

The Impact of Individualized Fluid Therapy Strategies on the Prognosis of Sepsis Patients: A Mediation Effect Analysis Based on Inflammatory Levels

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Abstract: Objective: To assess the impact of individualized fluid therapy on the prognosis of sepsis patients and evaluate the mediating effect of inflammatory markers.

Methodology: A retrospective single-center study of 74 adult sepsis patients, comparing an individualized fluid therapy group (n=42) using bedside ultrasound measurements and a conventional therapy group (n=32) with standard fluid management. Logistic regression models identified factors including mean arterial pressure (MAP), lactate (LAC), triglycerides (TG), and total cholesterol (TC). A mediation analysis was conducted to assess the influence of these inflammatory markers on patient outcomes, with inflammatory levels quantified by a composite score.

Results: Individualized fluid therapy significantly reduced ICU stay, mechanical ventilation days, and 28-day mortality. Key prognostic factors included APACHE II score (OR=1.17, 95% CI: 1.01–1.33), hypertension (OR=2.38, 95% CI: 1.92–2.84), LAC (OR=1.08, 95% CI: 1.01–1.15), CVP (OR=0.90, 95% CI: 0.80–0.99), ICU length of stay (OR=1.08, 95% CI: 1.02–1.14), TC (OR=1.13, 95% CI: 1.06–1.20) and TG (OR=1.06, 95% CI: 1.01–1.11). Inflammatory markers mediated 20.3% of the hypertension effect on outcomes and 10.4% of the LAC effect.

Conclusions: Individualized fluid management, by modulating inflammation, enhances sepsis prognosis, suggesting a need for tailored therapeutic approaches to improve outcomes in sepsis.

Keywords: Individualized Fluid Therapy; Prognosis; Sepsis; Inflammatory Levels; Mediation Effect Analysis

Introduction

Sepsis, a life-threatening condition characterized by a dysregulated host response to infection, remains a major global health challenge, with approximately 48.9 million cases and 11 million sepsis-related deaths reported each year (1). Despite advances in critical care, mortality rates for severe sepsis and septic shock can reach as high as 40–60%, underscoring the need for optimized treatment strategies (2, 3). Timely and effective fluid resuscitation is a cornerstone of

sepsis management, intended to restore hemodynamic stability and prevent organ dysfunction; however, the optimal fluid management approach is still under active investigation (4-8).

Traditional fluid therapy in sepsis often involves standardized protocols aimed at achieving specific hemodynamic targets, such as central venous pressure (CVP) and mean arterial pressure (MAP), to stabilize the patient (9, 10). However, recent research has shown that individualized fluid therapy, which tailors fluid resuscitation based on patient-specific factors and dynamic assessments of fluid responsiveness, may offer significant advantages over a one-size-fits-all approach (11, 12). Techniques such as bedside ultrasound allow for real-time monitoring of parameters like the inferior vena cava (IVC) diameter, enabling adjustments in fluid therapy that could prevent fluid overload, a common complication of standardized fluid therapy that has been linked to increased inflammation and poorer outcomes in septic patients.

Inflammation is central to the pathophysiology of sepsis, and elevated levels of inflammatory markers are often correlated with disease severity and prognosis (13). Markers such as lactate (LAC), triglycerides (TG), and total cholesterol (TC) are associated with the inflammatory and metabolic disturbances common in sepsis. Elevated LAC levels, for instance, are strongly linked to tissue hypoperfusion and mortality risk, making them a critical focus in sepsis management (14). Additionally, MAP and lipid levels such as TG and TC have been implicated in the inflammatory response and immune dysregulation observed in septic patients (15, 16).

This study investigates the impact of individualized fluid therapy on sepsis prognosis, focusing on the role of specific inflammatory markers as mediators (17). By using a mediation analysis framework, we aim to elucidate the indirect effects of individualized fluid therapy on sepsis outcomes, mediated by inflammatory levels, specifically LAC, MAP, TG, and TC. Understanding these relationships may provide valuable insights into how tailored fluid therapy can modulate harmful inflammatory responses in sepsis, ultimately improving patient prognosis and survival rates.

Methodology

Study Design and Population

This retrospective, single-center study was conducted on sepsis patients admitted to the intensive care unit (ICU) at Affiliated Hospital of Hebei University of Engineering between December 2022 and February 2024. A total of 74 adult patients aged 40–70 years were included, all meeting the diagnostic criteria for sepsis according to the Sepsis-3 guidelines. Patients were divided into two groups based on their fluid therapy approach: the individualized therapy group (ITG, n=42), receiving fluid resuscitation based on bedside ultrasound measurements of

the inferior vena cava (IVC) diameter, and the conventional therapy group (CTG, $n=32$), receiving standard fluid management.

Inclusion criteria were: (1) confirmed sepsis diagnosis, (2) presence of bacterial infection or purulent foci, (3) abnormal temperature ($>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$), heart rate (>90 bpm), respiratory rate ($>20/\text{min}$ or $\text{PaCO}_2 <32$ mmHg), or white blood cell count ($>12,000/\text{mm}^3$ or $<4,000/\text{mm}^3$), and (4) survival beyond the initial 24 hours after ICU admission. Exclusion criteria included significant cognitive impairment, malignancy, or hepatic/renal dysfunction. The study protocol was approved by the Affiliated Hospital of Hebei University of Engineering Ethics Committee, and informed consent was obtained from all participants or their guardians.

Treatment Protocols

The CTG received fluid resuscitation per established protocols aiming for a central venous pressure (CVP) of 8-12 mmHg, mean arterial pressure (MAP) ≥ 65 mmHg, urine output ≥ 0.5 mL/kg/h, and central venous oxygen saturation $\geq 70\%$. This group underwent standard interventions, including corticosteroids for hemodynamic instability, red blood cell transfusions if hemoglobin levels fell below 7.0 g/dL, and infection source control within 12 hours (18).

The ITG received early fluid resuscitation based on IVC diameter monitoring via bedside ultrasound. Initial resuscitation was performed with a 30 mL/kg bolus of lactated Ringer's solution within the first 3 hours, with subsequent adjustments based on dynamic assessments. Fluid therapy was modified according to the patient's response, with a goal of achieving a net-zero or slightly negative fluid balance within 72 hours. For patients with chronic kidney disease, heart failure, or acute lung injury, fluid tolerance and responsiveness were closely monitored using ultrasound-guided measurements of IVC variability, passive leg raise tests, and pulse pressure variation. Adjustments were made to avoid fluid overload, guided by arterial blood pressure and tissue perfusion indicators.

Data Collection and Outcomes

Data on demographic characteristics, clinical history, and treatment outcomes were collected from medical records. Key variables included resuscitation parameters (fluid infusion volume, urine output, and lactate clearance rate) recorded at 6, 12, and 24 hours post-resuscitation. Baseline and post-resuscitation levels of lactate (LAC), MAP, and CVP were also documented. Primary outcomes were ICU length of stay, duration of mechanical ventilation, and 28-day in-hospital mortality.

Statistical Analysis

All statistical analyses were performed using R version 4.3.2. Descriptive statistics summarized the baseline characteristics of the study population. Continuous variables were expressed as means $\pm$ standard deviation (SD), and categor-

ical variables as frequencies (n) and percentages (%). Independent t-tests were used to compare continuous variables between the treatment groups, while chi-square tests or Fisher's exact tests were applied to categorical variables.

Multivariate logistic regression models were employed to evaluate associations between various risk factors and patient prognosis. Model I adjusted for age and gender. Model II included additional adjustments for body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, smoking status, alcohol consumption, hypertension, diabetes, chronic kidney disease, MAP, LAC, CVP, mechanical ventilation days, and ICU length of stay. Model III further adjusted for lipid indicators, including triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for all models, with significance set at $P < 0.05$.

To assess the mediating role of inflammatory markers, a mediation analysis was conducted using the 'mediation' package in R. This analysis evaluated both direct effects of individualized fluid therapy on patient prognosis and indirect effects mediated by inflammatory levels. Inflammatory levels were represented by a composite score that integrated LAC, MAP, TG, and TC, each reflecting aspects of the inflammatory and metabolic response in sepsis. These variables were standardized and combined to form an overall inflammatory index, calculated as follows:

$$\text{Inflammatory Index} = \frac{LAC - \text{mean}(LAC)}{SD(LAC)} - \frac{MAP - \text{mean}(MAP)}{SD(MAP)} - \frac{TG - \text{mean}(TG)}{SD(TG)} - \frac{TC - \text{mean}(TC)}{SD(TC)}$$

where each term represents the standardized (z-score) contribution of each inflammatory marker, allowing for the combination of variables with different units into a single index. This composite inflammatory index provided a single mediator for assessing the indirect effects. CVP was also included individually as an inflammatory-related variable.

Three main estimates were reported: (i) total effects, (ii) direct effects, and (iii) indirect effects mediated by the inflammatory index and CVP, with statistical significance set at $P < 0.05$.

Results

A total of 74 sepsis patients were included in the study, with 32 patients in the Conventional Therapy Group (CTG) and 42 in the Individualized Therapy Group (ITG). The mean age of the study population was 56.94 ± 5.31 years, with no significant difference in age distribution between the two groups ($P = 0.570$). The overall proportion of males was 51.4%, with no significant gender difference between the CTG and ITG ($P = 0.501$).

The baseline characteristics are summarized in Table 1. There were no significant differences between the two groups in BMI ($P = 0.896$), Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ($P = 0.325$), smoking status ($P = 0.651$), alcohol consumption ($P = 0.874$), hypertension ($P = 0.413$), diabetes

($P=0.651$), chronic kidney disease ($P=0.874$), or LAC levels ($P=0.807$). However, the ITG had a significantly higher MAP compared to the CTG (69.18 ± 4.34 mmHg vs. 67.15 ± 3.65 mmHg, $P=0.036$) and a lower CVP (8.39 ± 1.15 cmH₂O vs. 9.05 ± 1.07 cmH₂O, $P=0.014$). In terms of clinical outcomes, patients in the ITG had a shorter duration of mechanical ventilation (8.23 ± 1.41 days vs. 10.15 ± 2.04 days, $P<0.001$) and a reduced ICU length of stay (15.32 ± 1.64 days vs. 18.64 ± 2.54 days, $P<0.001$) compared to those in the CTG. Additionally, the 28-day mortality rate was significantly lower in the ITG (9.5%) than in the CTG (28.1%, $P=0.037$). Finally, for lipid indicators, including TG, TC, LDL, and HDL, there were no significant differences between the groups, with P -values of 0.542, 0.371, 0.675, and 0.488, respectively.

Table 1. Baseline Characteristics of Sepsis Patients by Treatment Group (n=74)

Variables	Total (n=74)	CTG (n=32)	ITG (n=42)	P-value
Age (mean $\pm$ SD)	56.94 $\pm$ 5.31	56.61 $\pm$ 5.34	57.32 $\pm$ 5.29	0.570
Gender (n, %)				
Male	38 (51.4)	15 (46.9)	23 (54.8)	0.501
Female	36 (48.6)	17 (53.1)	19 (45.2)	0.501
BMI (kg/m ² , mean $\pm$ SD)	24.65 $\pm$ 3.08	24.78 $\pm$ 3.12	24.54 $\pm$ 3.06	0.896
APACHE II score (mean $\pm$ SD)	20.52 $\pm$ 1.25	20.38 $\pm$ 1.27	20.67 $\pm$ 1.23	0.325
Smoking status (n, %)				
Current smoker	32 (43.2)	14 (43.8)	18 (42.9)	0.651
Non-smoker	42 (56.8)	18 (56.3)	24 (57.1)	0.651
Alcohol Consumption (n, %)				
Current drinker	30 (40.5)	14 (43.8)	16 (38.1)	0.874
Non-drinker	44 (59.5)	18 (56.3)	26 (61.9)	0.874
Hypertension (n, %)	35 (47.3)	17 (53.1)	18 (42.9)	0.413
Diabetes (n, %)	30 (40.5)	14 (43.8)	16 (38.1)	0.651
Chronic Kidney Disease (n, %)	20 (27.0)	9 (28.1)	11 (26.2)	0.874
MAP (mmHg)	68.72 $\pm$ 4.00	67.15 $\pm$ 3.65	69.18 $\pm$ 4.34	0.036
LAC (mmol/L)	3.45 $\pm$ 0.35	3.46 $\pm$ 0.37	3.44 $\pm$ 0.33	0.807
CVP (cmH ₂ O)	8.72 $\pm$ 1.10	9.05 $\pm$ 1.07	8.39 $\pm$ 1.15	0.014
Mechanical Ventilation (days, mean $\pm$ SD)	9.12 $\pm$ 1.82	10.15 $\pm$ 2.04	8.23 $\pm$ 1.41	0.000
ICU Length of Stay (days, mean $\pm$ SD)	16.52 $\pm$ 2.09	18.64 $\pm$ 2.54	15.32 $\pm$ 1.64	0.000
28-day Mortality (n, %)	13 (17.6)	9 (28.1)	4 (9.5)	0.037
Lipid Indicators				
TG (mmol/L)	1.54 $\pm$ 0.47	1.58 $\pm$ 0.50	1.51 $\pm$ 0.45	0.542
TC (mmol/L)	4.62 $\pm$ 0.98	4.71 $\pm$ 1.02	4.55 $\pm$ 0.95	0.371
LDL (mmol/L)	2.56 $\pm$ 0.81	2.60 $\pm$ 0.85	2.53 $\pm$ 0.78	0.675
HDL (mmol/L)	1.15 $\pm$ 0.31	1.13 $\pm$ 0.32	1.17 $\pm$ 0.30	0.488

Mean Arterial Pressure (MAP); Lactate (LAC); Central Venous Pressure (CVP); Triglycerides (TG); Total Cholesterol (TC); Low-Density Lipoprotein (LDL); High-Density Lipoprotein (HDL) *CTG: Conventional therapy group; ITG: Individualized therapy group

The results of the multivariate logistic regression analysis are presented in Table 2. After adjusting for age, gender, BMI, APACHE II score, and other clinical factors, several variables remained significantly associated with patient prognosis. In Model II, hypertension (OR = 19.52, 95% CI: 3.98–152.39), APACHE II score (OR = 1.20, 95% CI: 1.02–1.38), MAP (OR = 1.08, 95% CI: 1.02–1.14), LAC (OR = 1.09, 95% CI: 1.01–1.18, $P = 0.033$), CVP (OR = 0.89, 95% CI: 0.78–0.99), and ICU length of stay (OR = 1.07, 95% CI: 1.00–1.15) were significantly associated with poorer prognosis. Similarly, in Model III, which included APACHE II score (OR=1.17, 95% CI: 1.01–1.33), hypertension (OR=2.38, 95% CI: 1.92–2.84), LAC (OR=1.08, 95% CI: 1.01–1.15), CVP (OR=0.90, 95% CI: 0.80–0.99), ICU length of stay (OR=1.08, 95% CI: 1.02–1.14), TC (OR=1.13, 95% CI: 1.06–1.20) and TG (OR=1.06, 95% CI: 1.01–1.11). Figure 1 shows the forest plot of significant influencing factors for patient prognosis.

Table 2. Logistic Regression Analysis of Factors Associated with Prognosis in Sepsis Patients

Variables	Estimate	Standard Error	Adjusted OR*	Lower CI*	Upper CI*	P-value
Model I						
Age	0.03	0.04	1.03	0.95	1.11	0.512
Male	0.10	0.45	1.10	0.45	2.66	0.843
Model II						
Age	0.05	0.05	1.05	0.96	1.15	0.316
Male	0.28	0.90	1.32	0.23	7.63	0.732
BMI	-0.02	0.15	0.98	0.71	1.34	0.915
APACHE II score	0.18	0.08	1.20	1.02	1.38	0.029
Smoking Status	-1.15	0.88	0.32	0.07	1.58	0.312
Alcohol Consumption	0.82	0.77	2.28	0.52	10.03	0.329
Hypertension	2.97	0.92	19.52	3.98	152.39	0.001
Diabetes	0.41	0.79	1.51	0.34	7.14	0.612
Chronic Kidney Disease	1.08	0.87	2.94	0.57	15.12	0.222
MAP	0.08	0.03	1.08	1.02	1.14	0.015
LAC	0.09	0.04	1.09	1.01	1.18	0.033
CVP	-0.12	0.06	0.89	0.78	0.99	0.042
Mechanical Ventilation (days)	0.06	0.04	1.06	0.98	1.12	0.072
ICU Length of Stay (days)	0.07	0.05	1.07	1.00	1.15	0.048
Model III						
Age	0.04	0.08	1.04	0.92	1.18	0.581
Male	1.38	1.72	1.29	0.20	2.36	0.403
BMI	-0.08	0.22	0.92	0.56	1.59	0.762
APACHE II score	0.16	0.09	1.17	1.01	1.33	0.008
Smoking Status	-1.98	1.22	0.76	0.09	1.52	0.271
Alcohol Consumption	1.09	1.14	2.98	0.79	9.12	0.258
Hypertension	3.20	2.41	2.38	1.92	2.84	0.000
Diabetes	-0.05	1.22	2.48	0.85	4.27	0.992

Chronic Kidney Disease	1.04	0.98	2.83	0.50	15.52	0.211
MAP	0.07	0.03	1.07	1.01	1.15	0.022
LAC	0.08	0.04	1.08	1.01	1.15	0.039
CVP	-0.11	0.06	0.70	0.60	0.80	0.000
Mechanical Ventilation (days)	0.07	0.05	1.07	1.01	1.13	0.068
ICU Length of Stay (days)	0.08	0.04	1.08	1.02	1.14	0.045
TG	0.06	0.03	1.06	1.01	1.11	0.021
TC	0.13	0.04	1.13	1.06	1.20	0.009
LDL	0.08	0.05	1.08	0.98	1.25	0.249
HDL	0.15	0.13	1.15	0.92	1.65	0.356

Mean Arterial Pressure (MAP); Lactate (LAC); Central Venous Pressure (CVP); *Adjusted OR: Adjusted Odds Ratio; Lower CI: The lower limit of the 95% confidence interval for the reported adjusted OR value; Upper CI: The upper limit of the 95% confidence interval for the reported adjusted OR value. Model I: adjusted for age and gender; Model II: adjusted for age, gender, BMI, APACHE II score, smoking status, alcohol consumption, hypertension, diabetes, chronic kidney disease, MAP, LAC, CVP, mechanical ventilation, and ICU length of stay; Model III: includes all factors from Model II plus lipid indicators (TG, TC, LDL, and HDL).

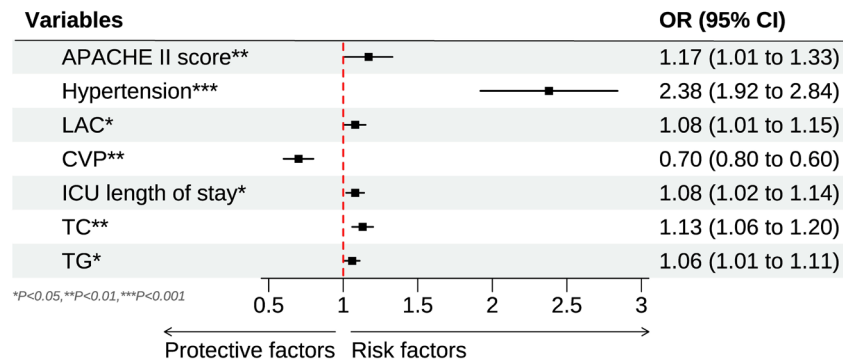


Figure 1. Forest plot of significant influencing factors for patient prognosis. Adjusted for all cofounders.

The mediation analysis demonstrated that specific inflammatory markers significantly mediated the relationship between individualized fluid therapy strategies and sepsis prognosis (Figure 2). Specifically, LAC, MAP, and lipid levels (TG and TC) accounted for 20.3% of the total effect of hypertension on adverse outcomes (indirect effect: $\beta=0.21$, $P<0.01$), with effect being statistically significant. Additionally, the mediation effect of these inflammatory markers accounted for 10.4% of the relationship between elevated LAC levels and poor prognosis (indirect effect: $\beta=0.10$, $P=0.03$). However, the mediation effects of these inflammatory markers on associations between other clinical factors, such as BMI and CVP, with sepsis prognosis were not statistically significant.

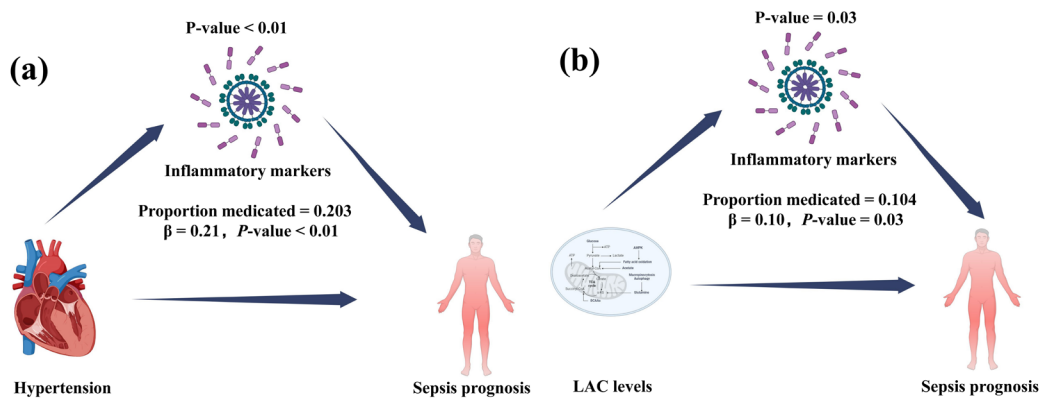


Figure 2. Path diagram of mediation analysis of relationship between hypertension/LAC levels, inflammatory markers and Sepsis prognosis; (a) hypertension; (b) LAC levels

Discussion

This study demonstrates that individualized fluid therapy strategies, guided by patient-specific parameters such as IVC diameter, have a significant impact on the prognosis of sepsis patients. Patients in the ITG showed reduced ICU length of stay, shorter duration of mechanical ventilation, and a lower 28-day mortality rate compared to those in the CTG. Additionally, the mediation analysis revealed that inflammatory markers, specifically LAC, MAP, TG, and TC, significantly mediated the relationship between individualized fluid therapy and sepsis prognosis. These findings suggest that by tailoring fluid therapy based on real-time physiological measurements, it may be possible to modulate inflammation and improve patient outcomes in sepsis (19-21).

Fluid resuscitation is a cornerstone of sepsis management aimed at restoring hemodynamic stability and optimizing tissue perfusion. Traditional fluid therapy approaches, which often follow standardized protocols, aim to meet specific hemodynamic targets but may overlook individual variations in fluid responsiveness (22, 23). Recent studies have highlighted the drawbacks of a one-size-fits-all approach, including the risk of fluid overload, which can exacerbate inflammation, impair gas exchange, and contribute to worse outcomes (24, 25). In contrast, individualized fluid management, as applied in our study, tailors resuscitation to each patient's hemodynamic status, which can help minimize fluid overload and its associated risks (26). Our findings align with previous research that suggests individualized strategies may reduce complications associated with excessive fluid administration and improve clinical outcomes (19, 27).

The role of inflammation in sepsis is well-established, with elevated inflammatory markers often indicating a poorer prognosis. Lactate, an indicator of tissue hypoperfusion, is widely used in clinical practice to assess sepsis severity, as high lactate levels are associated with increased mortality (21, 28, 29). In our study, lactate emerged as a significant mediator, suggesting that individualized fluid therapy may influence outcomes by reducing lactate levels, possibly through

improved perfusion and metabolic stabilization. MAP, another significant mediator in our analysis, is essential for maintaining organ perfusion and is a primary target in sepsis management (30, 31). Studies have shown that individualized fluid therapy can better maintain stable MAP levels, reducing the need for vasopressors and minimizing hemodynamic instability (32, 33).

Furthermore, our results identified TG and TC as mediators in the relationship between fluid therapy and prognosis. Dyslipidemia is common in critically ill patients and is increasingly recognized as a marker of inflammation and immune dysregulation in sepsis (20, 33, 34). Elevated TG and TC levels have been linked to increased inflammation and adverse outcomes, potentially reflecting the body's metabolic response to severe infection (23, 35, 36). By tailoring fluid therapy to individual needs, it may be possible to positively influence lipid metabolism and, in turn, reduce inflammatory activity. These findings add to the growing body of evidence suggesting that lipid markers, alongside traditional indicators like lactate and MAP, could provide insights into the effectiveness of therapeutic interventions in sepsis (21, 28, 37).

Despite the promising findings, our study has several limitations. As a retrospective, single-center study, the generalizability of our results may be limited. Additionally, while we used a composite index of inflammatory markers, other unmeasured markers may also play a role in sepsis progression and response to therapy (38, 39). Future studies could incorporate a broader array of biomarkers to provide a more comprehensive view of inflammation in sepsis (40-42). Another limitation is the relatively small sample size, which may limit the statistical power to detect smaller effects. Nevertheless, this study provides valuable insights into the potential benefits of individualized fluid therapy and the mechanisms through which it may improve outcomes in sepsis patients (43-45).

Conclusion

This study demonstrates that individualized fluid therapy strategies, guided by patient-specific parameters like IVC diameter, significantly improve sepsis outcomes by reducing ICU stay, mechanical ventilation duration, and 28-day mortality compared to conventional therapy. Mediation analysis indicated that inflammatory markers, partially mediated these effects, suggesting that tailored fluid management may positively influence outcomes through inflammation modulation. Despite limitations, such as the single-center, retrospective design, our findings underscore the potential of individualized fluid strategies in enhancing sepsis prognosis by addressing key inflammatory processes.

Authors contribution

Jing An was responsible for conceptualization, methodology, formal analysis, validation, investigation, and drafting and editing the manuscript. Linlin Feng and Zijiang Guo were responsible for conceptualization, methodology, formal

analysis and drafting the manuscript. Mingchao Chen contributed to conceptualization, manuscript review, supervision, project administration, and funding acquisition.

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The views expressed in this publication are those of the authors.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

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