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Original Research Article

Outcomes of a Positive Fluid Balance on Mortality in Patients with Septic Shock at the Intensive Care Unit of a Tertiary Hospital in Cameroon: A 4-Years Retrospective Study

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Abstract: ***Background:*** Early aggressive fluid resuscitation is beneficial in the management of septic shock (SS). Recent studies show that more positive or higher fluid balances after initial resuscitation in septic shock are associated with adverse outcomes. This study aimed to determine the impact of fluid balance on intensive care unit (ICU) mortality, and length of stay (LOS). ***Methods:*** A 4-year longitudinal retrospective study was conducted at the ICU of the Douala General Hospital (DGH). We reviewed file records of patients ≥ 18 years old, and with an ICU LOS of > 12 hours, admitted with a diagnosis of SS. We recorded the sociodemographic data, comorbidities, severity of illness as measured by the Sequential Organ Failure Assessment (SOFA), and modified Acute Physiologic and Chronic Health Evaluation (mAPACHE) II scores, treatment details, and patient's outcome. We followed the fluid intake and balance during the first 3 days. Data were analyzed using a the software SPSS version 26. Survival analysis was done for different fluid balance quartiles. Multivariate logistic regression was used to control for confounders. Statistical significance was set at a p-value < 0.05. ***Results:*** 99 patients with an ICU mortality rate of 60.6% were recruited. Survivors had a significantly higher mean cumulative fluid intake within 48h (4.76 vs 3.64 L, p = 0.007) and 72 h (6.45 vs 4.53 L, p = 0.002). Non-survivors had a significantly higher mean fluid balance within 24 h (1.81 vs 0.64 L, p < 0.001) and cumulative fluid balance within 72 h (3.00 vs 1.45 L, p = 0.005). In multivariate logistic regression, mean cumulative fluid intake and fluid balance within 72 h were independently associated with ICU mortality (p = 0.016 (OR: 0.999) and 0.005 (OR; 1.001) respectively). There was no significant association between fluid balance and ICU LOS. ***Conclusions:*** Aggressive fluid resuscitation in septic shock is beneficial; however, a more positive fluid balance cumulatively over 3 days is associated with increased ICU mortality. There is no significant association between fluid balance and ICU LOS.

Keywords: Septic shock, fluid balance, resuscitation, mortality, length of stay.

INTRODUCTION

Despite drastic improvements in the knowledge of the pathogenesis, diagnosis, and management of sepsis and septic shock (SS), the mortality of septic patients remains high in the range of 30-50% in severe sepsis and increasing to 50-87% in septic shock patients [1]. The surviving sepsis campaign bundle recommends the use of intravenous (IV) fluids, along with antibiotics, source control, vasopressors, and inotropic agents for the

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early management of SS [2]. This Early Goal-Directed Therapy (EGDT), which stresses the importance of aggressive fluid resuscitation, has been used for severe sepsis and SS in the ICU and provides significant benefits concerning the outcome of patients with severe sepsis and SS. In a prospective randomized study of the EGDT, it was noticed that at the first 6-hour mark, the EGDT group who received larger fluid volumes, compared to the standard group were associated with significantly lower mortality [3]. However, recent evidence shows that a more positive fluid balance following resuscitation in SS patients is associated with increased mortality, ICU, and hospital length of stay [4–7]. This implies an emphasis on fluid balance as well. As yet, no recommendations exist as to when to discontinue or reduce the IV fluids' administration rate during the resuscitation of SS patients [8]. Though the patient outcome is not solely dependent on fluid resuscitation in SS patients, the effects of fluid balance on this population which is usually at risk of fluid overload are relevant. To improve management guidelines in SS, we aimed to assess the outcome; mortality and length of stay (LOS) of a more positive fluid balance in ICU patients with SS by conducting a 4-year retrospective cohort study at a tertiary hospital in Cameroon.

MATERIALS AND METHODS

A retrospective longitudinal study was conducted at the Douala General Hospital (DGH) including patients ≥ 18 years old, who were admitted to the ICU between January 2018 to December 2021 with a diagnosis of SS, and an ICU LOS ≥ 12 hours. Patients with mixed forms of shock and incomplete files were excluded from this study and convenience sampling was used. Ethical reference 2022/1597-01/UB/SG/IRB/FHS was obtained from the Institutional Review Board (IRB) of the Faculty of Health Sciences (FHS), University of Buea (UB), Cameroon, and authorizations from the DGH too. For all patients, data concerning demographics, preexisting conditions, the severity of illness as measured by the sequential Organ Failure Assessment (SOFA) and the modified Acute Physiologic and Chronic Health Evaluation II (mAPACHE) scores, treatment details, fluid balance, and outcome of patients. Fluid intake and balance were followed during the first 72 hours. Data were analyzed using SPSS 26. The primary outcome was ICU mortality and the secondary outcome was ICU length of stay. Categorical variables were expressed as frequency distributions. Continuous variables were reported as means with standard deviation, and the median with an interquartile range. The Chi-square test was used to compare differences between groups for qualitative variables. The Mann-Whitney test was used for quantitative variables that were not normally distributed. The ANOVA test was used for quantitative variables with more than two categories. The fluid balance was divided into quartiles for statistical analysis [5]. Kaplan-Meier curves were used to evaluate mean fluid balance within 24 h and cumulative fluid balance within 72 h and mean fluid balance quartiles were then compared with the log-rank test. Variables that were significant to the $p < 0.2$ on bivariate analysis were entered into the multivariable logistic regression analysis. Multivariate logistic regression was done with backward elimination to determine the variables independently associated with ICU mortality. Cox proportional hazard models were used to select factors associated with ICU LOS. Age, mAPACHE II, and SOFA scores were adjusted. All statistics were two-tailed and the value $p < 0.05$ was statistically significant.

RESULTS

During the 4 years, 99 patients diagnosed with SS were enrolled in this study. The ICU mortality was 60.6%. Males were 51 (52%). The median age was 59 (38-65) years old. There was no significant age difference between survivors and non-survivors. Non-survivors statistically had greater severity of illness; SOFA score of 8.75 (2.30) vs 6.28 (2.20), $p < 0.001$ and mAPACHE II score of 14.72 (4.55) vs 9.64 (4.96), $p < 0.001$ with a greater proportion of those mechanically ventilated too (Table 1). The fluid balance was more positive in the first 24hours with a cumulative value of fluid intake greater than 5l at the 72nd hour. Non-survivors had a significantly higher mean fluid balance (FB) within 24 h and cumulative fluid balance (CFB) within 72 h (1.81 vs 0.64 L, and 3.00 vs 1.45 L, $p < 0.001$ and 0.005 respectively). Survivors statistically had a higher cumulative mean fluid intake (CFI) within 48 and 72 h (4.76 vs 3.64 L, and 6.45 vs 4.53 L, $p = 0.007$ and 0.002 respectively) (table 2). After multivariate logistic regression, the cumulative fluid intake and balance within 72hours, patient's status and patients coming from other hospitals were factors associated to mortality the following factors were found to be independently associated with ICU mortality (table 3).

Table 1: Baseline characteristics and fluid volumes of patients with septic shock in the ICU

Variables	All Patients (*n*=99)	Survivors (n=39)	Non-Survivors (n=60)	*p*
Male *n*, (%)	51	22	29	0.28
Age (IQR)	59 (38-65)	58 (30-65)	59 (49.25-65.75)	0.27
mAPACHE II score	12.72 (5.3)	9.64 (4.96)	14.72 (4.55)	<0.001
SOFA score	7.78 (2.6)	6.28 (2.20)	8.75 (2.30)	<0.001
ICU Length of Stay (SD)	3 (1.5)	5.62 (6.63)	3.51 (4.68)	0.07

Source of ICU admission *n*, (%)				
General wards	46 (46.5)	16 (41.0)	17 (28.3)	0.19
Emergency room	33 (33.3)	18 (46.2)	28 (46.7)	0.96
Other hospitals	20 (20.2)	5 (12.8)	15 (25)	0.14
Community-acquired infection *n*, (%)	72 (73)	28 (71.8)	44 (73.3)	0.87
Source of infection *n*, (%)				
Respiratory	40 (40.4)	17 (43.6)	23 (38.3)	0.60
Gastrointestinal	26 (26.3)	11 (28.2)	15 (25)	0.72
Integumentary	19 (19.2)	6 (15.4)	13 (21.7)	0.44
Primary bacteremia	17 (17.7)	5 (12.8)	12 (20)	0.36
Urinary	3 (3)	1 (2.6)	2 (3.3)	0.83
Mechanical ventilator support *n*, (%)	60 (60.6)	16 (41)	44 (73.3)	0.001

n: number of participants; IQR: Interquartile range;SD: standard deviation; mAPACHE: modified acute physiologic and chronic health evaluation II; SOFA: sequential organ failure assessment

Table 2: Fluid assessment across survivors and non survivors

VOLUME (L)	ALL PATIENTS N (SD)	SURVIVORS N (SD)	NON-SURVIVORS N (SD)	*P*
Fluid balance				
0 to 24 h	0.64 (1.46)	0.64 (1.81)	1.81 (1.29)	**0.000**
24 to 48 h	0.51 (1.32)	0.51 (1.49)	0.76 (0.16)	0.374
48 to 72 h	0.29 (0.91)	0.29 (0.99)	0.44 (0.86)	0.419
Cumulative fluid intake				
Within 24 h	2.42 (1.03)	2.47 (0.89)	2.39 (1.13)	0.731
Within 48 h	4.08 (2.03)	4.76 (1.85)	3.64 (2.03)	**0.007**
Within 72 h	5.29 (3.06)	6.45 (2.70)	4.53 (3.06)	**0.002**
Cumulative fluid balance				
Within 72 h	2.39 (2.72)	1.45 (2.70)	3.00 (2.43)	**0.005**

SD: standard deviation

Table 3: Factors independently associated with ICU mortality

Variable	*p*	OR
Patients from other hospitals	0.03	0.081
SOFA score	0.06	1.396
mAPACHE II score	0.02	1.295
Mean cumulative fluid intake within 72 h	0.002	0.999
Mean cumulative fluid balance within 72 h	0.005	1.001

Kaplan-Meier survival curves, estimated by mean fluid balance (FB) within 24 h and mean cumulative fluid balance (CFB) within 72 h are shown in Figures 1 and 2 below respectively. Patients with excessive fluid balance (quartile 1 < 2 < 3 < 4) within 0 to 24 h showed lower survival rates in the ICU (11.5, 10, 8, and 3.7 days respectively). Significant differences between the quartiles of fluid balance within 0 to 24 h and cumulative fluid balance within 72 h (0.03 and 0.02 respectively) were deduced from the log-rank test. A cumulative fluid balance within 72hours closer to zero ensure showed better survival time (quartile 2 with 10.3 days survival time) (table 4).

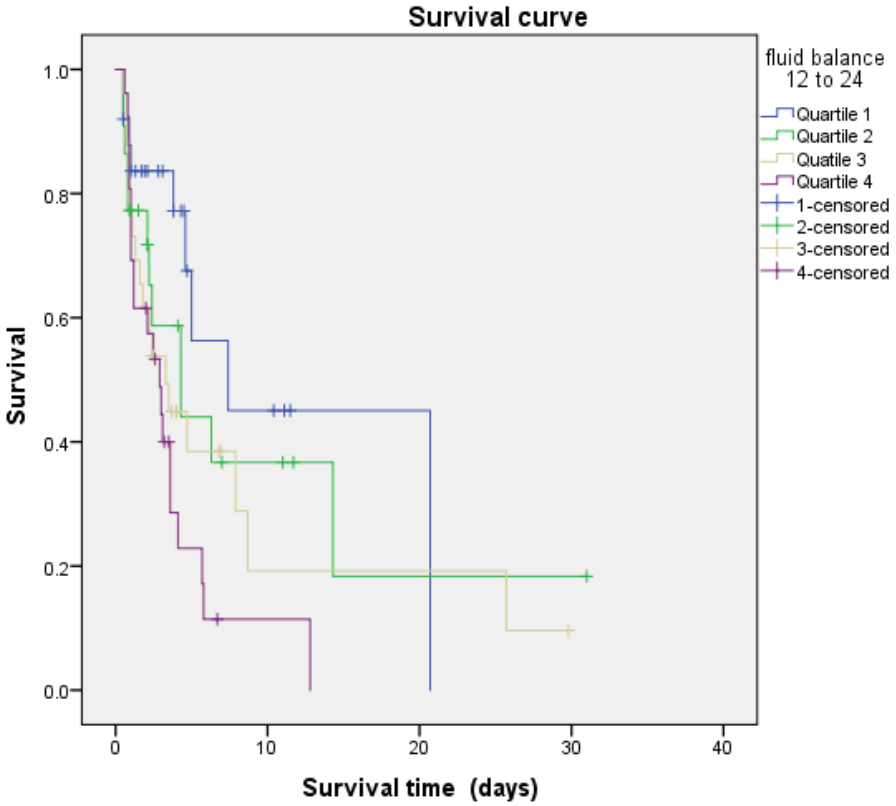

Figure 1: Kaplan-Meier survival curve for quartiles of fluid balance within 24 h

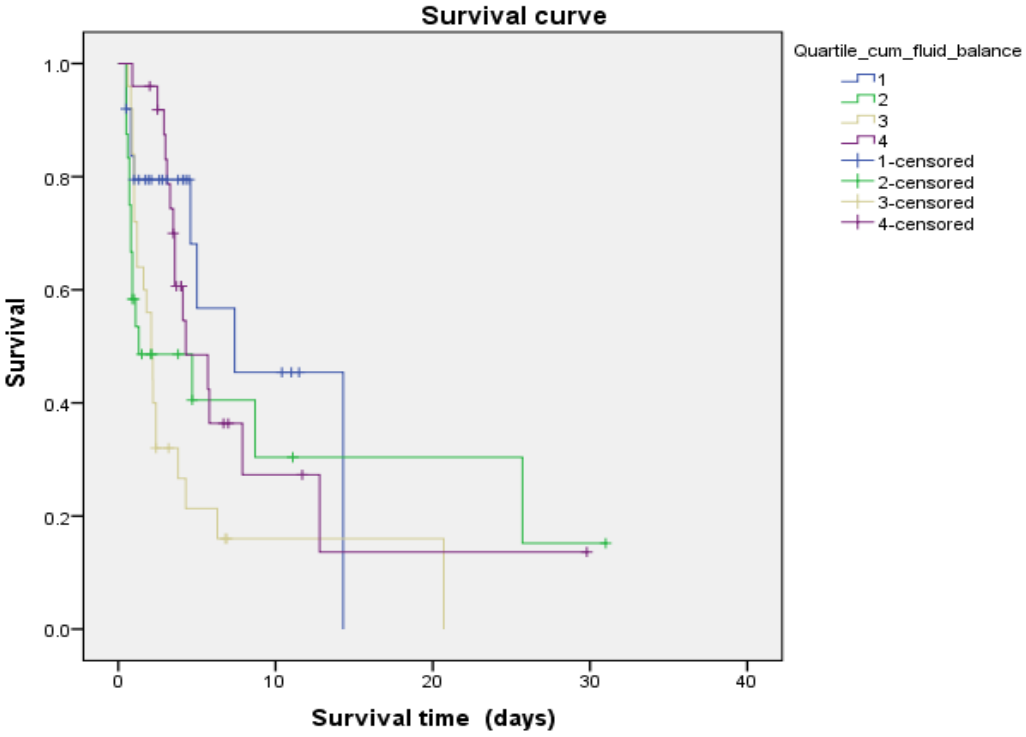

Figure 2: Kaplan-Meier survival curve for fluid quartiles of mean cumulative fluid balance within 72 h

Table 4: Mean survival time and LOS at the ICU for fluid quartiles for fluid balance within 24 h and 72 h

Fluid quartiles (L)	Mean survival time (days)	Mean LOS at the ICU (days)
FB: 0 to 24 h		
1 (-2.85-0.61)	11.5	4.5
2 (0.70-1.15)	10	5.1
3 (1.20-2.25)	8	5
4 (2.40-4.80)	3.7	3
CFB within 72 h		
1 (-7.50-0.75)	8.6	4.1
2 (0.80-2.13)	10.3	4.4
3 (2.17-3.90)	5.1	3.2
4 (3.96-10.15)	9	5.7

DISCUSSION

Fluid resuscitation is inevitable in the management of SS patients. In this study, the association between fluid balance and outcomes in SS patients was explored. Males were more affected, the median age was 59 years, with a mortality rate of 60.6 %. There were no significant age or sex differences between ICU survivors and non-survivors. However, non-survivors had greater severity of illness measured by the SOFA and mAPACHE II scores. Kooonrangsesomboon *et al.,* [5] in Thailand and Acheampong *et al.,* [9] in Belgium reported similar results however but they had lower mortality rates of 47 and 34 % respectively. These differences could exist because, in our study, we excluded patients with ICU LOS of less than 12 hours. We found a dose-response relationship between fluid balance within 24 hours and ICU mortality. Non-survivors had a significantly higher mean fluid balance within 0 to 24 h and cumulative fluid balance within 72 h. However, on multivariate logistic regression analysis, apart from factors like the severity of illness, mean cumulative fluid balance within 72 h from the onset of SS was a significant predictor of ICU mortality. Several other studies show similar results [5,6,8].

Fluid resuscitation in SS patients according to the EGDT remains controversial. In our study, within 24 h there was no significant difference in the amount of fluid received between survivors and non-survivors, however, survivors received more fluid than non-survivors within 48 and 72 h. One could say that receiving more fluid initially during resuscitation in SS patients is beneficial, however, applying conservative fluid strategies over the next few days is key to improved outcomes. A prospective multicenter observational study [10] reported that patients who initially received more fluid had improved survival compared to patients who received less, despite comparable severity of illness on admission. Lee *et al.,* [11] also reported in a retrospective study that the initial fluid volume received was greater in survivors than in non-survivors. Another study [12] sort out that patients with SS complicated by acute respiratory failure managed with a combination of adequate initial fluid resuscitation and conservative fluid strategies in the subsequent days had lower in-hospital mortality. Fluid accumulation is common in critically ill patients due to aggressive hemodynamic resuscitation. Hence, when fluid accumulation is likely to contribute to adverse patient outcomes fluid removal strategies are indicated.

Several mechanisms may explain the relationship between more positive fluid balance and adverse outcomes in SS patients. Positive fluid balance could increase extravascular lung water, and prolong mechanical ventilator days, hence increasing the occurrence of ventilator-associated pneumonia [13]. In our study, non-survivors were significantly more mechanically ventilated than survivors. This could be explained by the greater severity of illness in non-survivors. A similar study conducted [14] in the same ICU, reported that mechanical ventilation was significantly associated with ICU mortality in SS patients. Also, a more positive fluid balance may increase intravascular pressure and vascular permeability, causing fluid leakage, resulting in tissue oedema, decreased oxygenation index, increased intra-abdominal pressure, and increased mortality [15,16]. Furthermore, a more positive fluid balance has been associated with delayed renal recovery and an increased risk of acute kidney injury [17,18].

Our study had some strengths and limitations that have to be considered when interpreting these results. This being a retrospective study we were unable to determine a causal relationship between fluid balance and outcomes. Also, we did not estimate the amount of early fluid administration within 3-6 hours from the onset of septic shock. The results of this study, given its single-centered nature, may not be generalizable to other ICUs. The single-centre nature of our study may be seen as a limitation. Still, it could also be a strength as it limits variability in patient management as different centres may have different fluid management protocols. This is among the few studies in Cameroon and Africa that explore the association between fluid balance and outcomes in SS patients.

CONCLUSION

Aggressive fluid resuscitation in SS is beneficial however, a more positive fluid balance cumulatively over 3 days from the onset of septic shock is associated with increased ICU mortality. There is no significant correlation between more positive fluid balance and ICU lengths of stay.

Ethics approval and consent to participate: Ethical approval from the University of Buea Cameroon, consent to participate from each patients.

Consent for publication: Consent from all the authors.

Conflict of interest: The authors have not declared any conflict of interests Consent for publication.

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Author's contributions: all the authors contributed to the study.

- Study design, data collection, review, analysis, discussion: Metogo Mbengono Junette, Taku Angwa Samuel, Mbapah Tasha Lesli, Anyope Onoke Kevin
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