Research Article

Impact of positive fluid balance on mortality and length of stay in septic shock patients

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Abstract

Background: Fluid management is important in critically patients. The aim of this study was to determine the relationship between fluid balance and adverse outcomes of septic shock. **Methods:** A retrospective study was conducted in the medical Intensive Care Unit (ICU) of a tertiary university hospital in Thailand, over a 7-year period. **Results:** A total of 1048 patients with an ICU mortality rate of 47% were enrolled. The median cumulative fluid intake at 24, 48, and 72 h from septic shock onset were 4.2, 7.7, and 10.5 L, respectively. Nonsurvivors had a significantly higher median cumulative fluid intake at 24, 48, and 72 h (4.6 vs. 3.9 L, 8.2 vs. 7.1 L, and 11.4 vs. 9.9 L, respectively, $P < 0.001$ for all). Nonsurvivors also had a significantly higher cumulative and mean fluid balance within 72 h (5.4 vs. 4.4 L and 2.8 vs. 1.6 L, $P < 0.001$ for both). In multivariate logistic regression analysis, mean fluid balance quartile within 72 h, was independently associated with an increase in ICU and hospital mortality. Quartile 3 and 4 have statistically significant increases in mortality compared with quartile 1 (odds ratio [95% confidence interval] 3.04 [1.9–4.48] and 4.16 [2.49–6.95] for ICU mortality and 2.75 [1.74–4.36] and 3.16 [1.87–5.35] for hospital mortality, respectively, $P < 0.001$ for all). In addition, the higher amount of mean fluid balance was associated with prolonged ICU stays. **Conclusions:** Positive fluid balance over 3 days is associated with increased ICU and hospital mortality along with prolonged ICU stays in septic shock patients.

Keywords: Fluid, fluid balance, mortality, prognostic factor, septic shock

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Introduction

Septic shock is a life-threatening condition with a high mortality rate.[1-3] It requires aggressive treatment and close monitoring in the Intensive Care Unit (ICU). Intravenous fluids, vasopressor administration, early and appropriate antibiotic therapy, source of infection control as well as ventilator support are essential for the treatment of these patients.[2,4]

Intravenous fluid administration is important for stabilizing hemodynamic status and improving tissue oxygenation. However, once there has been adequate fluid resuscitation, further fluid administration may increase intravascular pressure along with vascular permeability, causing fluid leakage which results in tissue edema, decreased oxygenation index, increase intra-abdominal pressure and increased mortality.[1,5-8]

Rivers *et al*. reported a prospective, randomized study of the early goal-directed therapy (EGDT) in severe

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sepsis and septic shock patients.[9] At the first 6 h mark, the EGDT group who received larger fluid volumes, compared to the standard group were associated with a significantly lower mortality. Consequently, aggressive fluid resuscitation, during the first 6 h, has been essential for the management of patients with septic shock.[2] The observational cohort studies of severe sepsis and septic shock patients have demonstrated the benefit of aggressive fluid management. Higher fluid volume resuscitation in the first 3 h, and during the first 3 days of these patients was associated with a significantly lower mortality.[10,11] However, several studies showed contrary results. In a large survey of patients with sepsis, a positive fluid balance was the strongest prognostic factor of ICU mortality.[1] An analysis of the septic shock patients from the Vasopressin and Septic Shock Trial (VASST) showed that a more positive fluid balance at 12 h and cumulatively over 4 days was associated with an increased risk of mortality.[6] A recent retrospective study showed that excessive positive fluid balance was an independent risk factor for mortality in severe sepsis patients.[12,13] Thus, the amount of intravenous fluid administration in septic shock management is still highly controversial.

We, therefore, conducted this study to determine the relationship between fluid balance within 72 h after the onset of septic shock, ICU, and hospital mortality along with the length of stay in the ICU.

Methods

This study was conducted at a tertiary referral university teaching hospital in Southern of Thailand. We studied retrospectively, consecutive patients admitted with septic shock to mixed medical-coronary ICU from January 2005 through until December 2011. Patients with a length of stay <24 h were excluded from this study. This study was approved by the Institutional Ethics Committee.

Definitions

Infection was identified based on clinical history, physical examination, laboratory findings as well as the administration of antibiotics. It was defined according to the International Sepsis Forum Consensus Conference.[14] Septic shock was defined as systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg for a duration of at least 1 h, despite adequate fluid resuscitation or the use of any vasopressors. The onset of septic shock was defined as; the time of vasopressor initiation. Severity was evaluated using the Acute Physiology and Chronic Health Evaluation II (APACHE) II[15] and the Sequential Organ Failure Assessment (SOFA) scores.[16] Organ failure was defined as; a SOFA score of >2 for each involved organ.[1] Community-acquired infection was defined as: Manifestation of infection before or within 48 h after admission, whereas hospital-acquired infection manifested later than 48 h after hospital admission. Acute respiratory distress syndrome (ARDS) was defined according to Berlin definition.[17]

Fluid intake was calculated as the sum of any intravenous fluid and oral feeding, which patients received from the onset of septic shock. Fluid output included urinary output and other outputs such as drainage, thoracentesis, paracentesis, and ultrafiltration. Fluid balance was calculated as the difference between total fluid intake and total output within the first 3 days of admission to the ICU. The mean fluid balance was the calculated for each day during a 3-day admission to the ICU.

Data collection

Our data were derived from a previous prospectively registered data of severity score and sepsis. Patients demographic, laboratory, and clinical data were gathered. This included: Age, gender, source of ICU admission, severity of illness (based on the APACHE II and SOFA scores), site of infection, positive cultures, ARDS, vasopressor use, ICU and hospital outcome, and ICU lengths of stay. The medical electronic database for fluid intake and output, during the first 3 days of an ICU stay was retrospectively reviewed.

Statistical analysis

The primary outcome was ICU mortality, while the secondary outcomes were hospital mortality and ICU lengths of stay. Categorical data were expressed as frequency distributions, using the Chi-squared test to determine if differences existed between groups. Continuous data were reported as; the median with interquartile range and compared by the Wilcoxon's rank sum test. Fluid intake and fluid balance were divided into quartiles for statistical analysis. Kaplan–Meier curves were used to evaluate 24-h fluid intake, and mean fluid balance quartiles then compared with the log-rank test. Variables found to be significant to $P < 0.2$ on univariate analysis were entered into the multivariate logistic regression analysis. We performed multivariate logistic regression, with backward elimination, to determine the variables independently associated with the ICU and hospital mortality. Cox proportional hazards model was used to select factors associated with ICU lengths of stay. The multicollinearity was assessed by using a variance inflation factor and any variable with variance factors >2.5 were rejected from the model.[18]

The mean fluid balance was used in the models due to high multicollinearity with cumulative fluid balance. All statistics were two-tailed and the value $P < 0.05$ was considered to be statistically significant. The analyses were performed using R 3.1 software and Stata 7 software (Stata Corporation, College Station Tx, USA).

Results

During the 7-year period 1048 patients, diagnosed with septic shock, were enrolled in this study. The ICU and hospital mortalities were 47% and 57.8%. The baseline characteristics in addition to the fluid volumes are shown in Table 1. Nonsurvivors were statistically younger had greater severity of illness (measured by the APACHE II and SOFA scores), shorter lengths of ICU stay, fewer community-acquired infections, along with a higher frequency of ARDS [Table 2]. Nonsurvivors had a significantly higher median cumulative fluid intake within 24, 48, and 72 h, cumulative fluid balance and mean fluid balance within 72 h [Table 2]. Nonsurvivors also received daily fluid intakes at 48 and 72 h at a higher rate than survivors (3.69 [2.71–4.9] vs. 3.11 [2.27–4.13]) and (3.36 [2.44–4.27] vs. 2.61 [2–3.38]), $P < 0.001$ for both [Figure 1]. The fluid intake at 24 h was significantly higher in patients with nosocomial-acquired septic shock than those with community-acquired septic shock (4.38 [3.32–5.72] vs. 4.1 [3.08–5.37], $P = 0.02$). However, cumulative mean fluid balance within 72 h was not clinically significant between these patients (2.07 [1.4–3.38] vs. 1.99 [0.99–3], $P = 0.02$). Mean fluid intake at 24 h and cumulative mean fluid balance within 72 h were comparable between septic shock patients with or without ARDS (4.05 [3.24–5.28] vs. 4.2 [3.12–5.68] and 1.98 [1.23–3.09] vs. 2.04 [1.14–3.14], respectively).

Table 1: Baseline characteristics and fluid volumes

Variables	All patients (*n*=1048)
Age (year)	59 (44.75-73)
Male *n*, (%)	611 (58.3)
APACHE II score	27 (21-34.5)
SOFA score	10 (8-13)
ICU stays	4 (2-8)
Source of ICU admission *n*, (%)	
General wards	614 (58.6)
Emergency room	339 (32.3)
Other hospitals	95 (9.1)
Community-acquired infection *n*, (%)	625 (59.6)
Source of infection *n*, (%)	
Respiratory tract	499 (47.6)
Gastrointestinal	166 (15.8)
Primary bacteremia	96 (9.2)
Urinary tract	80 (7.6)
Positive hemoculture *n*, (%)	354 (33.8)
ARDS *n*, (%)	216 (20.6)
Mechanical ventilator support *n*, (%)	954 (91)
Renal replacement therapy *n*, (%)	360 (34.5)
Central venous catheterization *n*, (%)	880 (83.9)
Low dose corticosteroid *n*, (%)	463 (44.2)
Cumulative fluid volume (L)	
Within 24 h	4.2 (3.2-5.6)
Within 48 h	7.7 (5.9-9.8)
Within 72 h	10.5 (8.3-13.2)
Fluid balance within 72 h (L)	5.1 (2.7-3.1)
Mean fluid balance within 72 h (L)	2.0 (1.2-3.1)

Unless otherwise indicated, numbers are given as medians with interquartile range. APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; ICU: Intensive Care Unit; IQR: Interquartile range; SOFA: Sequential Organ Failure Assessment

Kaplan–Meier survival curves, estimated by 24-h fluid intake and mean fluid balance within 72 h, are shown in Figures 2 and 3, respectively. Patients with excessive fluid balance showed a lower survival rate. At 24 h, the risk of survival in quartile 4 was significantly lower than in quartile 1, 2, and 3. ($P < 0.001$, Figure 2). The median survival time for 24 h fluid quartile 1, 2, 3, and 4 was 15, 10, 10, and 6 days, respectively. Similarly, cumulative fluid balance within 72 h, quartile 4 showed a significant increase in mortality than other quartiles ($P < 0.001$, Figure 3). The patients in quartile 4 of cumulative fluid balance within 72 h had a shorter median survival time than patients in quartile 3, 2, and 1 (2, 6, 14, and 16 days, respectively).

Univariate analysis showed that several factors were associated with a significantly higher ICU mortality in patients with septic shock these being: Age ($P = 0.021$), APACHE II score ($P < 0.001$), SOFA score ($P < 0.001$), ICU stays ($P < 0.001$), hospital-acquired infection ($P < 0.001$), urinary tract infection ($P < 0.001$), primary bacteremia ($P < 0.001$), positive hemoculture ($P = 0.022$), ARDS ($P < 0.001$), vasopressor use ($P = 0.027$), fluid intake within the first 24 h ($P < 0.001$), 48 h ($P < 0.001$), and 72 h ($P < 0.001$), and mean fluid balance within 72 h ($P < 0.001$). However, after multivariate logistic regression analysis parameters showed independent predictors of increased risk of ICU or hospital mortality are presented in Table 3. Mean cumulative fluid balance at day 3 shows a strong impact on the ICU and hospital mortality. Quartiles 3 and 4 have statistically significant increases in both the ICU and hospital mortality, compared with quartile 1 [Table 3]. However, quartile 2 showed a nonsignificant trend to increased mortality. In addition to this, the higher amount of mean fluid balance within 72 h was associated with an increase in ICU stays (quartile 3 hazard ratio 2.19, 95% confidence interval [CI]: 1.62–2.96, and quartile 4 h 2.54, 95% CI: 1.86–3.48, $P < 0.001$ for both) when adjusting for age, APACHE II, SOFA scores, and comorbidities.

Discussion

In this study, the association between fluid volume and unfavorable outcomes in patients with septic shock

Table 2: Clinical characteristics of ICU survivors and non-ICU survivors

Variables	ICU survivors (*n*=555)	Non-ICU survivors (*n*=493)	*P*
Age (year)	62 (47-73.5)	56 (42-72)	0.016
Male *n*, (%)	327 (58.9)	284 (57.6)	0.713
APACHE II score	23 (18-27)	34 (28-40)	<0.001
SOFA score	8.6 (3.3)	12.2 (3.4)	<0.001
ICU stays (days)	5 (2-9)	2 (1-7)	<0.001
Sources of ICU admission *n*, (%)			
General wards	289 (52.1)	325 (65.9)	<0.001
Emergency room	212 (38.2)	127 (25.8)	<0.001
Other hospitals	54 (9.7)	41 (8.3)	0.4
Hospital-acquired infection *n*, (%)	178 (32.1)	245 (49.7)	<0.001
Source of infection *n*, (%)			
Respiratory tract	250 (45)	249 (50.5)	0.088
Gastrointestinal	87 (15.7)	79 (16)	0.945
Primary bacteremia	34 (6.1)	62 (12.6)	<0.001
Urinary tract	63 (11.4)	17 (3.4)	<0.001
Positive hemoculture *n*, (%)	171 (30.8)	185 (37.5)	0.026
ARDS *n*, (%)	80 (37)	136 (62.9)	<0.001
Cumulative fluid volume (L)			
Within 24 h	3.92 (2.94-5.16)	4.64 (3.48-5.98)	<0.001
Within 48 h	7.08 (5.53-9.24)	8.23 (6.42-10.96)	<0.001
Within 72 h	9.88 (8.0-12.5)	11.43 (9.17-14.89)	<0.001
Fluid balance within 72 h (L)	4.38 (1.84-6.59)	5.42 (3.49-8.12)	<0.001
Mean fluid balance within 72 h (L)	1.57 (0.74-2.26)	2.83 (1.81-4.04)	<0.001
Quartile 1	−1.67-0.74	−1.58-1.81	<0.001
Quartile 2	0.75-1.57	1.82-2.83	<0.001
Quartile 3	1.58-2.26	2.84-4.04	<0.001
Quartile 4	2.27-7.8	4.05-15.6	<0.001

Unless otherwise indicated, numbers are given as medians with interquartile range. APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment

Table 3: Multivariate logistic regression analysis of independent risk factors for ICU and hospital mortality

Variables	ICU mortality OR (95% CI)	*P*	Hospital morality OR (95% CI)	*P*
Mean fluid balance quartile 1	Reference		Reference	
Mean fluid balance quartile 2	1.37 (0.91-2.05)	0.13	1.44 (0.99-2.08)	0.06
Mean fluid balance quartile 3	3.04 (1.9-4.84)	<0.001	2.75 (1.74-4.36)	<0.001
Mean fluid balance quartile 4	4.16 (2.49-6.95)	<0.001	3.16 (1.87-5.35)	<0.001
APACHE II score (/point)	1.15 (1.12-1.19)	<0.001	1.16 (1.13-1.19)	<0.001
ARDS	2.72 (1.84-4.01)	<0.001	2.49 (1.69-3.68)	<0.001
Hospital-acquired infection	1.77 (1.28-2.46)	0.001	2.16 (1.57-2.98)	<0.001
SOFA score (/point)	1.06 (1.0-1.13)	0.04		
Length of ICU stay (/day)	0.97 (0.95-0.99)	0.02		

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; CI: Confident interval; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; OR: Odds ratio

was explored. We found a dose-response between 24-h fluid intake and 72-h mean fluid balance quartiles and

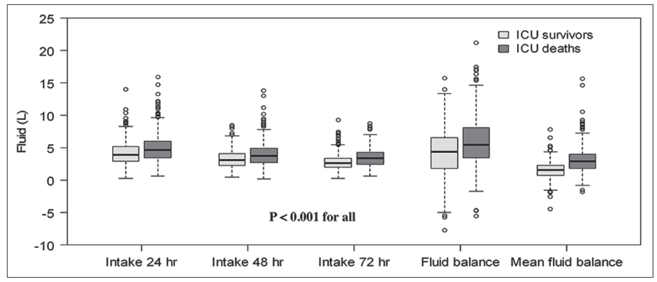

Figure 1: Box plots depicting daily fluid intake and fluid balance within 72 h

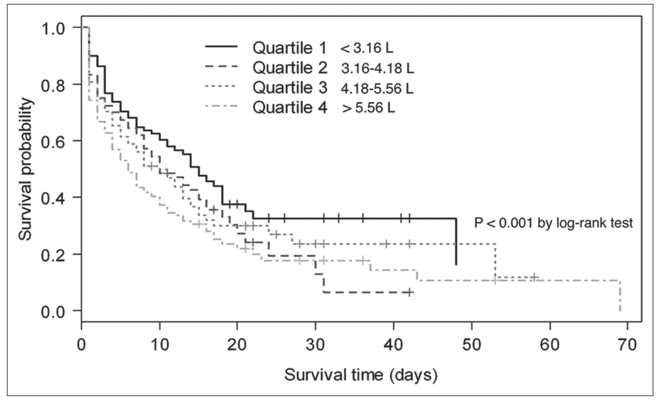

Figure 2: Kaplan–Meier survival curve for 24-h fluid intake quartiles

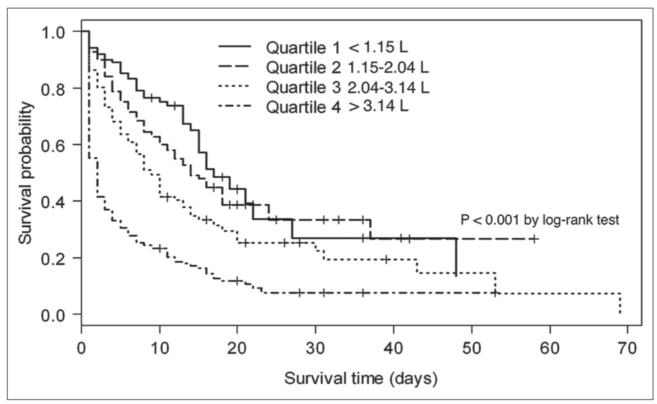

Figure 3: Kaplan–Meier survival curve for mean fluid balance quartiles within 72 h

ICU mortality. Whereas multivariate logistic regression analysis indicated that only mean fluid balance within 72 h of the onset of septic shock was a significantly independent risk factor for ICU and hospital mortality coupled with the increase of ICU lengths of stay.

Early and aggressive fluid resuscitation is essential for the management of patients with severe sepsis and septic shock.[2,9] However, a more positive fluid balance was associated with the adverse outcome in these patients. Two retrospective studies showed that positive fluid balance was associated with an increased mortality in patients with septic shock.[13,19] The large European study, Sepsis Occurrence in Acutely Ill Patients, demonstrated that positive fluid balance within the first 72 h of onset of sepsis did correlate with ICU mortality.[1] In the VASST trial, positive fluid balance at both 12 h and over a period of 4 days correlated significantly with increased 28-day mortality.[6] Similar to our study, quartiles of fluid balance within 72 h were associated with an increased risk of mortality in septic shock patients.

Several studies have found relationships between positive fluid balance and the worse outcome in other groups of critically ill patients. Fluid accumulation in patients with acute lung injury was associated with increased mortality[19] and the length of stay.[5] In surgical critically ill patients, excessive positive fluid balance was related to mortality[20-22] and ICU complications.[22] de Almeida *et al.* reported that positive fluid balance was independently associated with mortality in critically ill cancer patients.[23] Teixeira *et al*. established that a higher fluid balance is correlated with 28-day mortality in critically ill patients with acute kidney injury.[24]

Early and aggressive fluid resuscitation have been recommended for management in septic shock patients.[2] Several studies have demonstrated that aggressive fluid resuscitation during 3 and 6 h of severe sepsis and septic shock are associated with a decrease in mortality. Data from EGDT showed that the EGDT group, who received larger fluid volumes within the first 6 h was associated with significantly lower 60-day mortality.[9] Recent retrospective study found that higher fluid resuscitation within the first 3 h is associated with a decrease in hospital mortality in severe sepsis and septic shock.[11] Cumulative fluid accumulation is common in critically ill patients due to aggressive hemodynamic resuscitation. However, after hemodynamic stabilization, further fluid administration depended on the individual basis of physical examination, blood chemistry, and clinical course.[7,25] Fluid removal is indicated when fluid accumulation contributes or is likely to contribute to patient morbidity. Intravenous diuretics or continuous ultrafiltration should be used to promote negative fluid balance.[25,26] Therefore, intensivists must find a balance among fluid resuscitation, hemodynamic stability, and organ perfusion while avoiding excessive fluid accumulation.

This study demonstrated that excessive fluid balance correlated with prolonged ICU stays when adjusted with severity of illness and comorbidities. Our results are consistent with previous studies conducted on other groups of critically ill patients. Stein *et al.* found a significant association between fluid overload and the length of the ICU stay in cardiac surgical patients.[27] Fluid and catheter treatment trial showed that conservative fluid management shorted duration of ICU stays in acute lung injury patients.[5]

There are several mechanisms for explaining the correlation of positive fluid balance and adverse outcomes in sepsis patients. Positive fluid balance could increase extravascular lung water,[28] prolong mechanical ventilator days,[5] and contribute to the occurrence of ventilator-associated pneumonia. In addition, the positive fluid balance could also result in intra-abdominal hypertension along with abdominal compartment syndrome contributing to the development of organ dysfunction.[7,28] Furthermore, positive fluid balance is associated with delayed renal recovery[29,30] and increased risk of acute kidney injury.[27]

Our study included a larger number of septic shock patients with higher disease severity than previous reports.[6,10,12,13] However, this study has some limitations. First, this being a retrospective study, we were unable to determine a causal relationship between fluid balance and outcomes. Severity of illness, hemodynamic monitoring techniques and endpoints, types of fluid, and fluid management protocol may be possible confounders and may not be fully accounted for in are retrospective analysis. Hence, we would suggest further randomized controlled trials, so as to best determine the fluid balance in the fluid management of patients with septic shock. Second, this study was performed in the mixed medical-coronary ICU of a tertiary university teaching hospital. Due to these factors the cases-mixed could be more severe, and the results may not be generalizable to other types of institutions or ICUs. Third, we did not estimate the amount of early fluid administration during first 3–6 h. Finally, the consideration of the fluid balance without considering the time of recovery from shock would change the mean cumulative fluid balance.

Conclusions

A more positive cumulative fluid balance over the period of 3 days from the onset of septic shock is associated with higher ICU and hospital mortality as well as ICU length of stay. Physicians should carefully assess the need for fluids in both early and late resuscitation periods. Restrictive fluid protocols need further study to determine the efficacy when compared to the standard fluid resuscitation protocols.

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Conflicts of interest

There are no conflicts of interest.

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