Original article

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Balanced salt solution versus normal saline solution as initial fluid resuscitation in pediatric septic shock: A randomized, double-blind controlled trial

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Abstract

Objective: **Initial fluid resuscitation is mandatory in treatment of septic shock. Current sepsis guidelines do not have the recommendation for either balanced salt or normal saline solution for initial fluid resuscitation. The objective of this study was to determine the impact of balanced salt solution (BS) versus normal saline solution (NS) in pediatric septic shock as initial fluid resuscitation.**

Design: **A double-blind randomized controlled trial study.**

Setting: **A single tertiary care center in Bangkok, Thailand.**

Patients and participants: **Children aged 1 month to 18 years who were diagnosed with septic shock. We excluded patients who received fluid resuscitation in the 24 hours prior to septic shock, end-stage disease, and refusal of informed consent.**

Interventions: **Patients were randomly assigned into 2 groups after being diagnosed with septic shock and required fluid resuscitation (NS or BS).**

Measurements and results: **Demographic data, vasoactive-inotropic scores, and outcomes were evaluated. The primary outcome was incidence of hyperchloremic metabolic acidosis. Sixty-one septic shock children were enrolled into this study (NS=31 patients, and BS=30 patients). Baseline characteristics between two groups were not different. The incidence of hyperchloremic metabolic acidosis was 17 (54.8%) and 10 (33.3%) in NS and BS groups, respectively (p=0.091). The hospital mortality and prevalence of acute kidney injury were not different between groups.**

Conclusion: **In pediatric septic shock, the initial fluid resuscitation with balanced salt solution and normal saline was associated with similar clinical outcomes. However, normal saline solution had a trend toward more frequent hyperchloremic metabolic acidosis in children with septic shock when compared to balanced salt solution.**

Key words: Balanced salt solution, normal saline solution, pediatric septic shock, Ringer's acetate, initial fluid resuscitation, hyperchloremic metabolic acidosis.

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Introduction

Pediatric sepsis is defined as the infectious condition with systemic inflammatory manifestations, whereas septic shock is sepsis with cardiovascular organ dysfunction that is from imbalance between oxygen delivery and oxygen consumption. (1) Early recognition and initial fluid resuscitation are the essential management in children with shock. Intravenous fluid serves to increase intravascular volume which augmenting oxygen delivery. Current guidelines for pediatric septic shock advocate initial fluid resuscitation of 20 ml/kg, titrated to achieve adequate blood pressure and organ perfusion, up to 40-60 ml/kg. (2) Pediatric sepsis guidelines recommend initial isotonic crystalloid as initial fluid resuscitation. However, there is no clear consensus on the type of isotonic crystalloid. Normal saline solution (NS) is a chloride-rich fluid that alters acid-base equilibrium and reduces strong ion difference (SID), whereas balanced salt solution (BS) including Ringer's lactate or Ringer's acetate have an SID similar to plasma. (3) In addition, large amounts of NS can induce hypernatremia, hyperchloremia, and metabolic acidosis. (4,5) These can produce renal vasoconstriction, decrease glomerular filtration rate, (6) and reduce gastric mucosa perfusion. (7) Several studies have shown resuscitation with NS had been associated with unfavorable outcomes in animal studies, (8) human volunteers, (9) and observational studies. (10,11) Furthermore, there is evidence of an increased incidence of acute kidney injury (AKI), needing renal replacement therapy (RRT) (12) and associated with a higher risk of mortality in adults. (3,13,14) However, large randomized controlled trials showed no difference in outcomes on AKI and mortality between BS and NS in critically ill adults. (15,16)

In pediatric shock, there has been limited data comparing clinical outcomes between NS and BS. A prior study showed children with dengue shock syndrome who received BS were slower to recover from shock than NS. (17) Recently, a matched retrospective study showed that the mortality was not different between BS and NS groups in pediatric sepsis. (18) A large observational cohort study in pediatric severe sepsis showed patients who received exclusively BS at 72 hours had lower mortality, prevalence of AKI and vasoactive use. (19) However, no double-blinded randomized controlled study to date has evaluated the outcomes of the types of initial isotonic crystalloids fluid bolus in pediatric septic shock.

Materials and methods

This study was a prospective, randomized controlled trial that compared the use of NS with BS in pediatric septic shock at a tertiary care center. The study protocol was approved by the institutional review board (IRB) and all participants provided informed written consent. This trial was registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02336620. The primary objective was to evaluate the incidence of hyperchloremic metabolic acidosis within 48 hours of study. The secondary outcomes were prevalence of AKI, need for RRT, length of pediatric intensive care unit (PICU) stay, and in-hospital mortality. We also investigated the association between the clinical risk factors, circulating biomarkers and in-hospital mortality.

Patient population

Patients from 1 month to 18 years who were admitted to a PICU from January 2015 to December 2017 and had a diagnosis of septic shock and required fluid resuscitation were enrolled to this study. Exclusion criteria were patients who received fluid resuscitation 24 hours prior to septic shock, end-stage disease, chronic kidney disease, congenital heart disease, other causes of shock and refusal of informed consent.

The sample size calculation was based on the previous study reporting the incidence of hyperchloremic metabolic acidosis. (4) This study aimed to reduce the incidence rate from 95% to 65%. Using an alpha (two sides) of 0.05 and beta of 0.2, the sample size calculated was 27 patients in each group. Considering the possible loss of follow-up and a drop-out rate of 10%. Total sample size required was 60 patients.

Definitions

Patients were identified as sepsis, and septic shock based on the 2005 International Sepsis Definitions Conference. (1) Septic shock is defined as a state of persistent hypotension in sepsis patients, despite adequate volume resuscitation with fluid more than 40 to 60 ml/kg.

Initial fluid resuscitation is defined as fluid bolus 20 ml/kg infusions within 15-20 minutes and up to 40 to 60 ml/kg as patients needed within 60-90 minutes.

Hyperchloremic metabolic acidosis is defined as strong ion difference (SID) below 40 mEq/l and serum chloride more than 108 mmol/l. (4)

Vasoactive Inotropic Score (VIS) is equal to dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 10,000 x vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min). (20)

Acute kidney injury (AKI) stage 2 is defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) as increase in serum creatinine 2.0-2.9 times from baseline or urine output below 0.5 ml/kg/hours for 12 hours. (21)

Strong ion difference (SID) is the difference between the charge of strong cations (sodium, potassium, calcium, and magnesium) and strong anions (chloride, lactate). (22)

Time to fluid bolus, time to inotropes, time to vasopressor, and time to antimicrobials are defined as the interval time from presentation with shock to start of the first fluid bolus, the first inotropic medications, the first vasopressors medications, and appropriate antimicrobial medications, respectively.

Time to hemodynamic stability is defined as the interval time from presentation with shock to hemodynamic stability, which included all of the following: normal heart rate for age, normal mental status, systolic blood pressure more than 5th percentile for age, urine output more than 1 ml/kg/hour, and no further increased doses of inotrope or vasopressor medications required.

Methods

We recruited patients suspected of sepsis who intent to administer fluid bolus. We randomly assigned into two groups by stratified block of four using computer-generated assignment. The patients, treating physicians, and research personnels were all blinded to the study fluid allocation. Both fluids were clear, colorless and odorless solution. A pharmacist not involved in the patient care prepared the isotonic crystalloids. After preparation, the printed prescription was kept in a sealed opaque envelope. Patients received 20 ml/kg intravenous isotonic crystalloids bolus within 15 minutes for at least 2 to 3 doses as prescribed by the treating physician: 0.9% sodium chloride (NS group) versus Ringer's acetate (BS group). Decisions regarding frequency, total volume of initial fluid resuscitation, and type of the maintenance fluid were made by the treating physician. Inotropes and vasopressor administration followed the surviving sepsis campaign guideline. (2) The supportive therapies, such as mechanical ventilation, antimicrobials, nutrition, and renal replacement therapy, were decided by attending staff according to the routine practice. Baseline characteristics were recorded, including age, gender, underlying disease, source of infection, fluid balance, electrolytes prior to ICU admission within 1 month, Pediatric Risk of Mortality (PRISM) III score, and VIS. Laboratory data were recorded, including electrolytes, renal function test, serum lactate, troponin-T, pro B-type natriuretic peptide (proBNP) and cystatin-C at 0 (at enrollment), 6 hours, 24 hours, and 48 hours after enrollment. We used the Consolidated Standards of Reporting Trials (CONSORT 2010) guideline in the reporting of the methods, results, and discussion of this study. (23)

Statistical analysis

SPSS software (version 20.0; IBM, Armonk, NY) was used for statistical analysis. Patient demographics and clinical outcomes were reported using median (interquartile range [IQR]) or number (percent). The comparison of data between the two groups used Chi-square or Fisher's exact test for categorical variables. The Student's t-test was used for continuous data with normal distribution or Mann-Whitney U test for continuous data without normal distribution. Logistic regression was used to measure the association between the clinical variables and in-hospital mortality. Risk factors were determined to be clinically significant a priori on the bivariable model and clinical relevance. A p value of less than 0.05 was considered statistically significant.

Results

A total of 110 children were eligible during the study period, from whom 49 patients were excluded as **Figure 1**. Sixty-one septic shock patients were randomized into the NS group (n=31) and the BS group (n=30). Median age was 5.35 years, and 36 (58.1%) of patients were male. All patients required inotropic and vasopressor medications. The average volume of initial fluid resuscitation was 54.4 (±SD 19.3) ml/kg. There were 43 (70.5%) patients who received NS after initial fluid resuscitation. Nobody had hyperchloremic metabolic acidosis at the initial enrollment. The incidence of hyperchloremic metabolic acidosis within 48 hours was 44.3%. A totol of 32 (52.4%) patients were positive for bacteria in blood culture. In-hospital mortality, length of PICU stay, and length of hospital stay were 15 out of 61 (24.6%) patients, median (IQR) 3.24 days (1.71-5.61) and 33.48 days (17.45-62.17), respectively.

The baseline characteristics were not different in both groups (**Table 1**). Time to initial fluid resuscitation, time to inotropes, time to vasopressor, and time to antimicrobials administration were not different in both groups. Serum chloride had a trend to higher increased at 6 hours in NS group than BS group with mean difference (±SD) 3.81 (±11.63) vs 2.00 (±4.95), p=0.056. Clinical outcomes were not significantly different between both groups (**Table 2**). Normal saline solution group had a trend toward more frequent hyperchloremic metabolic acidosis than balanced salt solution group (17 [54.8%] vs 10 [33.3%], p=0.091).

The clinical risk factors of in-hospital mortality were analyzed and showed that higher PRISM III (p<0.001), higher VIS at 6 hours (p=0.004), and positive fluid balance at 24 hours (p=0.032) were significantly associated with in-hospital mortality. The multiple logistic regression analysis, adjusted for the clinical variables, which were significantly associated with mortality (age, gender, type of initial fluid, PRISM III, VIS at 6 hours, hyperchloremic metabolic acidosis, and fluid balance at 24 hours), showed that only higher PRISM III scrore was significantly associated with in-hospital mortality (OR 1.264, 95%CI 1.056-1.513, p=0.011). The SID in the BS group was higher than that in the NS group at 6 hours after enrollment with median (IQR) 37.19 (25.96-43.53) vs 30.39 (20.23-36.54), p=0.050. The SID at 6 hours after enrollment was significantly higher in the survived patients than the non-survived patients with median (IQR) 34.61 (25.99-43.39) vs 25.18 (10.19-36.54), p=0.038 (**Figure 2**). Serum cystatin-C, lactate, troponin-T, and proBNP level at initial, 6, 24, and 48 hours were not different between the two fluid groups. However, the non-survived patients had significantly higher serum cystatin-C, lactate, troponin-T, and proBNP level than the survived patients at some points of the study course (**Figure 3**).

Discussion

Initial fluid resuscitation is the cornerstone therapy in pediatric septic shock. A recent meta-analysis reviewed the effectiveness of different fluids resuscitation in adult critically ill patients. The result showed no significant difference in mortality outcomes between balanced salt solution and normal saline solution (OR 0.91, 95%CI [0.79-1.05]). (24) A recent large cohort study in pediatric severe sepsis with propensity score matching showed using exclusively BS up to 72 hours was associated with improved survival when compared with using only NS; however, no differences in mortality and incidence of acute kidney injury were found when compared between those exclusively receiving BS up to 24 hours and NS. (19) Recently open-label pragmatic randomized controlled trial in 50 children with sepsis who showed no difference in mortality and adverse events between Ringer's lactate and NS. (25) This study showed NS group had higher incidence of hyperchloremic metabolic acidosis within 48 hours than BS group. However, the clinical outcomes such as AKI and mortality were not different in both groups. The results are similar to a previous large retrospective study. (18) Interestingly, the reduced strong ion difference was associated with higher mortality in pediatric septic shock similar to the adult study. (26) The strong ion difference depends on strong cations and strong anions. Strong anions are not only chloride but also lactate, ketoacid, and other anions. This study showed non-surviving patients had lower strong ion difference than surviving patients. Furthermore, this study showed non-surviving patients had higher serum lactate than surviving patients while serum chloride was not different in both groups. We can explain this because serum lactate is one of the important strong anions, which can determine strong ion difference and mortality. Previous study showed increased serum lactate and unmeasured anions, but not chloride, were associated with increased mortality in critically ill adults. (27) We suggest monitoring of serial serum lactate and measuring strong ion difference in children with septic shock for determining clinical outcomes.

Several studies showed the circulating biomarker could predict the morbidity and mortality. (28-30) This study measured cardiac biomarkers (proBNP, troponin-T), kidney biomarker (cystatin-C), and lactate. Cardiac dysfunction can occur in children with septic shock. Higher proBNP and troponin-T are associated with early cardiac dysfunction. (28) Several studies of adults with severe sepsis have shown high cardiac biomarkers are associated with poor outcomes. (29) This study showed high serum proBNP and troponin-T in the first day were significantly associated with higher mortality in pediatric septic shock. However, our study showed no difference in cardiac biomarkers between NS and BS groups. Cystatin C is one of the kidney biomarkers to detect acute kidney injury. Prior study showed serum cystatin C has a higher level in septic AKI patients than septic shock patients without AKI. (30) This study showed serum cystatin C significantly increased in the non-survived patients than the survived patients, but showed no difference between the fluid groups.

Strengths and limitations

To our knowledge, this study is the first study of a double blind randomized controlled trial of different types of initial fluid resuscitation in children with septic shock. Our study addressed a very basic question of which type of resuscitation fluid should be used as initial bolus. The result of this study showed the type of initial fluid resuscitation did not alter morbidity and mortality outcomes. In addition, this study showed initial fluid resuscitation affected the strong ion difference in the short period as shown in **Figure 2A**. As clinical practice, physicians adjust the maintenance fluid depending on clinical scenario and serum electrolytes. We suggest adjusting the maintenance fluid in each patient relying on clinical scenario and laboratory values.

This study had some limitations. First, it was limited to a single center with a relatively small population. Furthermore, the sample size was calculated for the primary outcome. Therefore, it might be low power to conclude the association between initial fluid resuscitation and the clinical outcomes. A large multicenter randomized controlled trial (RCT) evaluating type of initial fluid resuscitation is warranted. Second, the maintenance fluid infusion was adjusted by treating physicians, which might have affected patients' electrolytes and outcomes. However, this study was not designed to discuss the choice of maintenance fluid irrespective of the initial fluid resuscitation. Further study should be considered. Last, renal replacement therapy is our objective, but a clinician's decision to initiate this procedure may be susceptible to treatment bias. However, we reduced this bias by using a randomized controlled trial study.

Conclusion

Normal saline solution had a trend to increase risk of hyperchloremic metabolic acidosis in children with septic shock when compared with Ringer's acetate as initial fluid resuscitation.

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Authors' contributions

NA is the primary contributor to the origination of the ideas and the study protocol. NA, ST, RL collected the data. NA analyzed the data and drafted the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Clinical and biochemical characteristics at the enrollment in normal saline and balanced salt solution groups

Variables	Normal saline (n=31)	Balanced salt (n=30)	p
Age (years)	5.35 (1.6-11.0)	5.2 (1.1-11.8)	0.931
Male, n (%)	22 (70.9)	14 (46.7)	0.071
BSA (m^2)	1.0 (0.3-1.0)	1 (0-1)	0.674
PRISM III score	9 (3-17)	7.5 (3-13)	0.696
Comorbidities, n (%)			0.089
- Oncology	14 (45.2)	11 (36.7)	
- Gastroenterology	7 (22.6)	6 (20.0)	
- Neurology	2 (6.4)	3 (10.0)	
- Others	8 (25.8)	10 (33.3)	
Source of infection, n (%)			0.134
- Blood	11 (35.5)	14 (46.7)	
- Lungs	5 (16.1)	8 (26.7)	
- Abdomen	6 (19.3)	1 (3.3)	
- Others	4 (12.9)	6 (20.0)	
- Unknown	5 (16.1)	1 (3.3)	
Prior MV, n (%)	4 (12.9)	4 (13.3)	0.960
Initial arterial lactate (mmol/l)	2.4 (1.5-3.3)	1.7 (1.2-2.6)	0.163
Initial ScvO2 (%)	74 (57-88)	73 (63-88)	0.917
Initial sodium (mmol/l)	137 (134-138)	138 (135-138)	0.688
Initial chloride (mmol/l)	103 (101-106)	103 (99-107)	0.732
Time to fluid bolus (min)	15 (0-25)	11 (0-21)	0.826
Time to inotropes (min)	95 (65-180)	140 (75-185)	0.240
Time to antimicrobials (min)	35 (20-90)	40 (0-94)	0.685
Time to hemodynamic stable (min)	230 (125-380)	235 (165-517)	0.289

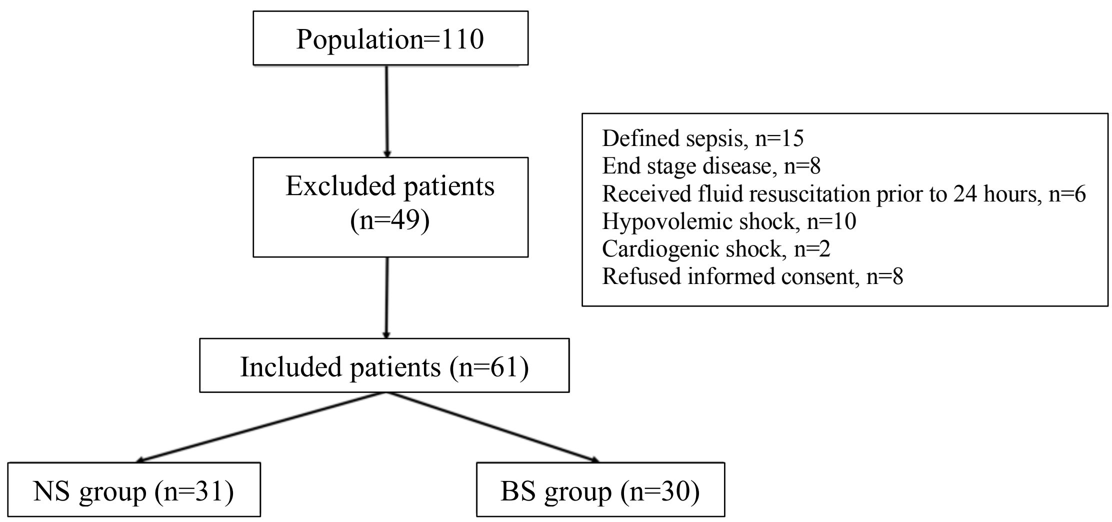
Legend: Values are median (IQR). BSA=body surface area; PRISM III=Pediatric Risk of Mortality III; MV=mechanical ventilation; ScvO2=central venous oxygen saturation.

Table 2. Clinical outcomes in normal saline and balanced salt solution groups

Variables	Normal saline (n=31)	Balanced salt (n=30)	p
Hyperchloremic acidosis, n (%)	17 (54.8)	10 (33.3)	0.091
Vasoactive inotropic score			
- At 1 hour	10 (9.5-10)	10 (5-10)	0.331
- At 6 hours	10 (10-23.5)	15 (10-21)	0.734
- At 24 hours	11 (5-30)	10 (5-27)	0.891
Fluid balanced (ml)			
- 1 hour	510 (400-800)	430 (235-1057)	0.399
- 6 hours	495 (200-996)	505 (187-1553)	0.593
- 24 hours	845 (50-1370)	480 (285-1272)	0.994
Acute kidney injury, n (%)	5 (16.1)	6 (20)	0.749
Need RRT, n (%)	1 (3.2)	1 (3.3)	0.981
LOS in hospital (day)	31.6 (17.9-62.0)	33.7 (12.1-67.4)	0.931
LOS in PICU (day)	3.5 (1.3-4.7)	2.9 (1.7-11.0)	0.925
Hospital mortality, n (%)	7 (22.6)	8 (26.7)	0.711
30-day mortality, n (%)	2 (6.4)	3 (10.0)	0.614
90-day mortality, n (%)	6 (19.3)	7 (23.3)	0.704

Legend: Values are median (IQR). RRT=renal replacement therapy; LOS=length of stay; PICU=pediatric intensive care unit.

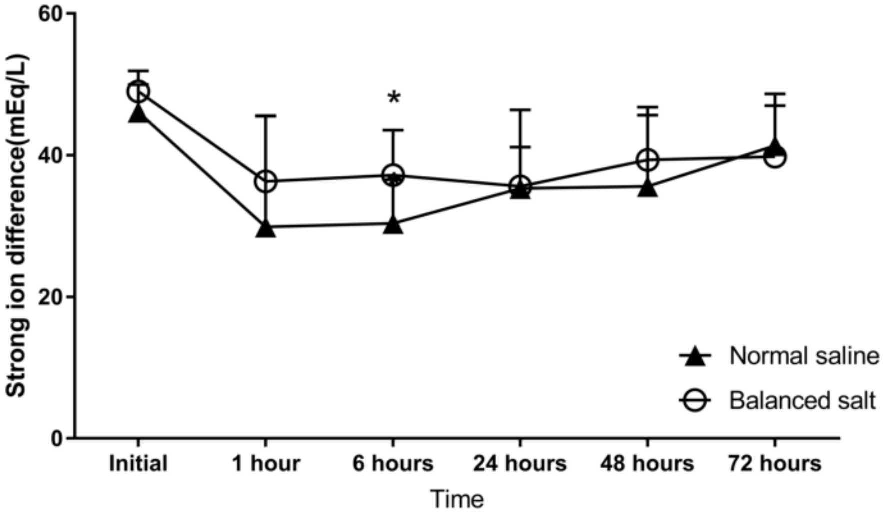
Figure 1. Flow diagram showing the screening, enrollment and follow-up of patients according to the Consolidated Standards of Reporting Trials guidelines



Legend: NS=normal saline solution; BS=balanced salt solution.

Figure 2. Strong ion difference
2A. Comparison between normal saline and balanced salt solution groups
2B. Comparison between non-survivors and survivors

2A



2B

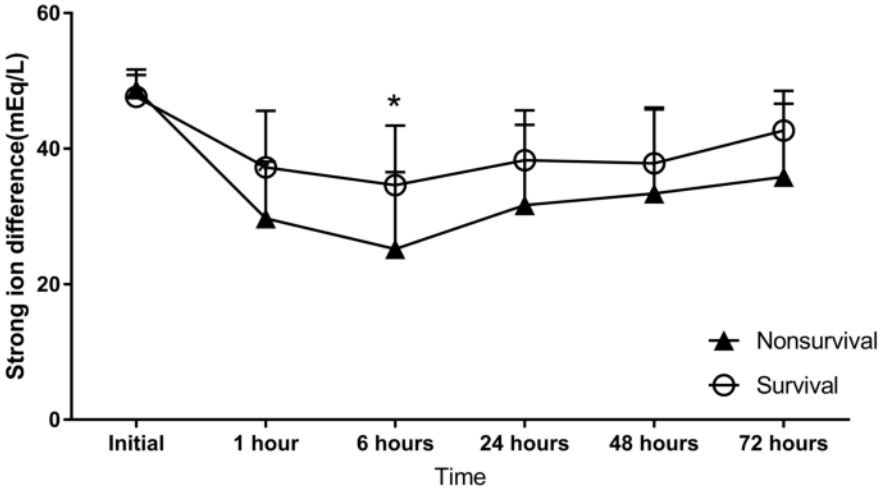
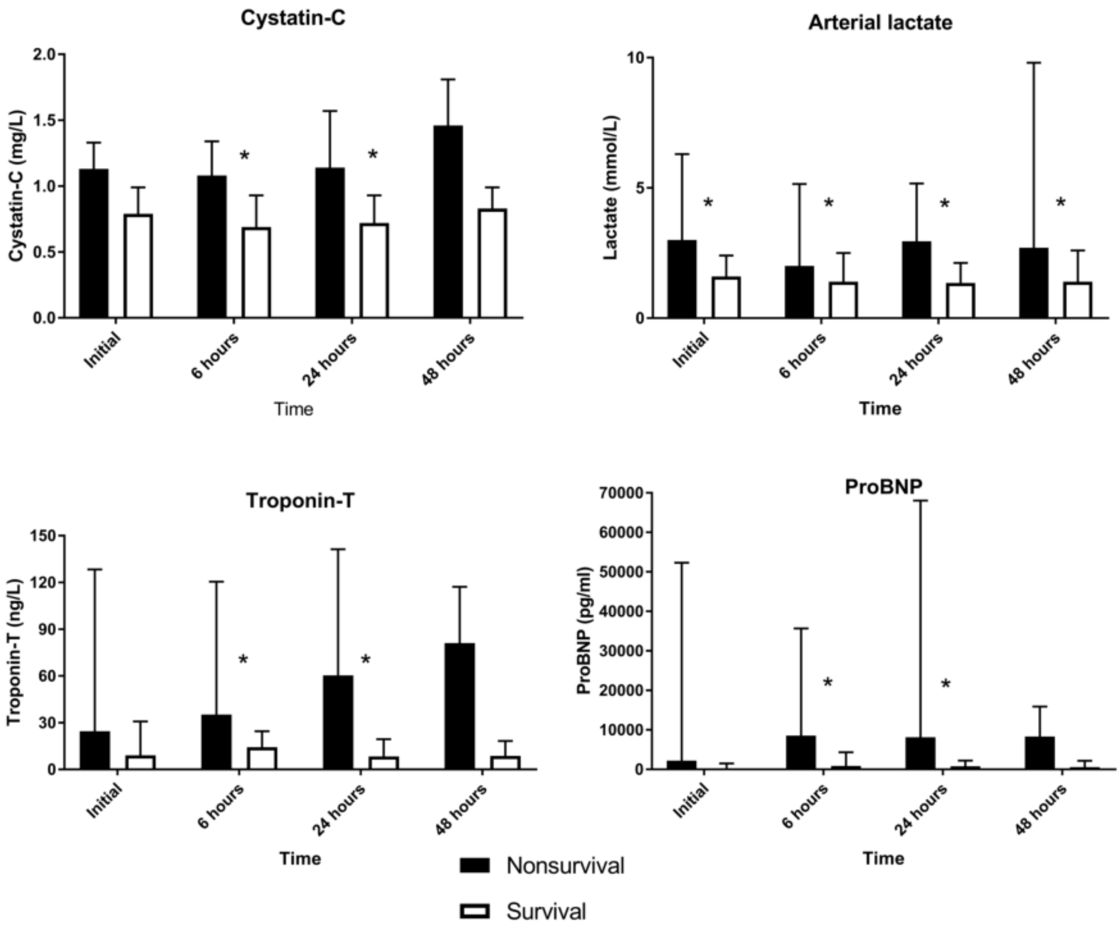


Figure 3. The association between mortality and serum cystatin-C, arterial lactate, troponin-T, and proBNP level



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