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Impact of Cumulative Fluid Balance During the First Three ICU Days in Septic Patients with Heart Failure: A Propensity Score-Matched Cohort Study

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ABSTRACT

Background: Septic patients with heart failure may be more sensitive to intravenous fluid infusion and are at risk for fluid overload. Methods to assess fluid overload status and how fluid accumulation relates to prognosis in these patients remain unknown. Based on these results, we aimed to explore how cumulative fluid balances during the initial three days in the ICU affect the prognosis of septic patients with heart failure.

Methods: Data for this retrospective study were obtained from the MIMIC IV2.2 database. According to the daily cumulative fluid balance status, patients were divided into negative fluid balance group (CFB<0%) and positive fluid balance group (CFB≥0%). The main outcome of this study was all-cause in-hospital mortality. Cox regression analysis was conducted to investigate the association between the daily CFB and the risk of mortality. Subgroup analyses were conducted to investigate the consistency of the prognostic value of the daily CFB status (day1-day3) in septic patients with reduced ejection fraction (HFrEF,LVEF<50%) and preserved ejection fraction (HFpEF,LVEF≥50%).

Results: A total of 1150 patients were included in this study, including 776 survivors and 374 deaths.The median age was 65 ± 12 years, with males comprising 58.0% of the sample. CFB-day3 (AUC=0.765) had a better predictive ability for mortality than CFB-day2(AUC=0.727) or CFB-day1 (AUC=0.530). Similar results were observed in the HFrEF and HFpEF population. Subgroup analysis showed that a positive fluid balance of CFB-day1 was associated with a 78% increased risk of mortality among patients with HFrEF(LVEF<50%). However, a positive fluid balance of CFB-day1 was associated with a 52% reduced risk among patients with HFpEF(LVEF≥50%). In exploratory analyses, the proportional effect of a positive fluid balance of CFB-day2 or CFB-day3 on mortality was consistent across all eight pre-specified subgroups, regardless of whether the patient had a preserved ejection fraction or a reduced ejection fraction (all P for interaction >0.05).

Conclusions: In septic patients with HFpEF, positive fluid balance of CFB-day1 might improve the prognosis of patients. However, from the second day, fluid overload was associated with poor prognosis. Therefore, we propose that on the first day of fluid resuscitation, the therapy should be considered according to the LVEF level. Furthermore, diuretics or CRRT should be utilized as much as possible on the second or third day to achieve a negative fluid balance.

INTRODUCTION

Sepsis is a syndrome characterized by life-threatening organ dysfunction and is a frequently encountered serious complication of critical illnesses such as trauma, infection, and shock Shankar-Hari et al. (2016). According to statistics, there are over 19 million sepsis patients worldwide annually, with approximately half of them being incurable. Sepsis causes approximately 6 million deaths each year Perner et al. (2018). In recent years, significant advancements have been made in the monitoring, diagnosis, and treatment of sepsis and septic shock, owing to the ongoing deepening of research in this field. Sepsis can now be detected early within the first few hours of onset, and timely management may enhance patient outcomes. The cornerstone of sepsis treatment consists of early rapid intravenous fluid resuscitation, antibiotic therapy and control of the infection source Levy et al. (2018). The primary objective of fluid resuscitation is to enhance cardiac output by augmenting cardiac preload, which in turn improves tissue perfusion and mitigates organ dysfunction. Both the 2016 and 2021 Surviving Sepsis Campaign (SSC) guidelines advocate for the intravenous administration of a minimum of 30 mL/kg of crystalloid fluid within the initial three hours of resuscitation Rhodes et al. (2016), Evans et al. (2021). The 2018 updated SSC bundle treatment guidelines

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present more positive treatment recommendations, advocating for the initiation of fluid resuscitation at a rate of 30 mL/kg within the first hour Levy et al. (2018). Several studies have reported a significant association between positive fluid balance (FB) and adverse outcomes, including an increased incidence of acute kidney injury (AKI) and mortality Sakr et al. (2017), Acheampong et al. (2015), Sadaka et al. (2014), Boyd et al. (2011). However, it is important to note that the majority of these studies have concentrated solely on the absolute volume of FB, which does not adequately capture the dynamic changes in fluid accumulation. Most prior studies have concentrated on data collected at various time points within the first 72 hours following admission to the intensive care unit (ICU) Kharadi et al. (2022), Vincent et al. (2006), Sirvent et al. (2015). Despite the controversy surrounding early goal-directed therapy (EGDT) and the fact that subsequent sepsis treatment guidelines no longer endorse its use, the importance of initiating fluid resuscitation as early as possible remains emphasized. Nevertheless, a sustained positive fluid balance during the ICU period has been linked to increased mortality in patients with sepsis Acheampong et al. (2015), Brotfain et al. (2016), Shen et al. (2018), Van Mourik et al. (2020). Septic patients with heart failure may be more sensitive to intravenous fluid infusion and are at risk for fluid overload Pellicori et al. (2015), Claure-Del Granado et al. (2016). The impact of fluid resuscitation on outcomes in these patients focuses primarily on the clinical effects of sepsis treatment bundle implementation but ignores cardiac function. Methods to assess fluid overload status and how fluid accumulation relates to prognosis in these patients remain unknown. Based on these results, we aimed to explore how cumulative fluid balances during the initial three days in the ICU affect the prognosis of septic patients with heart failure.

METHODS

Study population

The researchers conducted a retrospective observational study using data from the publicly accessible Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which can be found at https://mimic.mit.edu Johnson et al. (2023). In this study, data were analyzed retrospectively using an observational design. Ding yu Lu, as one of the authors, fulfilled the prerequisites to gain access to the database and undertook the task of data extraction. patient cohort for this research comprised individuals with a confirmed diagnosis of sepsis complicated with heart failure, following the guidelines outlined in the International Classification of Diseases, 9th and 10th Revision. Ethical review and approval were waived for this study, due to reason: The use of the MIMIC-IV database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

The data is publicly available, therefore, the ethical approval statement and the requirement for informed consent were waived for this study. This study followed the STROBE statement, and detailed results of filling out the STROBE checklist are provided in the attachment.

The inclusion criteria were as follows: 1)Age>18 years old; 2) ICU stay>72 hours; 3) Patients who meet the diagnosis of sepsis and heart failure at the ame time. The definition of sepsis refers to the diagnostic criteria for sepsis recommended in the 2016 Surviving Sepsis Campaign Singer et al. (2016), which is life-threatening organ dysfunction caused by a dysregulated host response to infection, SOFA score≥2 points. The exclusion criteria were as follows:1)The body weight and LVEF data on admission are missing, and the daily fluid output and intake data are missing;2) cardiopulmonary resuscitation before ICU admission, artificial valve prosthesis or severe mitral pathology.

Data collection

To conduct the data extraction, we utilized PostgresSQL (version 13.7.2) software and Navicate Premium (version 16) tool by employing Structured Query Language (SQL). The extraction process prioritized four categories of potential variables: demographic factors, vital signs, laboratory parameters, comorbidities and treatment during ICU stay. Vital signs and laboratory measurements from the initial 24 hours of ICU admission were included in the analysis. In instances where there were multiple outcomes, the average measurement was employed. To mitigate any potential bias, variables containing missing values surpassing 20% were eliminated. To handle variables with less than 20% missing data, the research team employed the multiple imputation (miss Forest R) technique Blazek et al. (2021). Calculate the patient's daily fluid balance and cumulative fluid balance (CFB) after admission to the ICU. Daily fluid balance=[Daily intake (L)-Daily output (L)]/body weight at admission (kg). CFB is the sum of the natural numbers of daily fluid balance.

Grouping: According to the daily cumulative fluid balance status, patients were divided into negative fluid balance group (CFB<0%) and positive fluid balance group (CFB≥0%). According to the LVEF levels, patients were divided into heart failure with reduced ejection fraction group (HFrEF,LVEF<50%) and heart failure with preserved ejection fraction group(HFpEF,LVEF≥50%).

Outcomes

The main outcome of this study was all-cause in-hospital mortality.

Statistical analysis

Continuous variables were presented as the mean±SD or median and interquartile range (IQR).

The comparison of continuous variables was performed using t-test or ANOVA, or using Mann-Whitney U-test or Kruskal-Wallis test, as appropriate. Categorical variables were expressed as numbers or percentages (%), and their analysis was implemented by means of Fisher's exact test or Pearson chi-square test.

Kaplan-Meier survival analysis was used to assess the cumulative incidence of in-hospital mortality with different CFB status in HFrEF group and HFpEF group respectively. The log-rank test was employed to examine any observed disparities.

Cox regression analysis was conducted to investigate the association between the daily CFB and the risk of mortality. Variables that showed clinical significance and had a level of P<0.1 were included in the multivariable Cox proportional hazards model by controlling for the following confounders: Age, gender, BMI, CVP, MAP, WBC, platelet, hemoglobin, lactate, creatinine,the use of ventilation,CRRT,SOFA score and SIRS score. HRs were counted and the findings were presented with 95% confidence intervals (CI).

In addition, Z test was used to compare the predictive value of CFB-day1,CFB-day2 and CFB-day3 in HFrEF and HFpEF group respectively by comparing the area under curves (AUC) of the receiver operating characteristic curves (ROC).

Finally, subgroup analyses were conducted to investigate the consistency of the prognostic value of the daily CFB status (day1-day3) across different subgroups. These subgroups were categorized based on age (<65 versus ≥65 years), gender (female versus male), BMI (<30 versus≥30kg/m2), LVEF (<50 versus ≥50%), the presence of specific medical histories including hypertension, diabetes, and whether to use ventilation or CRRT.Likelihood ratio tests were employed to evaluate the association between the daily CFB status and the variables used for stratification. The data analyses were conducted using R software (version 4.2.2). For all analyses, a 2-side P<0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 1150 patients were included in this study. Table 1 presents the baseline characteristics of all septic patients with heart failure, including 776 survivors and 374 deaths. The in-hospital mortality rate was 32.5%. The median age of the participants was 65 ± 12 years, with males comprising 58.0% of the sample. Compared with survivors, non-survivors tended to have a higher lactate level (2.45 ± 1.93 vs. 2.17 ± 1.70, P=0.011), SOFA scores (7.7 ± 3.7 vs. 6.9 ± 3.4, P<0.001), SIRS scores (2.93 ± 0.86 vs. 2.76 ± 0.89, P=0.001), a higher proportion of HFrEF (45.7% vs. 32.5%, P<0.001), AKI stage-3(54.5% vs.35.7%, P<0.001), a higher utilization of CRRT (23.8% vs. 9.7%, P<0.001) and vasoactive drugs (56.7% vs.50.5%, P=0.049). Non-survivors were less likely to receive positive fluid balance therapy on the first day after ICU admission (65.2% vs.71.8%, P=0.024), but more likely to receive positive fluid balance therapy on the second day (86.4% vs.54.6%, P<0.001) and on the third day (89.6% vs.43.6%, P<0.001). There was no statistical difference in hospitalization time and ICU stay between the death group and the survival group.

Association between daily CFB status, daily fluid balance and hospital mortality

The prediction of in-hospital mortality was analyzed using univariate and multivariate Cox proportional hazards regression. Factors with P<0.1 in univariate analysis were included in multivariate analysis. The results showed that compared with negative fluid balance, the risk of in-hospital mortality among patients with positive fluid balance of CFB-day1 was reduced by 47% after adjusting for age, gender, BMI, CVP,MAP,WBC, platelet, hemoglobin, lactate, creatinine, the utilization of ventilation and CRRT, SOFA score and SIRS score, which was a protective factor (HR,95%CI=0.53, 0.42-0.68,P<0.001). Patients in the positive fluid balance of CFB-day2 group had a 3.61-fold higher risk of mortality, representing a significant risk factor (HR,95%CI=3.61, 2.63- 3.65,P<0.001). Furthermore, the risk of mortality continued to rise obviously on the third day (HR,95%CI=5.11, 3.11- 8.42,P<0.001). However, daily fluid balance calculated without using body weight was not associated with prognosis (Table 2).

Association between daily CFB status and hospital mortality in HFrEF and HFpEF population

The association between the daily CFB status and hospital mortality in HFrEF and HFpEF population was analyzed respectively using Kaplan-Meier survival analysis curves (Figure 1).

Figure 1: Association between the in-hospital mortality and daily CFB status in HFrEF population. (a)Survival curves for mortality according to FB status of CFB-day1;(b) Survival curves for mortality according to FB status of CFB-day2;(c) Survival curves for mortality according to FB status of CFB-day3.

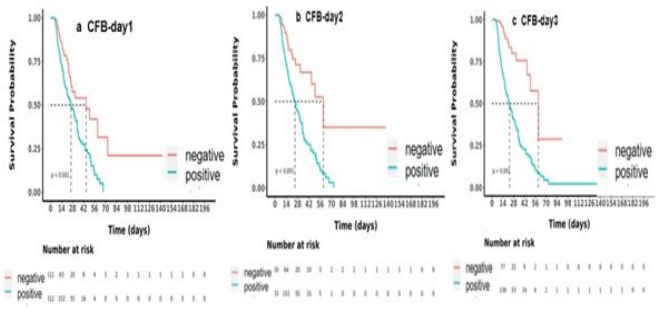


Table 1: Baseline characteristics of the Survivors and Non-survivors groups

Variable	Overall n = 1150	Survivors n = 776	Non - survivors n = 374	P
Age	65 ± 12	65 ± 12	65 ± 12	0.757
Male, n (%)	667 (58.0%)	481 (62.0%)	186 (49.7%)	<0.001
BMI	32 ± 10	32 ± 10	32 ± 10	0.45
CVP, mmHg	13.3 ± 4.0	13.3 ± 4.0	13.4 ± 4.2	0.608
MAP, mmHg	78 ± 18	78 ± 18	78 ± 20	0.737
WBC, K/uL	14 ± 11	14 ± 8	15 ± 16	0.297
Platelet, K/uL	204 ± 108	199 ± 105	215 ± 112	0.023
Hemoglobin, g/dL	10.32 ± 2.40	10.32 ± 2.44	10.32 ± 2.33	0.97
Lactate, mg/dl	2.36 ± 1.87	2.17 ± 1.70	2.45 ± 1.93	0.011
Creatinine, mg/dL	1.88 ± 1.73	1.88 ± 1.64	1.89 ± 1.91	0.885
CFB-day1				0.024
Negative, n (%)	349 (30.3%)	219 (28.2%)	130 (34.8%)	
Positive, n (%)	801 (69.7%)	557 (71.8%)	244 (65.2%)	
CFB-day2				<0.001
Negative, n (%)	403 (35.0%)	352 (45.4%)	51 (13.6%)	
Positive, n (%)	747 (65.0%)	424 (54.6%)	323 (86.4%)	
CFB-day3				<0.001
Negative, n (%)	477 (41.5%)	438 (56.4%)	39 (10.4%)	
Positive, n (%)	673 (58.5%)	338 (43.6%)	335 (89.6%)	
LVEF_ group				<0.001
LVEF< 50%, n (%)	423 (36.8%)	252 (32.5%)	171 (45.7%)	
LVEF≥ 50%, n (%)	727 (63.2%)	524 (67.5%)	203 (54.3%)	
SOFA	7.2 ± 3.5	6.9 ± 3.4	7.7 ± 3.7	<0.001
SIRS	2.81 ± 0.88	2.76 ± 0.89	2.93 ± 0.86	0.001
Hypertension, n (%)	357 (31.0%)	257 (33.1%)	100 (26.7%)	0.028
Diabetes, n (%)	467 (40.6%)	326 (42.0%)	141 (37.7%)	0.163
AKI-stage				<0.001
None, n (%)	47 (4.1%)	40 (5.2%)	7 (1.9%)	
stage-1, n (%)	145 (12.6%)	110 (14.2%)	35 (9.4%)	
stage-2, n (%)	477 (41.5%)	349 (45.0%)	128 (34.2%)	
stage-3, n (%)	481 (41.8%)	277 (35.7%)	204 (54.5%)	
Ventilation, n (%)	818 (71.1%)	549 (70.7%)	269 (71.9%)	0.68
CRRT, n (%)	164 (14.3%)	75 (9.7%)	89 (23.8%)	<0.001
Vasoactive drugs, n (%)	604 (52.5%)	392 (50.5%)	212 (56.7%)	0.05
Antibiotic, n (%)	1136 (98.8%)	765 (98.6%)	371 (99.2%)	0.567
Glucocorticoids, n (%)	317 (27.6%)	210 (27.1%)	107 (28.6%)	0.582

The results showed that for patients with HFrEF, patients with positive fluid balance of CFB-day1 had a lower cumulative survival rate than those with a negative fluid balance. However, for patients with HFpEF, the result was opposite (Figure 2).

Predictive value of CFB-day1, CFB-day2 and CFB-day3 for in-hospital mortality

In overall population, the study compared CFB-day3 with CFB-day2 and CFB-day1, showing that CFB-day3 (AUC=0.765) had a better predictive ability for in-hospital mortality than CFB-day2(AUC=0.727) or CFB-day1 (AUC=0.530). Similar results were observed in the HFrEF and HFpEF population (Figure 3).

Subgroup analysis

We estimated the relationship between daily CFB status and in-hospital mortality among subgroups. The results showed that a positive fluid balance of CFB-day1 was associated with a 78% increased risk of mortality compared with a negative fluid balance among patients with HFrEF(LVEF<50%). However, a positive fluid balance of CFB-day1 was associated with a 52% reduced risk of death among patients with HFpEF (LVEF≥50%) (Figure 4).

Table2: Cox regression analysis for in-hospital mortality

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age	1	0.99- 1.01	0.936			
Male	0.77	0.63- 0.94	0.011	0.9	0.73- 1.11	0.341
BMI	1.01	1.00- 1.02	0.254			
CVP	1.01	0.98- 1.03	0.673			
MAP	1	0.99- 1.00	0.353			
WBC	1.01	1.00- 1.01	0.097	1	1.00- 1.01	0.277
Platelet	1	1.00- 1.00	0.045	1	1.00- 1.00	0.482
Hemoglobin	1.01	0.97- 1.05	0.635			
Lactate	1.15	1.02- 1.30	0.034	1.1	0.90- 1.21	0.112
Creatinine	1.01	0.96- 1.06	0.726			
CFB-day1						
Negative	reference					
Positive	0.83	0.67- 1.03	0.095	0.53	0.42- 0.68	<0.001
CFB-day2						
Negative	reference					
Positive	3.32	2.46- 4.47	<0.001	3.61	2.63- 3.65	<0.001
CFB-day3						
Negative	reference					
Positive	5.72	4.10- 7.97	<0.001	5.11	3.11- 8.42	<0.001
LVEF< 50%	reference					
LVEF≥ 50%	0.72	0.59- 0.88	0.002	0.73	0.59- 0.90	0.004
Fluid balance-day1	1	1.00- 1.00	<0.001	1	1.00- 1.00	0.481
Fluid balance-day2	1	1.00- 1.00	<0.001	1	1.00- 1.00	0.282
Fluid balance-day3	1	1.00- 1.00	<0.001	1	1.00- 1.00	0.956
Ventilation	1.06	0.84- 1.33	0.624			
CRRT	2.06	1.62- 2.62	<0.001	1.4	1.06- 1.85	0.016
SOFA	1.05	1.02- 1.08	<0.001	1	0.97- 1.03	0.778
SIRS	1.23	1.09- 1.39	<0.001	1.09	0.96- 1.24	0.166

Figure 2: Association between the in-hospital mortality and daily CFB status in HFpEF population. (a)Survival curves for mortality according to FB status of CFB-day1;(b) Survival curves for mortality according to FB status of CFB-day2;(c)Survival curves for mortality according to FB status of CFB-day3.

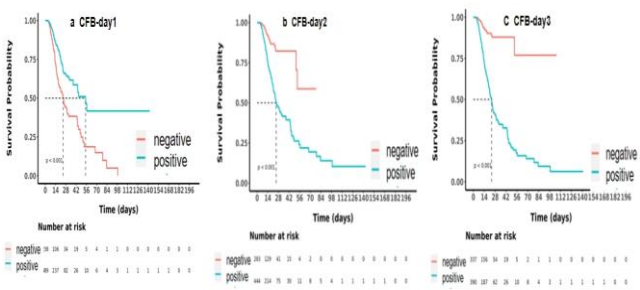


Figure 3: Predictive value of daily CFB status for in-hospital mortality. (a) ROC curves of overall population;(b) ROC curves of HFrEF population;(c) ROC curves of HFpEF population.

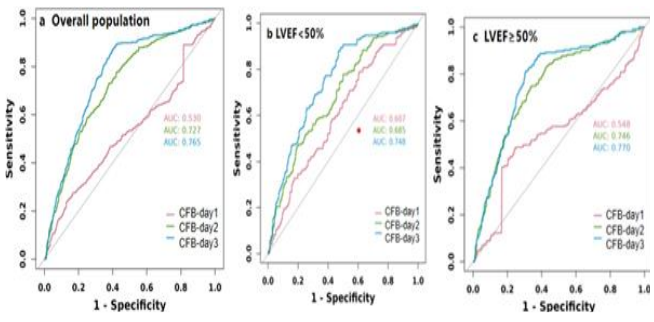
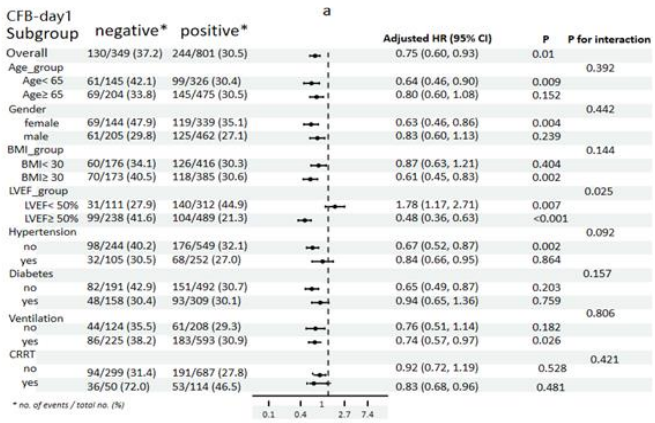


Figure 4: The relationship between CFB-day1 status and in-hospital mortality among subgroups.



In exploratory analyses, the proportional effect of a positive fluid balance of CFB-day2 or CFB-day3 on mortality was consistent across all eight pre-specified subgroups, regardless of whether the patient had a preserved ejection fraction or a reduced ejection fraction (all P for interaction >0.05) (Figure 5, Figure 6).

Figure 5: The relationship between CFB-day2 status and in-hospital mortality among subgroups.

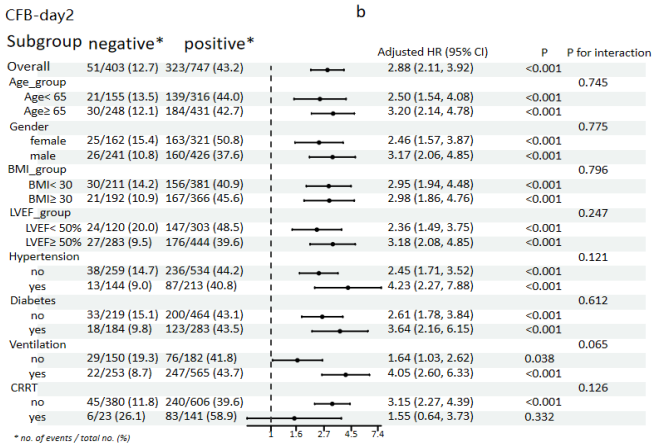
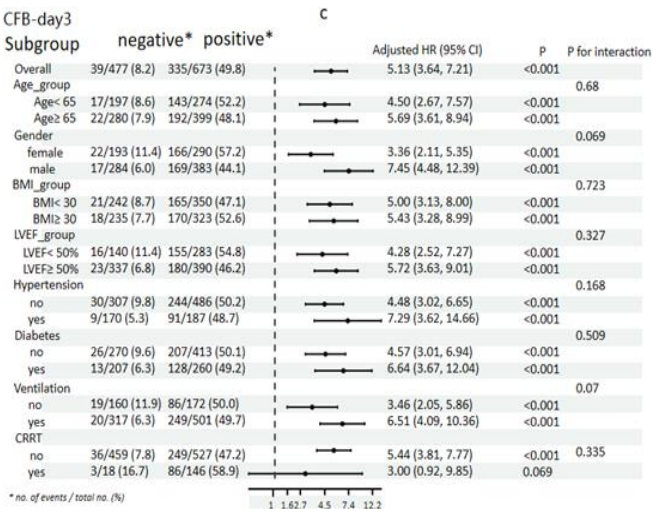


Figure 6: The relationship between CFB-day3 status and in-hospital mortality among subgroups.



DISCUSSION

Patients with sepsis often experience fluid accumulation during resuscitation, which is attributed to substantial fluid infusion, capillary leakage, and acute kidney injury. This fluid overload can result in pulmonary edema and edema of other organs, hindering oxygen diffusion and exacerbating hypoxia Hippensteel et al. (2019), Brooks et al. (2014). Consequently, fluid overload is closely associated with a poor prognosis in affected patients Sakr et al. (2017), Acheampong et al. (2015), Sadaka et al. (2014), Boyd et al. (2011). Simultaneously, cardiac function should be regarded as a complicating factor in the administration of intravenous fluids; patients with cardiac dysfunction are prone to hypervolemia and may develop hypoperfusion-induced organ injury. Previous studies have confirmed that both left ventricular diastolic and systolic dysfunction are predictors of mortality in patients with sepsis Sanfilippo et al. (2015), Sanfilippo et al. (2017), Gonzalez et al. (2016). Building on these findings, we sought to investigate how daily CFB status during the first three days in the ICU influence the prognosis of septic patients with heart failure.

This study has 4 main contributions: Firstly, our results indicated that in septic patients with heart failure, an increased risk of mortality was associated with daily CFB status, rather than daily absolute volume of FB. The risk of in-hospital mortality among patients with positive fluid balance of CFB-day1 was reduced by 47%, which was a protective factor. However, positive fluid balance of CFB-day2 or CFB-day3 was associated with an increased risk of mortality. Secondly, we found that for septic patients with HFrEF, patients with positive fluid balance of CFB-day1 had a lower cumulative survival rate than those with a negative fluid balance, which suggested that the restrictive fluid infusion on the first day might be benefit among these patients. Additionally, we found that regardless of cardiac function in patients with sepsis, CFB-day3 had the greatest value in predicting mortality risk. Finally, subgroup analysis suggested that in septic patients with HFrEF, positive fluid balance of CFB-day1 might be a risk factor of mortality. Therefore, we propose that on the first day of fluid resuscitation, the therapy should be considered according to the LVEF level.

Furthermore, diuretics or CRRT should be utilized as much as possible on the second or third day to achieve a negative fluid balance.

In exploring the connection between fluid management and prognosis, daily absolute volume of fluid balance is often assessed, which does not adequately capture the dynamic changes in fluid accumulation. Shen et al. were the first to define Fluid Accumulation Index (FAI) to capture the dynamic state of fluid accumulation. Their research indicated that the effect of FB on mortality among septic patients was mediated by FAI, whereas FB

did not show such an association Shen et al. (2021). The current definition of fluid overload remains ambiguous. However, most researchers define a cumulative fluid volume exceeding 10% of body weight as fluid overload Sakr et al. (2017), Casas-Aparicio et al. (2018). Our research also used this definition to distinguish the fluid balance status.

CONCLUSIONS

In septic patients with HFpEF, positive fluid balance of CFB-day1 might improve the prognosis of patients. However, from the second day, fluid overload was associated with poor prognosis. Therefore, we propose that on the first day of fluid resuscitation, the therapy should be considered according to the LVEF level. Furthermore, diuretics or CRRT should be utilized as much as possible on the second or third day to achieve a negative fluid balance.

LIMITATIONS

However, our study also had several limitations. Firstly, as this study was retrospective in nature, it was unable to definitively establish causality. Despite the use of multivariate adjustment and subgroup analyses, there was still a possibility of residual confounding factors influencing the clinical outcomes. This also influenced the variables utilized for the adjustments; therefore, the variables that had P values of less than 0.10 in the univariate analysis were incorporated into the multivariate analysis. Secondly, this study only used LVEF to evaluate left ventricular systolic function and ignored the evaluation of diastolic function and right heart function. Thirdly, this research could not distinguish the left ventricular dysfunction resulting from sepsis or prior conditions, which may limit the conclusions. Furthermore, the retrospective nature of the research hampered the evaluation of the relationship between LV function and fluid balance, as physician typically take care when giving intravenous fluids to those with LV dysfunction. As a result, these factors could be interrelated. Finally, the clinical parameters were insufficiently comprehensive, such as the source of infection, the administration of diuretics. These elements may significantly influence the accuracy of the results. Therefore, further research is essential to comprehensively explore how these bias impacts clinical outcomes.

DECLARATIONS

Ethics approval and consent to participate

The use of the MIMIC-IV database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. All patient information was anonymized, therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Data availability statement

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

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Author contributions

Conceptualization, Jian Liao; Methodology, Jian Liao; Validation, Maojuan Wang; Formal Analysis, Hong Xie; Data Curation, Dingyu Lu; Writing-Original Draft Preparation, Jian Liao; Writing-Review & Editing, Hong Xie; Supervision, Dingyu Lu. All authors read and approved the final draft.

Competing interests

The authors declare no competing interests.

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