

CORRESPONDENCE



Interaction between serum chloride increase and baseline chloride level

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Initial correspondence from Drs. Shen, Yan, and Cai

Dear Editor,

Recently, Dr. Barhight et al. reported an association between chloride increase and high mortality in critically ill children [1]. Although well designed, their study presents several limitations. First, the number of deaths in the cohort is small (4%, 71/1935). However, 21 variables were included in the logistic regression model (Table 2). Although no consensus has been reached, the rule of thumb is that at least 10 events per variable [2] are needed to avoid bias in multivariable regressions. Thus, the robustness of Barhight's findings needs careful evaluation. Second, multicollinearity issues resulting from highly correlated predictors also play an important role in bias [2]. While the correlations in this study (for instance, the correlation between serum sodium and chloride) may be minimized by the fact that the continuous variables were translated into categorized variables, the result of a multicollinearity test should be reported. Third, the major finding is that chloride increase is an independent risk factor for mortality. We suspect that this association may be influenced by the baseline serum chloride. For instance, in a patient with hypochloremia, would the chloride increase be associated with high mortality? To address this question, we performed a rough simulation using data from the Medical Information Mart for Intensive Care III (MIMIC III) database [3]. A significant interaction between baseline chloride and chloride increase was found (in a predominantly adult data set). Chloride increase was found to be associated with decreased mortality when baseline chloride was less

than 85 mmol/L (Fig. 1). Furthermore, the detrimental effect of chloride increase was greater with increasing baseline chloride levels.

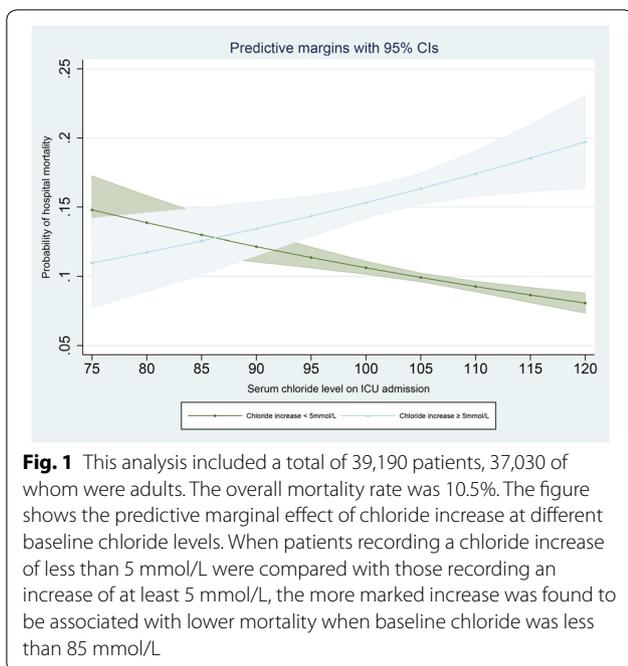
Note: All the data were extracted from the MIMIC III database, and adult patients were also included in this rough estimation. Thus, this finding cannot be considered transferable to pediatric patients because of the significant heterogeneity.

Rebuttal from Drs. Barhight and Brinton

We appreciate Drs. Shen, Yan, and Cai's comments and agree that our study has limitations. As the commenters state, there is no clear consensus on the correct number of events per variable. Studies evaluating this have led to a general consensus of a minimum of 5–10 events per variable for logistic regression [4]. We reviewed our analysis to see if following this "rule of thumb" would change our estimated effect. When we remove variables that were highly correlated or offered no univariable explanation (age, height, weight, sepsis, oncologic, or transplant diagnoses), the new estimated effect is greater in magnitude and direction, aOR of 3.1 (95% CI 1.5–6.3) (Supplementary Table 1). We agree about collinearity concerns, therefore "We tested the three-way interactions as well as successive two-way interactions to evaluate if there was improvement in the model fit" [1]. None were identified (Supplementary Table 2). We have reached out to the journal with a request to append the results of our multicollinearity testing to the manuscript. Concerning the possible interaction with baseline chloride, our final adjusted model included the admission chloride. The commenters present interesting findings. We agree that there may be an interactive effect between baseline chloride and change in chloride (Fig. 1). The differences in findings may be related to the differences between our two populations. Ours has only 0.2% ($n=4$) of patients with admission chloride values less than 86 mEq/L, as it

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is uncommon to have that degree of hypochloremia in pediatric patients.

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest

All authors declare that they have no conflict of interest.

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