JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Use of inferior vena cava guided fluid therapy in the treatment of septic shock: A randomised controlled trial

Sohom Ghosh[1], Rajesh Padhi[1], Samir Sahu[1], Meghanad Meher[1], Parshav Jain[1], Sambeet Kumar Subudhi[1], Jonnalagadda Vihari[1], Archana Samal[1], Anita Kumari Sahu[1]

[1] Department of Medicine, Institute of Medical Sciences & SUM Hospital, Siksha O Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India

Abstract

Introduction: By administering inferior vena cava (IVC) directed fluid, it is possible to avoid the use of additional fluid and fluid overload in patients with septic shock (SS) and sepsis-induced hypoperfusion (SIH).

Methodology: In patients with SIH and SS, we conducted prospective observational research on fluid therapy. A time-motion trace of the IVC diameter was created using M-mode imaging. The ability to predict fluid responsiveness was based on the IVC collapsibility index (cIVC) > 40%. Participants were randomised into 2 groups using a permuted block-of-four randomization list, with the investigators being blinded prior to patient allocation. They were split equally between the usual-care (UC) group, which received sepsis-guided fluid treatment, and the interventional ultrasound-guided fluid therapy (UGFT) group.

Results: The average age of the participants was 63.2 years (62.8 years for the UGFT group and 63.7 years for the UC group). Co-morbid health conditions were practically the same in both arms at baseline. Prior to enrolment, both groups received the same quantity of fluid as part of resuscitation (UGFT arm received 2.4 0.6 L, UC group received 2.2 0.7 L). The UGFT group outperformed the UC group with a P value of 0.02 due to a significantly lower positive fluid balance after 72 hours of ICU discharge (-1.37 L), which rendered the UGFT group superior to the UC group. Even after accounting for the fluids consumed before enrolment, there was still a sizable difference in the fluids infused. When the pre-enrolment fluids were counted at 72 hours, UGFT participants still displayed a decreased positive fluid balance. However, there was no discernible difference in the 30-day mortality rate overall (6.3% difference, UGFT: 15.7%, and UC: 22.0%).

Conclusions: In contrast to the UC group, the UGFT arm of our study demonstrated a statistically significant benefit of Point of Care USG (POCUS) guided fluid therapy during resuscitation in sepsis in reducing the positive fluid balance in 72 hours, preventing fluid overload, and reducing the need for dialysis and invasive ventilation. However, there was no statistically significant variation in the 30-day mortality rate.

Key words: IVC collapsibility index (cIVC); POCUS (Point of Care USG); septic shock; sepsis-induced hypoperfusion.

J Infect Dev Ctries 2024; 18(1):75-81. doi:10.3855/jidc.18489

(Received 05 May 2023 – Accepted 21 July 2023)

Introduction

Hospitals in India and around the world deal with a large burden from sepsis [1]. Particularly in patients with SIH & SS, sepsis has a higher mortality rate [2-4]. According to the surviving sepsis campaign package, an individual with septic shock should receive prompt delivery of isotonic crystalloid at the empirical amount of 30 mL/kg (UC approach) [5]. The UC method may result in either insufficient or excessive fluid delivery during the first few hours of resuscitation since not all patients are fluid-responsive. It has been linked in these situations to higher death rates among people with SS [6]. Fluid therapy can be customised during the first, important 6-hour resuscitation phase based on changes in IVC diameter during respiration [7]. In this work, we have used spontaneously breathing non-ventilated patients' respiratory collapse in IVC diameter. The respiratory disparity of the IVC (cIVC) was defined by Muller *et al.* [8] as [(DmaxDmin)/Dmin] 100% and it was discovered that a cIVC > 40% is typically associated with higher responsiveness in volume. In addition, a smaller research of 14 people found that a cIVC value of 15% or below had a 100% negative predictive value for responsiveness in volume [9]. With a clinical presentation of sepsis, low blood pressure that necessitates vasopressor treatment to maintain mean arterial pressure (MAP) 65 mmHg, and a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate resuscitation techniques, SS can be identified [10]. It is crucial to start fluid resuscitation within 30 minutes of sepsis and septic shock with appropriate fluid treatment to stop lactate levels from rising and avoid the needless use of vasopressors. Additionally, it shortens hospital stays and mortality rates [11-13]. In high-risk

individuals, a statistically significant correlation between the volume of fluid used in resuscitation and mechanical ventilation was discovered [14]. Studies on inferior vena cava guided fluid therapy in the resuscitation of septic shock have not been done in eastern Odisha.

Methodology

Between January 2021 and June 2022, this randomised controlled experiment was carried out at IMS and SUM, Tertiary Care Hospital, Bhubaneswar, Odisha.

Inclusion standards

Instances of SIH and SS in adults (18 years and older).

Exclusion standards

Acute pulmonary oedema, known cases of heart failure with reduced ejection fraction (HFrEF) (LVEF 40%), cases of pulmonary arterial hypertension (PAH), cases with ascites, significant bowel dilatation, cases of obesity with a body mass index of 30 kg/m^2, cases of concurrent asthma or COPD attacks, end-stage renal disease with or without dialysis, pregnancy, active bleeding, trauma cases, duplicated or masked cases of pulmonary embolism

Review of definitions

SIH covers patients with infection and systolic blood pressure less than 90 mm Hg or initial lactate less than 2 mmol/L at ED presentation [15,16]. Severe sepsis is defined as sepsis plus organ failure. The sequential organ failure assessment (SOFA) score was used to assess an individual's organ dysfunction [17].

Research Protocol

After meeting the inclusion criteria, people were recruited within one day (Figure 1). Clinical and demographic information including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [18], the diagnostic criteria for severe sepsis [19], pre-existing conditions, blood work including lactate, diagnostic investigations on organ function, and microbiologic workups including appropriate culture and sensitivity were gathered at hour 0 after enrolling the patients in the study. After getting the patient's or a relative's written informed consent, individuals were recruited. The MAP of 65 to 70 mmHg was advised by the trial protocol. The SOFA score was determined at presentation and 72 hours following therapy.

Measurements

A time-motion trace of the IVC diameter was obtained using M-mode imaging [20,21]. Over the course of one respiratory cycle, the maximum and minimum IVC diameters (Dmax and Dmin) were calculated. The formula used to calculate the IVC collapsibility index is cIVC = (Dmax-Dmin)/Dmax [22]. Enrolment, randomization, and data collection were performed online (InForm, Oracle) by well-trained physicians utilizing a Sonosite M-Turbo 2D Echo POCUS to perform ultrasonographic measurements. Participants were randomised into 2 groups using a permuted block-of-four randomization list, with the investigators being blinded prior to patient allocation. They were split equally between the usual-care (UC) group, which received sepsis-guided fluid treatment, and the interventional ultrasound-guided fluid therapy (UGFT) group. Following prompt randomization, patients received one of the following two approaches:

UGFT approach

In this arm, the patient's primary treating physician evaluated the IVC diameter. If an IVCCI > 40% was noted, the patient received 0.9% normal saline solution (NSS) at 10 mL/kg bolus without being deferred, and

Figure 1. Enrolments of participants in study.

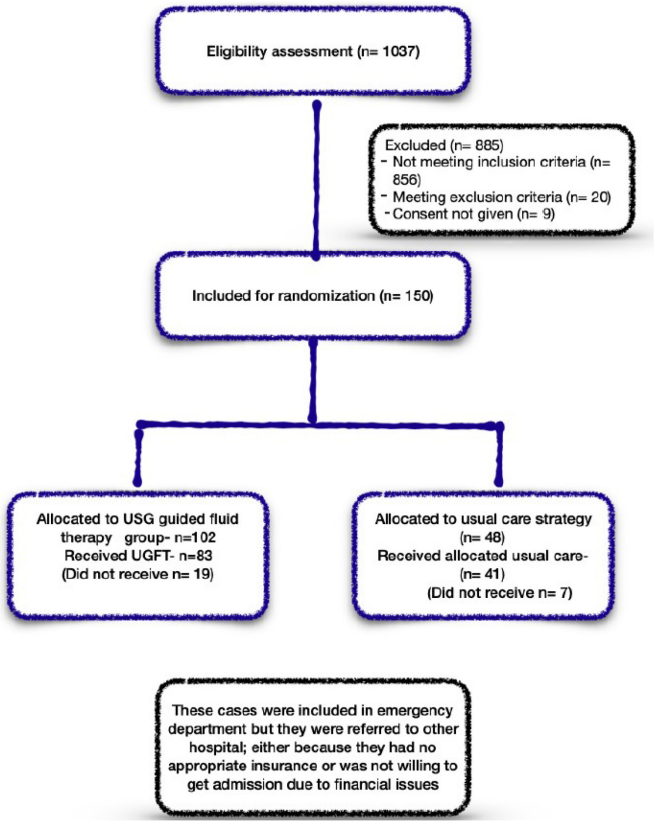


Table 1. Baseline characteristics of the study individuals in both groups.

PARAMETER	UGFT (N = 83)	UC (N = 41)
Age, Y		
Mean ± SD (No.)	61.8 ± 16.9 (83)	62.7 ± 15.0 (41)
Median (Q1, Q3)	65.0 (48.0,75.0)	63.0 (55.0,74.0)
Gender, % (n/N)		
Female	61.4 (51/83)	31.7 (13/41)
Male	38.6 (32/83)	68.3 (28/41)
Know or assumed infection, % (n/N)	100.0 (83/83)	100.0 (41/41)
SIRS criteria shown		
Mean ± SD (No.)	2.7± 0.7 (83)	2.8± 0.8 (41)
Median (Q1, Q3)	3.0 (2.0,3.0)	3.0 (2.0,3.0)
QSOFA		
Mean ± SD (No.)	1.9±0.7 (82)	2.1± 0.7 (40)
Median (Q1, Q3)	2.0 (1.0,2.0)	2.0 (2.0,3.0)
Serum lactate		
Mean ± SD (No.)	3.6±3.2 (66)	3.8 ± 3.6 (33)
Median (Q1, Q3)	2.5 (1.6,3.8)	2.0 (1.5,5.7)

measurements were routinely obtained shortly after each IV bolus fluid delivery. The IVCDI (distensibility index) was utilized in place of the IVCCI in this arm if the patients needed mechanical breathing within six hours of starting treatment. Every two hours up until six hours following the initial recruiting, the IVC assessment was performed. Using M-mode imaging, the IVC's diameter was assessed as 2 cm terminal to the hepatic vein's convergence.

$$IVCCI = \frac{IVC_{dmax} \times IVC_{dmin}}{IVC_{dmax}} \times 100$$

$$IVCDI = \frac{IVC_{dmax} \times IVC_{dmin}}{IVC_{dmin}} \times 100$$

Where: IVC_{dmax}=$IVC_{diamentermax}$, and IVC_{dmin}=$IVC_{diametermin}$.

UC approach

NSS was administered as a loading dose of 30 mL/kg to participants in this arm. During the six-hour research period, the treating physician used his or her discretion to decide whether to administer additional IV fluid or vasopressor support after the IV bolus was finished. Even after fluid therapy, MAP 65 mmHg was taken into consideration as a threshold for setting vasopressor support. It was noted when vasopressor was administered. Subsidiary fluid delivery was allowed in both arms, nevertheless, at the treating physician's discretion. In our investigation, additional supportive requirements such as the administration of colloids and central venous catheterization were allowed and employed as determined by the treating physicians. Our resuscitation regimen was terminated six hours after we began our treatment, and any additional care was administered at the treating physician's discretion.

Statistic evaluation

The *p* value was calculated using the Student's t-test and the chi-square test. The acquired data were assessed statistically using the SPSS programme version 20.0, and *p* values less than 0.05 were regarded as statistically significant.

Results

The average age of the participants was 63.2 years (62.8 years for the UGFT group and 63.7 years for the

Table 2. Primary and Secondary endpoints comparison between the UGFT and UC arms.

Parameter	UGFT [N = 83]	UC [N = 41]	Therapy distinction In Mean/ % (95% CI)	*p* value
Primary endpoint				
Fluid balance at 72 hours or ICU discharge (L)				
Mean ± SD (No.)	0.65 ± 2.85 (83)	2.02 ± 3.44 (41)	-1.37 (-2.53 to -0.21)	**0.02**
Median (Q1, Q3)	0.53 (-0.84, 2.53)	1.22 (-0.03, 3.73)	-	-
Secondary endpoints				
Need for dialysis, % (n/N)	5.1 (4/79)	17.5 (7/40)	-12.4% (-0.27 to -0.01)	**0.04**
Need for mechanical ventilation, % (n/N)	17.7 (14/79)	34.1 (14/41)	-16.42% (-0.33 to 0.0)	**0.04**
ICU stay length in days				
Mean ± SD (No.)	3.31 ± 3.53 (74)	6.22 ± 10.72 (35)	-2.91 (-6.67 to 0.85)	0.113
Median (Q1, Q3)	2.09 (0.85,3.75)	2.90(1.27, 3.80)	-	-
Use of vasopressor in hours				
Mean ± SD (No.)	40.74 ± 51.23 (55)	55.64 ± 87.42 (26)	-14.91 (-52.50 to 22.68)	0.426
Median (Q1, Q3)	20.98 (7.62, 45.27)	30.85 (13.75, 47.60)	-	-
Alteration in serum creatinine levels from 0 hr to 72 hr				
Mean ± SD (No.)	0.13 ± 1.10 (79)	0.04 ± 0.97 (34)	0.09 (0.34 to 0.52)	0.453
Median (Q1, Q3)	0.00 (-0.19, 0.23)	-0.11 (-0.39, 0.12)	-	-

UC group). Co-morbid health conditions were almost identical in both groups at baseline. The UGFT group had significantly more females (62.4%) than the UC group (30.7%). As part of resuscitation, the same amount of fluid was administered to both groups prior to enrolment (UGFT arm: 2.4 0.6 L, UC arm: 2.2 0.7 L). Table 1 shows the study participants' initial characteristics.

The UGFT group outperformed the UC group with a *p* value of 0.02 due to a significantly lower positive fluid balance after 72 hours or ICU discharge (-1.37 L), which rendered the UGFT group superior to the UC group. Table 2 compares the primary and secondary endpoints between the UGFT and UC groups.

From 0 hours to 72 hours, the change in serum creatinine levels was nearly identical in both arms (Figure 2).

Few patients needed invasive ventilation in the UGFT group (17.7%) compared to the UC group (34.1%) with a *p* value of 0.04 and few patients needed dialysis (5.1% vs. 17.5%). The average time required for vasopressor support and the length of the ICU stay were nearly identical in both arms (Figure 3 and 4). Individuals in the UGFT arm received fewer fluids in 72 hours than those in the UC arm. This distinction is made because the fluid continued to be statistically significant even after accounting for the pre-enrolment fluids. Individuals with UGFT even displayed a diminished positive fluid balance at 72 hours when the fluids given prior to enrolment were also taken into account (Figure 5). The 30-day mortality rate overall, however, did not change significantly (6.3% difference, UGFT: 15.7%, and UC: 22.0%) (Figure 6).

Discussion

In our study, we assessed the effectiveness of directing fluid and vasopressor infusion in patients with SIH and SS using an ultrasonographic assessment of the IVC in the first six hours. The results of our study confirm our hypotheses that when individuals with SIH and SS are managed using a dynamic fluid administration protocol as opposed to a fixed bolus therapy, the fluid balance is decreased and vital signs and organ function are improved, which is associated with a decrease in sepsis-associated mortality.

Figure 2. Change in serum creatinine level from baseline to 72 hours.

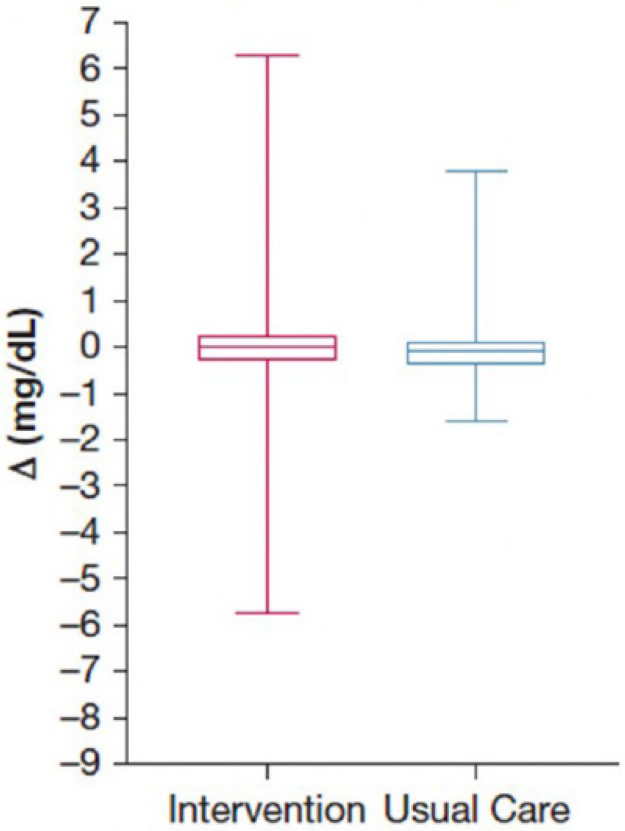


Figure 3. Length of ICU stay.

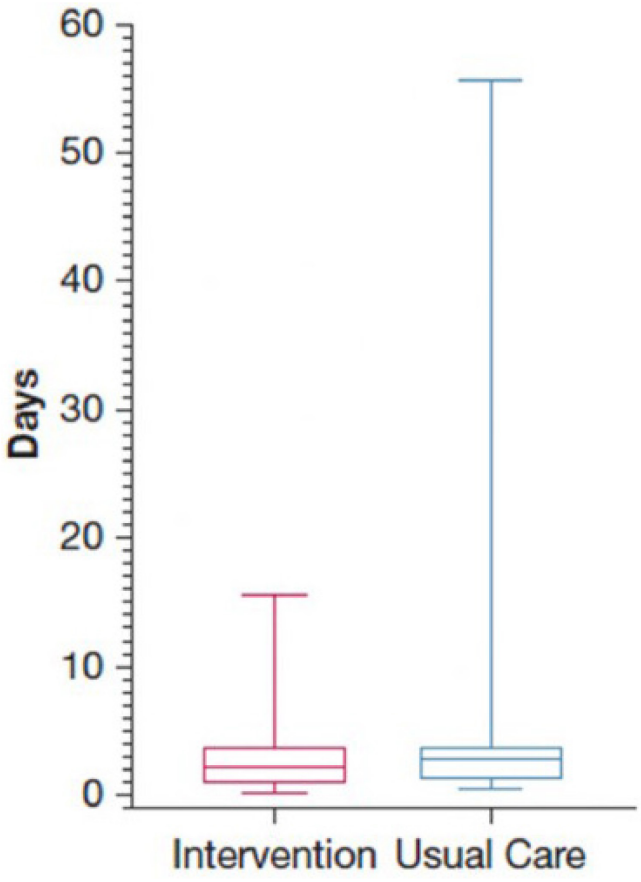


Figure 4. Average hours of vasopressor use.

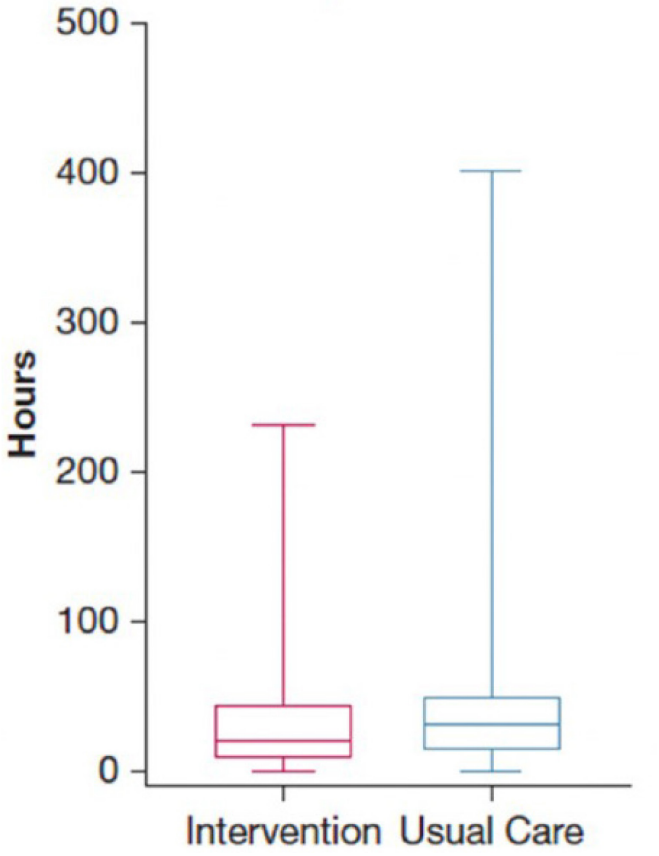


Figure 5. Fluid balance at 72 hours or discharge.

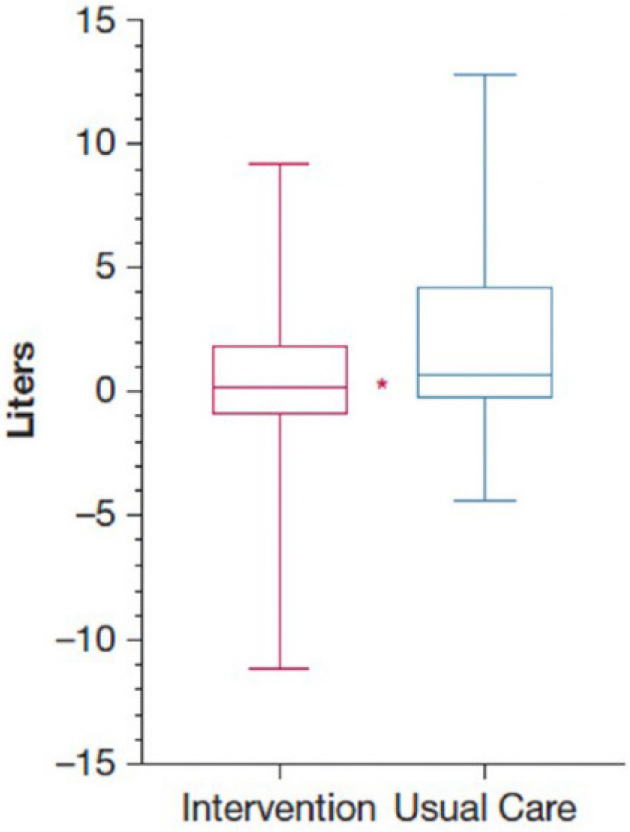
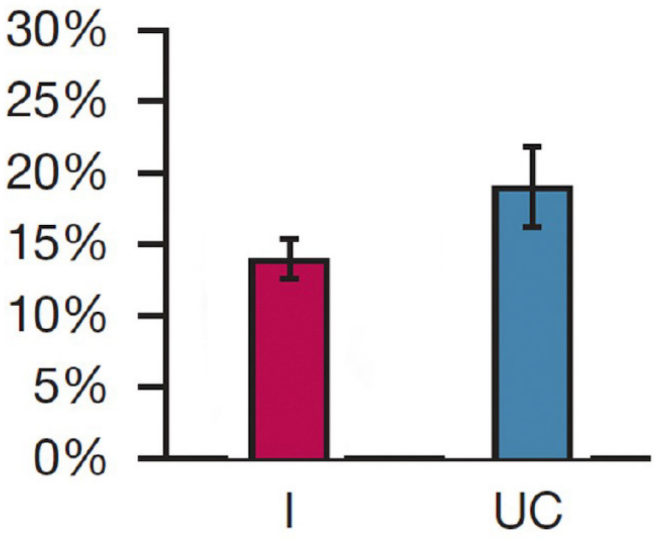


Figure 6. Overall 30-day mortality rate.



Similar to our study, a previous investigation from 2017 by Latham *et al.* demonstrated improved outcomes with guided fluid therapy as opposed to the "Usual Care"; they had used stroke volume [SV] to suggest fluid therapy. With a *p* value of 0.02, the SV group's net fluid balance was lower (1.77L) than it was in the UC group (5.36L), and the SV group also required less mechanical ventilation (RR, 0.51; $p = 0.0001$).

According to a recent work by Feissel *et al.* [6], we used M-mode to evaluate IVC diameter at 2 cm terminal to the convergence of the hepatic vein in our investigation. We should talk about the fact that we use cIVC in patients who spontaneously breathe. Particularly in cases of critically ill respiratory patients, this may be subjective to movement fluctuations during respiration. Recently, Kimura *et al.* [7] revealed that the breathing rhythm has a significant impact on cIVC. This needs to be considered when taking cIVC measurements.

The UGFT arm received considerably fewer fluids than the UC arm at 72 hours. Despite using less fluid and vasopressors, there was no increase in serum creatinine in the UGFT arm. Additionally, there was less need for mechanical ventilation and dialysis in the UGFT component. The length of stay in the ICU was reduced by roughly 2.91 days in the UGFT arm, even though this difference was not statistically significant. As a result of volume overload and elevated renal and central venous pressures, renal interstitial edoema increases, which in turn causes a decrease in filtration pressure and, ultimately, a decrease in glomerular filtration [9]. Similar to this, excessive lung fluid leads to deteriorating intrapulmonary shunting, progressive lung failure requiring mechanical ventilation, a longer hospitalisation in the intensive care unit, and ultimately mortality [10]. In both arms of this trial, the median volume of fluid given at the beginning of resuscitation in deceased subjects was noticeably higher than that of the last surviving. This incidental observation may suggest that an increase in early resuscitative fluid is associated with an increase in mortality. This can be clarified in the future with a more thorough investigation, though. Meyhoff *et al.* 2022 [8] have recently demonstrated in their recent study that limiting fluids may not connect with greater survival benefits at 90 days. However, their research does not demonstrate how drinking too much liquids might be harmful. Consequently, it is important to avoid administering unnecessary or irrational fluids during resuscitation. During the initial stage of resuscitation in sepsis, using IVC diameter determined by POCUS helps prevent "overload" and enables us to direct towards a cautious fluid restriction.

Conclusions

In the current study, it was demonstrated that POCUS-guided fluid therapy during resuscitation in sepsis reduced the positive fluid balance in 72 hours, prevented fluid overload, and reduced the need for dialysis and invasive ventilation in the UGFT arm compared to the UC arm. However, there was no statistically significant variation in the 30-day mortality rate.

Acknowledgements

We provide the corresponding author the right to make any adjustments required by the journal, to handle the remaining correspondence on our behalf, and to serve as the manuscript's guarantor. All individuals who contributed significantly to the study described in the book but are not authors are acknowledged in the acknowledgment and have given me or us written consent to do so. If I or we omit an acknowledgment, it signifies that no contributor has been left out and that I or we have not received significant contributions from non-contributors. The institutional ethical committee provided its ethical approval.

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Corresponding author
Dr. Meghanad Meher
Asst. Professor, Department of Medicine,
Institute of Medical Sciences & SUM Hospital,
Siksha O Anusandhan (deemed to be University),
Bhubaneswar, Odisha, India.
Tel: 94392 75371
Email: megha.hrt@gmail.com

Conflict of interests: No conflict of interests is declared.