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Effect of rapid fluid administration on the prognosis of septic shock patients with isolated hyperlactatemia: A prospective multicenter observational study

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ABSTRACT

Background: We aimed to investigate the association between initial fluid resuscitation in septic shock patients with isolated hyperlactatemia and outcomes.
Methods: This multicenter prospective study was conducted using the data from the Korean Shock Society registry. Patients diagnosed with isolated hyperlactatemia between October 2015 and December 2018 were included and divided into those who received 30 mL/kg of fluid within 3 or 6 h and those who did not receive. The primary outcome was in-hospital mortality; the secondary outcomes were intensive care unit (ICU) admission, length of ICU stay, mechanical ventilation, and renal replacement therapy (RRT).
Results: A total of 608 patients were included in our analysis. The administration of 30 mL/kg crystalloid within 3 or 6 h was not significantly associated with in-hospital mortality in multivariable logistic regression analysis ([OR, 0.8; 95% CI, 0.52–1.23, $p = 0.31$], [OR, 0.96; 95% CI, 0.59–1.57, $p = 0.88$], respectively). The administration of 30 mL/kg crystalloid within 3-h was not significantly associated with mechanical ventilation and RRT ([OR, 1.19; 95% CI, 0.77–1.84, $p = 0.44$], [OR, 1.2; 95% CI, 0.7–2.04, $p = 0.5$], respectively). However, the administration of 30 mL/kg crystalloid within 6 h was associated with higher ICU admission and RRT ([OR, 1.57; 95% CI, 1.07–2.28, $p = 0.02$], [OR, 2.08; 95% CI, 1.19–3.66, $p = 0.01$], respectively).
Conclusions: Initial fluid resuscitation of 30 mL/kg within 3 or 6 h was neither associated with an increased or decreased in-hospital mortality in septic shock patients with isolated hyperlactatemia.

1. Introduction

Despite the ongoing research and advances in management, sepsis and septic shock are still recognized as major public health problems and the leading cause of death with high mortality rates [1,2]. The incidence of sepsis has gradually increased, causing over 6 million deaths worldwide annually [2-4]. Furthermore, sepsis survivors often have long-term sequelae such as functional disability, persistent new cognitive impairment despite receiving medical treatment, and social implications [5].

Fluid resuscitation to replace intravascular volume depletion is one of the key components in managing patients with septic shock according to the current guidelines [6]. The 2016 Surviving Sepsis Campaign guideline strongly recommends the administration of at least 30 mL/kg of intravenous (IV) crystalloid fluid within the first 3-h in patients with hypotension or lactate ≥4 mmol/L as initial resuscitation [6]. However, the quality of evidence supporting the administration of fluid resuscitation is relatively low, and the recommended fluid volume is based on the

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average volume of fluid prior to randomization indicated in some clinical trials that used this volume in routine clinical practice at the early stages of resuscitation [7-10]. Even in patients with normal blood pressure (BP), sepsis-induced hypoperfusion can occur, which is indicated by elevated lactate levels, and the rapid administration of the same amount of fluid is also recommended in patients with isolated hyperlactatemia [11,12].

Avoiding fluid volume overload is as important as proper fluid resuscitation in critically ill patients, and the guideline warns against the excessive administration of fluid [6]. Several studies have reported that positive fluid balance and volume overload are associated with worse outcomes in patients with sepsis or septic shock [13-16]. Despite the absence of fluid overload, the current guideline does not indicate the difference between patients with hypotension and those with isolated hyperlactatemia (elevated lactate without hypotension) in terms of initial fluid resuscitation.

The paradigm of large-volume fluid resuscitation in patients with septic shock remains a challenge; moreover, the benefit of restrictive fluid approach with earlier use of vasopressors during the early stages of septic shock was recently reported [17-19]. On the contrary, no significant differences were observed between conventional liberal fluid resuscitation and restrictive fluid strategy in terms of mortality or fluid-related complication rates in patients with septic shock or severe sepsis [20,21]. In addition, mortality and severity were lower in septic shock patients with isolated hyperlactatemia defined by Sepsis-3 in a single-center observational study [22].

To the best of our knowledge, the data and evidence regarding the adequate initial fluid resuscitation for patients with sepsis-induced hypoperfusion, particularly for those with isolated hyperlactatemia, are limited. Hence, this study aimed to investigate the association between initial fluid resuscitation in septic patients with isolated hyperlactatemia (lactate ≥4 mmol/L without refractory hypotension) and outcomes. We hypothesized that the outcomes of patients with sepsis-induced hypoperfusion without refractory hypotension will not worsen if rapid fluid administration is performed as initial treatment.

2. Materials and methods

2.1. Study design and setting

We conducted a prospective multicenter observational study using data from the Korean Shock Society (KoSS) septic shock registry, which is a university-affiliated hospital-based research network. The KoSS registry enrolled patients aged 19 years or older who visited 1 of the 10 participating emergency departments (EDs) and met the eligibility criteria. Patients with evidence of hyperlactatemia or refractory hypotension with suspected or confirmed infection were included in the study [7,9,10,23]. Hyperlactatemia was defined as a serum lactate concentration of ≥4 mmol/L. Refractory hypotension was defined as persistent hypotension (mean arterial pressure < 70 mm Hg or systolic BP <90 mm Hg) after an IV fluid challenge of 30 mL/kg. Meanwhile, patients with "do not resuscitate" status, who only fulfilled the inclusion criteria 6 h after ED arrival, were transferred from other hospitals and did not meet the inclusion criteria upon ED arrival, or transferred to other hospital directly from the ED were excluded. Data collected via a standardized registry form were uploaded into an electronic database registry. The institutional review board of the participating hospitals ethically reviewed and approved the study, and the participating researchers obtained informed consent from the study participants prior to the collection of data. Further details of the KoSS septic shock registry were published prior to the conduct of the present study [23].

2.2. Study population and data extraction

To examine patients with sepsis-induced hypoperfusion, we included those with isolated hyperlactatemia without refractory hypotension from the KoSS registry, whose data were collected between October 2015 and December 2018. Patients transferred from other hospitals who lacked data on fluid administered prior to ED arrival were excluded. The registry collected the data of patients with a cumulative fluid amount of 30 mL/kg or more. The enrollment time was defined as the period when the lactate level was confirmed to be 4 mmol/L or higher and referred to as the "shock recognition time." The included patients were divided into two groups: those administered with 30 mL/kg of fluid within 3-h after shock recognition and those who did not receive fluid resuscitation. Then, the outcomes of the two groups were compared.

We extracted the following data and variables from the registry: 1) baseline characteristics [age, sex, vital signs upon ED arrival, comorbidities (hypertension, diabetes, cardiovascular disease, cerebrovascular accident, etc.)] and site of infection (respiratory, urinary tract, gastrointestinal, hepatobiliary, and pancreas), 2) laboratory findings, and 3) severity measures [Sequential Organ Failure Assessment (SOFA) score upon enrollment and Acute Physiology and Chronic Health Evaluation (APACHE) II score using the lowest score within 24 h upon ED arrival] [24,25].

2.3. Outcome variables and subgroup analysis

The primary outcome was in-hospital mortality. Meanwhile, ICU admission, length of ICU stay, frequency and days of mechanical ventilation, and renal replacement therapy (RRT) were compared between the two groups as secondary outcomes. Acute kidney injury was defined by Kidney Disease: Improving Global Outcomes (KDIGO) guideline. Initiation of renal replacement was at the discretion of treating physician though it was generally decided based on KDIGO and SSC guidelines [26,27]. Additional analysis was performed to determine whether the administration of 30 mL/kg of fluid within 6 h was associated with patient outcomes.

2.4. Statistical analysis

Continuous baseline variables were expressed as mean (standard deviation) or median (interquartile range) and analyzed using the Shapiro-Wilk test to determine the distribution. The Mann-Whitney test was used to compare the groups with unsatisfied to normally distributed continuous variables. Categorical variables were expressed as numbers and percentages and analyzed using a chi-square test. Two-tailed p values of <0.05 were considered significant. The logistic regression method was used for multivariable analysis to determine the association between the initial fluid resuscitation and in-hospital mortality, after adjusting for pre-defined confounding variables including age, sex, systolic BP, heart rate, site of infection (respiratory tract, urinary tract infection, gastrointestinal tract, and hepatobiliary/pancreas), and initial lactate level and SOFA score upon enrollment. The Hosmer-Lemeshow test was used to confirm the logistic model calibrations. We used propensity score matching to adjust for patient imbalances between fluid resuscitation volume below or above 30 mL/kg groups within 3 and 6-h using variables including age, sex, comorbidities, vital signs on ED arrival, source of infection, laboratory test results, SOFA score upon enrollment, and APACHE II score using the worst value within 24-h of the ED arrival. We performed 1-to-N matching with a caliper = 0.1 for each group. All covariates were used for the matching variables. Balance between 2 groups was evaluated based on standardized mean differences. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses.

3. Results

A total of 830 septic shock patients with isolated hyperlactatemia were registered in the KoSS registry during the study period; of them, 222 patients were transferred from other hospitals. Finally, 608 patients

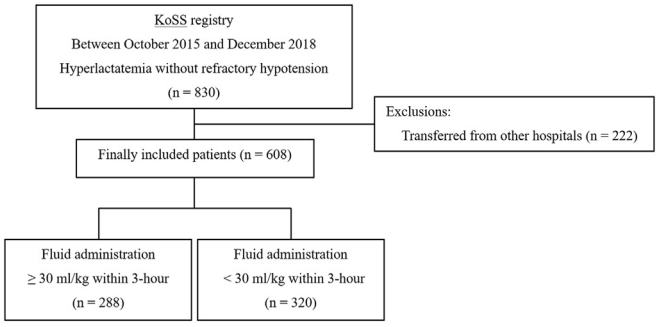

Fig. 1. Flow chart of the study process. KoSS: Korean Shock Society.

were included in our study and divided into two groups according to their fluid resuscitation status (Fig. 1; Supplemental Fig. 1).

The baseline characteristics of all included patients and the two groups are summarized in Table 1. Patients who received 30 mL/kg of fluid ($n = 288$, 47.4%) showed significantly lower systolic/diastolic BP as well as higher SOFA scores and initial lactate levels. Other variables including age, sex, heart rate, respiratory rate, body temperature, and APACHE II score were not significantly different between the two groups.

The primary and secondary outcomes in the two groups are summarized in Table 2. In-hospital mortality was not significantly different between the two groups ($p = 0.95$). Patients in the 30 mL/kg fluid administration group were more frequently admitted in the ICU ($p = 0.02$), frequently received RRT ($p = 0.02$), and had longer duration of mechanical ventilation ($p = 0.02$).

The odds ratios of receiving 30 mL/kg of fluid indicated in the univariable and multivariable analyses are summarized in Table 3. The administration of 30 mL/kg of fluid within 3-h was associated with a higher incidence of RRT (OR, 1.66; 95% CI, 1.08–2.55, $p = 0.02$) and ICU admission (OR, 1.46; 95% CI, 1.06–2.02, $p = 0.02$) as shown in the univariate analysis. However, the volume of fluid administered within 3-h was not associated with in-hospital mortality as shown in the univariate (OR, 1.01; 95% CI, 0.71–1.45, $p = 0.95$) and multivariable analyses (OR, 0.8; 95% CI, 0.52–1.23, $p = 0.31$). It was not also associated with the secondary outcomes, including RRT and ICU admission, after adjusting for influencing factors in the multivariable analysis using a logistic regression model.

Additional analysis of the administration of 30 mL/kg of fluid within 6 h was performed ($n = 353$, 58.1%); no association was also observed between the volume of fluid administered and in-hospital mortality. However, it was associated with ICU admission (OR, 1.57; 95% CI, 1.07–2.28, $p = 0.02$) and RRT (OR, 2.08; 95% CI, 1.19–3.66, $p = 0.01$) in the multivariable analysis (Table 4).

The number of patients included in propensity score matching analysis were 212 (106 patients administered more than 30 mL/kg, 106 patients administered less than 30 mL/kg within 3-h) and 210 (105 patients administered more than 30 mL/kg, 105 patients administered less than 30 mL/kg within 6-h). The balance between 2 groups were evaluated with standardized mean differences (Supplemental Table 1). Standardized mean differences after propensity score matching were lower than 0.2 except 2 variables (chronic lung disease and respiratory tract infection). The group who received 30 mL/kg of fluid administration within 3-h and 6-h did not show significant difference of in-hospital mortality in propensity score matching analysis (OR = 0.75, 1.19, respectively. $p = 0.32$, 0.56, respectively) (Table 5). There were no significant differences of other secondary outcomes (ICU admission, mechanical ventilation and renal replacement therapy) between group with fluid administration more 30 mL/kg and those with less within 3-h, whereas the OR of fluid administration more 30 mL/kg within 6-h for ICU admission was significantly higher (OR = 1.84, $p = 0.03$).

Table 1
Baseline characteristics stratified by volume of fluid admistration within 3-h.

Variables	Total ($n = 608$)	Fluid administration ≥30 mL/kg ($n = 288$)	Fluid administration <30 mL/kg ($n = 320$)	*p*-value
Age, years, median (IQR)	70 (61–78)	70 (62–78)	70 (60–78)	0.49
Sex, male (%)	378 (62.2)	184 (63.9)	194 (60.6)	0.41
Vital signs on ED arrival				
Systolic BP, mm Hg, median (IQR)	110 (88–137)	94 (74–120)	122 (103–144)	<0.01
Diastolic BP, mm Hg, median (IQR)	64 (54–80)	58 (47–71)	71 (60–83)	<0.01
Heart rate, per min, median (IQR)	115 (98–131)	116 (98–132)	113 (97–130)	0.63
Respiratory rate, per min, median (IQR)	21 (20–28)	22 (20–28)	20 (20–28)	0.26
Body temperature, Celsius, mediam (IQR)	37.8 (36.6–38.8)	37.9 (36.6–38.9)	37.8 (36.7–38.6)	0.2
Comorbidities				
Hypertension (%)	257 (42.3)	119 (41.3)	138 (43.1)	0.65
Diabetes (%)	196 (32.2)	87 (30.2)	109 (34.1)	0.31
Cardiovascular disease (%)	90 (14.8)	33 (11.5)	57 (17.8)	0.03
Cerebrovascular disease (%)	60 (9.9)	25 (8.7)	35 (10.9)	0.35
Chronic lung disease (%)	63 (10.4)	31 (10.8)	32 (10)	0.76
Nursing center/residence (%)	23 (3.8)	14 (4.9)	9 (2.8)	0.19
Metastatic cancer (%)	183 (30.1)	108 (37.5)	75 (23.4)	<0.01
Chronic renal disease (%)	45 (7.4)	19 (6.6)	26 (8.1)	0.47
Chronic liver disease (%)	96 (15.8)	55 (19.1)	41 (12.8)	0.03
Sites of infection				
Respiratory tract (%)	155 (25.5)	66 (22.9)	89 (27.8)	0.17
Urinary tract infection (%)	74 (12.2)	31 (10.7)	43 (13.4)	0.31
Gastrointestinal tract (%)	79 (13)	30 (10.4)	49 (15.3)	0.07
Hepatobiliary/Pancreas (%)	120 (19.7)	73 (25.4)	47 (14.7)	<0.01
Others (%)	50 (8.2)	22 (7.6)	28 (8.8)	0.62
First measured latate, mmol/l, median (IQR)	5.7 (4.5–8.3)	6.2 (4.7–8.8)	5.4 (4.4–7.5)	<0.01
SOFA score upon enrolment, median (IQR)	5 (3–7)	5 (4–8)	4 (3–6)	<0.01
APACHE II score using the lowest score within 24-h of the ED arrival, median (IQR)	19 (15–26)	19 (15–26)	19 (15–26)	0.92

Abbreviations: ED, emergency department; BP, blood pressure; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.
Continuous variables are presented as the median (Q1-Q3) and tested by using The Mann-Whitney test, and categorical variables are presented as N (%) and tested by using the chi-squared test.

Table 2
Primary and secondary outcomes of groups according to the volume of fluid administration within 3-h.

Outcomes	Fluid administration ≥30 mL/kg within 3-h ($n = 288$)	Fluid administration <30 mL/kg within 3-h ($n = 320$)	*p*-value
Primary outcome			
In-hospital mortality	79 (27.4)	87 (27.2)	0.95
Secondary outcomes			
Frequency of admission to the ICU	172 (59.7)	161 (50.3)	0.02
Duration of ICU stays, day ($n = 333$)	4 (3–9)	4 (3–8)	0.83
Frequency of mechanical ventilation	93 (32.3)	92 (28.8)	0.34
Duration of mechanical ventilation, day ($n = 185$)	6 (3–13)	4 (2–8)	0.02
Frequency of renal replacement therapy	59 (20.5)	43 (13.4)	0.02
Duration of hospitalization, day ($n = 603$)	13 (7–24)	12 (7–23)	0.45

Abbreviations: ICU, intensive care unit.
Continuous variables are presented as the median (Q1, Q3) and tested by using the Mann-Whitney test, and categorical variables are presented as N (%) and tested by using the chi-squared test.

Table 3
Odds ratio of administration fluid of 30 mL/kg within 3-h for primary and secondary outcomes with univariable and multivariable analysis.

Outcomes	Univariable analysis			Multivariable analysis		
	Unadjusted OR	95% CI for the OR	*p*-value	Adjusted OR	95% CI for the OR	*p*-value
	Administered fluid ≥30 mL/kg within 3-h					
Primary outcome						
In-hospital mortality	1.01	0.71–1.45	0.95	0.8	0.52–1.23	0.31
Secondary outcome						
Admission to the ICU	1.46	1.06–2.02	0.02	1.39	0.96–2.03	0.08
Mechanical ventilation	1.18	0.87–1.67	0.34	1.19	0.77–1.84	0.44
Renal replacement therapy	1.66	1.08–2.55	0.02	1.2	0.7–2.04	0.5

Abbreviations: OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Table 4
Odds ratio of administration fluid of 30 mL/kg within 6-h for primary and secondary outcomes with univariable and multivariable analysis.

Outcomes	Univariable analysis			Multivariable analysis		
	Unadjusted OR	95% CI for the OR	*p*-Value	Adjusted OR	95% CI for the OR	*p*-Value
	Administered fluid ≥30 mL/kg within 6-h					
Primary outcome						
In-hospital mortality	1.21	0.84–1.75	0.3	0.96	0.59–1.57	0.88
Secondary outcome						
Admission to the ICU	1.62	1.17–2.24	<0.01	1.57	1.07–2.28	0.02
Mechanical ventilation	1.32	0.93–1.88	0.13	1.44	0.92–2.24	0.11
Renal replacement therapy	2.28	1.52–3.66	<0.01	2.08	1.19–3.66	0.01

Abbreviations: OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

4. Discussion

In this study, we aimed to investigate the association between initial fluid resuscitation and outcomes, including in-hospital mortality, in septic patients with isolated hyperlactatemia. We found that the administration of 30 mL/kg of fluid within 3-h was not associated with in-hospital mortality or other outcomes such as ICU admission, mechanical ventilation, or RRT. However, the duration of mechanical ventilation was significantly longer in patients who received 30 mL/kg of fluid within 3-h. Furthermore, administration of 30 mL/kg of fluid

Table 5
Odds ratio of administration fluid of 30 mL/kg within 3-h and 6-h for primary and secondary outcomes with propensity score matching analysis.

Outcomes	Administered fluid ≥30 mL/kg within 3-h			Administered fluid ≥30 mL/kg within 6-h		
	OR	95% CI for the OR	*p*-value	OR	95% CI for the OR	*p*-value
Primary outcome						
In-hospital mortality	0.75	0.43–1.32	0.32	1.19	0.67–2.13	0.56
Secondary outcome						
Admission to the ICU	1.04	0.6–1.8	0.89	1.84	1.05–3.22	0.03
Mechanical ventilation	0.91	0.51–1.65	0.76	1.79	0.93–3.44	0.08
Renal replacement therapy	1.31	0.64–2.7	0.76	1.8	0.83–3.9	0.14

Abbreviations: OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

within 6 h was significantly associated with ICU admission and RRT. In propensity matching score analysis, the results were similar to main analysis though ICU admission was significantly higher in group administered more than 30 mL/kg of fluid within 6-h. However, due to relatively small number of patients included in propensity score matching analysis ($n = 212$ in 3-h and $n = 210$ in 6-h), our results regarding the effect of >30 mL/kg fluid administration in septic patients with isolated hyperlactatemia should be interpreted with caution.

Several previous studies have reported the association between higher mortality and positive fluid balance and recommended the careful assessment of patients who received fluid resuscitation. Positive cumulative fluid balance was an independent predictor of poor outcomes in an observational study of European adult ICU patients with sepsis [28]. In a single-center prospective observational study, Acheampong et al. reported that a persistent positive balance in critically ill patients increased the risk of death [16]. In a retrospective study, de Oliveira et al. showed that a positive fluid balance between 24th and 28th hours was associated with higher mortality [13]. Another retrospective study of septic shock noted that a positive net fluid balance within 24 h was a predictor of in-hospital mortality [29]. Furthermore, Kelm et al. reported that fluid overload on day 1 increased the need for fluid-related medical interventions [30]. Although the observation time for fluid administration in previous studies was longer and/or later than that in the present study and these studies were mostly conducted in ICU patients, the accumulating positive fluid balance upon ED arrival could have a negative effect and cause fluid overload-induced complications, especially in patients without hypotension. In the present study, the administration of 30 mL/kg of fluid within 3 or 6 h was not significantly associated with higher in-hospital mortality.

A recent retrospective study reported no significant differences in the incidence of intubation between liberal and restrictive fluid groups in high-risk patients with sepsis [20]. According to a previous randomized pilot study, a restrictive resuscitation strategy did not improve the incidence of mortality, organ failure, or adverse events [21]. One large observational study of protocolized sepsis bundle with 26,978 patients reported that the time to completion of the initial fluid administration of 30 mL/kg had no significant association with in-hospital mortality [31]. Hence, caution should be observed when interpreting these results to prevent the incidence of early fluid resuscitation. This is because critically ill patients are usually provided with fluid resuscitation at an early stage and that the mortality rate could possibly increase. The baseline characteristics of the group administered with 30 mL/kg of fluid were more severe. Moreover, higher SOFA score and lower BP were also observed in the present study. However, our analysis was adjusted for confounding factors to reduce the bias and address the independent association of fluid administration on various outcomes of septic shock patients with isolated hyperlactatemia.

To the best of our knowledge, this is the first study to investigate the effect of initial rapid crystalloid fluid administration in septic shock patients with isolated hyperlactatemia. The recommended volume of 30 mL/kg within 3-h based on the current guideline may not be harmful for septic shock patients with isolated hyperlactatemia. However, a large-scale randomized trial is needed to determine the ideal volume of initial fluid resuscitation in septic patients with isolated hyperlactatemia.

This study has several limitations. First, although the data collection and the registry review were performed prospectively, the aim was to analyze the association between the initial fluid resuscitation in septic shock patients with isolated hyperlactatemia, and the outcomes were not planned before the KoSS registry was established. However, the data of patients who received 30 mL/kg of fluid within 3 and 6 h were collected in our registry, and no data were missed. Second, data on the total fluid volume administered in each patient were not included in the registry, and patients who did not receive different infusion doses were classified into different groups and were possibly included in the analysis (e.g., 29 mL/kg vs. 31 mL/kg). However, the administration of 30 mL/kg of fluid is recommended by current guidelines and is widely used to manage septic shock. Third, critically ill patients are usually provided with fluids to maintain the blood pressure and require more mechanical ventilation and RRT. However, a multivariable analysis was performed to adjust the severity measures, including SOFA score and serum lactate level, and to determine their independent associations with fluid resuscitation. Fourth, although we tried to include and analyze the maximum number of variables as already known as important factors in previous sepsis studies, hidden confounders could exist, which could affect the outcomes unmeasured variables. Fifth, the accurate volume of fluid administered before enrollment was unknown. However, we excluded patients transferred from other hospitals to minimize the effect of the fluid volume administered prior to the study enrollment; and it was investigated whether the total amount of infusion before and after enrollment was 30 mL/kg in our registry. In addition, the median ED arrival to enrollment time of the included patients was 28 min. Therefore, the volume of fluid administered before enrollment was not relatively large. Sixth, this study focused on patients with early septic shock diagnosed in the ED. Therefore, it will be difficult to apply the results of this study to patients who developed septic shock after hospital admission. Seventh, there might be concern to the validity of our findings in patients who are the old or vulnerable to excessive fluid administration (ex. chronic kidney disease, chronic liver disease and cardiovascular disease). However, we did not find the association between initial fluid resuscitation and outcomes in those groups like main findings (Table S1). Finally, because of the nature of the multicenter registry-based study, the number of cases and the period of participation varied among hospitals. However, all the hospitals participating in this study managed patients using a standard protocol, which was based on the surviving sepsis campaign. Hence, we presume that the study results were less affected by the differences in the participating hospitals.

5. Conclusions

In the present study, an initial fluid resuscitation of 30 mL/kg within 3 or 6 h was neither associated with an increased or decreased in-hospital mortality in septic shock patients with isolated hyperlactatemia though administration of 30 mL/kg of fluid within 6-h was associated with higher ICU admission in propensity matching analysis. However, due to relatively small number of patients included in propensity score matching analysis our results regarding the effect of >30 mL/kg fluid administration in septic patients with isolated hyperlactatemia should be interpreted with caution. Our findings support the hypothesis that the currently recommended initial fluid may not be harmful in septic shock patients with isolated hyperlactatemia. Large randomized clinical trials are warranted to confirm these findings.

Funding information

None.

Author contributions

B.S. K. and W.Y. K.f conceived the idea. H. L., B.S. K. and W.Y. K.f wrote the manuscript. H. L., S.H. C., K. K., T.G. S., Y.S. P., S.M. R., G.J. S., W.Y. K.g, T.H. L., W.Y. K.f and B.S. K. collected data. K. K. and T.G. S. analyzed the data. D. S., Y.S. P. and S.M. R. performed statistical analysis. T.H. L. and W.Y. K.f supervised the whole study process. W.Y. K.f and T.H. L. assisted with study design and revised the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.07.003.

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