The effects of fluid therapy during the first 12 hours from septic shock onset in pediatric patients

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Abstract

Background: Initial fluid therapy is the cornerstone of hemodynamic resuscitation in pediatric patients suffering from septic shock. This study aimed to evaluate the association between fluid therapy during the first 12 hours from septic shock onset and clinical outcomes in a pediatric cohort.

Method: This was a retrospective, observational study of consecutive pediatric patients with septic shock admitted to our multidisciplinary pediatric intensive care unit (PICU) between January 2012 and December 2019. Total fluid administration within the first 12 hours from septic shock onset, patient characteristics, and outcome measurements were collected from validated electronic medical records.

Results: A total of 144 cases were included with an overall 28-day mortality rate of 20.1%. Among the survivors, the proportion of fluid received within the first 3 hours (36.9 % vs 25.4%, *p*=.004) and within the last 3 hours (18.9 % vs 21.3 %, *p*=.031) of the total amount administered over a 12 hour period from septic shock onset showed a significant difference compared with the non-survivors. The mortality rate was lower in the group receiving the highest proportion of the total administered fluid within the first 3 hours (13.9 % vs 26.4 %, *p*=.048). Patients receiving the highest proportion of fluid in the last 3 hours had a significantly higher mortality rate (29.6 % vs 14.4 %, *p*=.025). By multivariable logistic regression analysis, we also found that a higher proportion of administered fluid within the first and last 3 hours was associated with decreased mortality (OR, 0.951; 95% CI, 0.918-0.986; *p*=.028) and increased mortality (OR, 2.761; 95% CI, 1.175-6.495; *p*=.020), respectively.

Conclusions: An increased fluid intake within the first 3 hours of septic shock onset is associated with a decreased 28-day mortality. Moreover, a higher administration of fluids from 9 to 12 hours after this onset seems to be related to a poorer survival outcome. Treating pediatric septic shock cases with higher amounts of fluid within the first 3 hours of onset and then with more conservative levels thereafter may lead to better survival outcomes.

Background

Septic shock remains the leading cause of morbidity and mortality in children, with fatality rates of up to 60% [1]. In severe cases of sepsis and septic shock, the main therapeutic treatment approaches are intravenous fluids, appropriate antibiotics, source control, vasopressors, and ventilator support [2]. In 1991, Carcillo et al. reported that a decrease in mortality in pediatric septic shock cases was associated with higher volumes of initial fluid resuscitation [3]. In that study, the children who received a 40 ml/kg volume of resuscitation fluid or greater in the first hour from septic shock onset showed improved survival rates compared with cases that received smaller initial resuscitation fluid amounts. A growing body of evidence subsequently led to a consensus statement in 2002 for the hemodynamic support of pediatric and neonatal patients in septic shock [4]. These practice guidelines recommended aggressive fluid resuscitation that targets the normalization of vital signs and clinical evidence for perfusion in the first hour and then the subsequent titration of inotropes and vasopressors combined with ongoing

volume resuscitation. These guidelines were updated in 2007 and again in 2017 without significant changes to the continued focus on early and aggressive normalization of perfusion, initially using an aggressive volume followed by the addition of vasopressors and inotropes [5]. In 2020, Surviving Sepsis Campaign (SSC) guidelines recommended a 40–60 ml/kg administration of bolus fluid over the first hour if hypotension was present but did not provide distinct recommendations regarding subsequent fluid therapy [6].

It is now recognized however that a positive fluid balance in the intensive care unit (ICU) is associated with an increased risk of mortality in adult septic shock. This has indicated that aggressive volume resuscitation is no longer advantageous in these cases, and may even be harmful in some patient populations [7–10]. Optimal fluid resuscitation is still recognized as a critical component of clinical interventions upon septic shock onset, and key to the initial stages of sepsis resuscitation but it is now believed that the appropriate timing and level of fluid resuscitation may be crucial for improving survival. Notably however, there have been few studies on the association of fluid balance and the timing of fluid resuscitation with patient outcomes in pediatric septic shock.

In our current study, we aimed to describe the characteristics of a cohort of children with septic shock and determine whether the amount and distribution of resuscitation fluid over the first 12 hours after onset are associated with mortality outcomes.

Methods

Pediatric septic shock cases were obtained through a review of the electronic patient records from January 2012 to December 2019 in a tertiary PICU of Asan Medical Center Children's Hospital, Seoul, Korea. We screened all consecutive admissions to identify patients under the age of 18 who diagnosed with septic shock requiring vasoactive agents. The diagnosis of septic shock was based on the 2017 guidelines of the American College of Critical Care Medicine committee [3, 5]. We screened for patients who had 1) had a suspected infection manifested by hypothermia or hyperthermia, 2) had clinical signs of inadequate tissue perfusion that included any of the following: decreased or altered mental status, prolonged capillary refill greater than 2 seconds, diminished pulses, mottled cool extremities, flash capillary refill, bounding peripheral pulses and wide pulse pressure, or decreased urine output of less than 1 mL/kg/hr, and 3) required inotropics or vasopressor to maintain an adequate perfusion or blood pressure. We excluded children who could not receive fluid resuscitation in accordance with the septic shock protocol due to severe pulmonary hypertension or increased intracerebral pressure, and any cases for whom detailed medical data were not available.

This study was approved by the Asan Medical Center Institutional Review Board. The requirement for informed consent was waived because of the retrospective and observational nature of the study. All patients were treated in accordance with our institution's pediatric septic shock management protocol.

Data collection

We retrospectively reviewed the electric medical records of enrolled patients and collected data on their baseline demographics, Pediatric Risk of Mortality (PRISM) score Ⅲ, need of mechanical ventilatory support, need for renal replacement therapy, length of ICU stay, 28 day mortality, and initial lactate level. The onset time of septic shock was defined as the point at which fluid resuscitation or vasoactive drugs were first administered to improve inadequate tissue perfusion. The total intake and output volumes were taken from the electronic medical records and used to calculate the fluid given for the first 3 hours and then in every subsequent 3 hour period during the first 12 hours from the onset of septic shock. The intake volume refers to all fluids administered and includes all nutritional fluid (or products), drugs, resuscitation bolus fluid and blood transfusions. The output volume was calculated from urine, dialysis, drainage, stools and vomitus.

The proportion of the final total 12 hour fluid volume that was administered in every 3 hour period was calculated and compared between the survivors and non-survivors. The higher proportion group in each 3 hour period was defined as the patients receiving a larger than median distribution of fluid, and the lower proportion group as those with a smaller than median distribution in that same period. The 28-day mortality rates between the higher and lower proportion groups in the each time period were compared.

Statistical analysis

Statistical analyses were conducted using SPSS, version 21.0 (IBM Corp, Armonk, NY). Categorical variables were reported as numbers and percentages and analyzed using the Fisher's exact test or chi-squared test. Continuous variables were reported as medians (interquartile range, IQR). Two-tailed t-tests were used for normally distributed continuous variables, and the Mann-Whitney U test was employed for non-parametric data. Multivariable logistic regression was used to estimate variables associated with the 28-day mortality rates. Variables were selected for inclusion in the multivariable models based on an a priori clinical rationale, and included age, gender, and the PRISM score Ⅲ. For all tests, a two-sided $p < 0.05$ was considered statistically significant.

Results

Of the 167 children who initially met the inclusion criteria for this study, 23 were subsequently excluded. Fifteen patients did not have complete detailed data and the remaining eight cases were excluded as we could not challenge the fluid resuscitation due to severe pulmonary hypertension or increased intracerebral pressure. A total cohort of 144 children with septic shock was therefore enrolled. The characteristics of these cases and the results of the univariable analysis between the survivors and non-survivors are presented in Table 1. The median age and weight were 9.1 years and 20.6 kg, respectively. The overall 28-day mortality in the total study population was 22.1%. The most frequent underlying diseases were hemato-oncological disorders. However, the children in our current series with gastro-intestinal diseases had the highest mortality rate of 33.3%. There was significant difference in the PRISM Ⅲ score on the day of onset between the survivors and non-survivors.

Fluid balance and distribution over the first 12 hours

As shown in Table 2, a similar amount of fluid was administered over the first 12 hours in both the survivors and non-survivors. However, when subgrouped into 3 hour periods post septic shock onset, survivors were given more fluids in the first 3 hours (21.9 vs 16.1 ml/kg, $p = .239$) and a significantly smaller amount of fluid in the last 3 hours compared to non-survivors (9.4 vs 13.1 ml/kg, $p = 014$). There was no significant difference between survivors and non-survivors in the overall net fluid balance over the 12 hour period after septic shock. Figure 1 shows the distribution of administered fluid within every 3 hour period over these 12 hours. In the surviving children, the fluid administered in the first 3 hours accounted for the largest distribution with a gradual decline thereafter. In contrast, an even distribution of fluids over the 12 hours post septic shock was evident in the non-survivors.

The relationship between the 28-day mortality and the distribution of fluid

As shown in Fig. 2, when our subjects were divided into a higher and lower proportion group for the distribution of fluids in each 3 hour period, the higher proportion group for the first 3 hours showed a significantly lower 28-day mortality. Notably however, the higher proportion group in the last 3 hour period of the initial 12 hours after septic shock had a significantly higher 28-day mortality.

Table 3 presents the results of multivariable logistic regression analysis for possible risk factors for 28-day mortality from septic shock, including the PRISM □ score, higher proportion of fluid intake during the first 3 hours, and higher proportion group of fluid intake during 9–12 hours post septic shock. A higher proportion of fluid intake during the first 3 hours showed an association with a decreased 28-day mortality (OR, 0.951; 95% CI, 0.918–0.986; $p = .028$) and a higher proportion of fluid intake during 9–12 hours was associated with an increased 28-day mortality (OR, 2.761; 95% CI, 1.175–6.495; $p = .020$).

Discussion

We aimed in our present study to evaluate whether fluid management within the first 12 hours from the onset of septic shock in children affected the clinical outcomes. Our results indicated that the total amount of fluid given within the first 12 hours was similar between the children who survived and those that did not with no difference in the net fluid balance between these two groups. What made the difference between the survivors and nonsurvivors was the distribution of the fluid administered within the first 12 hours. Survivors tended to be given about 40% of the total administered fluids over 12 hours in the first 3 hour period with a gradual decrease in volume thereafter. However, the non-survivors showed a much more even distribution of administered fluid over the first 12 hours after septic shock. Of particular note, the higher proportion fluid group for the first 3 hour period after septic shock onset had a significantly low 28-day mortality whereas the patients in the higher proportion group for the last 3 hour period (i.e. 9–12 hours post septic shock) showed the opposite result and had a significantly high 28-day mortality.

The American College of Critical Care Medicine (ACCM) treatment guidelines for the first hour after the diagnosis of severe sepsis first and foremost recommend an aggressive fluid resuscitation of up to 60 mL/kg, followed by the titration of vasoactive medications based on the shock phenotype and, if necessary, additional fluids [4, 5, 11]. Even in the most recent SSC guidelines [6], the fluid therapy regimens have not changed. In practicality however, an aggressive resuscitation protocol of up to 60 mL/kg within 60 min is not easy to administer and it is for this reason that there is insufficient time to assess the effects or adverse effects of fluid resuscitation in pediatric cases. Moreover, increasing consideration is now being given to the mounting evidence that a significant volume overload beyond the initial period of resuscitation may be harmful [7, 8, 12]. Fluid resuscitation is one of the essential components of septic shock treatment and it is obvious that early fluid resuscitation in the initial stages of septic shock is key to a successful outcome, as indicated in many prior reports [2–4, 13–15]. In our current study of a pediatric septic shock, the survival rate was higher in the children who received more fluid in the first 3 hours. This is a very important finding in terms of the future management of these cases to improve perfusion i.e. the microcirculation in the initial period of septic shock. However it is difficult to define the appropriate fluid volumes and the optimal hemodynamic targets in children. The important determinant of the fluid resuscitation approach would be the fluid responsiveness but this is very difficult to estimate and there is no consensus on the assessment tools for this purpose in pediatric patients [16–19].

In our current cohort, a smaller volume of resuscitation fluid was administered than is recommended the ACCM guidelines, i.e. an approximately 20 ml/kg volume within the first 3 hours. Notably however, the mortality rate among our study subjects was no higher than that reported in other studies. Although our institute follows the guidelines recommended by the ACCM or SSC, the fluid resuscitation approaches in septic shock are at the discretion of the treating physicians. These clinicians consider a number of factors that could affect the patient's fluid responsiveness, and the possible adverse effects of fluid resuscitation, including the impacts on cardiac function, respiratory function or renal function. Hence, the children in our current analysis did not receive the aggressive fluid resuscitation regimen recommended by the existing guidelines. Importantly, this did not seem to increase the mortality rate. This is another important observation from our present analysis and raises questions about whether the currently recommended aggressive fluid resuscitation approaches are essential within the first hour of septic shock onset. The goal of fluid resuscitation is to increase the mean circulating pressure and stroke volume, thereby improving the tissue perfusion pressure. However, the ability of crystalloids to expand the intravascular volume is poor and several prior studies have reported that less than 5% of a crystalloid bolus remains in the intravascular space at one hour after the end of the infusion [20, 21]. Macro-circulatory goals such as blood pressure or central venous pressure are currently recognized as poor indicators of microcirculation, especially in sepsis and septic shock [22]. Moreover, the microvasculature plays an independent role in tissue perfusion and oxygenation that may not be influenced by macrovascular alteration [23]. In relation to fluid bolus therapy, some animal studies using intra vital microscopy and video imaging of the microcirculation have shown both improvement as well as persistence in microcirculatory dysfunction with bolus therapy [24]. Thus, fluid therapy targeted at the

macrocirculatory indicators can cause a fluid overload. The association of fluid overload and harm would be consistent in a broad spectrum of critically ill children. Most guidelines suggest an amount of fluid based on body weight and there is usually no accurate recommendation for fluid management after 1 hours. However, our present findings strongly indicate that basing the distribution of intake fluids over time on the patient's condition rather than body weight will have a far more beneficial impact on mortality outcomes in children with septic shock.

The recent Fluid Expansion as Supportive Therapy (FEAST) study, a Randomized Controlled Trial of fluid bolus therapy in over 3,000 acutely ill African children with sepsis and impaired perfusion, has been pivotal in generating interest in the potential harm from fluid resuscitation. The results of this trial indicated that both a higher early mortality (< 48 h) and higher late mortality (4 weeks) among children who received fluid boluses in response to impaired perfusion compared to those who did not receive fluid bolus [9]. Interestingly, in the post hoc analysis of the FEAST study, fluid boluses were found to have provided short-term benefit in terms of resolution of shock state, but the children who received these fluid boluses had increased mortality due to progression of cardiovascular dysfunction after this initial improvement [25, 26].

Abulebda et al. have described how the volume balance may influence the clinical course in pediatric patients with septic shock during the period after ICU admission [27]. These authors stratified their analysis based on the risk of mortality using their risk stratification tool and reported that an increased fluid intake and positive fluid balance after ICU admission are associated with poorer outcomes in pediatric septic patients with a low initial mortality risk, but not in patients with a moderate or high mortality risk. Their results deviate somewhat from what others have described in adults with septic shock [7, 8, 28–30] and show confounding outcomes according to the mortality risk. The reason for this limitation, as these authors pointed out, is the unavailability of data on the fluid balance of the subjects prior to their ICU admission. It is difficult to predict what the net effect on their results would have been if pre-ICU fluid balance data were available. On the other hand, a strength of our present study may be that the total intake fluid was estimated from the onset of shock regardless of the patient’s location, i.e. whether they were in the emergency room or general ward. The effects of early fluid therapy have therefore been more clearly demonstrated in our current investigation.

The existing reviews in the literature have revealed that a positive fluid balance recognized at different times during the first 24 hours in the ICU, leading to a cumulative positive balance at discharge, is predictive of a higher mortality [10, 12, 31–35]. Of note in particular, Merik et al. have demonstrated that a low volume resuscitation below that recommended by the SSC guidelines on the first ICU day in septic shock cases was associated with the reduction in mortality [33]. It is noteworthy also that our present results, in a comparable manner to previous studies, have revealed that increases in the intake volumes from 3 hours after the onset of septic shock increases mortality. Importantly, we show from our current data that a high intake volume from 9 to 12 hours post-onset has a significant association with high mortality in children with septic shock. These findings indicate that an aggressive fluid resuscitation approach from 3 hours after septic shock onset may be harmful.

Our study had several limitations of note. First, it was conducted in a single center and our results may therefore be lacking in general applicability. Second, our observational design incorporated a short period of only 12 hours, and we enrolled a smaller number of cases than other reports on fluid therapy. This limited our ability to determine a common relationship between fluid resuscitation and patient outcomes. Lastly, other factors such as antibiotic therapy, source control, and some other unmeasured clinical parameters may have contributed to our findings. For this reason, the prognosis of pediatric patients with septic shock cannot be explained simply by fluid therapy alone. It would thus appear difficult at present to standardize a single treatment protocol for these critically ill children or to draw clear conclusions from observational studies.

Conclusions

An increased fluid intake within the first 3 hours after septic shock onset in children is associated with a decreased 28-day mortality. Importantly however, an increased fluid intake after that time period seems to increase the mortality rate. Lower rates of mortality can thus be achieved in children diagnosed with septic shock who receive an adequate early fluid resuscitation regimen in the first 3 hours and conservative late fluid management from 3 to 12 hours after onset. We cautiously suggest therefore that a time-dependent fluid therapy strategy of ‘positive early in the first 3 hours, negative late’ will help to reduce morbidity and mortality in children with septic shock. However, because there is no current consensus on these strategies, high-quality tests in specific patient populations will be required in the future.

Declarations

Acknowledgements

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Authors’ contribution

WKJ, SJP designed the overall study. EJH and DHK carried out the collection and statistical analysis of the data. EJH drafted the manuscript. All authors contributed to the interpretation of the results and the revision of the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

Institutional review board of Asan Medical Center approved this study and waived the requirement for informed consent (study number: 2019-1269)

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Abbreviations

PICU: Pediatric Intensive Care U; SSC: Surviving Sepsis Campaign; PRISM score Ⅲ: Pediatric Risk of Mortality score Ⅲ; ACCM: The American College of Critical Care Medicine

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Tables

Table 1.

Baseline characteristics of the enrolled pediatric patients with septic shock

Variables	Total (n=144)	Survivors (n=115)	Non-survivors (n=29)	*P*-value
Age, years	9.1(1.6-14.3)	9.8(1.6-14.4)	4.1(1.6-13.9)	0.222
Boys, n (%)	89 (61.8)	61 (61.7)	18 (62.1)	0.576
Bwt, Kg	20.6 (7.7-43.0)	24.6 (7.4-44.0)	14.4 (9.2-42.8)	0.274
Underlying disease, n (%)				0.323
Hemato-oncology	61 (42.4)	47 (40.9)	14 (48.3)	
Neurology	23 (16.0)	21 (18.3)	2 (6.9)	
Cardiology	18 (12.5)	14 (12.2)	4 (13.8)	
Respiratory	16 (11.1)	14 (12.2)	2 (6.9)	
Gastro-intestinal	12 (8.3)	8 (7.0)	4 (13.8)	
Others	14 (9.7)	11 (9.6)	3 (10.3)	
PRISM III score	11.0 (8.0-17.0)	11.0 (8.0-15.0)	14.0 (11.0-20.0)	0.013
Micro-organism, n (%)				0.138
Fungus	10 (6.9)	6 (5.3)	4 (13.8)	
Gram positive	36 (39.6)	31 (38.6)	5 (44.8)	
Gram negative	57 (25.0)	44 (27.2)	13 (17.2)	
Mycoplasma	1 (0.7)	1 (0.9)	0 (0.0)	
Unproven	40 (27.8)	33 (28.9)	7 (24.1)	
Length of ICU stay, day	10 (5-22)	9 (5-22)	11 (3.5-23.5)	0.891
CRP, mg/dL	10.0 (2.8-18.3)	9.9 (3.2-18.7)	10.0 (2.4-16.7)	0.673
Lactic acid, mmol/L	2.1 (1.0-4.5)	2.0 (1.0-4.2)	3.8 (1.4-8.5)	0.052
Mechanical ventilation, n (%)	79 (54.9)	53 (46.1)	26 (89.7)	0.000
CRRT, n (%)	29 (20.1)	14 (12.2)	15 (51.7)	0.000
ECMO, n (%)	7 (4.9)	2 (1.7)	5 (17.2)	0.004

Values are expressed as numbers (%) or medians (IQR) unless otherwise indicated.

PRISM III score, Pediatric Risk of Mortality III score

CRP, C-reactive protein

CRRT, continuous renal replacement therapy

ECMO, extra-corporeal membrane oxygenator

Table 2.

Fluid administration pattern from the onset of septic shock in the pediatric patients

Variables	Total (n=144)	Survivors (n=115)	Non-survivors (n=29)	*P*-value
Amount of fluid received				
During the first 12 hours, ml/kg	56.5 (40.8-79.6)	54.7 (39.-79.4)	57.3 (43.0-85.3)	0.357
0-3 hours, ml/kg	21.4 (11.3-30.7)	21.9 (12.1-31.5)	16.1 (10.6-30.5)	0.239
3-6 hours, ml/kg	12.0 (7.4-17.9)	12.0 (7.2-16.4)	12.0 (9.9-21.6)	0.163
6-9 hours, ml/kg	11.2 (7.6-17.7)	10.9 (6.8 -17.8)	13.9 (9.7-17.7)	0.189
9-12 hours, ml/kg	10.1 (6.6-15.0)	9.4 (6.0-14.4)	13.1 (9.6-17.7)	0.014
Net fluid balance				
During the first 12 hours, ml/kg	20.9 (4.9-41.5)	20.7 (4.4-39.1)	23.9 (6.3-53.2)	0.404
0-3 hours, ml/kg	14.8 (4.3-27.3)	16.7 (4.8-27.7)	12.4 (3.6-23.0)	0.199
3-6 hours, ml/kg	4.0 (-2.9-10.0)	3.1 (-4.7-10.0)	4.9 (0.8-11.1)	0.044
6-9 hours, ml/kg	3.0 (-2.2-9.3)	3.1 (-2.8-9.4)	2.8 (-0.2-9.5)	0.363
9-12 hours, ml/kg	1.4 (-3.1-7.3)	0.8 (-3.6-6.5)	3.1 (-1.7-11.8)	0.156

Values are expressed as a median (IQR) unless otherwise indicated.

Table 3.

Multivariable logistic regression analysis of 28-day mortality risk factors in the pediatric patients with septic shock

Variables	Odds Ratio	95% Confidence Interval	*P*-value
PRISM III score	1.069	1.012-1.130	.017
Higher proportion fluid intake group during the first 3 hours	0.951	0.918-0.986	.028
Higher proportion fluid intake group during 9-12 hours	2.761	1.174-6.495	.020

PRISM III score, Pediatric Risk of Mortality III score

Figures

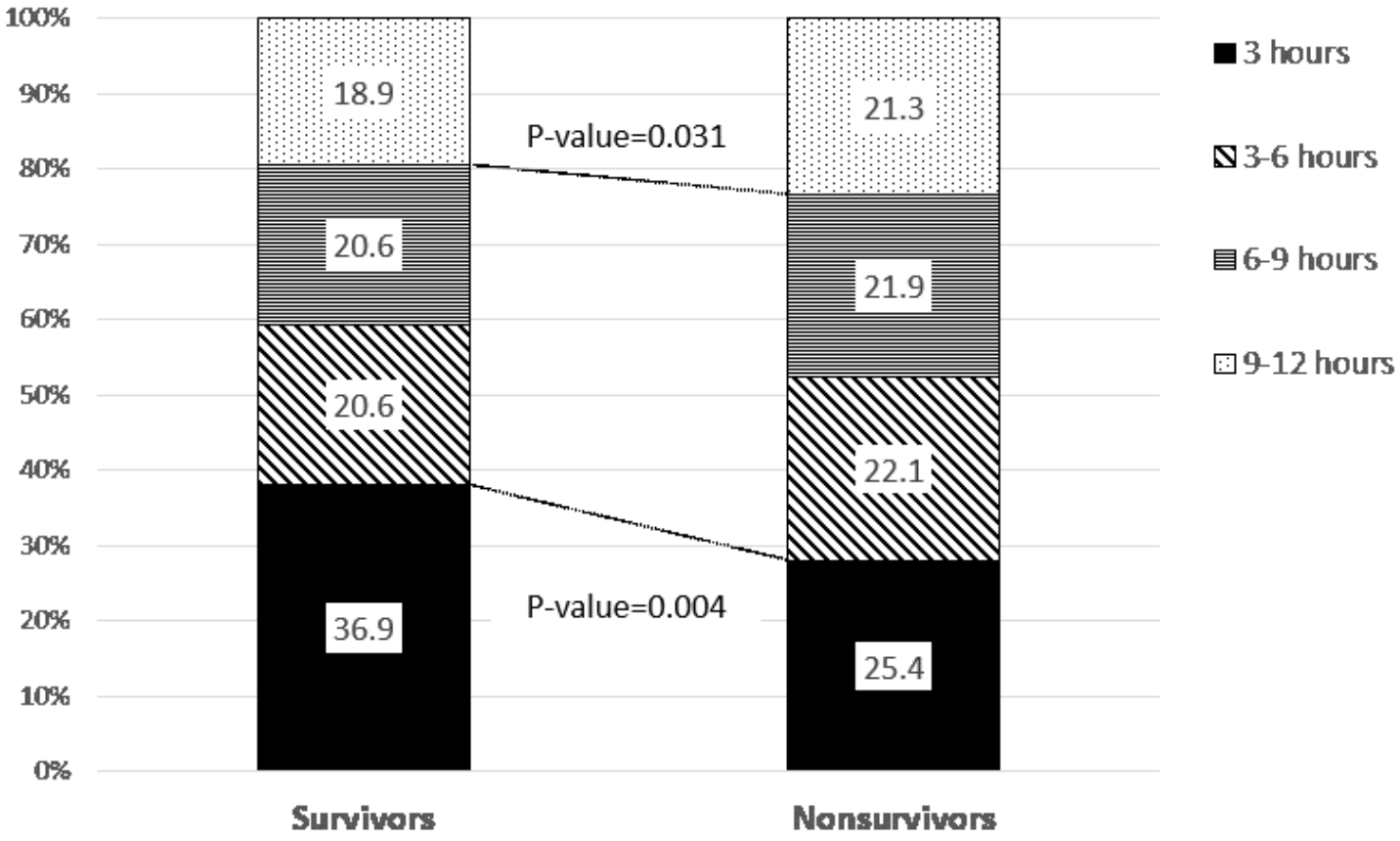

Figure 1

Distribution of the fluid administrated to the study patients during the 12 hour period from the onset of septic shock

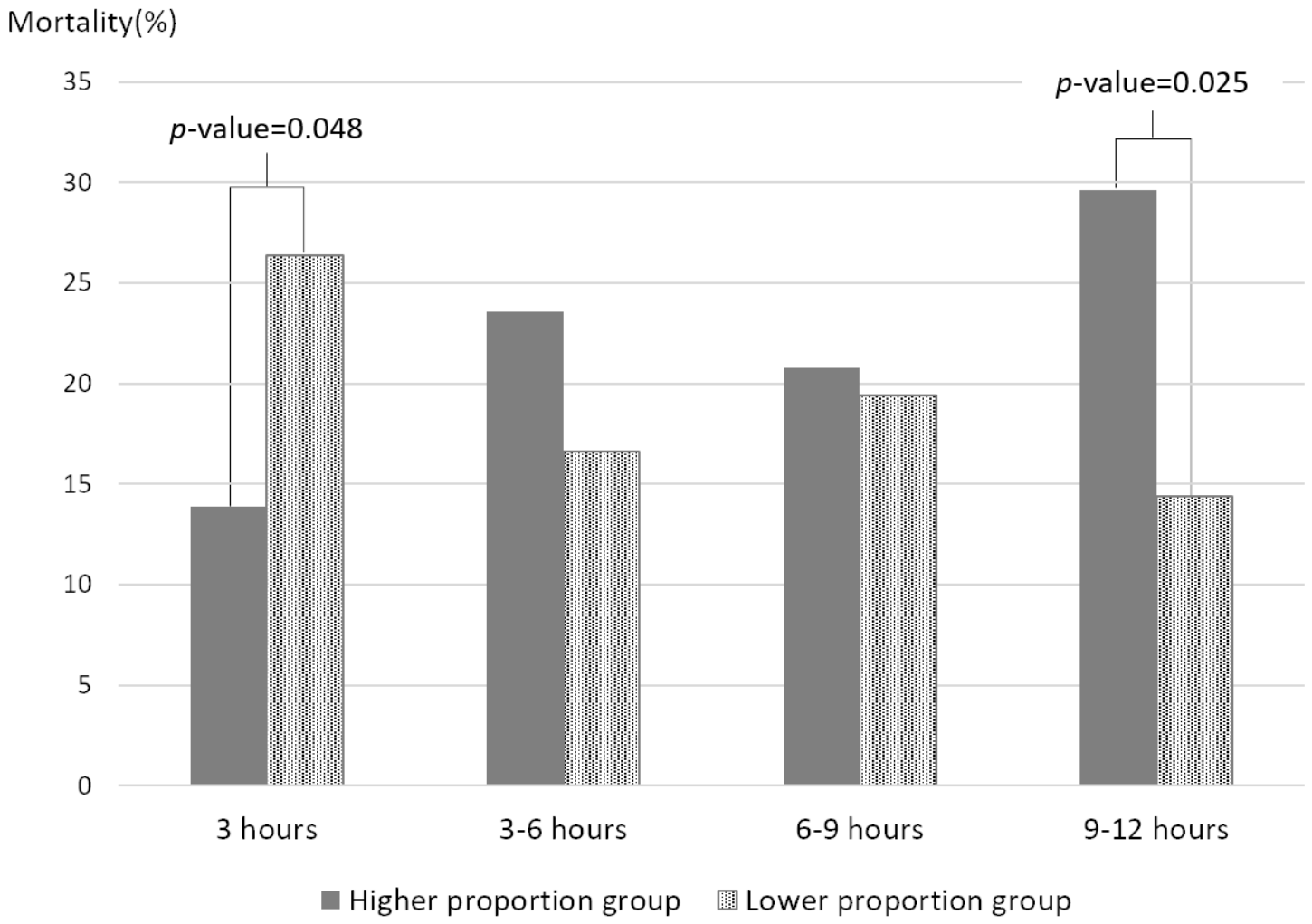

Figure 2

Comparison of mortality outcomes between the higher and lower fluid proportion groups stratified by the time from septic shock onset Higher proportion group, patients receiving a higher than median distribution of fluid within a discrete 3 hour period during the first 12 hours post septic shock Lower proportion group, patients receiving a lower than median distribution of fluid within a discrete 3 hour period during the first 12 hours post septic shock