

Low fluid intake volume during the first 24 h and persistent negative fluid balance from the second day are associated with favorable prognosis for patients with sepsis

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Abstract. For patients with sepsis and septic shock, it remains controversial when to restrict fluid intake and achieve a negative fluid balance. The present study aimed to evaluate the effects of the fluid intake volume during the first 24 h as well as fluid balance for 7 days on the prognosis of sepsis or septic shock. A total of 337 patients diagnosed with sepsis or septic shock at Ruijin Hospital (Shanghai, China) were enrolled in the present retrospective study. Patients with a low fluid intake volume during the first 24 h (fluid intake, 28.1±10.6 ml/kg) had lower in-hospital mortality rates (18.0 vs. 27.3%, P=0.043) and a shorter duration of mechanical ventilation [0 (0-6) vs. 3 (0-11), P=0.025] than the high-fluid volume intake group (62.6±17.6 ml/kg). Furthermore, survivors exhibited a daily negative net fluid balance from the second day (48 h), whereas non-survivors had a daily positive net fluid balance for 7 days, where fluid balance volumes were significantly lower in survivors compared with those in non-survivors. Finally, binary logistic regression analysis was used to determine whether the mean daily fluid balance (P<0.001) and the Acute Physiologic and Chronic Health Evaluation II score (P=0.048) were independent prognostic factors for patients with sepsis or septic shock. It was indicated that a low fluid intake volume during

the first 24 h and a persistent negative fluid balance from the second day were associated with favorable outcomes. The mean daily fluid balance was an independent prognostic factor or patients with sepsis or septic shock.

Introduction

Sepsis is a severe clinical syndrome with high morbidity and mortality (1,2). Hypovolemia is common in patients with severe sepsis. Therefore, reasonable early fluid resuscitation is considered to be the cornerstone for the treatment of patients with severe sepsis and septic shock (3,4). Sepsis management has recently been divided into four distinct but associated phases: Salvage, optimization, stabilization and de-escalation. Studies have suggested that liberal fluid management is performed during the salvage and optimization phases of sepsis, while excessive fluid overload is avoided during the stabilization and de-escalation phases (5-8). Excessive fluid administration may have deleterious effects, including increased cardiac preload, tissue edema, and damage to the kidneys and liver (9). In addition, aggressive fluid administration may result in fluid overload in patients with sepsis. Certain studies have demonstrated that fluid overload may increase the mortality of critically ill patients (10-18). Therefore, restricted fluid resuscitation may be a beneficial strategy for patients with sepsis (19-22). However, the optimal time-point of commencing the restriction of fluid intake and achieve a negative fluid balance for patients with sepsis remains controversial, particularly for those with septic shock.

The present study evaluated the effects of a low fluid intake volume during the first 24 h on in-hospital mortality and other clinical outcomes in patients with sepsis or septic shock. Furthermore, the association between the optimal time point required to reach a negative fluid balance and the prognosis of sepsis was investigated. In addition, it was determined whether an early negative fluid balance was an independent prognostic factor for patients with sepsis.

Patients and methods

Patients. Ruijin Hospital, which is affiliated to the Shanghai Jiaotong University School of Medicine (Shanghai, China),

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Abbreviations: APACHE II, Acute Physiologic and Chronic Health Evaluation II; CRP, C-reactive protein; EGDT, early goal-directed therapy; EICU, emergency intensive care unit; IQR, interquartile range; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment

Key words: fluid resuscitation, sepsis, septic shock, fluid balance

is a 2100-bed, tertiary-care university teaching hospital. The present single-center, retrospective study without a pre-planned protocol was approved by the Ethics Committee of Ruijin Hospital (reference no. 2017119). Information of each patient were only obtained from the medical records. Patient consent was not required due to the retrospective nature of the present study.

Enrolment criteria. All patients admitted to the emergency intensive care unit (EICU) between January 2014 and December 2018 were included if they met the following inclusion criteria: i) Age >18 years; ii) diagnosis of sepsis or septic shock (1); and iii) duration of EICU stay >24 h. Patients who did not have sepsis or septic shock at admission but developed the condition during their hospital stay were excluded.

Patients participating in other studies, those with incomplete medical data, those who died or were discharged within 24 h and those who required emergency operations after EICU admission were excluded from the study.

Data collection. The following baseline data were collected: Demographics; departments from which each patient was admitted; concomitant diseases; C-reactive protein (CRP), lactate and procalcitonin (PCT) levels; illness severity scores, including Sequential Organ Failure Assessment (SOFA) and Acute Physiologic and Chronic Health Evaluation II (APACHE II) scores (2), during the first 24 h of admission to the EICU, were collected. In addition, data regarding the duration of EICU and hospital stay, as well as the duration of mechanical ventilation, were collected. The in-hospital mortality rate was also recorded for the study population. The primary end-point was in-hospital mortality, while secondary end-points were the duration of hospital and EICU stay and mechanical ventilation, and whether the patients had undergone continuous renal replacement therapy (CRRT) or had used vasopressors or inotropes. Sepsis and septic shock were defined according to Sepsis-3 (1).

Daily fluid intake was measured while considering intravenous (e.g., medication, blood products, parenteral nutrition), oral and enteral fluid intake. Daily fluid output included urine, ultrafiltration and fluid loss from drains and tubes; insensible water loss was not considered. The daily net fluid balance for 7 days was calculated by subtracting the daily fluid output from the daily fluid input.

First, all the patients were divided into two groups based on the mean fluid input volumes (42.8 ml/kg): The low-(<42.8 ml/kg) and high-(≥42.8 ml/kg) fluid volume groups. Subsequently, all the patients were categorized as survivors or non-survivors. Furthermore, according to the conditions of the fluid balance on the second day, the patients were divided into the positive- and negative-fluid balance groups.

Statistical analysis. The Kolmogorov-Smirnov method was used for the normality test. Data for continuous variables are expressed as the mean with standard deviation or as the median and interquartile range (IQR). Data for categorical variables are presented as numbers and percentages. Student's t-test was used for comparison of two groups and one-way ANOVA followed by the Student-Neuman-Keuls test was

used for multiple groups (>2). Pearson's Chi-square, continuity correction, Fisher's exact, or likelihood ratio tests were used for categorical variables. Unpaired t-tests were used to analyze fluid intake and output volumes and net fluid balance, as well as cumulative fluid balance, among survivors and non-survivors over 7 days. The receiver operating characteristic (ROC) curve was used to demonstrate the predictive ability of fluid intake during the first 24 h for survival probability of patients with sepsis.

Binary logistic regression analysis was applied to analyze the association between indicators with statistical significance ($P<0.05$) and in-hospital mortality. Binary logistic regression model were performed using the following indicators: SOFA score, APACHE II score, CRP level, PCT level, mean net fluid balance, type of sepsis and time of disease onset. The median value was used as the demarcation point and the above indicators were assigned. Patients were then stratified into two groups based on the demarcation points.

A two-sided $P<0.05$ was considered to indicate statistical significance. Data analyses were performed using SPSS version 18.0 (SPSS Inc.).

Results

Characteristics of the study population. The data of 405 patients treated at our department were collected. Subsequently, 16 patients whose EICU stay duration was <24 h, 31 who did not meet the latest diagnostic criteria for sepsis or septic shock, 19 with incomplete medical data and 2 who required emergency operations during their EICU stay were excluded. Finally, the clinical and laboratory data of 337 patients, 263 (78.0%) of whom survived during the EICU stay, were analyzed (Fig. 1).

Table I presents the epidemiological data. Most subjects were male (61.4%). The median age of the study population was 64 years (IQR, 47-73 years), the mean body mass index was 23.60 ± 3.79 kg/m² and more than half (59.9%) of the cases had septic shock.

Hypertension, diabetes and coronary heart disease were the most common concomitant diseases among the patients. Furthermore, the most frequent type of infection was respiratory infection (57.0%), followed by abdominal infection (14.5%; Table I).

Low fluid intake volume during the first 24 h and persistent negative fluid balance from the second day are associated with a favorable prognosis. The mean fluid intake volume of the study population was 42.8 ± 22.0 ml/kg during the first 24 h. All patients were divided into the low- and high-fluid volume groups as per the mean fluid input volume during the first 24 h. Most of the baseline data of the two groups were comparable except BMI, some comorbidities and CRP levels (Table I). Patients in the low-fluid intake volume group had higher BMI, higher proportion of hypertension and CHD, as well as lower CRP levels than those in the high-fluid intake volume group ($P<0.05$). The results suggested that the patients in the low-fluid intake volume group had lower in-hospital mortality rates (18.0 vs. 27.3%, $P=0.043$), a shorter duration of mechanical ventilation [0 (0-6) vs. 0 (0-11), $P=0.025$] and a lower proportion of patients using vasopressors or inotropes (22.7 vs. 47.6%, $P<0.001$) than those in the high-fluid volume

Table I. Characteristics of patients in the low- and high-fluid intake volume groups.

Variable	Total patients (n=337)	Fluid input <42.8 ml/kg (n=194)	Fluid input ≥42.8 ml/kg (n=143)	P-value
Sex				0.792
Male	207 (61.4)	118 (60.8)	89 (62.2)	
Female	130 (38.6)	76 (39.2)	54 (37.8)	
Age (years)	64 (47-73)	66 (51-77)	57 (41-69)	0.074
BMI (kg/m ²)	23.60±3.79	24.35±4.96	22.58±3.56	<0.001
Sepsis category				0.799
Septic shock	202 (59.9)	114 (58.8)	88 (61.5)	
Sepsis	135 (40.1)	80 (41.2)	55 (38.5)	
Origin				
EICU	227 (67.4)	137 (70.6)	90 (67.2)	0.137
Medical emergency ward	72 (21.4)	40 (20.6)	32 (22.4)	0.697
Trauma surgery ward	10 (2.9)	2 (0.0)	8 (7.0)	0.864 ^b
Other	28 (8.3)	15 (7.7)	13 (9.1)	0.655
Comorbidities				
Hypertension	145 (43.0)	95 (49.0)	50 (35.0)	0.010
Diabetes	80 (23.7)	48 (24.7)	32 (22.4)	0.614
COPD	15 (4.5)	11 (5.7)	4 (2.8)	0.319 ^b
Arrhythmia	20 (5.9)	15 (7.7)	5 (3.5)	0.104
CHD	30 (8.9)	25 (12.9)	5 (3.5)	0.003
CKD	5 (1.5)	5 (2.6)	0 (0.0)	0.075 ^a
Cerebral infarction	15 (4.5)	13 (6.7)	2 (1.4)	0.039 ^b
Source of sepsis				
Gut tract	35 (10.4)	15 (7.7)	20 (14.0)	0.063
Lung	192 (57.0)	115 (59.3)	77 (53.8)	0.320
Urinary tract	19 (5.6)	13 (6.7)	6 (4.2)	0.324
Abdomen	49 (14.5)	23 (11.9)	26 (18.2)	0.103
Skin	11 (3.3)	10 (5.2)	1 (0.7)	0.050 ^b
Blood	8 (2.4)	6 (3.1)	2 (1.4)	0.824 ^b
Not determined	13 (3.9)	7 (3.6)	6 (4.2)	0.782
Other	10 (2.9)	5 (2.6)	5 (3.5)	0.623
SOFA score	5 (4-8)	5 (4-8)	6 (4-9)	0.793
APACHE II score	11±5	11±5	12±5	0.995
Creatinine	166.1±215.6	187.5±255.6	143.7±148.3	0.075
CRP	79.2 (22.9-171.5)	72.6 (23.3-136.8)	111.0 (23.0-192.0)	0.002
PCT	2.2 (0.5-12.1)	2.1 (0.5-11.1)	3.0 (0.8-14.5)	0.281
Lactate	1.9 (1.4-2.6)	1.95 (1.41-2.67)	1.83 (1.33-2.45)	0.616
Time of disease onset (days)	7 (3-12)	7 (3-12)	6 (3-11)	0.185

Normal range of parameters: Creatinine 62-115 μ mol/l; CRP 0-10 mg/l; PCT 0-0.5 ng/ml; Lactate 0.7-2.7 mmol/l. ^aFisher's exact test. ^bContinuity correction. Values are expressed as n (%), median (25-75th percentile) or mean \pm standard deviation. BMI, body mass index; EICU, emergency intensive care unit; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CKD, chronic kidney disease; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; PCT, procalcitonin.

group (Table II). As presented in Fig. 2, the receiver operating characteristic (ROC) curve demonstrated the predictive ability of fluid intake during the first 24 h for survival probability of patients with sepsis. With a cutoff value of 49.4 ml/kg, the fluid intake during the first 24 h achieved a sensitivity of 79.7%, a

specificity of 84.4% and an area under the ROC curve of 0.902 (95% CI, 0.865-0.939).

The fluid balance of survivors and non-survivors during the 7-day period was further compared. The daily fluid intake volumes of non-survivors were higher than those of survivors

Table II. Effects of fluid administration (ml/kg) of resuscitative measures delivered during the first 24-h study period on study outcomes.

Prognostic variable	Total patients (n=337)	Fluid input (<42.8 ml/kg) (n=194)	Fluid input (≥42.8 ml/kg) (n=143)	P-value
Mean fluid input (ml/kg)	42.8±22.0	28.1±10.6	62.6±17.6	<0.0001
Survival				0.043
Yes	263 (78.0)	159 (82.0)	104 (72.7)	
No	74 (22.0)	35 (18.0)	39 (27.3)	
Duration of hospital stay (days)	21 (13-34)	21 (13-30)	22 (13-38)	0.047
Duration of ICU stay (days)	14 (7-25)	12 (7-21)	17 (9-31)	0.062
Duration of mechanical ventilation (days)	0 (0-8)	0 (0-6)	0 (0-11)	0.025
CRRT				0.078
Yes	46 (13.6)	21 (10.8)	25 (17.5)	
No	291 (86.4)	173 (89.2)	118 (82.5)	
Vasopressors or inotropes				<0.001
Yes	112 (33.2)	44 (22.7)	68 (47.6)	
No	225 (66.8)	150 (77.3)	75 (52.4)	

Values are expressed as n (%) or the mean ± standard deviation. CRRT, continuous renal replacement therapy; ICU, intensive care unit.

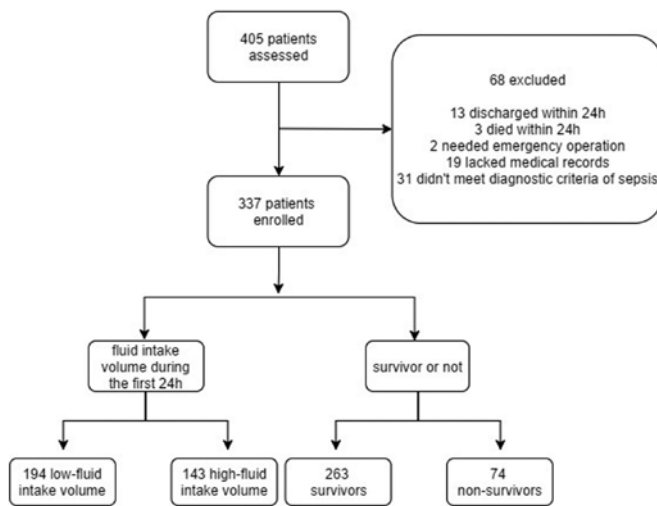


Figure 1. Flow chart illustrating the enrollment of the patients and outcomes assessed in the present study.

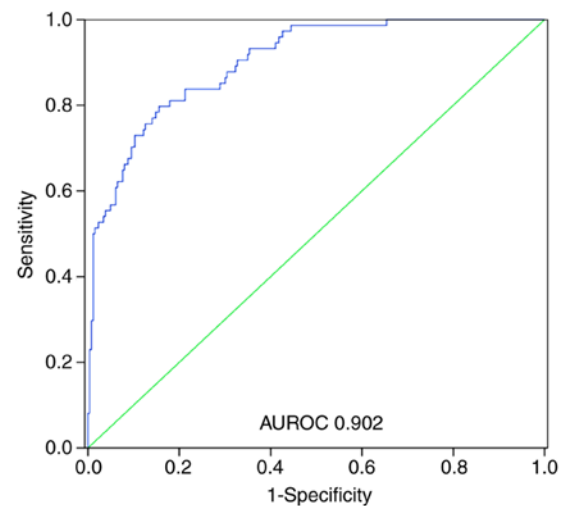


Figure 2. ROC curve of fluid intake during the first 24 h. $P<0.001$, cutoff value was 49.4 ml/kg. ROC, receiver operating characteristic; AUROC, area under the ROC curve.

every day for 7 days ($P=0.002$). However, the daily fluid output volumes were greater for survivors after admission ($P=0.014$; Fig. 3A). The number of survivors and non-survivors per day is stated in Fig. 3B. Number of patients were constant in the first 3 days and decreased because of discharge from hospital or death. The mean daily fluid input volume in the group of non-survivors was significantly higher than that in the group of survivors (47.5 ± 1.8 vs. 35.2 ± 2.9 ml/kg, $P<0.0001$). However, the output volumes were higher among the survivors (42.2 ± 2.6 vs. 37.4 ± 3.2 ml/kg, $P<0.0001$; Fig. 4).

The non-survivors had a daily positive net fluid balance over the 7 days, while the survivors had a daily negative net fluid balance from the second day. Fluid balance volumes of non-survivors were significantly higher compared with those

in survivors on all 7 days ($P<0.05$; Fig. 5). The net fluid balance was compared between survivors and non-survivors every day for 7 days and significant differences for each comparison were obtained ($P<0.01$). Furthermore, both the cumulative negative fluid balance of the survivors and the cumulative positive fluid balance of the non-survivors increased over time (Fig. 6). The cumulative fluid balance of the survivors and non-survivors was significantly different during the 7-day period ($P<0.001$).

Significant differences were observed in the fluid balance observed between survivors and non-survivors from the second day. Therefore, based on whether patients were able to reach a negative fluid balance during the second day, all of the patients were divided into the positive fluid balance

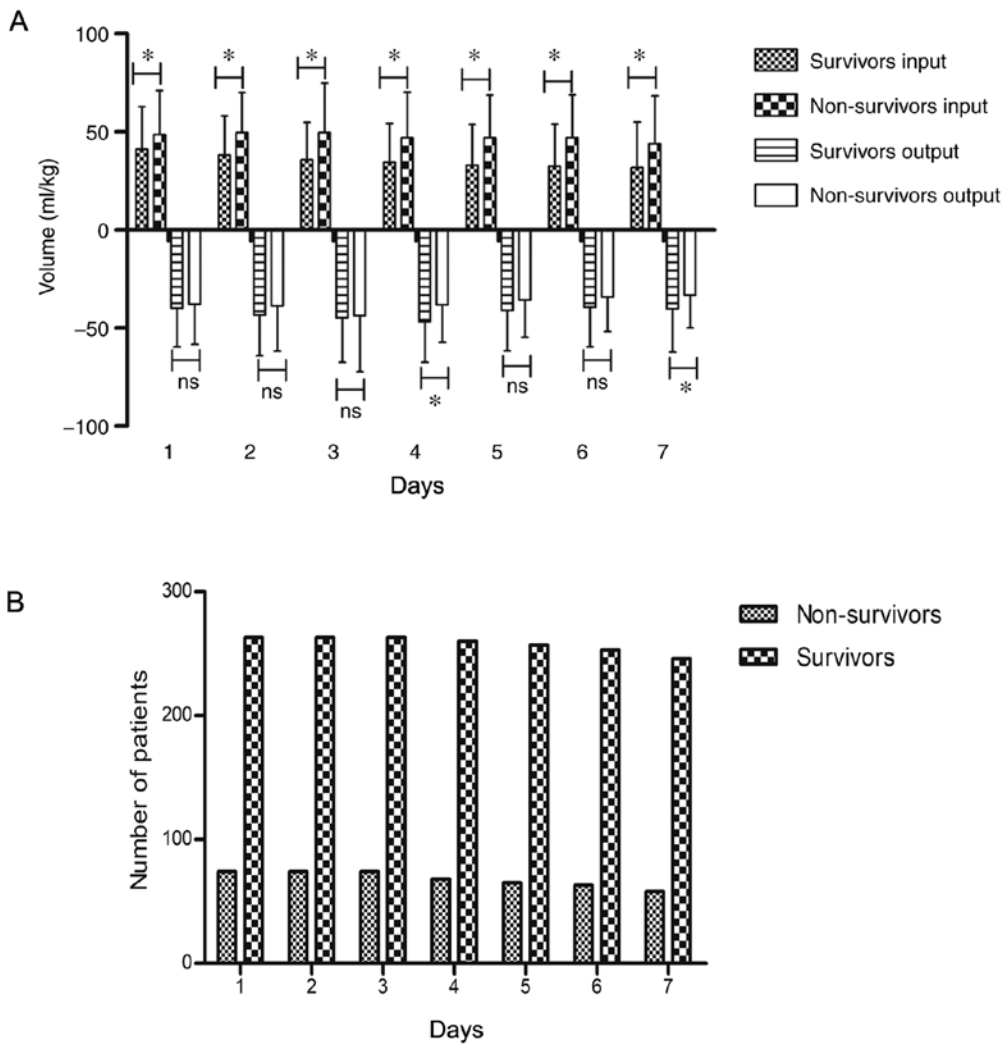


Figure 3. Fluid intake and output volumes of survivors and non-survivors. (A) Fluid intake and output volumes of survivors and non-survivors per day for 7 consecutive days after the onset of sepsis. (B) Number of patients in the survivors and non-survivors groups every day for 7 days. *P<0.05; ns, no significance.

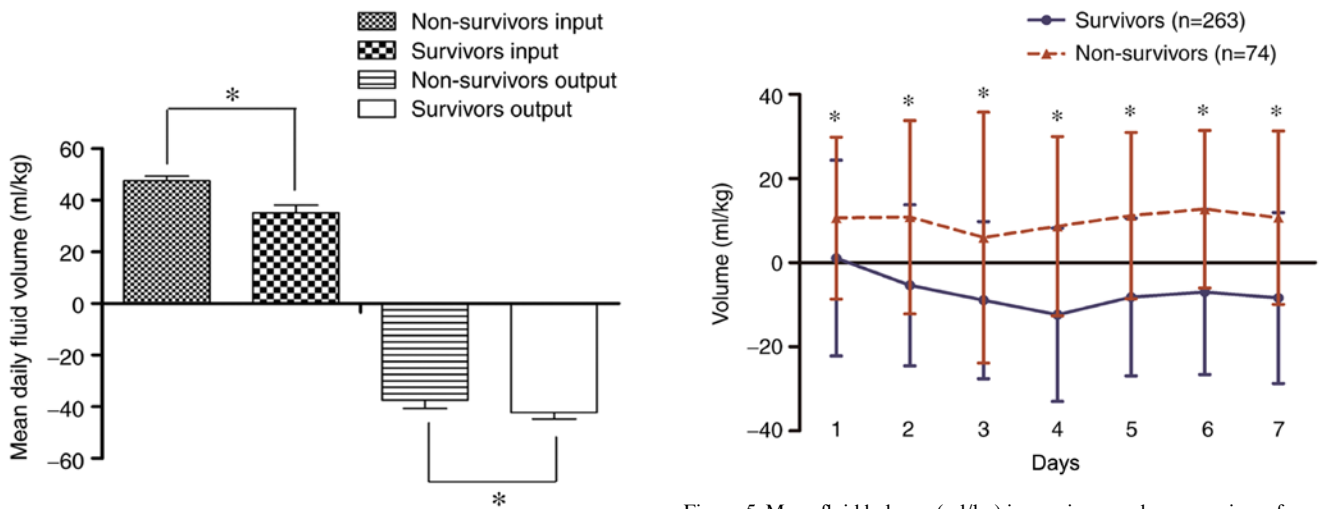


Figure 4. Mean fluid intake and output volumes (ml/kg) in survivors and non-survivors over 7 consecutive days after the onset of sepsis. *P<0.05.

Figure 5. Mean fluid balance (ml/kg) in survivors and non-survivors for each day for 7 consecutive days after the onset of sepsis. *P<0.05, survivors vs. non-survivors.

group (n=163, 48.4%) and negative fluid balance group (n=174, 51.6%; Table III). Patients in the negative fluid balance group

had a lower average in-hospital mortality rate (12.1 vs. 32.5%, P<0.001), a shorter duration of mechanical ventilation [0 (0-6) vs. 2 (0-12), P=0.001] and a lower proportion of patients

Table III. Characteristics of prognosis of patients who achieved negative fluid balance or positive fluid balance on the second day.

Prognostic variable	Patients with negative fluid balance (n=174)	Patients with positive fluid balance (n=163)	P-value
Survival			<0.001
Yes	153 (87.9)	110 (67.5)	
No	21 (12.1)	53 (32.5)	
Duration of ICU stay (days)	14 (8-23)	14 (7-27)	0.738
Duration of mechanical ventilation (days)	0 (0-6)	2 (0-12)	0.001
CRRT			0.005
Yes	15 (8.6)	31 (19.0)	
No	159 (91.4)	132 (81.0)	
Vasopressors or inotropes			0.003
Yes	45 (25.9)	67 (41.1)	
No	129 (74.1)	96 (58.9)	

Values are expressed as n (%). CRRT, continuous renal replacement therapy; ICU, intensive care unit.

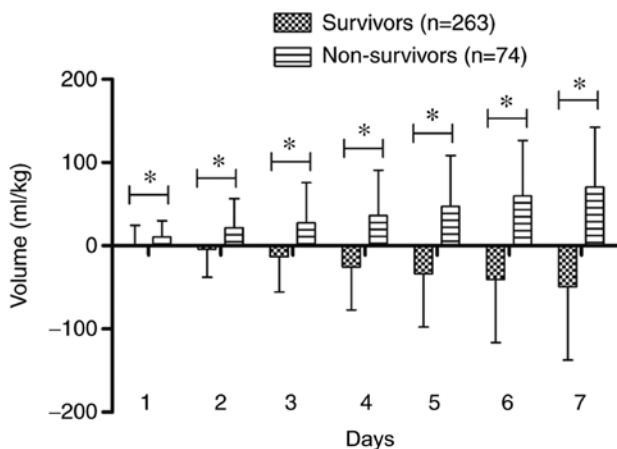


Figure 6. Cumulative fluid balance volumes of survivors and non-survivors for each day of the 7-day period after the onset of sepsis. *P<0.05.

undergoing CRRT (8.60 vs. 19.0%, P=0.005) or using vasopressors or inotropes (25.9 vs. 41.1%, P=0.003) than those in the positive fluid balance group.

Average net fluid balance is an independent prognostic factor.

Binary logistic regression analyses were performed with the following indicators, which were significantly different between survivors and non-survivors (Tables IV and V): SOFA score, APACHE II score, CRP level, PCT level, mean net fluid balance, type of sepsis and time of disease onset. According to the results of the binary logistic regression analysis, the mean net fluid balance (P<0.001) and APACHE II scores (P=0.048) were independently associated with higher in-hospital mortality in patients with sepsis or septic shock (Table VI).

Discussion

Fluid resuscitation is one of the most important strategies for the management of patients with sepsis. Early goal-directed

therapy (EGDT), proposed by Rivers *et al* (23) in 2001, was once regarded as the standard of care. However, three large clinical trials challenged EGDT for its aggressive fluid resuscitation strategies that were able to increase the risk of mortality in patients with sepsis (24-26). An increasing number of studies have indicated that restricted fluid resuscitation may be more beneficial for patients with sepsis (19,20,27). The Surviving Sepsis Campaign Guidelines (28) recommend that, during resuscitation from sepsis-induced hypoperfusion, at least 30 ml/kg of intravenous crystalloid fluid should be given within the first 3 h, as supported by observational evidence (29,30). A conceptual model was proposed that defined four phases for the treatment of sepsis and septic shock: The salvage, optimization, stabilization and de-escalation phases (5,6). Liberal fluid management is recommended during the salvage and optimization phases for enhancing the cardiac output and avoiding further damage to organ function. The aims during the stabilization and de-escalation phases are organ support and the prevention of adverse effects resulting from excessive fluid overload (7). However, in the present study, a low fluid intake volume during the first 24 h after EICU admission was associated with a better prognosis. According to the mean fluid intake volumes during the first day, all patients were divided into low- and high-fluid intake volume groups. Although the lower fluid intake volume group had a higher BMI, CHD and cerebral infarction rates and lower CRP levels, the SOFA and APACHE II scores were not significantly different between the high- and low-fluid volume groups, which indicated that the severity of the disease was similar between the two groups. Further analysis suggested that patients in the low-fluid intake volume group had lower in-hospital mortality rates, a shorter duration of mechanical ventilation and a lower proportion of patients using vasopressors or inotropes than those in the high-fluid volume group. The ROC curve indicated that a fluid volume of <49.4 ml/kg during the first 24 h was more beneficial for patient survival. The earliest possible restriction of the fluid intake volume and immediate and reasonable use of vasoactive drugs may benefit patients with sepsis or septic shock.

Table IV. Characteristics of the survivors and non-survivors.

Variable	Survivors (n=263)	Non-survivors (n=74)	P-value
Sex			0.694
Male	163 (62.0)	44 (59.5)	
Female	100 (38.0)	30 (40.5)	
Age (years)	64 (44-73)	61 (51-78)	0.321
BMI (kg/m ²)	23.78±3.87	22.94±3.40	0.091
Sepsis category			0.010
Septic shock	148 (56.3)	54 (73.0)	
Sepsis	115 (43.7)	20 (27.0)	
Origin			
EICU	165 (62.7)	62 (83.8)	0.001
Medical emergency ward	66 (25.1)	6 (8.1)	0.002
Trauma surgery ward	10 (3.8)	0 (0.0)	0.126 ^a
Other	22 (8.4)	6 (8.1)	0.944
Comorbidities			
Hypertension	112 (42.6)	33 (44.6)	0.758
Diabetes	61 (23.2)	19 (25.7)	0.658
COPD	12 (4.6)	3 (4.1)	0.851 ^b
Arrhythmia	11 (4.2)	9 (12.2)	0.010
CHD	25 (9.5)	5 (6.8)	0.463
CKD	4 (1.5)	1 (1.4)	0.915 ^b
Cerebral infarction	10 (3.8)	5 (6.8)	0.276
SOFA score	5 (4-8)	7 (5-10)	<0.001
APACHE II score	11±5	15±5	<0.0001
Chalson score	2 (0-3)	3 (1-4)	0.037
CRP (mg/l)	73.3 (21.0-151.0)	119.7 (39.8-192.0)	0.016
Creatinine (μmol/l)	157.0±208.3	198.0±202.8	0.156
PCT (ng/ml)	2.1 (0.5-8.9)	4.9 (0.8-21.0)	0.005
Lactate (mmol/l)	1.94 (1.36-2.49)	1.90 (1.32-2.95)	0.424
Time of disease onset (days)	7(3-10)	9 (5-14)	0.002
Duration of hospital stay (days)	22 (13-34)	20 (13-31)	<0.001
Duration of ICU stay (days)	15 (8-25)	12 (7-23)	0.057
Duration of mechanical ventilation (days)	0 (0-5)	7 (3-15)	<0.001
CRRT			0.002
Yes	28 (10.7)	18 (24.3)	
No	235 (89.3)	56 (75.7)	
Vasopressors or inotropes			<0.001
Yes	66 (25.1)	46 (62.2)	
No	197 (74.9)	28 (37.8)	

^aFisher's exact test. ^bContinuity correction. Values are expressed as n (%), median (25-75th percentile) or mean ± standard deviation. BMI, body mass index; EICU, emergency intensive care unit; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CKD, chronic kidney disease; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; PCT, procalcitonin.

The fluid balance is an intuitive reflection of fluid resuscitation in patients with sepsis. Several studies have explored the association between fluid balance and mortality. Boyd *et al* (31) indicated that a more positive fluid balance both early in resuscitation and cumulatively over 4 days was associated with an increased risk of mortality in patients with septic shock. Another study by Sirvent *et al* (12)

reported a similar conclusion that suggested a strong correlation between the accumulated positive fluid balance at 48, 72 and 96 h and higher mortality rate of intensive care unit (ICU)-admitted patients with sepsis or septic shock. Brotfain *et al* (14) collected data from 297 patients with sepsis or septic shock and indicated that a positive cumulative fluid balance at discharge from ICU was an independent prognostic

Table V. Assignment instructions of indicators analyzed by binary logistic regression analysis.

Variable	One point ^a	Two points ^b
SOFA score	≤5	>5
APACHE II score	≤11	>11
CRP (mg/l)	≤79.2	>79.2
PCT (ng/ml)	≤2.24	>2.24
Mean net fluid balance (ml/kg/day)	≤-1.94	>-1.94
Sepsis category	Sepsis	Septic shock
Time of disease onset (days)	≤7	>7
Duration of ventilatory support (days)	0	>0

^aValues of indicators less than median value were assigned to 1-point group. ^bValues of indicators more than median value were assigned to 2-point group. SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; PCT, procalcitonin.

Table VI. Results of the binary logistic regression analysis (multivariate analysis).

Variable	P-value	OR	95% CI
SOFA score	0.205	0.611	0.285-1.310
APACHE II score	0.048	0.611	0.285-1.310
CRP (mg/l)	0.298	0.494	0.245-0.995
PCT (ng/ml)	0.792	0.710	0.373-1.352
Time of disease onset (days)	0.107	1.099	0.546-2.211
Mean daily fluid balance (ml/kg/day)	<0.001	0.583	0.303-1.123
Sepsis category	0.157	0.136	0.063-0.293

SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; PCT, procalcitonin; OR, odds ratio.

factor of mortality; furthermore, patients who reached a negative cumulative fluid balance on day 3 at the ICU had a lower chance of readmission to the ICU. The present study also focused on the correlation between fluid balance and in-hospital mortality of patients with sepsis or septic shock. In a single-center population of 337 septic patients, the overall in-hospital mortality was 22.0%, which was much lower than that in a previous study (mortality rate, 34.1%) by Acheampong and Vincent (10). Furthermore, in the present study, the patients in the negative-fluid balance group had a lower in-hospital mortality rate, a shorter duration of mechanical ventilation and a lower proportion of patients undergoing CRRT or using vasopressors or inotropes than those in the positive-fluid balance group. The above results suggested that a negative fluid balance is beneficial for the survival of patients with sepsis. Next, these conclusions were verified by

binary logistic regression analysis. The results indicated that the net fluid balance was an independent prognostic factor for patients with sepsis and its prognostic value was better than that of the APACHE II score.

Although the association between a negative fluid balance and favorable prognosis has been reported in numerous studies, the optimal time-point of patients with sepsis or septic shock reaching a negative fluid balance remains to be determined. In a retrospective study, Acheampong and Vincent (10) indicated that the mean fluid balance in survivors became negative between days 4 and 5 and remained negative, while the mean fluid balance in non-survivors remained positive. Another study concluded that a high fluid balance from the first 24 h until discharge from the ICU increased the risk of mortality in patients with severe sepsis and septic shock. Furthermore, high fluid volume resuscitation in the first 3 h and low fluid volume therapy in the first 24 h have been observed to provide survival benefits (32). An observational cohort study by Peake *et al* (26) suggested that the fluid balance was more positive in non-survivors than in survivors and that these differences became more evident on the third day, when the fluid balance in survivors was negative. Huang *et al* (33) indicated that the 72-h cumulative fluid balance was correlated with the likelihood of developing multiple-organ dysfunction syndrome and of mortality in patients with septic shock. The present results exhibited certain differences from those of the previous studies aforementioned. Survivors had much less positive fluid balance volumes than non-survivors and reached a negative net fluid balance from the second day, which was much earlier than that reported in other studies. The fluid intake volumes of non-survivors were much higher than those of survivors every day for 7 days; however, the output volumes did not exhibit any significant differences between the two groups except for days 4 and 7. The main output volumes came from urine and these results indicated kidney function between the two groups was similar. Therefore, the most important way of achieving a negative fluid balance is to decrease fluid intake. Fluid administration appears to be the most relevant modifiable factor to prevent fluid overload. Our group is currently performing a prospective study regarding the efficacy of restricted fluid resuscitation in patients with sepsis or septic shock to further clarify this issue.

Acute kidney injury (AKI) is also an important factor affecting the prognosis of patients with sepsis or septic shock. Therefore, creatinine levels and the proportion of subjects receiving CRRT were compared between patients in the low- and high-fluid intake volume groups during the first 24 h. There was no significant difference in the above results, suggesting that the effect of the fluid intake volume during the first 24 h on prognosis was not caused by AKI. Furthermore, non-survivors had a longer duration of mechanical ventilation; this correlated well with the results of a previously published prospective study on 717 patients at 28 ICUs (34). A longer duration of mechanical ventilation may aggravate or initiate pulmonary inflammation and cause lung injury.

The present study had certain advantages over other previous/relevant studies. First, there was a lack of unified time-points in previous studies. Fluid resuscitation was a

dynamic and changing process that was based on the patient's condition and doctors were required to evaluate the volumes and types of fluid administration not only at the beginning but also during the subsequent days. Thus, in the present study, the fluid balance was evaluated during the first 7 days after admission to the EICU, as it was assumed to be more meaningful to study a time period rather than a small number of time-points. Furthermore, the definition and diagnostic criteria were revised, resulting in changes in the inclusion criteria of patients. Furthermore, there remains to be a lack of relevant studies in China; most of these studies did not include a sufficient number of patients with sepsis. Therefore, it is worthwhile to study the association between the net fluid balance and in-hospital mortality in Chinese patients with sepsis or septic shock.

Of note, the present study had certain limitations. First, it was performed at a single center with an insufficient number of patients, was retrospective in nature and did not include any pre-planned protocol. This reduced the external validity of the data. Therefore, larger, multi-center, prospective studies are required to confirm the present results. Furthermore, data were collected every 24 h without considering the data of the early hours after the onset of sepsis, which may have been more meaningful. In addition, the clinical parameters recorded were not sufficiently comprehensive and certain factors such as the type of bacteria and use of antibiotics were neglected; this may also have influenced the accuracy of the present results. Finally, binary logistic regression analysis was used to determine independent prognostic factors for patients with sepsis or septic shock, as the independent variables included both categorical and continuous variables; however, the correction for confounding factors may have been insufficient.

In conclusion, although the present study was a single-center retrospective study, the results indicated that a low fluid intake volume during the first 24 h and persistent negative fluid balance from the second day were associated with favorable outcomes. Furthermore, the mean daily fluid balance in patients with sepsis or septic shock from China was an independent prognostic factor. The present data provide a basis for conducting large randomized controlled clinical trials to explore the effects of restricted fluid administration strategies and negative fluid balance on the prognosis of patients with sepsis or septic shock.

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Availability of data and materials

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

Authors' contributions

YMW and YC analyzed data and were major contributors in writing the manuscript. EZC and EQM were involved in the conceptualization and supervision of the work. YJZ and YCH contributed to acquisition of data. WWC, RJ and LLX contributed to analysis and interpretation of data. ZTY and HQS contributed to acquisition of data. HPQ contributed to analysis and interpretation of data. ZTY, HQS and HPQ agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This single-center and retrospective study was approved by the ethics committee of Ruijin Hospital (reference no. 2017119). All procedures performed in this study involving human participants were part of routine clinical evaluations in accordance with the institutional ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The requirement of patient consent was waived by the ethics committee as this study was retrospective.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, *et al*: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315: 801-810, 2016.
2. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, Jaton K, Giulieri S, Delaloye J, Opal S, *et al*: Sepsis: A roadmap for future research. *Lancet Infect Dis* 15: 581-614, 2015.
3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, *et al*: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 39: 165-228, 2013.
4. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, *et al*: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 36: 296-327, 2008.
5. Vincent JL and De Backer D: Circulatory shock. *N Engl J Med* 369: 1726-1734, 2013.
6. Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, Kellum JA, Mythen MG and Shaw AD; ADQI XII Investigators Group: Four phases of intravenous fluid therapy: A conceptual model. *Br J Anaesth* 113: 740-747, 2014.

7. Besen BA and Taniguchi LU: Negative fluid balance in sepsis: When and how? *Shock* 47 (1S Suppl 1): S35-S40, 2017.
8. Cinel I, Kasapoglu US, Gul F and Dellinger RP: The initial resuscitation of septic shock. *J Crit Care* 57: 108-117, 2020.
9. Marik PE and Lemson J: Fluid responsiveness: An evolution of our understanding. *Br J Anaesth* 112: 617-620, 2014.
10. Acheampong A and Vincent JL: A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care* 19: 251, 2015.
11. Bagshaw SM, Brophy PD, Cruz D and Ronco C: Fluid balance as a biomarker: Impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care* 12: 169, 2008.
12. Sirvent JM, Ferri C, Baró A, Murcia C and Lorenzo C: Fluid balance in sepsis and septic shock as a determining factor of mortality. *Am J Emerg Med* 33: 186-189, 2015.
13. Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y and Manthous CA: Negative fluid balance predicts survival in patients with septic shock: A retrospective pilot study. *Chest* 117: 1749-1754, 2000.
14. Brotfain E, Koyfman L, Toledano R, Borer A, Fucs L, Galante O, Frenkel A, Kutz R and Klein M: Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. *Am J Emerg Med* 34: 2122-2126, 2016.
15. de Oliveira FS, Freitas FG, Ferreira EM, de Castro I, Bafi AT, de Azevedo LC and Machado FR: Positive fluid balance as a prognostic factor for mortality and acute kidney injury in severe sepsis and septic shock. *J Crit Care* 30: 97-101, 2015.
16. Sakr Y, Rubatto Birri PN, Kotfis K, Nanchal R, Shah B, Kluge S, Schroeder ME, Marshall JC and Vincent JL; Intensive Care Over Nations Investigators: Higher fluid balance increases the risk of death from sepsis: Results from a large international audit. *Crit Care Med* 45: 386-394, 2017.
17. de Almeida JP, Palomba H, Galas FR, Fukushima JT, Duarte FA, Nagaoka D, Torres V, Yu L, Vincent JL, Auler JO Jr and Hajjar LA: Positive fluid balance is associated with reduced survival in critically ill patients with cancer. *Acta Anaesthesiol Scand* 56: 712-717, 2012.
18. Dhondup T, Tien JC, Marquez A, Kennedy CC, Gajic O and Kashani KB: Association of negative fluid balance during the de-escalation phase of sepsis management with mortality: A cohort study. *J Crit Care* 55: 16-21, 2020.
19. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD and Harabin AL: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354: 2564-2575, 2006.
20. Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, Blackwood B and Fan E: Conservative fluid management or dereuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: A systematic review and meta-analysis. *Intensive Care Med* 43: 155-170, 2017.
21. Douglas IS, Alapat PM, Corl KA, Exline MC, Forni LG, Holder AL, Kaufman DA, Khan A, Levy MM, Martin GS, *et al*: Fluid response evaluation in sepsis hypotension and shock: A randomized clinical trial. *Chest*: Apr 27, 2020 (Online ahead of print).
22. Shen Y, Ru W, Huang X and Zhang W: Time-related association between fluid balance and mortality in sepsis patients: Interaction between fluid balance and haemodynamics. *Sci Rep* 8: 10390, 2018.
23. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E and Tomlanovich M; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345: 1368-1377, 2001.
24. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, *et al*: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 372: 1301-1311, 2015.
25. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, *et al*: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 370: 1683-1693, 2014.
26. ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, *et al*: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 371: 1496-1506, 2014.
27. Skrypnik D, Mostowska A, Jagodzinski PP and Bogdański P: Association of rs699947 (-2578 C/A) and rs2010963 (-634 G/C) single nucleotide polymorphisms of the VEGF gene, VEGF-A and leptin serum level, and cardiovascular risk in patients with excess body mass: A case-control study. *J Clin Med* 9: 469, 2020.
28. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, *et al*: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 43: 304-377, 2017.
29. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, *et al*: The surviving sepsis campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 38: 367-374, 2010.
30. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, Osborn T, Lemeshow S, Chiche JD, Artigas A and Dellinger RP: Surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 43: 3-12, 2015.
31. Boyd JH, Forbes J, Nakada TA, Walley KR and Russell JA: Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 39: 259-265, 2011.
32. Tigabu BM, Davari M, Kebriaeezadeh A and Mojtahedzadeh M: Fluid volume, fluid balance and patient outcome in severe sepsis and septic shock: A systematic review. *J Crit Care* 48: 153-159, 2018.
33. Huang AC, Lee TY, Ko MC, Huang CH, Wang TY, Lin TY and Lin SM: Fluid balance correlates with clinical course of multiple organ dysfunction syndrome and mortality in patients with septic shock. *PLoS One* 14: e0225423, 2019.
34. Soares M, Caruso P, Silva E, Teles JM, Lobo SM, Friedman G, Dal Pizzol F, Mello PV, Bozza FA, Silva UV, *et al*: Characteristics and outcomes of patients with cancer requiring admission to intensive care units: A prospective multicenter study. *Crit Care Med* 38: 9-15, 2010.



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