

Original Article

Ultrasound-guided circulatory management strategy for improving microcirculatory dysfunction and promoting organ function recovery in critically ill shock patients

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Abstract: Aims: To evaluate whether ultrasound-guided circulatory management improves microcirculatory perfusion, accelerates organ function recovery, and enhances clinical outcomes in critically ill shock patients compared with standard care. Methods: Our retrospective cohort study was performed in the adult ICUs of Xuanwu Hospital and consecutive screening of ICU admissions of January 1, 2022 to December 31, 2025. In total, 200 eligible shock patients were categorized in accordance with the leading initial circulatory management approach following shock detection: conventional guideline consistent care (control, n=100) and organized point-of-care ultrasound guided care (observation, n=100) on the basis of protocolized evaluation at pre-arranged decision points to phenotype hemodynamics and progressively oversee the administration of fluids and vasoactive introduction/adjustment with reassessment. The primary outcome was organ support-free days until day 28 (death = 0). While time to shock resolution, shock-free days to day 7, ICU/hospital length of stay, ICU mortality, ICU readmission, discharge disposition, and 90-day EQ-5D were some of the secondary outcomes. Mechanistic endpoints included 0-6 h metrics of resuscitation, 24-h hemodynamic/ultrasound phenotype, SOFA trajectory, day 5 and baseline/24-h biomarkers. Results: Compared with usual care, the ultrasound-guided strategy reduced early fluid exposure and net fluid balance within 6 h ($P=0.004$ and $P=0.001$, respectively) and lowered norepinephrine dose and norepinephrine ≥ 0.30 $\mu\text{g/kg/min}$ use at 6 h ($P<0.001$ and $P=0.010$). At 24 h, patients receiving ultrasound-guided management had higher MAP, improved cardiac performance, and less vasopressor dependence (all $P\leq 0.015$), with a lower prevalence of moderate-severe LV dysfunction ($P=0.001$). Clinically, the intervention shortened time to shock resolution ($P<0.001$) and increased organ support-free days to day 28 ($P<0.001$). SOFA scores improved more rapidly ($P<0.01$ at 24 h; $P<0.001$ at 48 h, 72 h, and 5 days), accompanied by better renal perfusion and lower injury biomarkers (all $P<0.001$). Conclusion: Optimized early resuscitation (less fluid and lower vasopressor exposure), better 24-h hemodynamic and renal microcirculatory phenotypes, faster SOFA recovery, more organ support-free days, and faster shock resolution, with at least a partial association with reduced renal injury, were observed in patients receiving ultrasound-guided circulatory management. These findings indicate potential benefits but do not establish causality due to the retrospective, single-center study design.

Keywords: Point-of-care ultrasound, shock, hemodynamic resuscitation, microcirculation, organ support-free days

Introduction

Shock is still a major factor of morbidity and mortality in critically ill patients, yet there has been significant progress in resuscitation science and intensive care management [1, 2]. Conventionally, shock-induced circulatory resuscitation has been concerned with the recovery of macrocirculatory parameters that include blood pressure, cardiac output and central venous pressure [3, 4]. There is however, an

increasing amount of evidence that normalization of global hemodynamic variables does not guarantee sufficient tissue perfusion or cellular oxygen consumption. Continued microcirculatory dysfunction (mimicking impaired appearances of capillary flow, heterogeneity of perfusion, and endothelial dysfunctional activities) has arisen as one of the pathophysiological processes that explain persisting organ dysfunction and adverse prognosis in shock conditions [5, 6].

Microcirculation is the key factor of supply of oxygen, nutrients and removal of metabolic waste at the tissue level [7, 8]. Microvascular changes can continue despite the observed and claimed hemodynamic recovery in shock patients who are in a critical state, and this phenomenon is also known as the loss of hemodynamic coherence. This is the dissociation between macro- and microcirculation that has been reported in various types of shock such as septic, cardiogenic, and hypovolemic shock and is closely related to the onset of multiple organ dysfunction syndrome and excessive mortality [9]. As a result, there is a growing consensus that shock management must not only seek to implement macrocirculatory stability but should also include measures aimed at identifying and rectifying microcirculatory infirmity.

Ultrasound has quickly become an essential bedside device in critical care, providing real-time, noninvasive and repeatable evaluation of cardiovascular structure and cardiovascular functions [10]. Circulatory management guided by ultrasound allows dynamic measuring of cardiac preload, afterload, contractility, and fluid responsiveness and can indirectly assess tissue perfusion through parameters such as venous congestion, organ blood flow, and indices related to perfusion [11]. With such multimodal ultrasound results, clinicians can now personalize resuscitation strategies, optimize fluid and vasoactive therapy and prevent the harmful consequences of under- and over-resuscitation which have been identified to worsen microcirculatory dysfunction.

Recent conceptual advances further support a physiology-guided approach to shock resuscitation. In the newly proposed “Five Differences” framework, critical illness is viewed as a dynamic and convergent biological process shaped by differences in host characteristics, primary etiologies, host/organ unregulated responses, interventions, and final clinical phenotypes. Within this model, hemodynamic instability and critical unit injury are central drivers of progressive microcirculatory failure, organ ischemia-hypoxia, and adverse outcomes. Importantly, the framework emphasizes that inappropriate or non-individualized interventions may themselves aggravate secondary injury, whereas continuous hemodynamic monitoring and individualized evaluation may help prevent pro-

gression [12]. In this context, critical care ultrasound is particularly valuable because it enables repeated bedside assessment of both macro- and microcirculatory perfusion, facilitates multidimensional monitoring, and may reduce iatrogenic harm. Therefore, ultrasound-guided circulatory management is biologically plausible as a precision-resuscitation strategy to restore hemodynamic coherence, optimize organ perfusion, and promote organ function recovery in critically ill patients with shock. Dynamic changes in cerebral oxygen saturation during a passive leg raising challenge may provide additional bedside information on perfusion adequacy and early brain dysfunction in sepsis and septic shock, and could complement ultrasound-based hemodynamic assessment in precision resuscitation [13].

The present paper aims to review and synthesize existing evidence on the use of ultrasound-guided circulatory management strategies in shock and specifically how they can be used to enhance microcirculatory dysfunction and to support organ function recovery. We aim to give a detailed outline of the physiological explanation, clinical uses, and possible drawbacks of this methodology to enable its role in the enrichment of the state of the art practice in critical care, as well as aid in future studies, in a field that is currently progressing in leaps and bounds.

Methods

Case section

The study was a single-center, retrospective cohort study conducted in Xuanwu Hospital in the adult ICUs at Sichuan University. Through the electronic medical record system, off-line screening of ICU admissions between January 1, 2022 and December 31, 2025 was performed sequentially and we identified patients who presented or developed shock in the ICU within 6 h following admission. Shock was operationally defined as acute circulatory failure requiring active resuscitation, characterized by (I) sustained hypotension (MAP <65 mmHg or SBP <90 mmHg) despite initial measures or the need for vasopressors to maintain perfusion pressure, together with (II) objective evidence of tissue hypoperfusion (≥ 1 of the following around “time zero”: lactate elevation, oliguria, altered mental status, mottled/cool extremi-

ties, delayed capillary refill, or clinician-documented hypoperfusion). Participants were required to be 18 years old and were required to receive fluid resuscitation and/or vasoactive therapy at the point of shock recognition (the initial time hemodynamic resuscitation was documented) and must have had sufficient records available to determine exposure assignment and other important baseline covariates. We excluded patients who were pregnant; had ICU length of stay <24 h or died/were transferred before exposure could be reliably classified; were transferred after prolonged resuscitation outside the study center such that “time zero” was not attributable; had do-not-resuscitate/comfort-measures-only orders instituted at or near shock recognition; received extracorporeal life support (e.g., VA-ECMO) initiated at or immediately after shock recognition; had indeterminate or crossover management without a clearly dominant initial strategy; or had irretrievable missingness in exposure, primary outcomes, or core covariates. Two hundred patients were used to fulfill the criteria and were stratified according to the type of primary early circulatory management applied once the shock was detected; a control group (n=100 cases) received a conventional standard circulatory management based on routine clinical assessment and guideline consistent targets whereas an observation group (n=100 cases) received a structured ultrasound-guided circulatory management strategy where protocolized point of care ultrasonography was used to phenotype hemodynamics and make iterative decisions regarding the use of fluids, vasoactive, initiation/titration, and reassessment. The study was approved by the ethical committee of Xuanwu Hospital and informed consent was waived because the design of the research was retrospective and the data was not identifiable.

Data extraction

The electronic medical record and study case-report forms contained the data that were prospectively extracted by trained investigators with a standardized data dictionary in place, including predetermined variables and time-dependent windows of reference to enrollment. The following baseline variables were used: demographics, shock phenotype (septic, cardiogenic, hypovolemic, or obstructive), suspect-

ed source of infection and blood culture status (when available), chronic comorbidities (hypertension, diabetes, coronary artery disease, chronic heart failure, chronic kidney disease, chronic liver disease/cirrhosis, COPD, active malignancy, immunosuppression, and chronic atrial fibrillation), and baseline severity indices (including total SOFA score and serum lactate). The initial 6 h resuscitation was recorded, such as achievement and time to sustained (generally) MAP 65 mmHg, cumulative fluid and net fluid balance (0-6 h), norepinephrine use and dosing (including high-dose exposure limits) and absence or presence of dynamic tests of fluid responsiveness and fluid challenges. The variables of hemodynamic and ultrasound phenotyping were obtained at 24 h, which included heart rate, MAP, vasopressor use, cardiac index, LVOT VTI, left ventricular ejection fraction, the presence of moderate-to-severe LV systolic dysfunction, IVC maximum diameter, IVC distensibility (in ventilated patients), and a classification of the fluid responsiveness. Total and component SOFA scores of the organ dysfunction were longitudinally monitored according to prespecified timepoints (baseline and 24, 48, 72 h, and 5 days) and organ-specific biomarkers of perfusion/injury were collected before intervention and at 24 h (renal resistive index, plasma NGAL, serum creatinine, procalcitonin, AST, and ALT). The extracted clinical outcomes were time to shock resolution, shock-free days to day 7, organ support-free days to day 28, length of stay in the ICU as well as in the hospital, ICU mortality, ICU readmission during the index hospitalization, discharge disposition, and 90-day health-related quality of life (EQ-5D index). The completeness and the plausibility of the data were checked at predetermined checkpoints, the second reviewer checked the main exposures and result with the source records and confirmed the discrepancies by consensus, and the adjudication was documented.

Outcome measures

The main outcome was organ support-free days to day 28, the number of days alive and without vasopressors/inotropes, invasive mechanical ventilation and renal replacement therapy during the randomization period through day 28 (non-survivors received 0 days). Time to shock resolution was a secondary outcome, shock-

free days to day 7, ICU length of stay, hospital length of stay, ICU mortality, ICU readmission on the index hospitalization, discharge disposition, and 90-day health-related quality of life (EQ-5D index) were secondary outcomes. Pre-specified mechanistic endpoints included early resuscitation variables (0-6 h), 24-h hemodynamic/ultrasound phenotype, longitudinal SOFA (baseline to day 5), and organ-specific perfusion/injury biomarkers (renal resistive index, plasma NGAL creatinine, procalcitonin, AST, ALT).

Statistical analysis

Analyses were performed on an intention-to-treat basis, with patients analyzed according to randomized group assignment. Continuous variables were summarized as mean $\pm$ SD or median (IQR) as appropriate, and categorical variables as number (percentage). Between-group comparisons used Student's t test or the Mann-Whitney U test for continuous data and the χ^2 test or Fisher's exact test for categorical data, as indicated by distributional assumptions. Within-group changes from baseline (e.g., biomarkers before vs. 24 h) were evaluated using paired t tests or Wilcoxon signed-rank tests. The primary recovery endpoint (organ support-free days to day 28) was further examined using multivariable linear regression to estimate adjusted β coefficients with 95% confidence intervals, prespecifying covariates reflecting demographics (age, sex), shock phenotype (septic vs. non-septic), baseline severity (total SOFA and lactate), major comorbidity (chronic kidney disease), and early resuscitation variables (time from shock onset to randomization, cumulative fluid input 0-6 h, and norepinephrine dose at 6 h); a second model additionally incorporated 24-h renal microcirculatory and injury markers (renal resistive index and plasma NGAL). All tests were two-sided with a significance threshold of $P < 0.05$.

Results

The demographic and baseline clinical characteristics

The distribution of shock phenotypes was also similar: septic shock was the predominant type in both arms, with comparable proportions of cardiogenic, hypovolemic, and obstructive shock, as well as similar distributions of prima-

ry infection sites and rates of positive blood cultures (all $P > 0.05$; e.g., septic shock $P = 0.873$, cardiogenic shock $P = 0.831$, hypovolemic shock $P = 0.788$, obstructive shock $P = 0.774$; pneumonia $P = 0.776$, intra-abdominal infection $P = 0.852$, urinary tract infection $P = 0.800$, skin/soft tissue/other $P = 0.809$; positive blood cultures $P = 0.777$). Baseline chronic comorbidities, including hypertension, diabetes mellitus, coronary artery disease, chronic heart failure, chronic kidney disease, chronic liver disease/cirrhosis, COPD, active malignancy, and chronic atrial fibrillation, did not differ significantly between groups (all $P > 0.05$; e.g., hypertension $P = 0.887$, diabetes mellitus $P = 0.768$, coronary artery disease $P = 0.747$, chronic heart failure $P = 0.856$, chronic kidney disease $P = 0.845$, chronic liver disease/cirrhosis $P = 0.818$, COPD $P = 0.825$, active malignancy $P = 0.800$, and chronic atrial fibrillation $P = 0.836$). Overall, there were no statistically significant differences in any recorded demographic or baseline clinical characteristic between the two groups at enrollment (all $P > 0.05$) (**Table 1**).

Comparison of early hemodynamic resuscitation variables within 6 h of enrollment between the two groups

Early fluid exposure was lower in the observation group, with reduced cumulative fluid input and a less positive net fluid balance over 0-6 h ($P = 0.004$ and $P = 0.001$, respectively). Dynamic assessments of fluid responsiveness were performed substantially more often ($P < 0.001$), whereas the proportion of positive fluid responsiveness among tested patients did not differ between groups ($P = 0.107$). The proportion of patients receiving any norepinephrine within 0-6 h was similar ($P = 0.521$), but the observation group required a lower norepinephrine dose at 6 h ($P < 0.001$) and had fewer patients needing norepinephrine ≥ 0.30 $\mu\text{g/kg/min}$ at 6 h ($P = 0.010$) (**Table 2**).

Comparison of Hemodynamic and ultrasound phenotype at 24 hours of enrollment between the two groups

At 24 h, the observation group exhibited a more favorable hemodynamic profile, characterized by a lower heart rate ($P = 0.003$) and higher MAP ($P = 0.003$), alongside reduced vasopressor requirements, including a lower norepinephrine dose ($P < 0.001$) and a smaller proportion of

Ultrasound-guided circulatory management in patients during shock

Table 1. The demographic and baseline clinical characteristics

Variable	Control group (n=100)	Observation group (n=100)	p value
Age, years	66.59 ± 13.62	66.25 ± 13.56	0.860
Male sex, n (%)	62 (62.0)	59 (59.0)	0.664
Body mass index, kg/m ²	24.42 ± 4.26	25.08 ± 3.65	0.243
Time from shock onset to randomization, h	4.88 ± 1.34	4.59 ± 1.26	0.117
Shock type and etiology			
Septic shock, n (%)	73 (73.0)	74 (74.0)	0.873
Cardiogenic shock, n (%)	13 (13.0)	12 (12.0)	0.831
Hypovolemic shock, n (%)	8 (8.0)	7 (7.0)	0.788
Obstructive shock, n (%)	6 (6.0)	7 (7.0)	0.774
Primary infection focus - pneumonia, n (%)	44 (44.0)	46 (46.0)	0.776
Primary infection focus - intra-abdominal, n (%)	18 (18.0)	17 (17.0)	0.852
Primary infection focus - urinary tract, n (%)	9 (9.0)	8 (8.0)	0.800
Primary infection focus - skin/soft tissue/other, n (%)	10 (10.0)	9 (9.0)	0.809
Positive blood cultures, n (%)	52 (52.0)	50 (50.0)	0.777
Chronic comorbidities			
Hypertension, n (%)	57 (57.0)	56 (56.0)	0.887
Diabetes mellitus, n (%)	35 (35.0)	37 (37.0)	0.768
Coronary artery disease, n (%)	27 (27.0)	25 (25.0)	0.747
Chronic heart failure, n (%)	18 (18.0)	19 (19.0)	0.856
Chronic kidney disease (stage ≥3), n (%)	15 (15.0)	16 (16.0)	0.845
Chronic liver disease/cirrhosis, n (%)	11 (11.0)	10 (10.0)	0.818
COPD, n (%)	12 (12.0)	11 (11.0)	0.825
Active malignancy, n (%)	9 (9.0)	8 (8.0)	0.800
Chronic atrial fibrillation, n (%)	14 (14.0)	13 (13.0)	0.836

Note: COPD: Chronic Obstructive Pulmonary Disease.

Table 2. Comparison of early hemodynamic resuscitation variables within 6 h of enrollment between the two groups

	Control group (n=100)	Observation group (n=100)	p value
Achieved MAP ≥65 mmHg within 6 h, n (%)	78 (78.0)	92 (92.0)	0.006
Time to first sustained MAP ≥65 mmHg, h	3.24 ± 1.57	2.27 ± 1.33	<0.001
Cumulative fluid input 0-6 h, mL	2446.54 ± 894.83	2127.19 ± 624.01	0.004
Net fluid balance 0-6 h, mL	2188.77 ± 801.63	1835.24 ± 613.10	0.001
Dynamic test of fluid responsiveness performed*, n (%)	31 (31.0)	81 (81.0)	<0.001
Positive fluid responsiveness among tested, n (%)	21 (67.7)	31 (31.0)	0.107
Any norepinephrine use 0-6 h, n (%)	86 (86.0)	89 (89.0)	0.521
Norepinephrine dose at 6 h, µg/kg/min	0.26 ± 0.06	0.20 ± 0.06	<0.001
Patients on norepinephrine ≥0.30 µg/kg/min at 6 h, n (%)	34 (34.0)	18 (18.0)	0.010

Note: MAP: Mean Arterial Pressure. *Defined as documentation of at least one dynamic bedside assessment of fluid responsiveness within the first 6 h after enrollment.

patients remaining on any vasopressor support (P=0.015). Indices of forward flow and cardiac performance were higher in the observation group, with greater cardiac index (P<0.001), higher LVOT VTI (P<0.001), and higher left ven-

tricular ejection fraction (P=0.001), accompanied by a lower prevalence of moderate-to-severe LV systolic dysfunction (P=0.001). The observation group also had a smaller IVC maximum diameter (P<0.001) and a greater propor-

Table 3. Comparison of hemodynamic and ultrasound phenotype at 24 of enrollment between the two groups

	Control group (n=100)	Observation group (n=100)	p value
Heart rate, beats/min	98.97 ± 18.51	91.70 ± 14.93	0.003
MAP, mmHg	68.29 ± 8.74	72.05 ± 8.84	0.003
Norepinephrine dose, µg/kg/min	0.22 ± 0.01	0.14 ± 0.01	<0.001
Proportion still on any vasopressor, n (%)	82 (82.0)	67 (67.0)	0.015
Cardiac index (thermodilution/echo), L·min ⁻¹ ·m ⁻²	2.50 ± 0.08	2.89 ± 0.07	<0.001
LVOT VTI, cm	17.29 ± 3.23	19.25 ± 4.09	<0.001
Left ventricular ejection fraction, %	48.85 ± 9.78	53.13 ± 8.47	0.001
Moderate-severe LV systolic dysfunction, n (%)	29 (29.0)	10 (10.0)	0.001
IVC maximum diameter, mm	20.14 ± 3.82	18.30 ± 3.29	<0.001
Patients classified as fluid responsive at 24 h, n (%)	19 (19.0)	36 (36.0)	0.007

Note: MAP: Mean Arterial Pressure; LVOT VTI: Left Ventricular Outflow Tract Velocity-Time Integral; IVC: Inferior Vena Cava.

Table 4. Comparison of major clinical outcomes between the two groups

	Control group (n=100)	Observation group (n=100)	p value
ICU mortality, n (%)	28 (28.0)	17 (17.0)	0.063
Time to shock resolution*, days	3.78 ± 1.07	2.83 ± 1.17	<0.001
Shock-free days to day 7	2.40 ± 0.57	3.55 ± 0.77	<0.001
Organ support-free days through day 28†	10.82 ± 3.51	16.04 ± 4.72	<0.001
ICU length of stay, days	12.13 ± 4.23	9.33 ± 3.33	<0.001
Hospital length of stay, days	20.33 ± 4.83	17.88 ± 4.51	<0.001
Proportion discharged home (vs. rehabilitation or other facility), n (%)	37 (37.0)	55 (55.0)	0.011
Health-related quality of life at 90 days (EQ-5D index)	0.57 ± 0.09	0.64 ± 0.03	<0.001
Readmission to ICU during same hospitalization, n (%)	9 (9.0)	5 (5.0)	0.268

Note: ICU, Intensive Care Unit; EQ-5D, EuroQol 5-Dimension. *Time to shock resolution was calculated from the time of shock recognition to the documented resolution of shock. †Organ support-free days to day 28 were defined as the number of days alive and free from vasopressors/inotropes, invasive mechanical ventilation, and renal replacement therapy through day 28; patients who died before day 28 were assigned 0 days.

tion of patients were classified as fluid-responsive at 24 h (P=0.007) (**Table 3**).

Comparison of major clinical outcomes between the two groups

The observation group showed more rapid clinical stabilization, with a shorter time to shock resolution (P<0.001) and more shock-free days through day 7 (P<0.001), accompanied by a greater number of organ support-free days to day 28 (P<0.001). Resource utilization was lower in this group, reflected by shorter ICU length of stay (P<0.001) and hospital length of stay (P<0.001). Functional recovery favored the observation group, including a higher proportion discharged home rather than to rehabilitation or another facility (P=0.011) and better health-related quality of life at 90 days (EQ-5D

index, p<0.001). ICU mortality did not differ significantly between groups (P=0.063), and ICU readmission during the same hospitalization also did not differ between groups (P=0.268) (**Table 4**).

Comparison of SOFA scores between the two groups

Baseline total SOFA scores were broadly comparable between groups, but the observation group exhibited a significantly greater reduction by 24 h (P<0.01), with consistently lower total SOFA scores at 48 h, 72 h, and 5 days after intervention (all P<0.001). This overall improvement was accompanied by a marked attenuation in cardiovascular dysfunction: cardiovascular SOFA scores were lower in the observation group at 24 h and 48 h (both

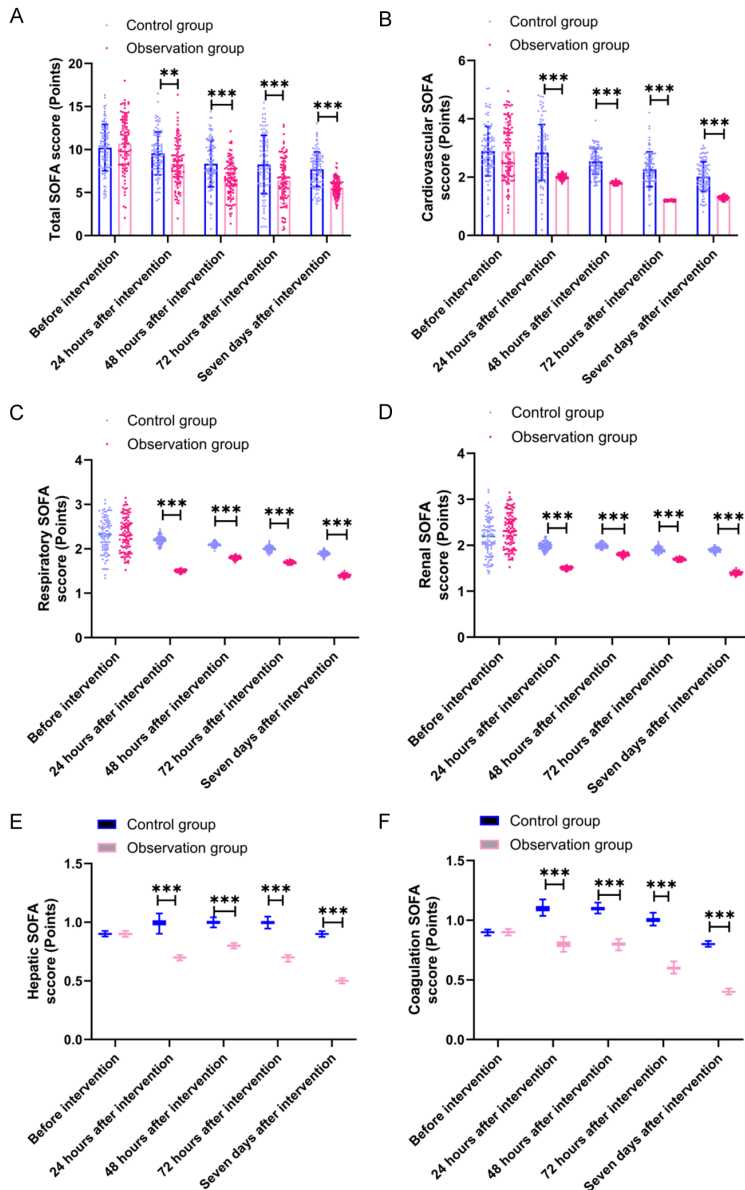


Figure 1. Comparison of SOFA scores between the two groups. (A) Total SOFA scores, (B) cardiovascular SOFA scores, (C) respiratory SOFA scores, (D) renal SOFA scores, (E) hepatic SOFA scores, and (F) coagulation SOFA scores, assessed before intervention and at 24, 48, and 72 h, as well as 5 days after intervention. Blue indicates the control group and red indicates the observation group; dots represent individual measurements and bars depict group-level summaries. Brackets denote between-group comparisons at each time point. ** $P < 0.01$, *** $P < 0.001$.

$P < 0.001$), remaining significantly lower at 72 h ($P < 0.01$), and persisted through day 5 ($P < 0.001$). Parallel between-group differences were also observed across other organ-specific SOFA components over the same time window, favoring the observation group ($P < 0.001$) (Figure 1).

Comparison of organ-specific perfusion and injury biomarkers between the two groups

By 24 h, the observation group demonstrated a more favorable renal phenotype, with a lower renal resistive index and reduced plasma NGAL compared with the control group (both $P < 0.001$), accompanied by significant within-group improvements from baseline (both $P < 0.001$). In contrast, markers of renal dysfunction and systemic/organ injury diverged over time: serum creatinine, procalcitonin, and hepatic transaminases (AST and ALT) increased from baseline in the control group (all $P < 0.001$), whereas they decreased in the observation group (all $P < 0.001$), yielding consistently lower levels in the observation group at 24 h (all between-group $P < 0.001$) (Figure 2).

Discussion

In critically ill shock patients, our study indicates that a well-organized ultrasound-based strategy of circulatory management was linked to a consistent chain of benefit, including reduced early fluid exposure (reduced early exposure to fluids and unfavorable 0-6 h fluid balance), reduced norepinephrine demand, as well as earlier reassessment of physiology and subsequent preferable 24-h hemodynamic/ultrasound phenotype (better MAP, improved forward flow, less LV dysfunction), and quicker remediation of global organ dysfunction. These early physiologic alarms expressed into clinically relevant recovery outcomes in shorter time to shock resolution and more organ support-free days to day 28 with additional better downstream recovery metrics (disposition and 90-day EQ-5D). The novelty of the study is that

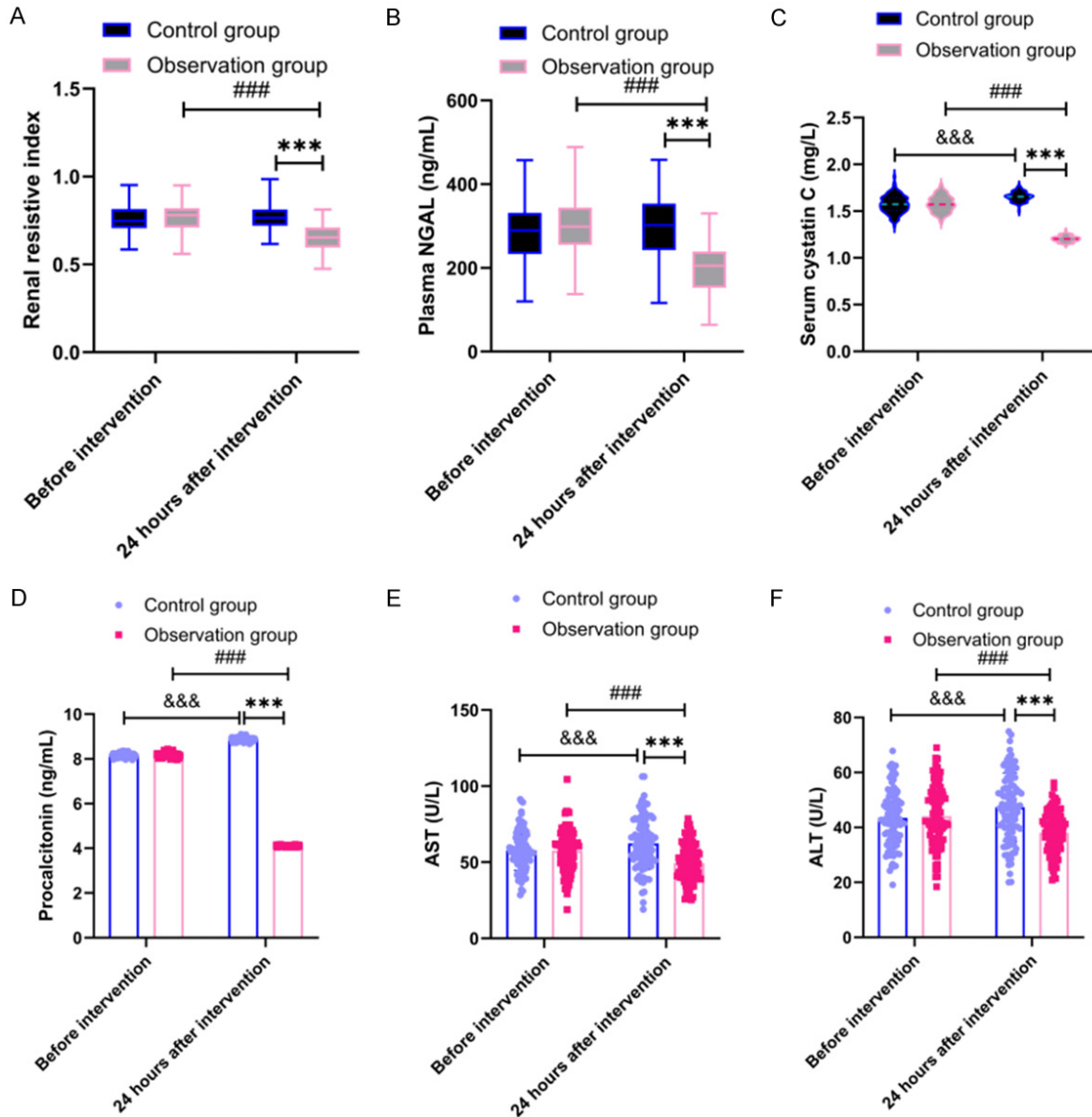


Figure 2. Comparison of organ-specific perfusion and injury biomarkers between the two groups. (A) Renal resistive index, (B) plasma NGAL, (C) serum creatinine, (D) procalcitonin, (E) aspartate aminotransferase (AST), and (F) alanine aminotransferase (ALT), measured before intervention and 24 h after intervention. Blue indicates the control group and pink indicates the observation group; symbols represent individual patients with group-level summaries overlaid. ***P<0.001 for between-group comparisons at the indicated time point; &&&P<0.001 vs. before intervention within the control group; ###P<0.001 vs. before intervention within the observation group.

it operationalized the concept of precision resuscitation at the bedside through repetitive phenotyping of the macrocirculation and organ perfusion through the point-of-care ultrasound and associated the changes to organ recovery, based on both multivariate and mediation models.

Our evidence confirms the idea that shock resuscitation needs to be transitioned to a

state where it is based on real-time physiology-informed, and individually adjusted hemodynamic targets, rather than fixed-volume, one-size-fits-all guidelines. Modern sepsis practices have focused on the serious understanding of early identification, prior stabilization, and constant review as well as the uncertainty regarding optimal fluid dosing and advising the deployment of dynamic variables where practical [14]. Our ultrasound-based approach in this

regard can be considered as a practical-use tool to translate guideline directive into replicable decisions in the bedside that is deliberately designed to convert clinical examination intent with inadequate clinical examination-based differentiators of preload responsiveness, contractile reserve, and afterload dysfunction, especially in mixed shock states. The clinical implication is not that the increased use of ultrasound is necessarily effective, but rather that guided ultrasound at selected decision points could decrease the tendencies of therapeutic inertia and avoid more catastrophic outcomes of frequent failure modes in conventional shock treatment, such as fluid overload and excessive exposure to catecholamines. Bed-side ultrasound may further improve resuscitation by enabling quantitative assessment of venous congestion, thereby helping clinicians distinguish clinically relevant hypervolemia from simple positive fluid balance and avoid organ injury related to fluid overload [15].

The fluid-sparing trend that we identified early is consistent with the increasing literature that associates positive fluid balance with unfavorable outcomes and dysfunction of organs in the case of sepsis and septic shock. The meta data analysis has indicated that the risk of mortality is related to increased cumulative fluid balance, which supports the biologic plausibility of unnecessary fluid accumulation avoidance delivering positive outcomes to organ recovery [16]. There have been no significant mortality benefits demonstrated in large randomized trials using restrictive vs liberal fluid approaches (as in CLASSIC and CLOVERS) and, although this approach has its own benefits, it has generally been shown to not favor restrictive measures [17, 18]. We hypothesize that fluid restriction can be effective only when it is not a fixed ceiling, but rather physiology-selected that is, selected because repeated measurements of forward flow, venous congestion/preload surrogates and responsiveness have identified it as such. In line with this process, the FRESH trial, has shown that responsiveness-driven resuscitation led to net fluid balance decreases and increased the risk of renal and respiratory failure was also lowered, which validates the principles that reassessment-driven downward trend may be converted into organ protective pathways [19]. These data, in clinical terms, warn against the fact that early hypotension

does not imply the need to supply the body with fluids universally, but rather the fact that fluid administration is more likely to exacerbate tissue edema, which thus becomes more challenging to oxygenate, as renal interstitial pressure rises, and hepatic congestion occurs.

Our finding of reduced dose of norepinephrine at 6 h or less, help to add to the literature of early and prudent use of vasopressors to promptly revive perfusion pressure with minimum fluid overload. The results of the CENSER trial showed that low-dose of norepinephrine started early enhanced shock control after 6 h with usual care, which prospectively supported the initiation of vasopressors as a component of balanced resuscitation [20]. Phenotyping by ultrasound could have been performed at an earlier stage in our cohort differentiating between vasodilatory and preload limitations, allowing for timely vasopressor to prevent excessive and timely de-escalation of the vasopressor as cardiac output and perfusion recovered. On the mechanistic level, lowering catecholamine exposure might reduce arrhythmogenicity, overexertion, and microcirculatory heterogeneity and prevent protracted hypotension a proven cause of organ damage [21]. The caution here is that early vasopressors should not be reflexive instead they should be combined with close evaluation of cardiac performance and volume tolerance to prevent the development of low-flow states in patients with occult myocardial depression.

The likely benefit of ultrasound-informed management in the detection and management of moderate-to-severe LV systolic dysfunction is demonstrated by the 24-h change in cardiac performance indices (cardiac index, LVOT VTI, and LVEF) and the decrease in severe-to-moderate LV systolic cardiomyopathy or mixed shock prevalence. According to the syntheses made by experts, point-of-care ultrasound is capable of describing preload, afterload, and contractility along with individualized resuscitation in sepsis and septic shock within seconds, but randomized evidence remains scarce and containing discrepant results [22, 23]. Our data build on this framework proposing that when the ultrasound evidence is incorporated into a systematic decision process (as opposed to being applied as a one-dimensional snapshot), they could be useful in assisting clinicians to

prevent maladaptive fluid loading of depressed systolic functioning, by choosing the right vaso-active format, thus tuning therapy to restoring acceptable forward motion. The larger point is that the process of macro-hemodynamic normalization cannot be effective unless it takes place through an approach that preserves ventriculo-arterial coupling as well as prevents the development of iatrogenic congestion, which can be identified by ultrasound well in advance.

This is supported by the fact that the renal signal, which is lower renal resistive index and decreased NGAL at 24 h, is biologically plausible and indicates the improvement of organization of the perfusion in the organ along with the reduction of the early tubular injury. It has been previously shown that high renal resistive index is linked with risk of AKI in sepsis and that its analysis has to consider systemic hemodynamics (including MAP) and vascular tone [24, 25]. Physiologic work also demonstrates that MAP change can induce changes in renal vascular resistance indices of septic shock, indicating that renal Doppler parameters of changing MAP may be an interaction between perfusion pressure, intrarenal vasoconstriction, and venous congestion and not the resultant effect of perfusion pressure. The higher MAP, better forward flow, and less positive fluid balance combination is plausible in our research: better effective renal perfusion with decreased interstitial edema/congestion could reduce renal vascular resistance, and less stress on the early tubules through lower NGAL.

This faster than time dependency in increasing the difference in SOFA scores indicates the intervention was, however, not limited to hemodynamic number measurements, but linked to multisystem organ recovery, which is in line with a perfusion-centered resuscitation philosophy. Peripheral perfusion trials (e.g. capillary refill directed approaches) have also helped to support the concept that targeted tissue perfusion is capable of beneficially modifying physiologic endpoints and may converge to better results than lactate-based approaches [26-28]. This direction is echoed by our findings, however they widen it by adding ultrasound-derived phenotyping, which would be used to inform the pulling of the lever (fluid vs vasoactive vs reassessment timing). These findings provide exploratory, non-confirmatory support

for a potential mechanistic pathway linking the intervention to improved outcomes. Specifically, improvements in organ dysfunction (Δ SOFA) and cardiac performance (cardiac index) showed the strongest statistical contribution to the association with organ support-free days, while renal microcirculatory and injury markers demonstrated smaller but significant associations. Given the retrospective design, mixed temporal measurement windows of candidate mediators, and the absence of formal structural equation modeling or path analysis to validate directional and hierarchical relationships, these results should be interpreted as indicative of convergent physiological signals rather than definitive causal mediation or dominance of specific pathways.

There are a number of limitations that should be highlighted. The retrospective, single-center design is prone to residual confounding, with other effects of selection, practice-pattern effects that cannot be completely overcome even after adjustment. Classification of exposure can be imperfect (strategy strength and protocol based on actual care is variable), and the ultrasound measurements depend on the operator and time. Phenotyping and biomarkers and ultrasound sampled at predefined windows which could not capture previous transient effects. Although the organ support-free days endpoint is a clinically relevant one, it may be affected by the local weaning practices. Lastly, mediation analyses rely on strong causal and temporal assumptions, including correct temporal ordering and no unmeasured mediator-outcome confounding. In our retrospective dataset, variables were derived from different and partly overlapping time windows, and we did not apply structural equation modeling or path analysis to formally validate directional relationships. Therefore, these mediation results should be interpreted as exploratory and hypothesis-generating rather than causal evidence.

In conclusion, a structured ultrasound-guided circulatory management strategy was associated with more physiology-concordant early resuscitation, including less fluid accumulation and lower vasopressor intensity, as well as more favorable 24-h hemodynamic and renal perfusion/injury phenotypes, faster recovery of organ dysfunction, and better clinical recovery

outcomes in critically ill shock patients. These findings suggest that ultrasound-enabled, repeatedly reassessed 'precision resuscitation' may be a promising management approach; however, given the single-center retrospective design, no causal relationship can be established, and prospective multicenter studies are required to confirm these associations, to identify the best-performing phenotypes, and to standardize implementation across diverse ICUs.

Disclosure of conflict of interest

None.

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