Received: 14 September 2023 | Accepted: 11 December 2023

DOI: 10.1002/ams2.914

ORIGINAL ARTICLE

ACUTE MEDICINE & SURGERY WILEY

Clinical parameter-guided initial resuscitation in adult patients with septic shock: A systematic review and network meta-analysis

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Abstract

Aim: To identify the most useful tissue perfusion parameter for initial resuscitation in sepsis/septic shock adults using a network meta-analysis.

Methods: We searched major databases until December 2022 for randomized trials comparing four tissue perfusion parameters or against usual care. The primary outcome was short-term mortality up to 90 days. The Confidence in Network Meta-Analysis web application was used to assess the quality of evidence.

Results: Seventeen trials were identified. Lactate-guided therapy (risk ratios, 0.59; 95% confidence intervals [0.45–0.76]; high certainty) and capillary refill time-guided therapy (risk ratios, 0.53; 95% confidence intervals [0.33–0.86]; high certainty) were significantly associated with lower short-term mortality compared with usual care, whereas central venous oxygen saturation-guided therapy (risk ratio, 1.50; 95% confidence intervals [1.16–1.94]; moderate certainty) increased the risk of short-term mortality compared with lactate-guided therapy.

Conclusions: Lactate or capillary refill time-guided initial resuscitation for sepsis/septic shock patients may decrease short-term mortality. More research is essential to personalize and optimize treatment strategies for septic shock resuscitation.

KEYWORD
capillary refill timecarbon dioxide gapcentral venous oxygen saturationlactatenetwork meta-analysissepsisseptic shock

INTRODUCTION

Sepsis is a life-threatening condition marked by organ dysfunction from a dysregulated response to infection.[1] Immediate treatment, particularly fluid resuscitation and vasopressors is critical in patients with possible impaired tissue perfusion or septic shock. Balancing fluid input is essential; excessive resuscitation can lead to complications such as pulmonary edema and increased risk of death.[2] Regular assessment of patients allows clinicians to adjust treatment, but there is uncertainty about which variables best optimize organ perfusion.

Currently, blood lactate assessment is standard for suspected sepsis because it is central to its definition.[1] Although elevated lactate levels are often associated with tissue hypoperfusion, they can also be influenced by other factors such as aerobic glycolysis or mitochondrial dysfunction, making them an imperfect and occasionally misleading indicator.[3] This uncertainty underscores the weak recommendation and low-quality evidence for

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lactate-guided therapy.[2] A trial of early goal-directed therapy (EGDT), specifically focused on central venous oxygen saturation ($ScvO_2$), showed no improvement over standard care.[4] Meanwhile, the veno-arterial difference in the partial pressure of carbon dioxide, also known as the PCO_2 gap, has been proposed as a potentially more dependable alternative to $ScvO_2$ or blood lactate in indicating tissue hypoperfusion.[5] A recent trial highlighted better outcomes using capillary refill time (CRT) over lactate monitoring, with the CRT group showing reduced Sequential Organ Failure Assessment (SOFA) scores and a trend of lower mortality at 28 days.[6]

Given the fragmented evidence and limited data on the best monitoring strategies and organ perfusion variables in sepsis, we undertook a network meta-analysis (NMA). Our goal was to determine which tissue perfusion or clinical parameter-guided therapy is most useful in improving outcomes for adults with sepsis or septic shock.

MATERIALS AND METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension statement for reporting NMAs (PRISMA-NMA) (Table S1**S1**). The protocol was registered on protocols.io (74175).

Eligibility criteria

We included randomized controlled trials (RCTs) analyzing the effectiveness of various tissue perfusion parameters, or comparing them to standard care, for initial resuscitation in adult sepsis/septic shock patients. Parameters studied were lactate, CRT, $ScvO_2$/mixed venous oxygen saturation (SvO_2), and the ratio of veno-arterial carbon dioxide tension difference to arterial–venous oxygen content difference $P(v–a)CO_2/C(a–v)O_2$. SvO_2-guided therapy was considered equivalent to $ScvO_2$.[7] EGDT trials were categorized under $ScvO_2$ because of its key role in septic shock resuscitation.[8] Usual care was resuscitation without specific tissue perfusion targets. In multi-arm trials, any of the two arms listed above, including usual care, were compared to reflect each comparison. Multi-arm trials assessing different goal settings of a single parameter were combined. Studies on mixed populations of critically ill patients involving the subgroup of patients with severe sepsis or septic shock were also included. The primary outcome was short-term mortality (up to 90 days) or in-hospital mortality if time-specific data was not provided. Secondary outcomes included intensive care unit (ICU) mortality, ventilator-free days at 28 days, and ICU length of stay.

Information sources and search

We searched the Cochrane Central Register of Controlled Trials, MEDLINE via PubMed, Web of Science, and the ICHUSHI database (a national database of Japanese research papers) until December 2022. Our detailed search strategy is available in Table S2. We also searched the World Health Organization International Clinical Trials platforms Search Portal and ClinicalTrials.gov. for ongoing trials up to December 2022.

Study selection and data collection process

Two of the five authors screened titles and abstracts, with full-text reviews for final inclusion. Disagreements were settled by a third researcher. Similarly, two reviewers independently extracted the data. Study authors were contacted to resolve any queries.

Risk of bias within individual studies

Two of the five reviewers assessed the risk of bias independently based on the Cochrane Risk of Bias tool version 2 (RoB 2). Any disagreement was handled by a third reviewer. We rated each risk of bias as "low risk," "some concerns," or "high risk" of bias.

Analyses

We conducted a pairwise meta-analysis for every direct comparison using RevMan 5.4. For categorical outcomes, the effect sizes were expressed as risk ratios (RR) with their 95% confidence intervals (CI), whereas weighted mean differences (MD) with 95% CI were used for continuous outcomes. We used random-effects models to estimate the pooled effect sizes. The NMA was conducted using Stata version 17 statistical software (Stata-Corp LP, College Station, TX, USA). We created network plots showing direct comparisons between tissue perfusion parameters. Pooled RRs or weighted MDs with their 95% CIs, as appropriate, were estimated using a multivariate random-effects meta-analysis. We also calculated the surface under the cumulative ranking curve (SUCRA) to estimate ranking probabilities of each parameter. Certainty of evidence for each outcome was evaluated using the Confidence in Network Meta-Analysis (CINeMA) approach.[9] To ensure our results' robustness, we conducted sensitivity analyses for the primary outcome by 1) excluding trials with high risk of bias, 2) excluding pre-2004 trials following the first Survival Sepsis Campaign, and 3) excluding trials in mixed critically ill patients with sepsis or septic shock.

RESULTS

Figure 1 shows the PRISMA flow diagram for study selection. Seventeen studies were finalized for analysis.

Network geometry

Figure 2 illustrates the network plot for primary and secondary outcomes. Eight trials compared $ScvO_2$-guided therapy with usual care,[10–17] four trials compared lactate-guided therapy with $ScvO_2$-guided therapy,[18–21] two trials compared lactate-guided therapy with usual care,[22,23] two trials compared CRT-guided therapy with lactate-guided therapy,[6,24] and one trial compared P(v–a)CO_2/C(a–v)O_2-guided therapy with $ScvO_2$-guided therapy.[25]

Study characteristics

Table 1 demonstrates the main characteristics of the selected studies. Three trials included mixed critically ill patients with sepsis or septic shock.[12,17,22] Of the remaining 14 trials of patients with sepsis/septic shock, two targeted patients with pneumonia and those 60 years old or older.[18,23]

Short-term mortality up to 90 days

Seventeen trials were included in the short-term mortality analysis. The results of pairwise meta-analysis are provided in Figure S1 and Table S3). Lactate-guided (RR, 0.59; 95% CI [0.45–0.76]; high certainty) and CRT-guided therapies (RR, 0.53; 95% CI [0.33–0.86]; high certainty) significantly reduced short-term mortality compared to usual care. In contrast, $ScvO_2$-guided (RR, 0.88; 95% CI [0.75–1.03]; moderate certainty) and P(v–a)CO_2/C(a–v)O_2-guided therapies (RR, 0.90; 95% CI [0.53–1.54]; very low certainty) did not. Considering lactate-guided therapy as the reference, neither CRT-guided therapy (RR, 0.91; 95% CI [0.61–1.36]; low certainty) nor P(v–a)CO_2/C(a–v)O_2-guided therapy (RR, 1.54; 95% CI [0.87–2.73]; low certainty) lowered short-term mortality, whereas $ScvO_2$-guided therapy (RR, 1.50; 95% CI [1.16–1.94]; moderate certainty) increased the risk of short-term mortality (Figure 3 and Table S4). The SUCRA statistic is shown in Table 2.

Secondary outcomes

ICU mortality was evaluated from five studies. Pairwise comparisons of the individual studies are presented in

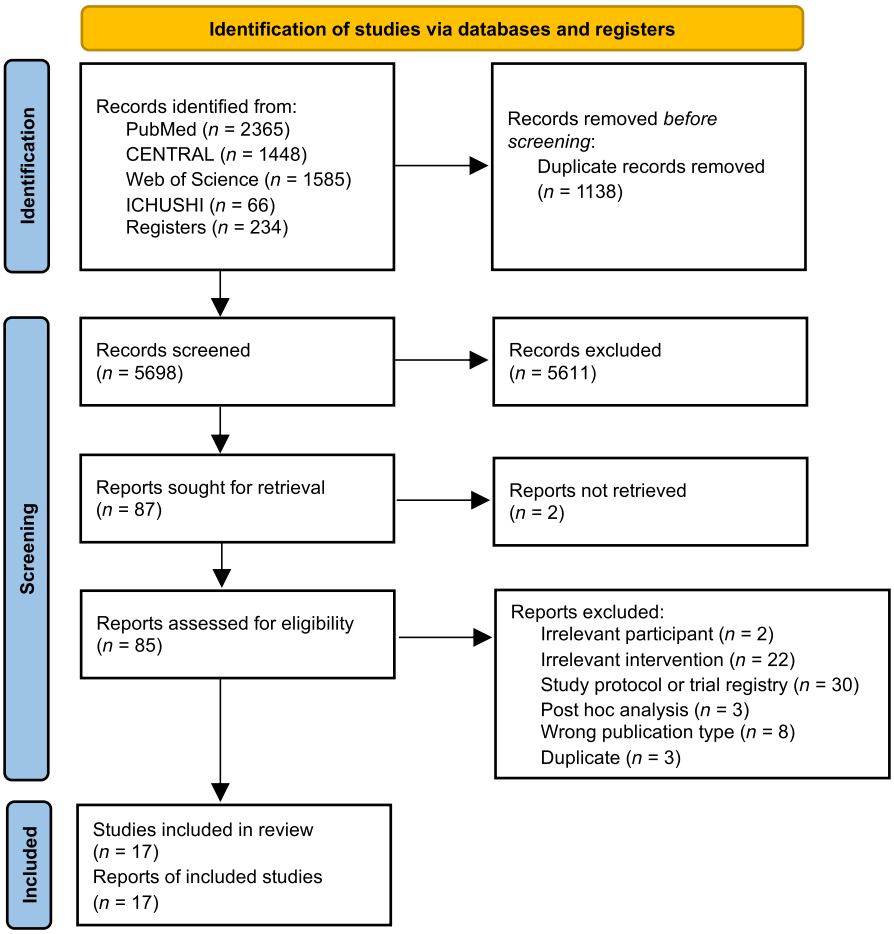


FIGURE 1 Flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) template.

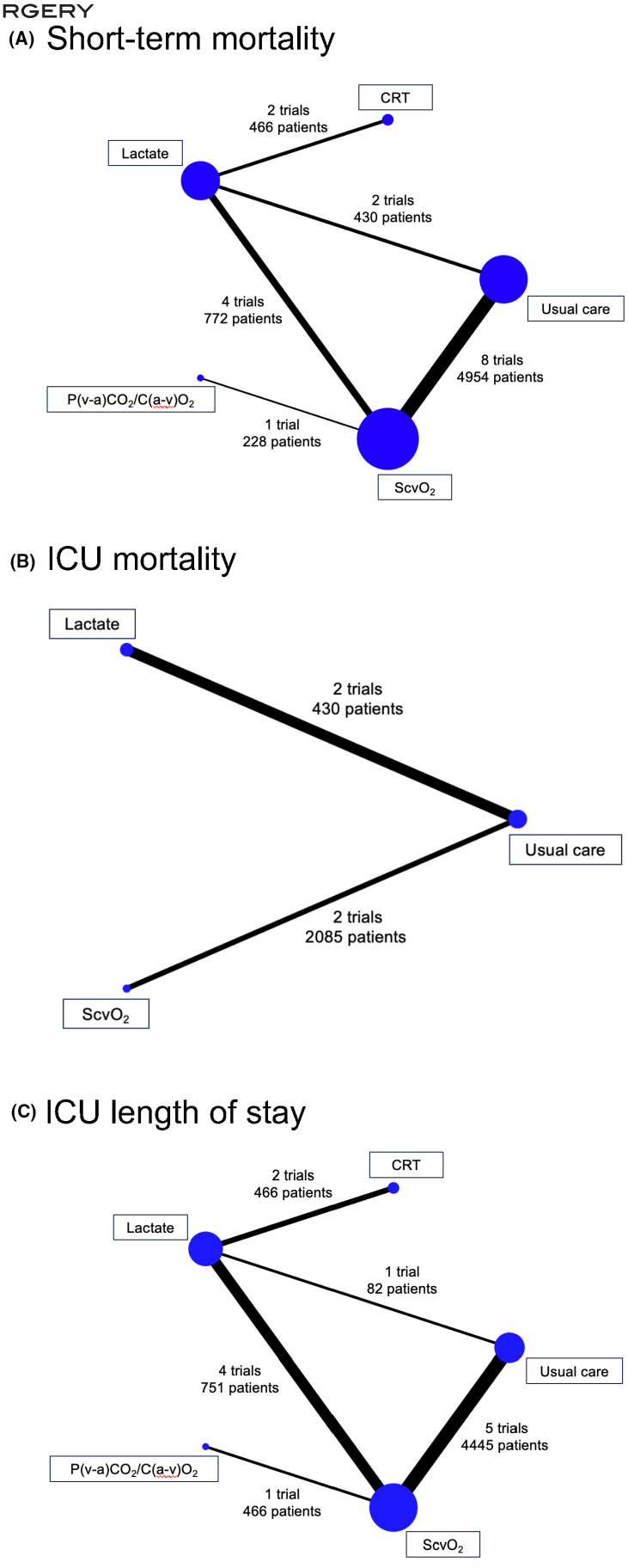


FIGURE 2 Network plots of short-term mortality up to 90 days, ICU mortality, and ICU length of stay for the different outcomes. CRT, capillary refill time; ICU, intensive care unit; $ScvO_2$, central venous oxygen saturation; $P(v–a)CO_2/C(a–v)O_2$, ratio of veno-arterial carbon dioxide tension difference to arterial–venous oxygen content difference.

TABLE 1 Main characteristics of included trials.

Source	Funding	Country	Total no. of patients	Participants	Exposure/ control age, mean (SD), year	Intervention	Comparison	Treatment period	Mortality assessed	Secondary outcomes assessed
Gattinoni *et al.*[17]	Eli Lilly Italy and Abbott Italy	Italy	762[a]	Critically ill (mixed)	62.4 (15.4)/61.3 (16.2)	SvO_2 (≥70%)	Usual	5 days	ICU	ICU mortality ICU length of stay
Rivers *et al.*[10]	Henry Ford Health Systems Fund for Research, a Weatherby Healthcare Resuscitation Fellowship, Edwards Lifesciences, and Nova Biomedical	US	263	Septic shock	67.1 (17.4)/64.4 (17.1)	EGDT ($ScvO_2$ ≥70%)	Usual	6 h	In-hospital	N/A
Wang *et al.*[11]	Undisclosed	China	33	Septic shock	33 (13)/36 (14)	EGDT ($ScvO_2$ ≥70%)	Usual	6 to 10 h	14-day	N/A
Chen *et al.*[12]	Undisclosed	China	273	Critically ill (MODS)	51.27 (16.76)/53.71 (16.62)	EGDT ($ScvO_2$ ≥70%)	Usual	6 h	ICU	ICU mortality
Jansen *et al.*[22]	Undisclosed	Netherlands	348	Critically ill (lactate level >3.0 mEq/L)	61 (15)/62 (18)	Lactate (decrease >10% every 2 h)	Usual	8 h	ICU	ICU mortality
Early Goal-Directed Therapy Collaborative Group of Zhejiang Province[13]	Zhejiang Provincial Medical and Health Key Scientific Research Project, Zhejiang Province Natural Science Foundation of China, and Zhejiang Provincial Health High-level Innovative Talent Fund Project	China	303	Severe sepsis or septic shock	68.9 (15.6)/67.7 (18.1)	EGDT ($ScvO_2$ ≥70%)	Usual	6 h	28-day	Ventilated days ICU length of stay
Jones *et al.*[19]	National Institutes of Health	US	300	Septic shock	59.8 (17.6)/61.6 (17.6)	Lactate (decrease >10% every 2 h)	$ScvO_2$ (≥70%)	6 h	In-hospital	Ventilated days Ventilator-free days ICU length of stay
Tian *et al.*[18]	Shandong Natural Science Funding	China	62[b]	Pneumonia with septic shock	51.86 (19.38)/46.18 (16.28)	Lactate (decrease >10% or 30% every 2 h)	$ScvO_2$ (>70%)	6 h	28-day	ICU length of stay
Yu *et al.*[20]	Hebei Province Medical Scientific Research Key Project	China	50	Septic shock	61 (12)/59 (18)	Lactate (decrease >10% every 3 h)	$ScvO_2$ (≥70%)	6 h	28-day	ICU length of stay

TABLE 1 (Continued)

Source	Funding	Country	Total no. of patients	Participants	Exposure/ control age, mean (SD), year	Intervention	Comparison	Treatment period	Mortality assessed	Secondary outcomes assessed
ARISE Investigators[14]	National Health and Medical Research Council of Australia and the Alfred Foundation	Australia and New Zealand, et al.	1588	Septic shock	62.7 (16.4)/63.1 (16.5)	EGDT ($ScvO_2$ ≥70%)	Usual	6 h	90-day	ICU mortality ICU length of stay
ProCESS Investigators[15]	National Institute of General Medical Sciences	US	1351[c]	Septic shock	60 (16.4)/62 (16.0)	EGDT ($ScvO_2$ ≥70%)	Usual	6 h	90-day	Ventilated days ICU length of stay
Mouncey *et al.*[16]	United Kingdom National Institute for Health Research Health Technology Assessment Programme	UK	1260	Septic shock	66.4 (14.6)/64.3 (15.5)	EGDT ($ScvO_2$ ≥70%)	Usual	6 h	90-day	Ventilator-free days ICU length of stay
Zhou *et al.*[21]	Health Scientific Research in the Public Interest Program	China	360	Septic shock	56 (44, 66)/56 (40, 67)	Lactate (decrease >10% every 2 h)	$ScvO_2$ (≥70%)	6 h	60-day	Ventilated days ICU length of stay
Su *et al.*[25]	N/A	China	228	Severe sepsis or septic shock	63 (17)/62 (17)	P(v–a)CO_2/C(a–v)O_2 ≥ 1.8	$ScvO_2$ (≥70%)	3 days	60-day	Ventilator-free days ICU length of stay
Hernández *et al.*[6]	Pontificia Universidad Católica of Chile	Argentina, Chile, Colombia, Ecuador, Uruguay	424	Septic shock	62 (17)/64 (17)	CRT (≤3 s)	Lactate (decrease >20% every 2 h)	8 h	90-day	Ventilator-free days ICU length of stay
Castro *et al.*[24]	FONDECYT Chile Grant project	Chile	42	Septic shock	51 (45, 75)/66 (55, 75)	CRT (≤3 s)	Lactate (decrease >20% every 2 h)	6 h	28-day	ICU length of stay
Chen *et al.*[23]	N/A	China	82	Septic shock (age ≥60)	72.4 (9.2)/70.9 (8.3)	Lactate (decrease >20% every 2 h)	Usual	6 h	ICU	ICU mortality Ventilated days ICU length of stay

Abbreviations: CRT, capillary refill time; EGDT, early goal-directed therapy; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; P(v–a)CO_2/C(a–v)O_2, ratio of veno-arterial carbon dioxide tension difference to arterial–venous oxygen content difference; SD, standard deviation; UK, United Kingdom; US, United States.

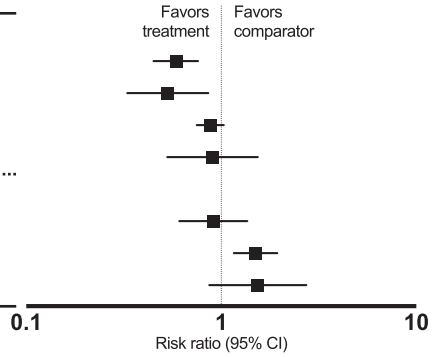
[a]Three-arm trials, including cardiac index group, which was out of our scope.

[b]Three-arm trials, including lactate clearance of 10%, 30%, and usual care.

[c]Three-arm trials comparing EGDT to protocol-based standard therapy, and usual care.

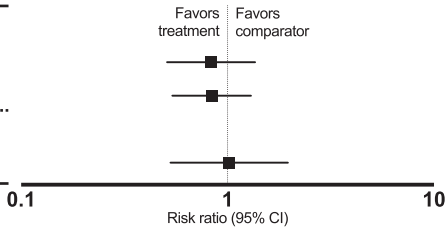
(A) Short-term mortality

Comparison	No. of trials	No. of patients	Quality of evidence	Network Risk Ratio (95% CI)
Usual care				Reference
Lactate	2	430	High	0.59 (0.45 to 0.76)
CRT	Indirect evidence	NA	High	0.53 (0.33 to 0.86)
$ScvO_2$	8	4954	Moderate	0.88 (0.75 to 1.03)
$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$	Indirect evidence	NA	Very low	0.90 (0.53 to 1.54)
Lactate				Reference
CRT	2	466	Low	0.91 (0.61 to 1.36)
$ScvO_2$	4	772	Moderate	1.50 (1.16 to 1.94)
$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$	Indirect evidence	NA	Low	1.54 (0.87 to 2.73)



(B) ICU mortality

Comparison	No. of trials	No. of patients	Quality of evidence	Network Risk Ratio (95% CI)
Usual care				Reference
Lactate	2	430	Very low	0.83 (0.51 to 1.36)
$ScvO_2$	2	2085	Very low	0.84 (0.54 to 1.30)
Lactate				Reference
$ScvO_2$	Indirect evidence	NA	Very low	1.02 (0.53 to 1.96)



(C) ICU length of stay

Comparison	No. of trials	No. of patients	Quality of evidence	Network Mean Difference (95% CI)
Usual care				Reference
Lactate	1	82	Moderate	–0.76 (–1.72 to 0.19)
CRT	Indirect evidence	NA	Low	–0.97 (–3.18 to 1.24)
$ScvO_2$	5	4445	Low	–0.02 (–0.56 to 0.52)
$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$	Indirect evidence	NA	Very low	0.58 (–1.78 to 2.94)
Lactate				Reference
CRT	2	466	Low	–0.21 (–2.20 to 1.79)
$ScvO_2$	4	751	Moderate	0.74 (–0.12 to 1.61)
$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$	Indirect evidence	NA	Very low	1.34 (–1.11 to 3.80)

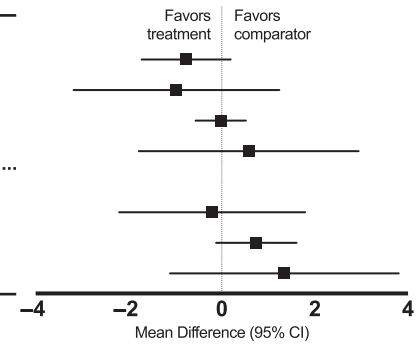


FIGURE 3 Forest plots for the association of tissue perfusion parameter-guided initial resuscitation with study outcomes. (A) Short-term mortality up to 90 days. (B) ICU mortality. (C) ICU length of stay. The certainty of evidence for each network meta-analysis estimate was evaluated based on the Confidence in Network Meta-Analysis approach. ICU, intensive care unit.

Figure S2 and Table S3. Compared to usual care as the reference, neither lactate-guided therapy nor $ScvO_2$-guided therapy was associated with decreased ICU mortality. Lactate-guided therapy was not superior to $ScvO_2$-guided therapy (Figure 3 and Table S4). SUCRA ranking is shown in Table 2.

Thirteen trials reported on ICU length of stay. Pairwise comparisons are provided in Figure S3 and Table S3). CRT-, lactate-, $ScvO_2$-, and $P(v–a)CO_2/C(a–v)O_2$-guided therapy were not associated with shorter ICU length of stay compared with usual care (Figure 3 and Table S4). Ranking probabilities is shown in Table 2.

Four trials reporting ventilator-free days were identified. Pairwise comparisons are shown in Figure S4 and Table S3. The limited number of trials providing information on ventilator-free days did not allow us to perform NMA.

Sensitivity analyses

After excluding trials with a high risk of bias, those before 2004, and those on mixed critically ill patients, lactate and CRT-guided therapies still showed lower short-term mortality than usual care, whereas $ScvO_2$-guided therapy had

TABLE 2 Treatment hierarchy using the SUCRA curve for study outcomes.

Rank	Usual care	CRT	Lactate	P(v–a)CO_2/C(a–v)O_2	ScvO_2
Short-term mortality					
Best	0.0	66.3	29.8	3.9	0.0
2nd	0.1	27.2	65.0	6.4	1.3
3rd	3.0	4.9	5.1	35.0	52.0
4th	33.7	1.3	0.1	20.3	44.7
Worst	63.2	0.3	0.0	34.5	2.0
Mean rank	4.6	1.4	1.8	3.8	3.5
SUCRA	0.1	0.9	0.8	0.3	0.4
ICU mortality					
Best	0.0		6.7		93.3
2nd	10.1		83.5		6.4
Worst	89.9		9.8		0.3
Mean rank	2.9		2.0		1.1
SUCRA	0.1		0.5		1.0
ICU length of stay					
Best	1.8	53.7	35.2	8.3	1.0
2nd	9.9	20.7	51.9	8.6	9.0
3rd	32.9	6.9	10.4	11.7	38.1
4th	39.1	9.8	2.0	8.2	40.9
Worst	16.4	8.8	0.6	63.3	11.0
Mean rank	3.6	2.0	1.8	4.1	3.5
SUCRA	0.4	0.8	0.8	0.2	0.4

Abbreviations: CRT, capillary refill time; ICU, intensive care unit; ScvO_2, central venous oxygen saturation; SUCRA, surface under the cumulative ranking; P(v–a)CO_2/C(a–v)O_2, ratio of veno–arterial carbon dioxide tension difference to arterial–venous oxygen content difference.

higher mortality risk than lactate-guided therapy (Table S5 and Figure S5).

DISCUSSION

Based on an NMA of 17 studies with 6850 participants across five interventions, lactate or CRT-guided resuscitation showed significantly lower mortality up to 90 days in adults with sepsis or septic shock compared to usual care, whereas ScvO_2-guided therapy had a higher mortality risk than lactate-guided therapy.

Our results align with recent meta-analyses, highlighting lactate-guided therapy's superiority in reducing ICU mortality over ScvO_2-guided therapy.[26] Past research indicated sepsis affects tissue oxygen balance, as evidenced by decreased ScvO_2 or SvO_2.[8] In 2001, the Rivers trial showed EGDT, primarily based on continuous ScvO_2 monitoring, improved ICU mortality compared to standard care.[10] However, three subsequent trials disagreed.[14–16] This inconsistency stems from differing initial ScvO_2 values across studies: 49% in the Rivers trial versus around 71% in the latter three. Therefore, many patients in the later trials might have already reached desired ScvO_2 levels at the start. Given ScvO_2's role in indicating tissue oxygenation and its link to mortality, those with "normal" ScvO_2 might not have received aggressive resuscitation.[27]

The 2004 Survival Sepsis Campaign promoted standardized care emphasizing large volume fluid resuscitation, although concerns about fluid overload emerged.[28] The ANDROMEDA-SHOCK trial compared CRT, a simple peripheral perfusion parameter, with lactate-guided therapy for septic shock. Despite similar 28-day mortality rates, CRT patients showed better 72-hour SOFA scores and received less initial fluid.[6] Post-hoc analyses revealed higher mortality in patients normalized by CRT, but further treated with lactate-guided fluids, suggesting curtailing aggressive resuscitation once CRT is normal.[29] Our NMA found no difference between the two therapies, but CRT had superior short-term mortality outcomes. P(v–a)CO_2/C(a–v)O_2-guided therapy showed no clear advantage in short-term mortality over usual care or lactate-guided therapy with very low and low certainty of evidence, respectively. The results may be difficult to interpret because of indirect evidence based on only a single study comparing P(v–a)CO_2/C(a–v)O_2-guided therapy and ScvO_2-guided therapy.[25]

Recent trials have tested individualized fluid resuscitation strategies, often using lactate levels or knee mottling as benchmarks.[30] Lactate-guided resuscitation is a mainstay for

septic shock, aligning with our NMA findings. Given sepsis's complexity, combining lactate with parameters such as CRT may be effective. Continued research is crucial to refine septic shock resuscitation guidelines.

This study has several limitations. First, the validity of NMA relies on the assumption of similar study populations, but five of 17 trials had diverse patient groups. Second, with evolving sepsis management guidelines, there is clinical variance across studies. Third, although our findings withstood sensitivity analyses, the few direct intervention comparisons led to sparse networks. Fourth, targets for lactate clearance varied between studies, and minimal data on ventilator-free days prevented an NMA on that outcome. Last, although long-term mortality was not examined because of an extreme paucity of studies addressing this specific outcome, our analysis of ICU mortality was similarly constrained by limited networks and few studies.

CONCLUSIONS

In this NMA, lactate or CRT guidance for septic shock resuscitation appears to reduce short-term mortality. However, because of significant heterogeneity and the need for individualized treatments, results should be interpreted cautiously. Further research is essential not only to examine ICU and long-term mortality, but also to explore other clinical outcomes and optimal treatment combinations for initial resuscitation, thereby creating a comprehensive evidence base for septic shock resuscitation strategies.

ACKNOWLEDGEMENTS

We thank Christine Burr for English editing of the article. We also like to thank the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2024 (J-SSCG 2024) committee for supporting this project.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Approval of the Research Protocol: N/A.
Informed Consent: N/A.
Registry and the Registration No. of The Study/Trial: The study protocol was registered on protocols.io (74175).
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yumoto T, Kuribara T, Yamada K, Sato T, Koba S, Tetsuhara K, et al. Clinical parameter-guided initial resuscitation in adult patients with septic shock: A systematic review and network meta-analysis. Acute Med Surg. 2023;10:e914. https://doi.org/10.1002/ams2.914