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# The authors reply

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In conclusion, we appreciate the comments by Luglio et al (1) and wish to reiterate that our study is one of only a few pediatric studies of capnography measures in mechanically ventilated children. We hope that as evidence accumulates, more pediatric intensivists will join us and begin to monitor and evaluate this important parameter.

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## Hyperchloremia Versus Nonhyperchloremia or Hyperchloremia Versus Normochloremia?

## To the Editor:

In a recent issue of *Critical Care Medicine*, we read with great interest the article by Neyra et al (1) presenting the association of hyperchloremia with hospital mortality in 1,940 ICU adult patients with severe sepsis or septic shock. The authors revealed that hyperchloremia (serum chloride [Cl] ≥ 110 mEq/L) at ICU admission, higher Cl levels, and within-subject worsening hyperchloremia at 72 hours of ICU stay were associated with all-cause hospital mortality even after adjusting base deficit, cumulative fluid balance, acute kidney injury, and other critical illness parameters. These findings add to the body of evidence showing harmfulness of hyperchloremia and seem to be attributable to the avoidance of chloride-rich solutions in critically ill patients, as well as the studies of Raghunathan et al (2) and Shaw et al (3).

We are curious of few things. First, authors divided enrolled cohort into two groups; patients with hyperchloremia ($Cl_0$ ≥ 110 mEq/L) and no hyperchloremia ($Cl_0$ < 110 mEq/L). The odds for outcomes were presented comparing the hyperchloremic group with the nonhyperchloremic group. We wonder what would have happened if authors had divided enrolled cohort into two groups; patients with hyperchloremia and normochloremia, excluding patients with hypochloremia. Serum chloride levels would exert bimodal effect, such as pH, WBC, and so on. Because hypochloremic patients were included in the nonhyperchloremic group in this study, statistical results would be more impactive if authors excluded hypochloremic patients. Also, the odds for outcomes comparing the hyperchloremic group with the normochloremic group may be more acceptable to the physicians.

Second, the study by Tani et al (4) would be better not to be mentioned in the discussion. Because Tani et al (4) tried to determine the prognostic value of hypochloremia in critically ill patients, it was out of focus to deal with hyperchloremia. Then, studies that evaluated the association of hyperchloremia with hospital mortality in critically ill patients showed consistent results as authors described (3, 5).

The authors have disclosed that they do not have any potential conflicts of interest.

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## The authors reply:

We reviewed Jo et al (1) correspondence in which they have raised an important question regarding the contribution of hypochloremia to our analysis (2). In our original study ($n$ = 1,940) (2), we stratified our primary cohort by the presence ($n$ = 615) or absence ($n$ = 1,325) of hyperchloremia (serum chloride ≥ 110 mEq/L) on ICU admission. Jo et al (1) suggested that the strength of the association between higher serum chloride levels and hospital mortality in the hyperchloremic group may perhaps be stronger if patients with hypochloremia were excluded from the nonhyperchloremic group for comparison.

Consequently, we identified 361 patients with hypochloremia (serum chloride ≤ 100 mEq/L) on ICU admission in

**TABLE 1. Association of Hospital Mortality With Serum Chloride Levels at 72 Hours of ICU Stay in a Secondary Cohort (n = 1,579) in Which Patients With Hypochloremia (Serum Chloride ≤ 100 mEq/L) on Admission Were Excluded**

| | Normochloremia at Admission ($Cl_0$ 101–109 mEq/L) | | Hyperchloremia at Admission ($Cl_0$ ≥ 110 mEq/L) | |
|---|---|---|---|---|
| | Odds Ratio | *p* | Odds Ratio | *P* |
| $Cl_{72}$ per 5 mEq/L increase, univariate | 1.05 (0.93–1.30) | 0.26 | 1.38 (1.13–1.68) | 0.002[a] |
| $Cl_{72}$ per 5 mEq/L increase, multivariate | 1.06 (0.87–1.30) | 0.05 | 1.27 (1.02–1.59) | 0.03[a] |

$Cl_0$ = serum chloride on ICU admission, $Cl_{72}$ = serum chloride at 72 hr of ICU stay.

[a]Statistically significant, *p* value < 0.05.

Multivariate models adjusted for age, gender, hypertension, acute kidney injury (Kidney Disease Improving Global Outcomes serum creatinine-based criteria), oliguria, cumulative fluid balance, vasopressor or inotrope requirements, mechanical ventilation, Sequential Organ Failure Assessment score, and base deficit. Multivariate models included all variables associated with hospital mortality on univariate analysis at *p* value < 0.10.

our primary cohort. To eliminate the effect of hypochloremia in our results, we performed a sensitivity analysis in a secondary cohort that excluded patients with hypochloremia on ICU admission. This secondary cohort consisted of 615 patients with hyperchloremia and 964 with normochloremia (101–109 mEq/L) on ICU admission. We obtained similar results and nearly identical univariate and multivariate logistic regression estimates for the association of higher serum chloride levels with hospital mortality in the hyperchloremic group as our published results (Table 1).

Small observational studies have demonstrated the association between hypochloremia and mortality in critically ill and postoperative patients (3, 4). Jo et al (1) raised the question of a possible bimodal effect of serum chloride levels on mortality outcomes. However, in our primary cohort, there was no association between serum chloride levels at 72 hours and hospital mortality in the hypochloremic group ($n = 361$): the univariate odds ratio for each 5 mEq/L decrease in serum chloride was 0.96 (95% CI, 0.77–1.21).

The study by Tani et al (4) comprised interesting observations of serum chloride levels and adverse hospital outcomes in critically ill patients. Importantly, in the multivariate model, serum chloride was not independently associated with hospital mortality. However, the authors also reported the frequency of hospital mortality in three subgroups (hypochloremia, normochloremia, and hyperchloremia) and found the highest risk for mortality in the hypochloremic group. The risk for hospital mortality was not different between the normochloremic and hyperchloremic groups: 14 of 364 (3.8%) versus three of 81 (3.7%). The lack of difference between these two subgroups is statistically evident by Fisher exact test ($p = 1.00$). We consider that this work constitutes a negative study for the association between hyperchloremia and hospital mortality as discussed in our article (2).

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## Association of Postoperative Hypoalbuminemia With Acute Kidney Injury Following Liver Transplantation

## To the Editor:

In a recent issue of *Critical Care Medicine*, we read with interest the article by Sang et al (1) assessing association of hypoalbuminemia within two postoperative days