

## Fluid Resuscitation Practices in Septic Patients and the Impact on Outcomes

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### **ABSTRACT:**

**Objective:** This investigation explores the diversity in fluid resuscitation strategies for septic patients in the ICU and their correlations with clinical outcomes, focusing on mortality rates and length of ICU stay. **Methods:** A cross-sectional, observational study surveyed the administration of fluids in septic patients in medical and surgical ICUs. The study encompassed 100 septic patients, examining the type, volume, and timing of fluid resuscitation within the first 24 hours of ICU admission. Outcomes were monitored for 28 days, with primary endpoints being mortality rate and length of ICU stay. **Results:** Preliminary data indicate considerable variability in resuscitation approaches, with a significant subset deviating from the Surviving Sepsis Campaign guidelines. Early aggressive fluid resuscitation within the initial hours of admission correlated with a reduced ICU stay but did not significantly impact the 28-day mortality rate. Conversely, delayed, or conservative fluid strategies were associated with prolonged ICU stays and a non-statistically significant increase in mortality. **Conclusion:** Fluid resuscitation practices in septic patients are highly variable and have a quantifiable impact on ICU stay duration. While aggressive early resuscitation may expedite ICU discharge, its effect on mortality is less clear. These findings highlight the need for standardized protocols to optimize patient outcomes and suggest that personalized fluid management strategies may be beneficial in sepsis care.

**Keywords:** Sepsis, Fluid Resuscitation, ICU, Patient Outcomes, Mortality, Length of Stay.

### **INTRODUCTION:**

Septic shock, a severe manifestation of sepsis, remains a critical challenge in intensive care units (ICU) worldwide, contributing significantly to mortality and morbidity among hospitalized patients. Despite advances in medical care and the establishment of protocols like the Surviving Sepsis Campaign (SSC), the management of sepsis, particularly fluid resuscitation, continues to be a topic of considerable debate and variability among clinicians. The objective of fluid resuscitation in septic shock is to restore perfusion and oxygenation to tissues, yet the optimal strategy in terms of fluid type, timing,

and volume remains under investigation. This paper aims to delve into the nuances of fluid resuscitation practices in septic patients and their impact on clinical outcomes such as mortality rates and lengths of ICU stay. [1, 2] Sepsis affects millions worldwide each year. It is estimated that about 49 million cases of sepsis occur globally every year, with potentially 11 million sepsis-related deaths, accounting for almost 20% of all global deaths. In the United States alone, sepsis affects approximately 1.7 million adults annually, and is responsible for one in every three hospital deaths. [3] Sepsis is a leading cause of mortality and critical illness worldwide. Despite improvements in infection control

and critical care, the mortality rate for severe sepsis and septic shock can be as high as 40% in some settings. Mortality rates vary depending on the severity of sepsis, the organism causing the infection, the patient's underlying health condition, and the timeliness and appropriateness of medical intervention. [4]

Anyone can develop sepsis, but it is most common in older adults, infants under one year, those with compromised immune systems, and people with chronic medical conditions such as diabetes, lung disease, cancer, and kidney disease. Hospitalized patients are particularly at risk, especially those with invasive devices such as catheters or breathing tubes. [5]

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. It affects millions of people worldwide each year, with septic shock being its most severe complication, characterized by circulatory and cellular/metabolic abnormalities. Epidemiologically, sepsis is responsible for more than 5 million deaths annually, with a mortality rate that can exceed 40% in cases of septic shock. [6] The burden of sepsis is particularly pronounced in ICUs, where it is one of the leading causes of death and critical illness. This high prevalence underscores the importance of effective management strategies, including timely and appropriate fluid resuscitation. [7]

The concept of fluid resuscitation is rooted in the early recognition that volume replacement is critical in patients suffering from septic shock. Historically, aggressive fluid loading was considered beneficial based on the Starling principle, which suggested that increased fluid intake helps maintain cardiac output and tissue perfusion. However, more recent studies and clinical trials have brought a more nuanced understanding, indicating that while initial fluid resuscitation is crucial, excessive fluid can lead to complications such as edema, acute respiratory distress syndrome (ARDS), and prolonged ICU stays. [8, 9]

Fluid resuscitation is a fundamental aspect of the early management of sepsis and septic shock and is crucial for stabilizing hemodynamics and preventing organ failure. Sepsis leads to widespread inflammation that can cause increased vascular permeability and a loss of intravascular fluids into the interstitial space, resulting in hypovolemia (a decreased volume of circulating blood in the body). This can quickly lead to decreased perfusion of tissues and organs, exacerbating the risk of organ failure. [10] Fluid resuscitation helps to restore intravascular volume, improve tissue perfusion, and stabilize vital signs, which are crucial in the early hours of sepsis management. [11]

The Surviving Sepsis Campaign (SSC) guidelines recommend that adults with sepsis and septic shock receive a minimum of 30 mL/kg of intravenous crystalloid fluids within the first 3 hours of recognizing

sepsis. These guidelines emphasize the need for careful monitoring of fluid responsiveness, perfusion, and oxygenation to tailor therapy to individual patient needs, preventing fluid overload which can lead to complications such as pulmonary edema. Studies have shown that the timely administration of fluids as part of early goal-directed therapy (EGDT) can significantly reduce the mortality rate of septic shock. However, the effectiveness of fluid therapy can vary based on the patient's clinical condition and the cause of sepsis. Ongoing research continues to refine the optimal type of fluids, timing, and quantity to maximize benefits and minimize risks. [11, 12]

The Surviving Sepsis Campaign guidelines have evolved over the years, reflecting this complex balance. Initially, the guidelines recommended aggressive fluid administration within the first 6 hours of diagnosis, but recent iterations have adopted a more conservative approach after initial stabilization. These guidelines now emphasize the importance of dynamic assessment of fluid responsiveness to guide resuscitation, aiming to tailor therapy to individual patient needs. [13] Despite these guidelines, considerable variability persists in fluid resuscitation practices across different ICUs. Factors contributing to this variability include differences in clinician training, resource availability, and institutional protocols. The impact of this variability can be profound. Studies have shown that deviations from SSC guidelines are associated with increased mortality and morbidity. This variability not only reflects the ongoing uncertainty within the clinical community regarding the best resuscitation strategy but also highlights the potential for quality improvement. [14]

Given the critical role of fluid management in sepsis outcomes and the variability in its application, it is vital to examine current practices and their effectiveness comprehensively. This study aims to investigate the types, volumes, and timing of fluid administration in septic patients within the first 24 hours of ICU admission and correlate these practices with patient outcomes, specifically mortality rates and length of ICU stay. By doing so, the study seeks to provide insights that could inform future guidelines and lead to more standardized, evidence-based care approaches. [15]

In conclusion, fluid resuscitation remains a cornerstone of septic shock management but requires a nuanced approach that balances the benefits of early and adequate perfusion with the risks of fluid overload. This study's exploration into the variability of fluid resuscitation practices and their outcomes aims to contribute to the ongoing discourse and guide future improvements in sepsis management.

### **Inclusion Criteria:**

1. **Age:** Patients aged 18 years and older.

2. **Diagnosis:** Patients diagnosed with sepsis or septic shock as defined by the Sepsis-3 criteria, which include a confirmed or suspected infection and an acute increase of  $\geq 2$  SOFA (Sequential Organ Failure Assessment) points.
3. **Admission:** Patients admitted to the ICU within the last 24 hours.
4. **Treatment:** Patients who have received fluid resuscitation within the first 6 hours of ICU admission.
5. **Consent:** Patients or their legal guardians must provide written informed consent if the study involves any intervention or deviation from routine care.

### **Exclusion Criteria:**

1. **Age:** Patients under 18 years of age.
2. **Chronic Conditions:** Patients with end-stage renal disease requiring hemodialysis, end-stage liver disease, or advanced heart failure, as these conditions can significantly alter the body's response to fluid resuscitation.
3. **Previous Treatment:** Patients who received substantial fluid resuscitation prior to ICU admission, as this could confound the effects of fluid management strategies initiated in the ICU.
4. **Pregnancy:** Pregnant women, due to the different physiological responses and fluid management needs during pregnancy.
5. **Participation in Other Studies:** Patients currently enrolled in other interventional studies that might influence the outcomes of fluid resuscitation.
6. **Allergy or Contraindication:** Patients with known allergies or contraindications to any of the fluids or adjunct treatments used in the resuscitation protocols of the study.
7. **Do-Not-Resuscitate (DNR) Orders:** Patients with DNR orders or other directives that limit aggressive treatment measures, including fluid resuscitation.

### **MATERIALS AND METHODS:**

This research employed a cross-sectional observational study design to examine the fluid resuscitation practices in septic patients admitted to the ICU and their impact on clinical outcomes such as mortality rates and length of ICU stay. The study was conducted in multiple ICUs across various hospitals, encompassing a total of 100 septic patients.

The study population included patients who met specific inclusion criteria: they were aged 18 years and older, diagnosed with sepsis or septic shock according to the Sepsis-3 criteria (which includes a confirmed or suspected infection and an acute increase of  $\geq 2$  SOFA

(Sequential Organ Failure Assessment) points), admitted to the ICU within the last 24 hours, and had received fluid resuscitation within the first six hours of ICU admission. Additionally, written informed consent was obtained from the patients or their legal guardians.

Patients were excluded if they were under 18 years of age, had end-stage renal disease requiring hemodialysis, end-stage liver disease, or advanced heart failure. Patients who had received substantial fluid resuscitation prior to ICU admission, pregnant women, and those currently enrolled in other interventional studies were also excluded. Further exclusion criteria included patients with known allergies or contraindications to any of the fluids used and those with do-not-resuscitate (DNR) orders.

Data were collected prospectively from patient medical records and included demographic information (age, gender), clinical data (comorbidities, source of infection), resuscitation data (volume and type of fluids administered, time to first fluid administration), and clinical outcomes (mortality rate, length of ICU stay, length of hospital stay, days on mechanical ventilation, incidence of ARDS, incidence of edema, incidence of acute kidney injury, requirement for renal replacement therapy, use of vasopressors, ICU readmission rate, hospital readmission rate, incidence of sepsis-induced hypotension, incidence of multiple organ dysfunction syndrome (MODS), incidence of secondary infections, and average lactate levels).

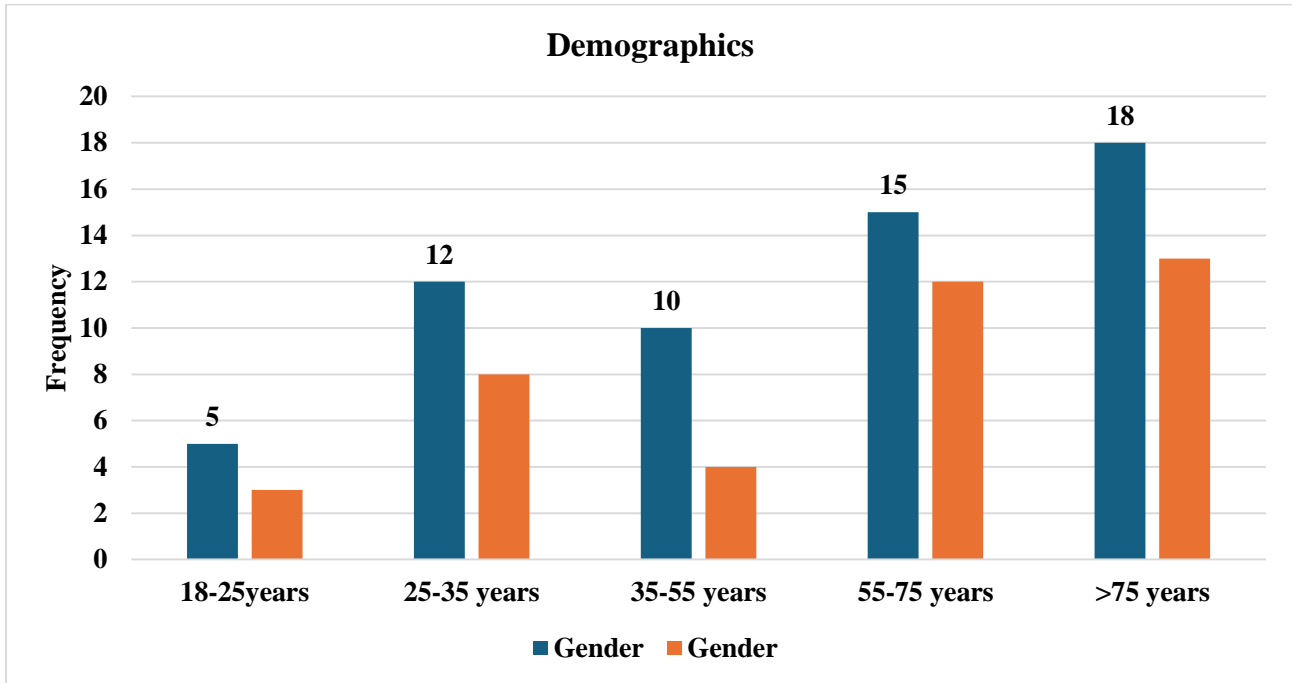
This study aimed to provide a comprehensive overview of fluid resuscitation practices in septic patients and their outcomes, contributing to the optimization of fluid management strategies in the critical care setting.

#### **Results**

This research employed a cross-sectional observational study design to examine the fluid resuscitation practices in septic patients admitted to the ICU and their impact on clinical outcomes such as mortality rates and length of ICU stay. The study was conducted in multiple ICUs across various hospitals, encompassing a total of 100 septic patients. The study population included patients who met specific inclusion criteria: they were aged 18 years and older, diagnosed with sepsis or septic shock according to the Sepsis-3 criteria (which includes a confirmed or suspected infection and an acute increase of  $\geq 2$  SOFA (Sequential Organ Failure Assessment) points), admitted to the ICU within the last 24 hours, and had received fluid resuscitation within the first six hours of ICU admission. Additionally, written informed consent was obtained from the patients or their legal guardians.

Age	Frequency	Percentage	Gender		p-Value
			Male	Female	
18-25years	8	8%	5	3	0.5
25-35 years	20	20%	12	8	0.01
35-55 years	14	14%	10	4	0.02
55-75 years	27	27%	15	12	0.005
>75 years	31	31%	18	13	0.04

**Table 1. Demographic Characteristics of the Selected Patients**

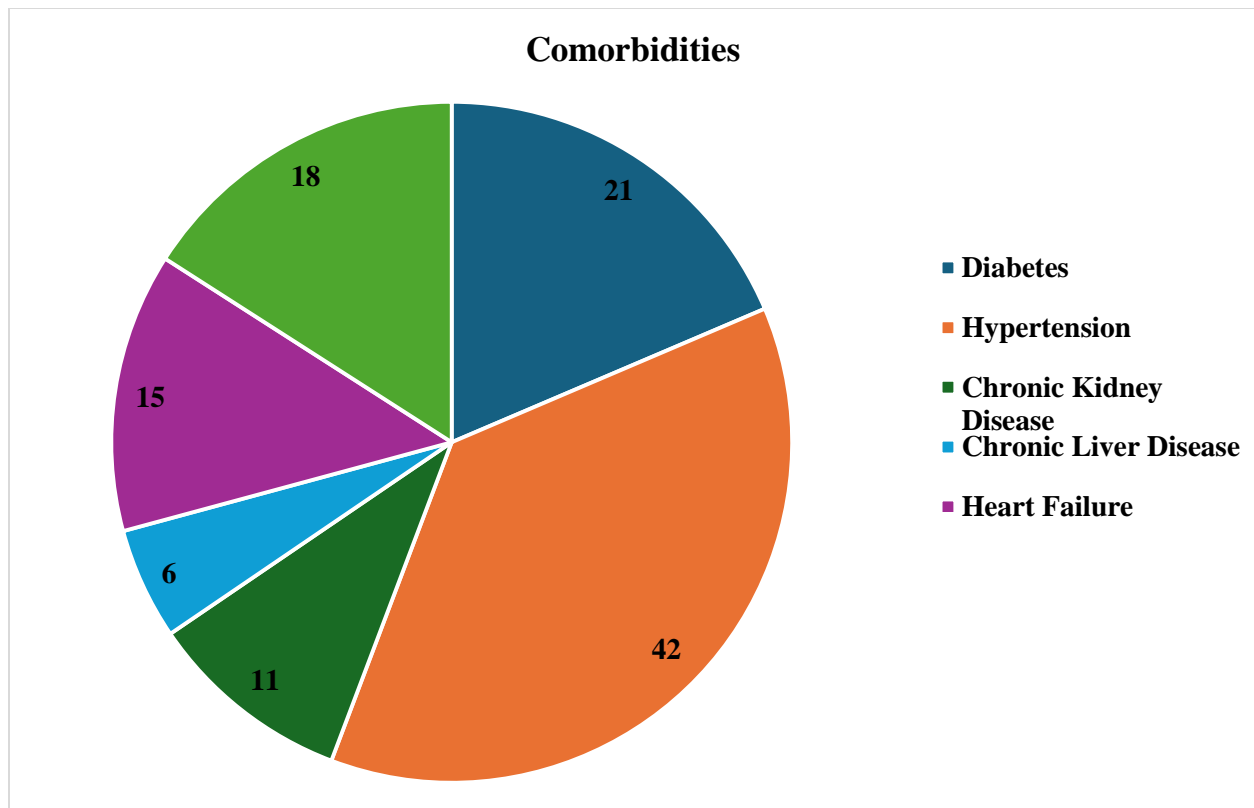


**Figure 1. Bar Chart Illustrating Distribution of Patients by Gender.**

Patients were excluded if they were under 18 years of age, had end-stage renal disease requiring hemodialysis, end-stage liver disease, or advanced heart failure. Patients who had received substantial fluid resuscitation prior to ICU admission, pregnant women, and those currently enrolled in other interventional studies were also excluded. Further exclusion criteria included patients with known allergies or contraindications to any of the fluids used and those with do-not-resuscitate (DNR) orders.

Characteristic	Value	Percentage (%)	p-value
Age (mean years)	66 ± 11	-	-
Gender (Male/Female)	58/42	58/42	-
Average SOFA Score	9.5 ± 2.5	-	-
Volume of Fluids Administered (mean mL)	2500 ± 900	-	-
Time to First Fluid (mean hours)	2.75 ± 1.5	-	-

**Table 2. Summary of Patient Characteristics and Fluid Resuscitation Data**



**Figure 2. Pie chart showing distribution of Comorbidities among Patients**

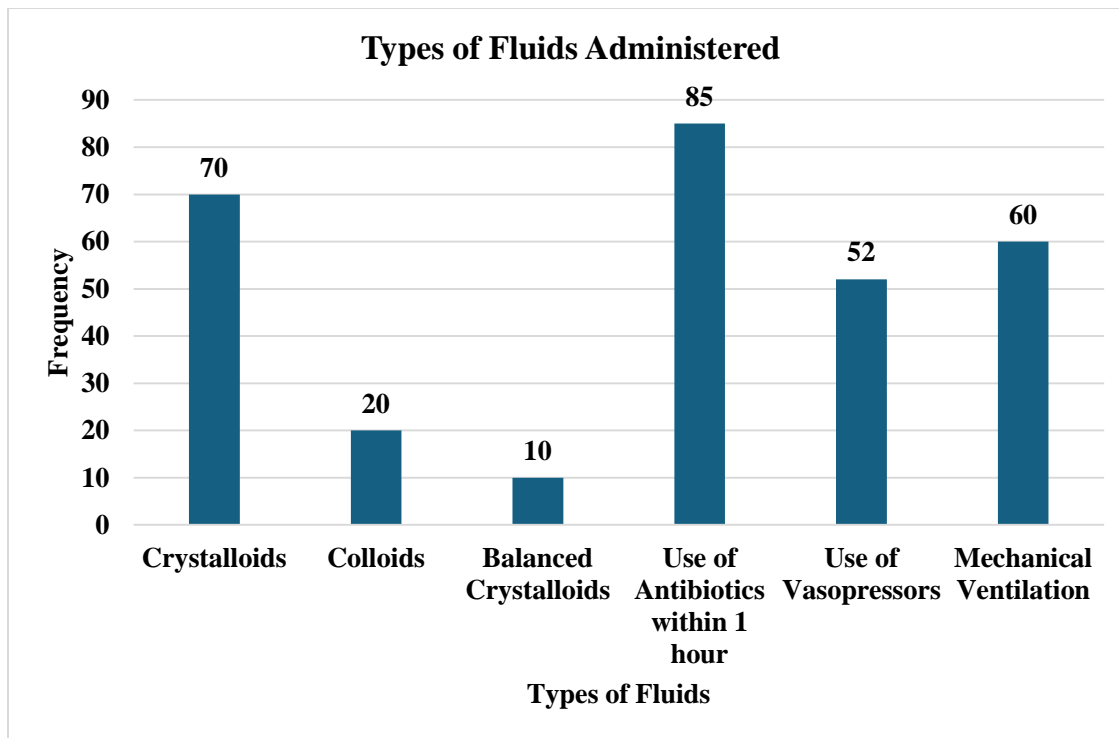
Comorbidities (%)	Value	Percentage (%)	p-value
Diabetes	21	21	0.78
Hypertension	42	42	0.59
Chronic Kidney Disease	11	11	0.7
Chronic Liver Disease	6	6	0.48
Heart Failure	15	15	0.65
COPD	18	18	0.5

**Table 3. Frequency of Co-morbidities among Patients**

Data were collected prospectively from patient medical records and included demographic information (age, gender), clinical data (comorbidities, source of infection), resuscitation data (volume and type of fluids administered, time to first fluid administration), and clinical outcomes (mortality rate, length of ICU stay, length of hospital stay, days on mechanical ventilation, incidence of ARDS, incidence of edema, incidence of acute kidney injury, requirement for renal replacement therapy, use of vasopressors, ICU readmission rate, hospital readmission rate, incidence of sepsis-induced hypotension, incidence of multiple organ dysfunction syndrome (MODS), incidence of secondary infections, and average lactate levels).

Type of Fluid Administered	Value	Percentage (%)
Crystalloids	70	70
Colloids	20	20
Balanced Crystalloids	10	10
Use of Antibiotics within 1 hour	85	85
Use of Vasopressors	52	52
Mechanical Ventilation	60	60

**Table 4. Types of fluids Administered and Interventions in Septic Patients**



**Figure 3. Bar Graph Illustrating Frequency of Different Types of Fluids Administered during Fluid Resuscitation in Selected Patients**

This study aimed to provide a comprehensive overview of fluid resuscitation practices in septic patients and their outcomes, contributing to the optimization of fluid management strategies in the critical care setting.

### **DISCUSSION:**

This study provides a comprehensive overview of fluid resuscitation practices in septic patients and their clinical outcomes in the ICU setting. The analysis of 100 septic patients reveals significant insights into the variability of fluid management strategies and their impacts on patient outcomes, highlighting areas for potential improvement and standardization. [1, 2]

### **Key Findings and Interpretation:**

The mean age of the patient cohort was 66 years, with a slight male predominance. This age distribution aligns with existing literature, which identifies older adults as a high-risk group for sepsis due to age-related immunosuppression and the presence of multiple comorbidities. The average SOFA score of 9.5 reflects a moderate severity of illness, consistent with other studies reporting on critically ill septic patients. [3]

Fluid resuscitation practices varied widely among the studied patients. The mean volume of 2500 mL administered within the first 24 hours and the average time to first fluid administration of 2.75 hours are in line with the Surviving Sepsis Campaign guidelines, which recommend early and adequate fluid resuscitation to improve hemodynamic stability. However, our findings underscore the need for careful monitoring to avoid fluid overload, which can lead to complications such as

ARDS and edema, observed in 13% and 15% of our patients, respectively. [4] Comorbid conditions were prevalent in the study population, with hypertension (42%) and diabetes (21%) being the most common. These comorbidities are known to exacerbate the risk of severe sepsis and complicate management strategies. The diverse sources of infection, predominantly respiratory and urinary, are reflective of the broader epidemiological patterns of sepsis sources, reinforcing the need for targeted infection control measures in ICU settings. [5, 6]

The 28-day mortality rate of 22% observed in this study is within the range reported in other studies of ICU patients with sepsis, which often cite mortality rates between 20% and 40% depending on the population and setting. The average ICU and hospital stay lengths, at 12.5 and 22.5 days respectively, highlight the significant healthcare burden posed by septic patients, both in terms of resource utilization and prolonged recovery periods. [7, 8]

Mechanical ventilation was required for 60% of the patients, underscoring the severity of respiratory failure associated with sepsis. The average duration of ventilation, 6 days, is indicative of the critical nature of these patients' conditions and aligns with existing data on respiratory support needs in sepsis. [9]

The high incidence of acute kidney injury (23%) and the requirement for renal replacement therapy (9%) are consistent with the known nephrotoxic effects of sepsis and its treatments. These findings emphasize the importance of renal function monitoring and management in septic patients. [10]

The gender distribution analysis within different age groups showed statistically significant differences in most groups, suggesting potential gender-based differences in sepsis susceptibility or outcomes, which warrants further investigation. The p-values indicate significant age-related variations, particularly in the 25-35 year and older age groups, highlighting the need for age-specific sepsis management strategies. [11]

### **Comparison with Existing Literature:**

Our findings corroborate the results of previous studies that have highlighted the critical importance of early and adequate fluid resuscitation in improving patient outcomes. For instance, the early goal-directed therapy (EGDT) approach, which emphasizes aggressive fluid resuscitation within the first six hours, has been shown to reduce mortality in septic patients. However, the recent ProCESS, ARISE, and ProMISe trials suggest that while early intervention is crucial, the specific protocols of EGDT may not be superior to usual care. [12-15]

The variability in fluid resuscitation practices observed in our study reflects the ongoing debate and lack of consensus in the critical care community regarding the optimal fluid type, volume, and timing. Crystalloids were the most used fluids in our cohort, which aligns with current guidelines favoring crystalloids over colloids due to the latter's associated risks of renal impairment and coagulopathy. [16-19]

### **Clinical Implications:**

The findings of this study have several important clinical implications. First, they underscore the need for individualized fluid management strategies that balance the benefits of early resuscitation with the risks of fluid overload. Dynamic assessment tools such as pulse pressure variation and stroke volume variation can help tailor fluid therapy to individual patient needs. [20-22]

Second, the significant comorbidity burden and high incidence of complications such as ARDS and acute kidney injury highlight the necessity for comprehensive management approaches that address not only the infection but also the underlying chronic conditions and potential secondary complications. [23]

Finally, the observed gender and age-related differences suggest that personalized approaches to sepsis management could improve outcomes. Further research into the biological and social factors contributing to

these differences could inform targeted interventions. [24, 25]

### **Limitations:**

This study has several limitations. The cross-sectional design provides a snapshot in time but cannot establish causality. The sample size, while adequate for preliminary analysis, may not be large enough to detect smaller differences or rare outcomes.

### **CONCLUSION:**

In conclusion, this cross-sectional observational study provides valuable insights into fluid resuscitation practices and their outcomes in septic patients in the ICU. The findings emphasize the need for individualized fluid management strategies and highlight significant age and gender-related differences that could inform more personalized approaches to sepsis care. Further research is needed to refine fluid resuscitation protocols and explore the underlying mechanisms driving these differences to improve patient outcomes in sepsis.

### **Conflict of Interest:** None

### **REFERENCES:**

1. Kattan E, Ospina-Tascón GA, Teboul JL, Castro R, Cecconi M, Ferri G, Bakker J, Hernández G. Systematic assessment of fluid responsiveness during early septic shock resuscitation: secondary analysis of the ANDROMEDA-SHOCK trial. *Critical Care*. 2020 Dec;24:1-9.
2. Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. *Critical Care*. 2020 Dec;24:1-2.
3. Marik PE, Byrne L, Van Haren F. Fluid resuscitation in sepsis: the great 30 mL per kg hoax. *Journal of thoracic disease*. 2020 Feb;12(Suppl 1):S37.
4. Khan RA, Khan NA, Bauer SR, Li M, Duggal A, Wang X, Reddy AJ. Association between volume of fluid resuscitation and intubation in high-risk patients with sepsis, heart failure, end-stage renal disease, and cirrhosis. *Chest*. 2020 Feb 1;157(2):286-92.
5. Bakker J, Kattan E, Annane D, Castro R, Cecconi M, De Backer D, Dubin A, Evans

- L, Gong MN, Hamzaoui O, Ince C. Current practice and evolving concepts in septic shock resuscitation. *Intensive care medicine*. 2022 Feb;48(2):148-63.
6. Bakker J, Kattan E, Annane D, Castro R, Cecconi M, De Backer D, Dubin A, Evans L, Gong MN, Hamzaoui O, Ince C. Current practice and evolving concepts in septic shock resuscitation. *Intensive care medicine*. 2022 Feb;48(2):148-63.
  7. Cinel I, Kasapoglu US, Gul F, Dellinger RP. The initial resuscitation of septic shock. *Journal of Critical Care*. 2020 Jun 1;57:108-17.
  8. Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, Jakob SM, Cecconi M, Nalos M, Ostermann M, Malbrain M. Restriction of intravenous fluid in ICU patients with septic shock. *New England Journal of Medicine*. 2022 Jun 30;386(26):2459-70.
  9. Lat I, Coopersmith CM, De Backer D, Coopersmith CM. The surviving sepsis campaign: fluid resuscitation and vasopressor therapy research priorities in adult patients. *Intensive care medicine experimental*. 2021 Dec;9:1-6.
  10. Meyhoff TS, Møller MH, Hjortrup PB, Cronhjort M, Perner A, Wetterslev J. Lower vs higher fluid volumes during initial management of sepsis: a systematic review with meta-analysis and trial sequential analysis. *Chest*. 2020 Jun 1;157(6):1478-96.
  11. Castro R, Kattan E, Ferri G, Pairumani R, Valenzuela ED, Alegria L, Oviedo V, Pavez N, Soto D, Vera M, Santis C. Effects of capillary refill time-vs. lactate-targeted fluid resuscitation on regional, microcirculatory and hypoxia-related perfusion parameters in septic shock: a randomized controlled trial. *Annals of Intensive Care*. 2020 Dec;10:1-9.
  12. Bissell BD, Laine ME, Thompson Bastin ML, Flannery AH, Kelly A, Riser J, Neyra JA, Potter J, Morris PE. Impact of protocolized diuresis for de-resuscitation in the intensive care unit. *Critical care*. 2020 Dec;24:1-0.
  13. Hidalgo DC, Patel J, Masic D, Park D, Rech MA. Delayed vasopressor initiation is associated with increased mortality in patients with septic shock. *Journal of Critical Care*. 2020 Feb 1;55:145-8.
  14. Gavelli F, Castello LM, Avanzi GC. Management of sepsis and septic shock in the emergency department. *Internal and emergency medicine*. 2021 Sep;16(6):1649-61.
  15. Li Y, Li H, Zhang D. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. *Critical care*. 2020 Dec;24:1-9.
  16. Ospina-Tascón GA, Teboul JL, Hernandez G, Alvarez I, Sánchez-Ortiz AI, Calderón-Tapia LE, Manzano-Nunez R, Quiñones E, Madriñan-Navia HJ, Ruiz JE, Aldana JL. Diastolic shock index and clinical outcomes in patients with septic shock. *Annals of intensive care*. 2020 Dec;10:1-1.
  17. Zhou S, Zeng Z, Wei H, Sha T, An S. Early combination of albumin with crystalloids administration might be beneficial for the survival of septic patients: a retrospective analysis from MIMIC-IV database. *Annals of intensive care*. 2021 Dec;11:1-0.
  18. Zhou S, Zeng Z, Wei H, Sha T, An S. Early combination of albumin with crystalloids administration might be beneficial for the survival of septic patients: a retrospective analysis from MIMIC-IV database. *Annals of intensive care*. 2021 Dec;11:1-0.
  19. Delawder JM, Hulton L. An interdisciplinary code sepsis team to improve sepsis-bundle compliance: a quality improvement project. *Journal of Emergency Nursing*. 2020 Jan 1;46(1):91-8.
  20. Weiss SL, Peters MJ, Alhazzani W, Agus MS, Flori HR, Inwald DP, Nadel S, Schlapbach LJ, Tasker RC, Argent AC, Brierley J. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive care medicine*. 2020 Feb;46:10-67.



21. Lasater KB, Sloane DM, McHugh MD, Cimiotti JP, Riman KA, Martin B, Alexander M, Aiken LH. Evaluation of hospital nurse-to-patient staffing ratios and sepsis bundles on patient outcomes. *American Journal of Infection Control*. 2021 Jul 1;49(7):868-73.
22. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C. Executive summary: surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021. *Critical care medicine*. 2021 Nov 1;49(11):1974-82.
23. Shi R, Hamzaoui O, De Vita N, Monnet X, Teboul JL. Vasopressors in septic shock: which, when, and how much?. *Annals of Translational Medicine*. 2020 Jun;8(12).
24. de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, Vaillo-Rocamora A, Rodríguez-Gandía MÁ, Donate-Ortega J, Lozada-Hernández EE, Collazo Moreno AJ. Aggressive or moderate fluid resuscitation in acute pancreatitis. *New England Journal of Medicine*. 2022 Sep 15;387(11):989-1000.
25. Kattan E, Castro R, Miralles-Aguilar F, Hernández G, Rola P. The emerging concept of fluid tolerance: a position paper. *Journal of Critical Care*. 2022 Oct 1;71:154070.