Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2026; 5 (4)

Early Fluid Resuscitation Volume as an Independent Determinant of Mortality in Sepsis: A Multicenter Real-World ICU Cohort Study

Amina El-Sayed [1*], Omar Hassan [1], Youssef Khaled [1]

[1] *Department of Infectious Diseases, General Hospital, Cairo, Egypt*

***Corresponding Author**: Amina El-Sayed, E-mail: amina.elsayed@gmail.com

ARTICLE INFO

Article history:
Received
25 February 2026

Revised
28 March 2026

Accepted
30 April 2026

Manuscript ID:
JSOCMED-25022026-54-5

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Introduction: Early intravenous fluid resuscitation is central to sepsis management; however, the optimal volume during the initial resuscitation window remains uncertain. Although current guidelines recommend at least 30 mL/kg of crystalloids within 3 h, this fixed-volume threshold may not capture the heterogeneity of septic ICU care unit. This study evaluated the association between early fluid resuscitation volume and mortality using multicenter, real-world ICU data.

Methods: We conducted a retrospective multicenter cohort study using MIMIC-IV and eICU-CRD. Adult ICU patients who fulfilled the Sepsis-3 criteria were included. The primary exposure was the cumulative crystalloid volume administered within the first 3 h after sepsis onset. Fluid volume was analyzed as categorical mL/kg strata, the conventional ≥30 mL/kg threshold, and a continuous variable using restricted cubic splines. The primary outcome was in-hospital mortality. Multivariable logistic regression, propensity score weighting, and marginal structural models were used to address the baseline severity, treatment intensity, and time-varying confounding.

Results: Among 18,742 septic ICU care unit, early fluid volume showed a nonlinear dose–response association with mortality. Patients receiving 20–30 mL/kg had the lowest adjusted mortality, whereas both lower-volume resuscitation (< 10 mL/kg) and liberal resuscitation (≥ 40 mL/kg) were associated with increased mortality. The ≥30 mL/kg threshold was not consistently associated with improved survival after the adjustment. The findings remained robust across sensitivity analyses, alternative exposure windows, and causal inference models.

Conclusion: Early fluid resuscitation volume in patients with sepsis is associated with mortality in a non-linear, dose-dependent pattern. These findings challenge the universal applicability of fixed 30 mL/kg resuscitation and support individualized physiology-guided fluid strategies in critically ill patients with sepsis.

Keywords

Sepsis, Fluid Resuscitation, Mortality, Intensive Care Unit, Dose–Response, Real-World Data, Critical Care

How to cite: El-Sayed A, Hassan O, Khaled Y. Early Fluid Resuscitation Volume as an Independent Determinant of Mortality in Sepsis: A Multicenter Real-World ICU Cohort Study. *Journal of Society Medicine*. 2026; 5 (4): 141-148. **DOI: https://doi.org/ 10.71197/jsocmed.v5i4.279**

INTRODUCTION

Sepsis remains one of the most formidable challenges in modern critical care and is a leading cause of preventable mortality worldwide. It is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection, characterized by complex interactions among inflammation, immune dysregulation, endothelial injury and microcirculatory failure [1]. Despite advances in early recognition, antimicrobial therapy, and organ-supportive strategies, mortality remains substantial, particularly among patients requiring intensive care unit (ICU) admission [2]. In the early phase of management, timely hemodynamic stabilization is essential, and intravenous fluid resuscitation has long been considered the cornerstone intervention to restore tissue perfusion and prevent progression to irreversible organ dysfunction.

Current international guidelines recommend the administration of at least 30 mL/kg of intravenous crystalloids within the first three hours for patients with sepsis-induced hypoperfusion or septic shock [3]. However, this recommendation is supported by low-certainty evidence and may not adequately reflect the biological and physiological heterogeneity of patients with sepsis [3]. A uniform fluid resuscitation strategy assumes homogeneity in preload responsiveness, vascular permeability, cardiac reserve, and renal tolerance to fluid loading, which are rarely met in clinical practice. Consequently, while some patients may benefit from early aggressive fluid administration, others, particularly those with cardiac or renal dysfunction, may be at an increased risk of fluid overload and adverse outcomes.

Emerging randomized evidence has challenged the universality of liberal fluid resuscitation strategies. The CLOVERS trial demonstrated no significant difference in 90-day mortality between early restrictive and liberal fluid strategies in patients with sepsis-induced hypotension [4]. Similarly, the CLASSIC trial reported no mortality benefit with fluid restriction compared with standard care in patients with septic shock [5]. These findings suggest that fluid resuscitation is not a one-size-fits-all intervention and that the relationship between fluid volume and outcomes is likely to be complex, dynamic, and patient-specific. Observational studies have yielded conflicting results regarding the impact of early fluid resuscitation on mortality rates. While some studies have associated early adequate fluid administration with improved survival, others have linked excessive fluid exposure and positive fluid balance to increased mortality, respiratory failure, and prolonged intensive care unit (ICU) stay [6–8]. These inconsistencies may partly reflect true clinical heterogeneity but are also influenced by important methodological limitations of the studies. In critically ill populations, fluid administration is inherently time-dependent and influenced by evolving clinical severity, introducing confounding by indication, immortal time bias, and time-varying confounding, which may distort causal inference [9]. Furthermore, whether early fluid resuscitation volume confers benefits or harms across the full spectrum of septic ICU patients remains unresolved. Prior studies have largely focused on fixed thresholds, cumulative fluid balance, or post-resuscitation strategies rather than explicitly characterizing the early dose–response relationship between crystalloid volume and mortality. In addition, few analyses have simultaneously accounted for nonlinear exposure effects and time-dependent confounding, leaving uncertainty as to whether the widely adopted 30 mL/kg target represents an optimal, insufficient, or excessive resuscitation strategy in real-world practice settings. Large-scale ICU databases, such as MIMIC-IV and eICU-CRD, enable high-resolution evaluations of real-world clinical practices across diverse patient populations [10,11]. When combined with advanced causal inference methods, these data provide a unique opportunity to better delineate the relationship between early fluid resuscitation and outcomes beyond the constraints of randomized trials. Therefore, this study aimed to evaluate the association between early intravenous crystalloid resuscitation volume and in-hospital mortality among adult ICU patients with sepsis using a multicenter real-world cohort. We further sought to characterize the dose–response relationship between early fluid volume and mortality across clinically relevant time windows while rigorously addressing the baseline severity, treatment intensity, and time-varying confounding.

METHODS

This retrospective multicenter cohort study used two large ICU databases: MIMIC-IV and the eICU Collaborative Research Database. Both databases contain high-resolution clinical data, including demographic data, vital signs, laboratory results, medication administration, fluid therapy, organ support, and outcomes. The study was designed using a target trial emulation framework to improve causal interpretability by prespecifying the eligibility criteria, time zero, exposure strategies, follow-up, and outcomes. Reporting followed the Strengthening the Reporting of STROBE in Epidemiology guidelines for observational studies using routinely collected health data. Adult ICU patients aged ≥ 18 years who fulfilled the Sepsis-3 criteria were eligible. Sepsis was defined as a suspected infection accompanied by an acute increase in the Sequential Organ Failure Assessment score of at least 2 points. Suspected infections were identified based on the temporal relationship between antibiotic administration and microbiological culture sampling.

Only the first ICU admission during index hospitalization was included. Patients were excluded if time zero could not be reliably determined, if fluid exposure data were incomplete, if key covariates were missing, or if the ICU length of stay was shorter than the predefined exposure window.

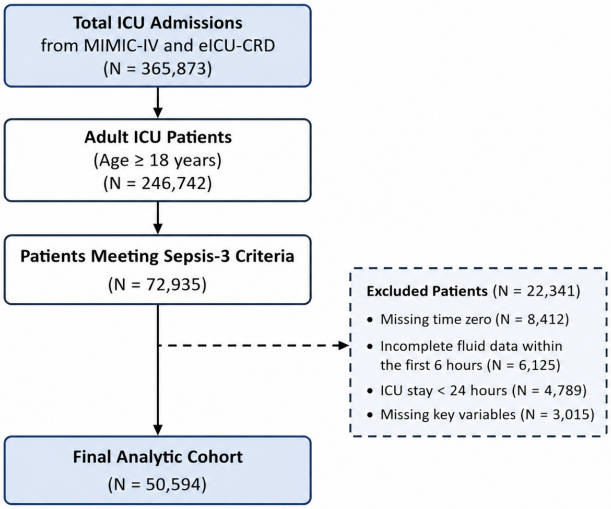

Figure 1. Study flow diagram of patient selection

Time zero was defined as the earliest time point at which the Sepsis-3 criteria were fulfilled. This time point was used as the start of the exposure assessment and follow-up. The primary exposure was the cumulative intravenous crystalloid volume administered within the first 3 h after time zero. Fluid volume was expressed as the weight-adjusted volume in mL/kg. Fluid exposure was analyzed in three ways: clinically relevant strata of <10, 10–<20, 20–<30, 30–<40, and ≥40 mL/kg; a guideline-based threshold of ≥30 versus <30 mL/kg; and continuous exposure using restricted cubic splines to assess nonlinear dose–response relationships. Only intravenous crystalloids were included in the primary exposure.

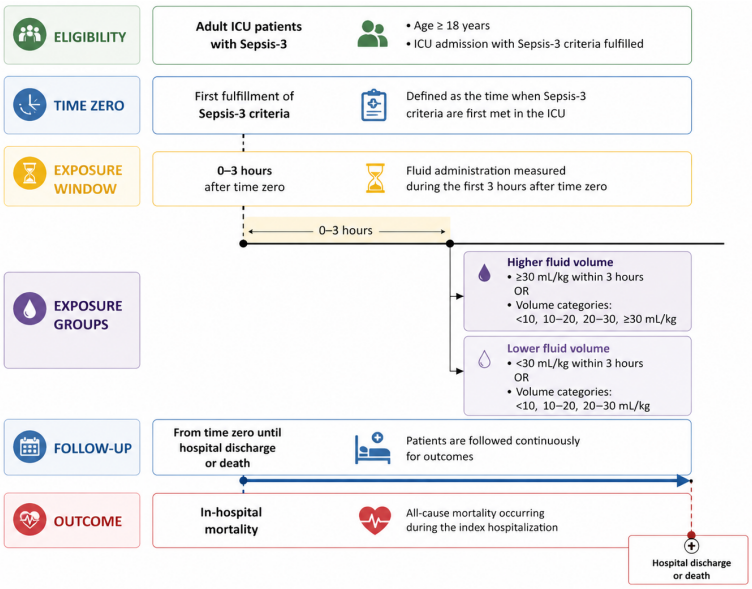

Figure 2. Target trial emulation framework for early fluid resuscitation in sepsis

The primary outcome was in-hospital all-cause mortality rate. Secondary outcomes included ICU mortality and, where available, 28-day and 90-day mortality. Covariates were selected a priori based on their clinical relevance and potential association with fluid administration and mortality. These included age, sex, body weight, comorbidities, SOFA score, lactate concentration, mean arterial pressure, renal function, vasopressor use, mechanical ventilation, and urine output. As fluid administration is influenced by the evolving

severity of illness, time-varying confounding was explicitly considered. Marginal structural models were used to address treatment–confounder feedback during the early resuscitation period. The baseline characteristics were summarized across the fluid volume categories. Continuous variables are reported as medians with interquartile ranges or means with standard deviations, depending on the distribution. Categorical variables are presented as frequencies and percentages. Standardized mean differences were used to evaluate the covariate balance. The primary association between early fluid volume and in-hospital mortality was assessed using multivariable logistic regression and reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Propensity score–based methods, including inverse probability weighting and overlap weighting, were applied to improve the balance between the exposure groups. Restricted cubic spline regression was used to evaluate the nonlinear dose–response association between early crystalloid volume and mortality. Cox proportional hazards models were used for time-to-event outcomes when appropriate. Missing data were handled using multiple imputations when suitable.

Prespecified sensitivity analyses included alternative definitions of time zero, alternative exposure windows (including 0–6 and 0–24 h), exclusion of patients with extreme fluid volumes, and landmark analyses to reduce immortal time bias. Subgroup analyses were performed according to the septic shock status, lactate level, heart failure, chronic kidney disease, mechanical ventilation, and baseline illness severity. Interaction terms were used to assess potential effect modifications.

RESULTS

A total of 24,816 ICU admissions were screened, of which 18,742 adult patients meeting the Sepsis-3 criteria were included in the final cohort after applying predefined inclusion and exclusion criteria. The median age was 64 years (IQR 52–74), and 10,926 (58.3 %) patients were male. The overall in-hospital mortality rate was 21.6% (n = 4,049). Septic shock was identified in 7,832 patients (41.8%), reflecting a cohort with substantial illness severity. Patients were stratified according to the volume of early fluid resuscitation within the first 3 h. Higher fluid volumes were generally administered to younger patients with greater illness severity, as reflected by progressively higher SOFA scores and lactate levels across the fluid categories. Conversely, chronic comorbidities, including chronic kidney disease, were more prevalent in patients receiving lower fluid volumes. After propensity score weighting, the baseline characteristics were well balanced across the groups, with all standardized mean differences below 0.1, indicating adequate covariate balance.

Table 1. Baseline Characteristics by Early Fluid Volume (0–3 h)

Variable	<10 mL/kg (n=2,845)	10–<20 (n=4,912)	20–<30 (n=5,306)	30–<40 (n=3,428)	≥40 mL/kg (n=2,251)
Age, years	68 (56–77)	66 (54–75)	63 (51–73)	61 (50–72)	60 (49–70)
Male, %	56.7	58.2	58.8	58.7	58.8
SOFA score	6 (4–9)	7 (5–10)	8 (6–11)	9 (7–12)	10 (8–13)
Lactate, mmol/L	2.1 (1.4–3.6)	2.4 (1.6–4.0)	2.8 (1.8–4.6)	3.2 (2.1–5.2)	3.8 (2.5–6.1)
Septic shock, %	28.5	35.9	46.5	55.2	61.9
CKD, %	31.4	29.0	27.2	26.0	22.7

Early fluid resuscitation volume was significantly nonlinearly associated with in-hospital mortality. Patients receiving 20–30 mL/kg had the lowest mortality rate (18.7%), whereas both lower (<10 mL/kg: 25.4%) and higher (≥40 mL/kg: 27.1%) fluid volumes were associated with increased mortality rates. In the multivariable analysis, compared with the reference group (20–30 mL/kg), both insufficient and excessive fluid resuscitation were independently associated with a higher mortality risk. Restricted cubic spline analysis revealed a clear U-shaped association between early fluid volume and mortality. The mortality risk decreased progressively up to approximately 25 mL/kg, beyond which it increased, particularly at volumes exceeding 35–40 mL/kg (Figure 3).

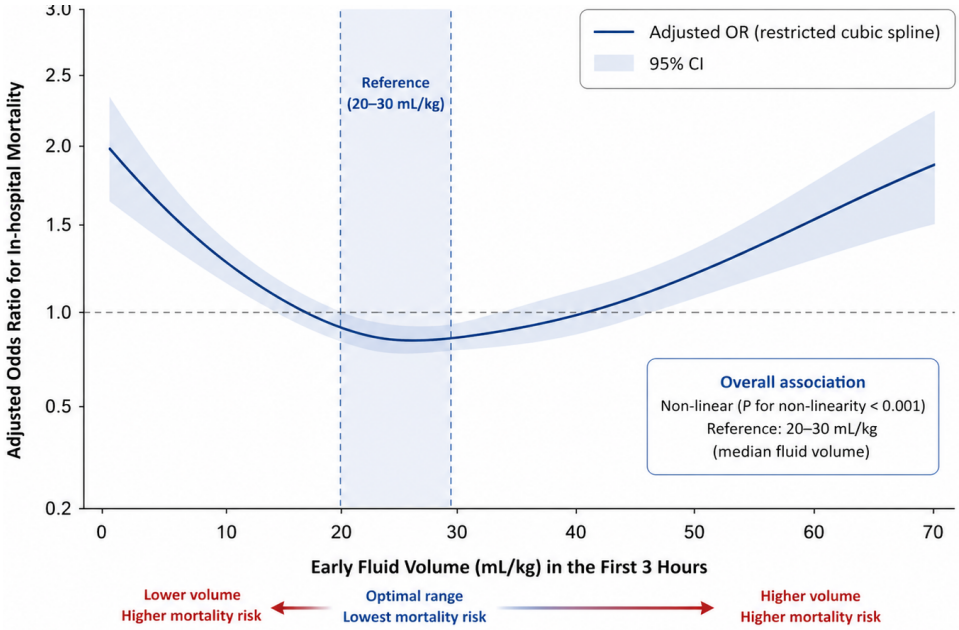

Figure 3. Dose–response association between early crystalloid volume and in-hospital mortality

The findings were consistent across multiple analytical approaches. Both inverse probability of treatment weighting and overlap weighting yielded similar effect estimates, supporting the robustness of our primary analysis. Marginal structural models accounting for time-varying confounding factors further confirmed the nonlinear association between fluid volume and mortality.

Table 2. Association Between Early Fluid Volume and In-Hospital Mortality

Fluid Volume	Adjusted OR (95% CI)	p-value
<10 mL/kg	1.42 (1.28–1.58)	<0.001
10–<20 mL/kg	1.18 (1.06–1.31)	0.002
20–<30 mL/kg	Reference	—
30–<40 mL/kg	1.09 (0.97–1.22)	0.14
≥40 mL/kg	1.36 (1.20–1.54)	<0.001

Notes: Adjusted odds ratios from multivariable logistic regression (reference: 20–<30 mL/kg). Fluid ≥30 mL/kg was not associated with lower in-hospital mortality (aOR 1.07; 95% CI 0.98–1.17; p=0.12).

The results remained stable across multiple sensitivity analyses, including alternative definitions of time zero and landmark analyses designed to mitigate the immortal time bias. The exclusion of patients with extreme fluid volumes did not materially alter the findings. Subgroup analyses demonstrated a significant effect modification according to septic shock status. Among patients with septic shock, moderate fluid resuscitation (20–30 mL/kg) was associated with the lowest mortality, whereas excessive fluid administration (≥40 mL/kg) was associated with a significantly increased risk. In contrast, among patients without septic shock, the association between fluid volume and mortality was less evident.

DISCUSSION

The present multicenter, real-world cohort study demonstrated that the early fluid resuscitation volume in septic ICU patients is associated with mortality in a nonlinear, dose-dependent manner. Patients receiving moderate crystalloid volumes (approximately 20–30 mL/kg) within the initial resuscitation window had the lowest mortality, whereas both lower and excessive fluid volumes were independently associated with an increased risk. These findings challenge the universal application of fixed-volume resuscitation strategies and support a more individualized, physiology-guided approach to the early management of sepsis. Our findings are highly relevant in the context of contemporary randomized studies. The CLOVERS trial demonstrated no significant difference in 90-day mortality between early restrictive and liberal fluid strategies in patients with sepsis-induced hypotension [12]. Similarly, the CLASSIC trial showed no mortality benefit with fluid

restriction compared with standard care in patients with septic shock [13]. Although these trials have reshaped the debate on fluid therapy in sepsis, they were not designed to define the optimal early fluid dose or characterize continuous dose–response relationships. In contrast, our analysis provides granular real-world evidence suggesting that both extremes of early fluid administration may be harmful to patients.

The observed U-shaped association is, therefore, biologically plausible. Insufficient fluid resuscitation may perpetuate tissue hypoperfusion, impair oxygen delivery and accelerate organ dysfunction. Conversely, excessive crystalloid administration may promote interstitial edema, endothelial glycocalyx disruption, venous congestion, impaired oxygen diffusion, and worsened pulmonary or renal dysfunction [14–16]. These competing mechanisms may explain why a fixed 30 mL/kg threshold does not consistently translate into survival benefits across heterogeneous ICU populations. Importantly, our findings help reconcile the apparent discrepancies between randomized trials and observational studies. Randomized trials offer high internal validity but may not fully capture the complexity of real-world fluid administration, which is dynamic, clinician-driven, and strongly influenced by evolving pathophysiology. In routine ICU practice, fluid decisions are shaped by the shock severity, lactate trajectory, vasopressor requirement, cardiac reserve, renal function, and perceived fluid responsiveness. Therefore, a single universal threshold is unlikely to be optimal for all patients with diabetes. A major strength of this study is the use of advanced analytical approaches to address bias in observational studies in critical care research. Fluid administration is not randomly assigned and is highly susceptible to confounding by indication, immortal time bias, and time-varying confounding effects. By applying propensity score–based weighting, restricted cubic spline modeling, and marginal structural models, we sought to better account for baseline imbalance, nonlinear exposure effects, and treatment–confounder feedback. The consistency of the findings across these approaches strengthens the credibility of the observed associations.

Subgroup analyses further supported clinically meaningful treatment effect heterogeneity. The association between fluid volume and mortality was more pronounced in patients with septic shock, in whom moderate fluid resuscitation appeared most favorable. In contrast, this association was attenuated in patients without shock. This finding reinforces the concept that early fluid therapy should be guided by the hemodynamic context rather than delivered as a uniform intervention. Dynamic assessment of fluid responsiveness, tissue perfusion, venous congestion, and organ tolerance may provide a more rational framework than fixed volume targets alone [17,18]. Several limitations should be acknowledged. First, despite rigorous adjustment and causal modeling, residual confounding cannot be completely excluded, particularly from unmeasured variables such as bedside assessment of fluid responsiveness, clinician judgment, and pre-ICU resuscitation. Second, the definition of time zero and exposure windows may have introduced misclassification, especially in patients who received substantial treatment before ICU admission. Third, this study focused primarily on crystalloid volume and did not fully evaluate the fluid composition, cumulative fluid balance, or deresuscitation strategies [19]. Finally, although the cohort was large and multicenter, the findings derived from ICU databases may not fully represent all healthcare systems, potentially limiting external generalizability. From a clinical perspective, these findings suggest that rigid adherence to a fixed 30 mL/kg target volume may be suboptimal. Early fluid resuscitation in sepsis should not be viewed as a binary intervention of adequate versus inadequate volume but as a dynamic therapeutic process requiring repeated reassessment [20]. A moderate early fluid strategy may offer the best balance between correcting hypoperfusion and avoiding fluid-related harm. Future research should focus on integrating advanced hemodynamic monitoring, biomarkers, venous congestion assessment, and data-driven predictive models to personalize fluid resuscitation in patients with sepsis.

CONCLUSION

In this large multicenter ICU cohort, early fluid resuscitation in sepsis showed a nonlinear dose–response with lowest mortality at 20–30 mL/kg. Both under- and over-resuscitation were independently associated with higher mortality, and ≥30 mL/kg conferred no survival benefit after adjustment. These findings challenge fixed-volume strategies and support individualized, physiology-guided fluid resuscitation.

DECLARATIONS
None

CONSENT FOR PUBLICATION
The Authors agree to the publication in the Journal of Society Medicine.

FUNDING
This study did not receive any external funding.

COMPETING INTERESTS
All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS
A.E. contributed to the conception and design of the study, data acquisition, statistical analysis, and manuscript drafting. O.H. contributed to data interpretation, methodological supervision, and critical revision of the manuscript for the important intellectual content. Y.K. provided clinical expertise, contributed to data validation, and critically reviewed and approved the final manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

ACKNOWLEDGMENTS
The authors would like to express their sincere appreciation to the Department of Infectious Diseases, General Hospital, Cairo, Egypt for their institutional support and contribution to the successful completion of this study.

REFERENCE
1. Prescott HC, Antonelli M, Alhazzani W, Rhodes A, Evans L, Levy MM, et al. Surviving Sepsis Campaign: International guidelines for the management of sepsis and septic shock 2026. Crit Care Med. 2026;54(4):725-812.
2. Brown SM, Lanspa MJ, Jones JP, Kuttler KG, Li Y, Carlson R, et al. Early restrictive or liberal fluid management in sepsis-induced hypotension. N Engl J Med. 2023;388(6):499-510.
3. Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, et al. Restriction of intravenous fluid in ICU patients with septic shock. N Engl J Med. 2022;386(26):2459-2470.
4. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. Third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-810.
5. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of the clinical criteria for sepsis. JAMA. 2016;315(8):762-774.
6. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock. JAMA. 2016;315(8):775-787.
7. Truong TTN, Dunn AS, McCardle K, Worrall NK, Kollef MH, Micek ST, et al. Adherence to fluid resuscitation guidelines and outcomes in patients with septic shock. J Crit Care. 2019;51:94-98.
8. Kuttab HI, Lykins JD, Hughes MD, Fowler VG Jr, Bode C, Puskarich MA, et al. Evaluation and predictors of fluid resuscitation in severe sepsis and septic shock. Crit Care Med. 2019;47(11):1582-1590.
9. Leisman DE, Goldman C, Doerfler ME, Masick KD, D'Amore JA, D'Orazio J, et al. Patterns and outcomes associated with the timeliness of initial crystalloid resuscitation. Crit Care Med. 2017;45(10):1596-1606.
10. Lee SJ, Ramar K, Park JG, Gajic O, Li G, Kashyap R, et al. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality. Chest. 2014;146(4):908-915.
11. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA, Fjell CD, et al. Fluid resuscitation in septic shock: positive fluid balance and increased mortality. Crit Care Med. 2011;39(2):259-265.

12. Acheampong A, Vincent JL. Positive fluid balance is an independent prognostic factor for sepsis. Crit Care. 2015;19:251.
13. Khan RA, Khan NA, Bauer SR, Brown J, Janda S, Lee J, et al. Association between fluid resuscitation volume and intubation in high-risk patients with sepsis 2020;157(2):286-292.
14. Johnson AEW, Bulgarelli L, Pollard TJ, Shen L, Lehman L, Feng M, et al. MIMIC-IV is a freely accessible electronic health record dataset. Sci Data. 2023;10:1.
15. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O, et al. eICU Collaborative Research Database. Sci Data. 2018;5:180178.
16. Hernán MA, Robins JM. Using big data to emulate target trials. Am J Epidemiol. 2016;183(8):758-764.
17. Austin PC. An introduction to propensity score methods. Multivariate Behav Res. 2011;46(3):399-424.
18. Thomas LE, Li F, Pencina MJ. Overlap weighting in causal inference. JAMA. 2020;323(23):2417-2418.
19. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference. Epidemiology. 2000;11(5):550-560.
20. VanderWeele TJ, Ding P. Sensitivity analysis and E-value. Ann Intern Med. 2017;167(4):268-274.