Fluid balance in sepsis and septic shock as a determining factor of mortality

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Abstract

Objective: The objective was to assess whether fluid balance had a determinant impact on mortality rate in a cohort of critically ill patients with severe sepsis or septic shock.

Design: A prospective and observational study was carried out on an inception cohort.

Setting: The setting was an intensive care unit of a university hospital.

Patients: Patients admitted consecutively in the intensive care unit who were diagnosed with severe sepsis or septic shock were included.

Interventions: Demographic, laboratory, and clinical data were registered, as well as time of septic shock onset, illness severity (Simplified Acute Physiology Score II, Sepsis-related Organ Failure Assessment), and comorbidities. Daily and accumulated fluid balance was registered at 24, 48, 72, and 96 hours. Survival curves representing 28-day mortality were built according to the Kaplan-Meier method.

Results: A total of 42 patients were included in the analysis: men, 64.3%; mean age, 61.8 ± 15.9 years. Septic shock was predominant in 69% of the cases. Positive blood cultures were obtained in 17 patients (40.5%). No age, sex, Sepsis-related Organ Failure Assessment, creatinine, lactate, venous saturation of O2, and troponin differences were observed upon admission between survivors and nonsurvivors. However, higher Simplified Acute Physiology Score II was observed in nonsurvivors, P = .016. Nonsurvivors also showed higher accumulated positive fluid balance at 48, 72, and 96 hours with statistically significant differences. Besides, significant differences (P = .02) were observed in the survival curve with the risk of mortality at 72 hours between patients with greater than 2.5 L and less than 2.5 L of accumulated fluid balance.

Conclusions: Fluid administration at the onset of severe sepsis or septic shock is the first line of hemodynamic treatment. However, the accumulated positive fluid balance in the first 48, 72, and 96 hours is associated with higher mortality in these critically ill patients.

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1. Introduction

In severe sepsis and septic shock, the main elements of treatment are intravenous fluids, appropriate antibiotics, source control, vasopressors, and ventilatory support [1]. For more than 10 years, the administration of intravenous fluids has been known as a key in the initial stages of sepsis resuscitation, as proven by a classic article on goal-based treatments [2]. Anyway, it is now recognized that the administration of excess fluid in sepsis may lead to worsened respiratory function, increased intraabdominal pressure, worsened coagulopathy, and increased probability of cerebral edema [3]. Some authors observed difficulty in fluid balance management in critically ill patients, and positive fluid balance is associated with increased mortality rates in patients with acute lung injury and septic shock [4,5]. For all these reasons, the present observational study was designed to assess whether fluid balance has a determinant impact on mortality in a well-defined cohort of patients with severe sepsis or septic shock.

2. Methods

2.1. Population and data collection

Our study includes the patients admitted consecutively in the intensive care unit (ICU) of a teaching hospital for 4 months (from October 2012 to January 2013) that were diagnosed with severe sepsis or septic shock. It is a prospective and observational study on an inception cohort. Patients with septic shock were identified by a specific team of intensivists. Demographic, laboratory, and clinical data were registered: age, sex, time of septic shock onset, focus of infection, presence of initial acute kidney injury, severity of illness based on the Simplified Acute Physiology Score (SAPS) II score [6], the Sepsis-related Organ Failure Score (SOF) [7], acute respiratory distress syndrome (ARDS) [8], and the presence of acute kidney injury [9].
2.3. Statistical analysis

Descriptive statistics of demographic and clinical variables included means and standard deviations for quantitative variables and percentages for qualitative variables. For unadjusted comparisons between or among groups, continuous variables were compared by using Student t test in case of normally distributed data or Mann-Whitney U test for nonnormally distributed data. Categorical variables were compared using the χ² test or Fisher exact test where appropriate. Comparative variables for mortality at 28 days were studied by means of bivariate analysis. Survival curves representing mortality at 28 days were constructed according to the Kaplan-Meier method and compared with the Mantel-Haenszel log-rank test. P < .05 was considered statistically significant for all comparisons. Statistical analyses were performed using SPSS (version 12; SPSS Inc, Chicago, IL).

3. Results

A total of 42 patients were included in the analysis. Epidemiologic results were as follows: predominance of men (64.3%); mean age was 61.8 ± 15.9 years; cases of septic shock were predominant (69%). Positive blood cultures were obtained in 17 patients (40.5% of the cases). The most frequent initial infectious focus was abdominal (48%), followed by respiratory (17%). Infections were community acquired in almost 70% of the cases. Severity scores upon ICU admission were 44.6 ± 16.1 and 7.1 ± 3.4 points in SAPS II and SOFA, respectively. Besides, 28-day mortality was observed in 15 patients (35.7%), all of them in the septic shock group. Five out of 26 patients (19.2%) were classified as having cardiac dysfunction by EF less than 45% (see population characteristics in Table 1).

Table 2 presents differences in fluid balance and variables between survivors and nonsurvivors. No age, sex, SOFA score, creatinine, lactate, venous saturation of O2 (SavO2), and troponin T differences were reported upon admission between survivors and nonsurvivors. However, higher SAPS II score was observed in nonsurvivors (52.5 ± 15.4 vs 40.2 ± 14.9, P = .016). Nonsurvivors also showed higher accumulated positive fluid balance at 24, 48, and 96 hours with statistically significant differences. Fig. 1 shows a box plot with the greater daily accumulated fluid balance in survivors and nonsurvivors. Other factors such as creatinine, lactate, SavO2, and the risk of survival at 72 hours between patients with greater than 2.5 L and less than 2 L of accumulated fluid balance, compared by log-rank test with significant differences (P = .02).

4. Discussion

Our observational study shows that the accumulated positive fluid balance at 48, 72, and 96 hours is associated with higher mortality in ICU-admitted patients with sepsis or septic shock. These results are consistent with those by Boyd et al [5], who showed that higher positive fluid balance in resuscitation over the first 4 days was associated with increased risk of mortality in septic shock patients. Other factors such as creatinine, lactate, SavO2, and

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Table 2
Fluid balance and variables between survivors and nonsurvivors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 27)</th>
<th>Non-survivors (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.9 (17.6)</td>
<td>66.9 (11.3)</td>
<td>.122</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>17 (62.9)</td>
<td>10 (66.6)</td>
<td>.810</td>
</tr>
<tr>
<td>SAPS II upon admission, points</td>
<td>40.2 (14.9)</td>
<td>52.5 (15.4)</td>
<td>.016</td>
</tr>
<tr>
<td>SOFA upon admission, points</td>
<td>6.3 (3.2)</td>
<td>7.6 (3.6)</td>
<td>.518</td>
</tr>
<tr>
<td>Initial creatinine (mg/dL)</td>
<td>1.5 (1.3)</td>
<td>1.9 (1.7)</td>
<td>.452</td>
</tr>
<tr>
<td>Initial lactate (mg/dL)</td>
<td>18.9 (14.7)</td>
<td>28.6 (18.6)</td>
<td>.072</td>
</tr>
<tr>
<td>Initial SavO2 (%)</td>
<td>77 (9)</td>
<td>72 (9)</td>
<td>.118</td>
</tr>
<tr>
<td>Troponin T hs (ng/dL)</td>
<td>32.5 (36.3)</td>
<td>115.6 (180.4)</td>
<td>.099</td>
</tr>
<tr>
<td>Fluid balance (mL) within 24 h</td>
<td>1710.4 (1955.4)</td>
<td>3153.5 (3118.9)</td>
<td>.096</td>
</tr>
<tr>
<td>Fluid balance (mL) within 48 h</td>
<td>1791.6 (2348.3)</td>
<td>4194.3 (3477.6)</td>
<td>.020</td>
</tr>
<tr>
<td>Fluid balance (mL) within 72 h</td>
<td>1128.1 (3132.6)</td>
<td>5401.6 (3961.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Fluid balance (mL) within 96 h</td>
<td>4612.8 (4220.0)</td>
<td>6678.6 (4656.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Fluid balance 24 h &gt; 2.0 L</td>
<td>10 (37.0)</td>
<td>11 (73.3)</td>
<td>.042</td>
</tr>
<tr>
<td>Fluid balance 48 h &gt; 2.5 L</td>
<td>12 (44.4)</td>
<td>11 (73.3)</td>
<td>.071</td>
</tr>
<tr>
<td>Fluid balance 72 h &gt; 2.5 L</td>
<td>11 (40.7)</td>
<td>12 (80.0)</td>
<td>.014</td>
</tr>
<tr>
<td>Fluid balance 96 h &gt; 2.5 L</td>
<td>10 (37.0)</td>
<td>12 (80.0)</td>
<td>.008</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>13 (48.1)</td>
<td>0 (0.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Septic shock</td>
<td>14 (51.8)</td>
<td>15 (100.0)</td>
<td>.980</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>11 (40.7)</td>
<td>6 (40.0)</td>
<td>.963</td>
</tr>
</tbody>
</table>

* Data are expressed as mean (SD).
† χ² or Fisher test for qualitative data and Student t or Mann-Whitney U test for quantitative data.
in patients with severe sepsis and septic shock needs further study to determine their relative efficacy compared to standard care therapy [8]. Associations between increased cumulative positive fluid balance and long-term adverse outcomes have been reported in sepsis patients [5]. In tests of liberal vs goal-based treatments or restrictive fluid strategies in patients with acute respiratory distress syndrome—particularly in perioperative patients [3,4]—restrictive fluid strategies were associated with reduced morbidity. However, because there is no consensus on the definition of these strategies, high-quality tests in specific patient populations are required [10].

The mechanisms by which positive fluid balance can adversely influence outcomes remain unknown. However, hypervolemia or hyperosmolarity might exacerbate capillary leak in septic shock patients, thus contributing to pulmonary edema. Positive fluid balance could also result in intraabdominal hypertension, thus contributing to organ hypoperfusion development and subsequent organ failure [11,12]. Acute renal failure coexisting with sepsis may worsen outcomes as well as lead to positive fluid balance [13].

Our study has important limitations. Firstly, it was performed in one only middle-sized and university hospital and may therefore have no external validity for other institutions. Secondly, our observational design and the lower number of studied patients than other studies of fluid balance, limit our ability to determine a causal relationship between fluid balance and outcomes. And thirdly, the fact that cardiac function was only studied in 26 of the 42 patients leaves out an important predictor of mortality. Finally, other factors such as antibiotic therapy, focus control, and some other unmeasured clinical parameters may have contributed to our findings. Recommendations in the guidelines for sepsis treatment are well known to have recently been questioned, specifically the early goal-directed treatment [14]. The same applies to the recommendations of the type of fluid used for sepsis and septic shock. For all these reasons, it is difficult to standardize a single treatment protocol for these critically ill patients, as well as to draw clear conclusions from observational studies.

Lastly, selection, timing, doses, and fluid balance in sepsis and septic shock should also be evaluated very carefully with the aim of maximizing efficacy and minimizing iatrogenic toxicity [15].

In conclusion, fluid administration upon the onset of severe sepsis or septic shock is the first line of hemodynamic treatment in this clinical situation. There is no doubt that the study of cardiac function by echocardiography helps us better understand the prognosis of these patients. However, the accumulated positive fluid balance in the first 48, 72, and 96 hours is associated with higher mortality in these critically ill, ICU-admitted patients.

**References**


