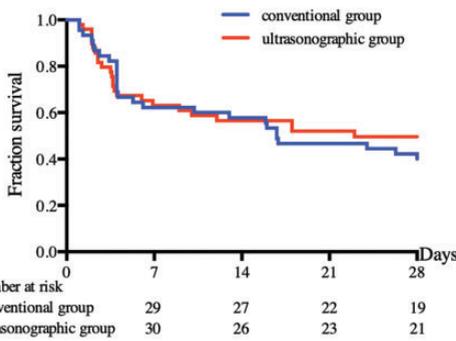


Figure 2. Comparison of 28-day mortality with Kaplan-Meier estimate ($p = 0.58$).

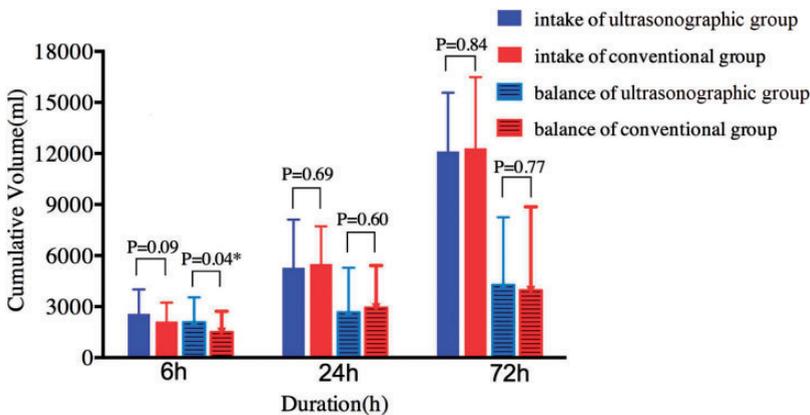


Figure 3. Comparison of cumulative volume intake and balance over time. * $p < 0.05$. At 24 and 72 hours, the data for patients who were dead or had been discharged from the hospital before that were analyzed as missing.

Table 3. Comparison of administrations, interventions, and secondary endpoints

Items	ICUS group (n = 50)	CON group (n = 44)	p value
Vasoactive and inotropic administrations			
Maximum dose of norepinephrine,* $\mu\text{g}/\text{kg}/\text{minute}$	0.75 (0.20–2.0)	1.00 (0.35–2.0)	0.15
Dobutamine	4 (8.2)	2 (4.4)	0.68
Vasopressin	1 (2.0)	4 (8.89)	0.19
Others [#]	8 (16.3)	5 (11.1)	0.49
Cardiac dysfunction	9 (18.4)	9 (20.0)	0.80
CRRT	24 (49.0)	26 (57.8)	0.58
PiCCO	11 (22.5)	10 (22.2)	0.97
Secondary outcomes			
Lactate clearance rate [§]	0.13 (–0.34–0.41)	0.17 (–0.23–0.44)	0.78
Time to lactate normalization, hours	18.5 (7.3–69.0)	19.0 (11.5–213.0)	0.61
Duration of vasopressor use, hours	48.0 (24.0–83.5)	69.0 (34.0–97.9)	0.08
ICU stay, hours	108.0 (63.5–286.8)	130.1 (96.0–296.7)	0.38
Duration of mechanical ventilation, hours	60.00 (18.7–152.6)	62.0 (24.0–120.0)	0.72

Data are presented as n (%) or median (interquartile range).

*The maximum dose did not include the use of vasopressors at the time of death.

[#]Others included digitalin, natriuretic peptide, adrenaline, dopamine, and esmolol.

[§]Lactate clearance rate = (first measurement within 1 hour after ICU admission – first measurement 6 hours after initial therapy) / first measurement within 1 hour after ICU admission.

ICUS, integrated cardiopulmonary ultrasonography; CON, conventional; CRRT, continuous renal replacement therapy; PiCCO, pulse index continuous cardiac output; ICU, intensive care unit.

Table 4. Findings of focused cardiopulmonary ultrasonography.

Ultrasonography findings	Measurements (n)
IVC diameter	< 10 mm/ \geq 20 mm/ other: 10/0/39
RV size	Normal/dilated: 47/2
Diffuse interstitial syndrome	Yes/no: 6*/43
LV systolic function	Hyperdynamic/normal/moderately impaired/ severely impaired: 2/42/5/0

*Two patients had combined moderate LV depression.

IVC, inferior vena cava; RV, right ventricular; LV, left ventricular.

This study examined the effect of focused cardiopulmonary sonography for initial evaluation of septic shock to answer specific questions regarding fluid requirement and vasoactive choices and to categorize the shock. Although the increased fluid administration based on sonography findings showed very good agreement with large-database research from real-world evidence,²¹ this increase did not continue

beyond 3 days. In total, 11 (22.4%) patients in the ICUS group and 17 (37.8%) patients in the CON group received restrictive resuscitation. Perhaps focused sonography enhanced the confidence of the physician in diagnosing septic shock while helping to exclude shock of cardiac origin in most cases. However, this needs further clarification because when early transesophageal echocardiography and Surviving Sepsis

Campaign guidelines were compared, the results showed obvious disagreement with the prescription of fluid loading in patients with septic shock.²² Notably, whether the increased fluid balance was associated with the patients' good clinical outcomes remains unclear; this might have been because there was no significant improvement in lactate clearance or organ function in the ultrasonographic group. Whether early resuscitation resulted in a shorter vasopressor duration also requires further investigation.

Prompt and adequate fluid resuscitation is a fundamental but challenging problem in patients with septic shock. Both deficient and excessive fluid resuscitation are associated with a poor prognosis.²³ According to the latest international guidelines, infusion of 30 mL/kg of a crystalloid within the hour-1 bundle is recommended²; however, this might not be appropriate for all patients with hypotensive sepsis. In fact, the determinant of fluid tolerance majorly relies on individual heart function. Sepsis-related myocardial dysfunction reportedly occurs in as many as 20% to 65% of patients.²⁴ Even at the Mayo Clinic, a study showed that the intensivists misjudged the ventricular function in about half of patients with septic shock before echocardiographic examination.¹¹ More importantly, the echocardiography findings changed the therapeutic plan in nearly one-third of the patients.¹¹ Because of the small sample size of this study, the differences in the initial fluid intake and fluid balance should be carefully estimated. Because no harm occurred, it would be worthwhile to perform a similar assessment in a larger clinical trial.

Dynamic values such as the IVC collapsibility/distensibility index are reportedly more instructive than the static IVC diameter, but their application is rigorous.²⁶ In the current study, about 75% of patients received assisted mechanical ventilation,

which prevented monitoring of the IVC collapsibility/distensibility index. The diameter and variation of the IVC depend on many factors, including the preload status, right heart function, difference between the thoracic and abdominal pressure, and others; therefore, the IVC alone is not a reliable index to predict preload.²⁷ Instead, the fluid resuscitation was guided by a combination of the LVEF and IVC parameters in this study. In another cohort study, the physicians changed the treatment plans in more than half of patients with suspected sepsis guided by a combination of the LVEF and IVC parameters.²⁵

One advantage of the present study is that lung ultrasound was integrated into the hemodynamic decision-making procedure. The amount of lung sonographic artifacts was well correlated with the extravascular lung water.^{17,28} Lung ultrasonography significantly influenced the therapeutic decisions in about 85.6% of mechanically ventilated critically ill patients.¹⁶ Fluid administration may be limited by lung sonography because of acute circulatory failure.²⁹⁻³¹ One study showed that instantaneous ICUS was associated with a shorter time to diagnosis and smaller fluid infusion volume in critically ill patients with acute pulmonary edema.³² Considering the above points, we intentionally chose ICUS to guide our hemodynamic management. However, few patients were affected, and several patients required urgent treatment because of atelectasis or mass pleural effusion.

A previous study indicated a strong positive correlation ($p < 0.001$, $r = 0.985$) between the cardiac output values measured by critical care echocardiography and PiCCO in pediatric patients.³³ In the present study, however, one main purpose for the use of ultrasonography for treatment guidance in the ICU was to reduce the need for invasive procedures. Therefore, PiCCO was not considered a routine

monitoring item. In addition, only 11 (22%) of the 49 patients in the ultrasonographic group underwent PiCCO monitoring, but the cardiac output values measured by ultrasonography were not totally consistent with those measured by PiCCO. One reason for the discrepancy between our study and the previous study of pediatric patients might be the higher quality and measurement accuracy of pediatric patients' cardiac ultrasound images. The present study may have contained some errors in the cardiac output measurement by echocardiography; this was also reported in a previous study.³⁴ Further studies involving larger sample sizes are needed.

This study has several limitations that should be noted. First, the Sepsis-3 criteria were not used to screen patients for eligibility because the participants were recruited before documentation of the new criteria. Second, the intervention was not blinded to the patients or attending intensivists; however, the latter might have acted more proactively to the therapeutic response. Third, the outcomes of a more detailed examination of echocardiographic effects was not performed. In particular, measurement of LV diastolic function should be involved in the decision-making process because LV diastolic function occurs more often than systolic depression and has prognostic value in sepsis-related myocardial dysfunction.^{24,35,36} The lack of diastolic function evaluation partly explains the low incidence of sepsis-related myocardial dysfunction in the present study. Moreover, repetitive echocardiographic examinations might assist in rapid evaluation of the responses to initial resuscitation and provide more reference for subsequent treatment, which may in turn help to improve the prognosis. Fourth, dynamic parameters of fluid responsiveness were not used to guide fluid management. For the convenience of comparison and decision-making, the CVP was not initially

monitored in the ultrasonographic group; therefore, we cannot make conclusions regarding the relationship between ultrasonographic signs and CVP. Finally, this study would have been more powered if the sample size had been larger.

In conclusion, initial focused ICUS evaluation had no effect on the clinical outcomes of patients with severe sepsis and septic shock, although it probably enhanced fluid administration and shortened vasopressor support. A multicenter or more productive randomized controlled trial is required to verify these results.

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Declaration of conflicting interest

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