Risk Potential for Organ Dysfunction Associated with Sodium Bicarbonate Therapy (SBT) in Critically Ill Patients with Hemodynamic Worsening

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Research

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Abstract

Background: The role of sodium bicarbonate therapy (SBT) remains controversial. This study aimed to investigate whether hemodynamic status before SBT contributed to the heterogeneous outcomes associated with SBT in acute critically ill patients.

Methods: We obtained data from patients with metabolic acidosis from the Medical Information Mart for Intensive Care (MIMIC)-III database. Propensity score matching (PSM) was applied to match the SBT group with the control group. Logistic regression and Cox regression were used to analyze a composite of newly “developed or exacerbated organ dysfunction” (d/eOD) within 7 days of ICU admission and 28-day mortality associated with SBT for metabolic acidosis.

Results: A total of 1765 patients with metabolic acidosis were enrolled, and 332 pairs obtained by PSM were applied to the final analyses in the study. An increased incidence of newly d/eOD was observed in the SB group compared with the control group (54.8% vs 44.6%, p<0.01). Multivariable logistic regression indicated that the adjusted OR of SBT for this composite outcome was no longer significant [OR (95% CI): 1.39 (0.9, 1.85); p=0.164]. This effect of SBT did not change with the quintiles stratified by pH. Interestingly, SBT was associated with an increased risk of the composite of newly d/eOD in the subgroup of patients with worsening hemodynamics before SBT [adjusted OR (95% CI): 3.6 (1.84, 7.22), p<0.001]. Moreover, the risk potential for this composite of outcomes was significantly increased in patients characterized by both worsening [adjusted OR (95% CI): 2.91 (1.54, 5.47), p<0.001] and unchanged hemodynamics [adjusted OR (95% CI): 1.94 (1.01, 3.72), p=0.046] compared to patients with improved hemodynamics before SBT. Our study failed to demonstrate an association between SBT and 28-day mortality in acute critically ill patients with metabolic acidosis.

Conclusions: Our findings suggested that SBT for metabolic acidosis was associated with an increased risk potential for subsequent d/eOD, while the hemodynamic status remained unstable during the acute phase of critical illness.

Background

Acute metabolic acidosis is a frequent and potentially life-threatening condition in patients admitted to intensive care units (ICUs) [1–4]. It has been demonstrated that low blood pH impairs cellular bioactivities, which contributes to organ dysfunction [5]. As shown in in vitro experiments and animal studies [6, 7], severe acidosis resulted in a reduction in the vascular contractile response to catecholamines and decreases in cardiac inotropism and ventricular arrhythmia, which led to cardiac dysfunction. Accordingly, intravenous administration of sodium bicarbonate (SB) to reverse severe metabolic acidosis (namely, sodium bicarbonate therapy, SBT) has become common in clinical practice [8]. According to previous reports, the proportion of patients receiving SBT ranged from 29–67% in a cohort of septic patients with metabolic acidosis [9], a mixed ICU population with metabolic acidosis [1] and cases characterized by severe lactic acidosis [10].
However, the role of SBT remains controversial [11, 12]. Findings in Jaber’s randomized controlled trial (RCT) and Zhang’s retrospective cohort study suggested that SBT conferred a potential benefit for outcomes in a highly selected subgroup of patients with acute kidney injury (AKI) [9, 13]. Furthermore, the pooled effect of SBT on either hemodynamic stability or mortality was inconclusive among critically ill patients with metabolic acidosis, although increased blood pH or excess alkalinity was evident [14–16]. On the other hand, SBT may be harmful owing to its potential induction of hypokalemia, hypernatremia, hypocalcemia, prolonged QTC interval, progression of vascular calcification, rebound metabolic alkalosis and increased lactate production. [17, 18]. Given these concerns, there are warnings associated with the use of SBT for the management of critically ill patients in the currently updated multidisciplinary guidelines [19–21].

It is well known that metabolic acidosis is largely attributable to poor tissue perfusion in the acute phase of critical illness, which plays an important role in the development of organ dysfunction [22]. Restoration of hemodynamics as early as possible has been strongly recommended for the initial management of critically ill patients in evidence-based guidelines, although the etiology of hypoperfusion is complex [19, 20]. Therefore, SBT should not be considered until hemodynamic optimization has been completed for these patients. However, there have been few previous studies reporting hemodynamic status before the administration of SB [9, 13–15].

Despite multiple factors, we hypothesized that hemodynamic status before SBT could be an important determinant of the heterogeneity of outcomes associated with SBT in acute critically ill patients. Based on the Medical Information Mart for Intensive Care (MIMIC-III) database, this study tested this hypothesis in a cohort of patients who were diagnosed with metabolic acidosis within 48 hours of ICU admission.

**Methods**

We obtained data from the MIMIC-III, which is a large US-based, open-access, deidentified critical care database. The newest version of MIMIC-III, v. 1.4, integrates 61,532 patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, Massachusetts, including 53,432 distinct hospital admissions for adult patients aged 16 years or above. The duration of the database covers from June 2001 to October 2012. Since our study was based on a third party anonymized publicly available database with pre-existing institutional review board (IRB) approval, IRB approval from our institution was exempted.

**Study population**

Our study included patients with severe metabolic acidosis within 48 hours after ICU admission who fulfilled all of the following criteria: (1) pH ≤ 7.3; (2) BE≤-8, or HCO$_3^-$ < 20 mmol/L if BE was missing; and (3) PaCO$_2$ < 50 mmHg, or without chronic obstructive pulmonary disease (COPD) in discharge diagnoses if PaCO$_2$ was unavailable. The lowest values of pH, BE, and HCO$_3^-$ and the highest value of PaCO$_2$ were selected when there were multiple measurements. The exclusion criteria included (1) age 16 or under; (2) diabetes history; (3) comorbidity of peripheral paralysis; (4) ICU stay over 100 days; (5) initiation of
sodium bicarbonate therapy before or 48 hours after ICU admission, or after a record of order for renal replacement therapy (RRT); and (6) death within the first 24 hours after ICU admission. For those who had multiple admissions to the ICU, only the initial visit was included.

**Definitions**

We defined a composite of newly “developed or exacerbated organ dysfunction” (d/eOD) as a net increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2 of at least one organ within 7 days of ICU admission over the baseline (SOFA score in the first 24 hours). The worst SOFA score was adopted if multiple measurements were documented from the second 24-hour period (or the day following SBT) until day 7 after ICU admission. Hemodynamic status during the initial resuscitation was defined as hemodynamic improvement, hemodynamic worsening and unchanged hemodynamics. The period of initial resuscitation was defined as the first 6 hours of ICU admission. However, it was modified to be the period from ICU admission to SB therapy when SB infusion was initiated earlier than 6 hours of ICU admission. The status of “hemodynamic improvement” or “hemodynamic worsening” was determined during initial resuscitation if 1) “the reduction from the highest level” or “the increase over the initial dosage” of intravenous continuous infusion of norepinephrine dosage (or identical dosage of other vasopressors, Table S1) was equal to or over 0.1 µg/min/kg (or ≥ 50% net change at least when the highest or initial dosage was below 0.1 µg/min/kg) for maintaining mean arterial pressure (MAP) ≥ 65 mmHg; or 2) the plasma lactate concentration was “decreased below” or “raised over” 2 mmol/L (or ≥ 10% net change) while vasopressor data were unavailable. If the change in vasopressors or plasma concentration of lactate did not fulfill either the hemodynamic improvement or hemodynamic worsening criteria, a status of unchanged hemodynamics during initial resuscitation was determined. Sepsis 3.0 definitions were used to categorize the enrolled patients as nonsepsis, sepsis or septic shock [23]. AKI stage was identified by the Kidney Disease: Improving Global Outcomes (KDIGO) classification system [24].

**Variables**

Characteristic data of patients were extracted, including age and sex; category of diseases (surgical vs medical), history of comorbidity and whether cardiopulmonary resuscitation (CPR) was experienced; and diagnosis of sepsis, shock and AKI (Table 1). Supportive interventions such as mechanical ventilation (MV) and RRT were recorded. Fluid balances at 24 hours and 48 hours after ICU admission and the total SB dosage administered within the first 48 hours were extracted. The SOFA score including each component was calculated every 24 hours if data were available. The Simplified Acute Physiology Score II (SAPSII) was calculated within the first 24 hours after ICU admission.

Laboratory variables included pH, actual bicarbonate (AB), base excess (BE), PaO₂, PaCO₂, hematocrit (Hct), hemoglobin (Hb), lactate concentration and electrolytes such as [Na⁺], [K⁺], and [Cl⁻]. We also calculated the anion gap (AG) by the formula AG=[Na⁺] + [K⁺] – [Cl⁻] – [HCO₃⁻] [25].
A composite of newly d/eOD within 7 days of ICU admission was used as the primary outcome of this study. The secondary outcome was 28-day mortality.

**Statistical analysis**

Single imputation was applied to fix missing data for variables (with missing data less than 20%), including pH, BE, PO$_2$, PCO$_2$, lactate, and the cumulative fluid balance [26]. Because only one data point was missing, we applied complete sample analysis for the missing AG data.

Propensity score matching (PSM) was applied to minimize either selection biases or potential confounders for SBT [9]. The propensity score was estimated by a multivariate logistic regression model using the following variables: the worst value of pH and BE during initial resuscitation, basic characteristics including age, sex and category of disease, variables with regard to severity of disease such as comorbidity, diagnosis of shock or AKI, and whether MV, CPR and RRT were received. A one-to-one nearest neighbor matching algorithm was applied using a caliper width of 0.02.

Continuous variables are expressed as the mean (standard deviation) or median (upper quantile, lower quantile), and a t-test or the Wilcoxon-test was used to compare the differences between groups. Categorical variables are depicted as the number of groups (the number of percentages), and the chi-squared test or Fisher’s exact test was applied.

Univariate logistic regression and Cox regression were used to evaluate the overall effectiveness of SBT without any adjustments. Multivariate logistic regression and Cox regression were applied to evaluate the overall effectiveness of SBT with adjustment for potential confounders suggested by clinical expertise and matching variables that remained imbalanced after PSM with $p < 0.05$. Further, logistic regression and Cox regression were implemented to evaluate the impact of hemodynamic status on SBT-associated outcomes among the SB group. Furthermore, we accounted for the collinearity among variables to be adjusted to select final independent variables. The proportional hazard assumption for each independent variable was evaluated based on Schoenfeld residuals.

All statistical analyses were performed by R (version 3.6.1). A p value less than 0.05 was indicative of statistical significance.

**Results**

**Characteristics of the enrolled patients**

Out of 61,532 ICU records in the MIMIC-III database, 2,733 admissions fulfilled the definition of severe metabolic acidosis within 48 hours after ICU admission. According to the inclusion and exclusion criteria, 1,765 patients were enrolled in this cohort. As shown in the flowchart of patient selection (Fig. 1), 332 propensity score-matched pairs were generated and applied to the final analyses.
The baseline characteristics of patients in the SB group and non-SB group were compared before and after PSM. There were higher SOFA and SAPSII scores, a larger proportion of patients receiving mechanical ventilation and vasopressors, higher cumulative positive fluid balances at 24-hour and 48-hour and more severe acidosis (i.e., blood gas analysis showed a significantly lower BE value, pH value, and AB value in the SB group than in the non-SB group before PSM) (Table S2). Most of variables were comparable after PSM. Moreover, a significant difference between the two groups remained for variables including fluid balance at 24 hours and 48 hours, SAPS II and SOFA scores, the proportion of patients with a diagnosis of sepsis receiving mechanical ventilation and vasopressors, and pH, PaCO₂ and BE (Table 1).
| Characteristics | SB (N = 332) | Non-SB (N = 332) | P-value |
|----------------|-------------|-----------------|---------|
| **General characteristics** |             |                 |         |
| Age (year)            | 66.5 (54.2, 77.6) | 66.2 (52.9, 79.9) | 0.705   |
| Sex [male, n (%)]     | 158 (47.6%)  | 163 (49.1%)    | 0.756   |
| With comorbidity, n (%) | 330 (99.4%) | 327 (98.5%) | 0.451   |
| Category [surgical, n (%)] | 88 (26.5%) | 79 (23.8%) | 0.474   |
| Sepsis, n (%)         | 164 (49.4%)  | 132 (39.8%)    | 0.016   |
| With shock, n (%)     | 285 (85.8%)  | 278 (83.7%)    | 0.517   |
| With AKI, n (%)       | 269 (81.0%)  | 272 (81.9%)    | 0.842   |
| Receiving RRT, n (%)  | 37 (11.1%)   | 40 (12.1%)     | 0.809   |
| Receiving MV, n (%)   | 219 (66.0%)  | 179 (53.9%)    | 0.002   |
| Receiving CPR, n (%)  | 34 (10.2%)   | 37 (11.1%)     | 0.802   |
| SAPS II score [M(IQR)] | 52 (40, 65) | 46 (36, 57) | < 0.001 |
| SOFA score [M(IQR)]   | 8 (6, 12)    | 6 (4, 9)       | < 0.001 |
| CFB 24-hr [L, M(IQR)] | 0.52 (0.28, 0.82) | 0.35 (0.12, 0.59) | < 0.001 |
| CFB 48-hr [L, M(IQR)] | 0.69 (0.36, 1.16) | 0.46 (0.20, 0.76) | < 0.001 |
| SB dosage [mmol, M(IQR)] | 60 (30, 150) | 0 | NA |
| **Laboratory tests** |             |                 |         |
| pH                    | 7.21 (7.15, 7.25) | 7.22 (7.18, 7.26) | 0.012   |
| PaCO₂ [mmHg, M(IQR)]  | 37.5 (31, 44)   | 41 (35, 45)    | < 0.001 |
| PaO₂ [mmHg, M(IQR)]   | 89 (61, 122)    | 67 (44, 95)    | < 0.001 |
| AB (mEq/L)            | 14.5 ± 3.7     | 14.6 ± 4.4     | 0.960   |
| BE (mEq/L)            | -12.5 (-16, -10) | -11 (-14, -9)  | 0.001   |
| Lactate (mmol/L)      | 3.2 (1.7, 6.2)  | 3.4 (1.8, 5.5) | 0.935   |

Note: Baseline characteristics were extracted within 6 hours of ICU admission or before SBT if it was initiated earlier. SB: Sodium bicarbonate; SBT: Sodium bicarbonate therapy; PSM: propensity score matching; SOFA: Sequential Organ Failure Assessment; MAP: mean arterial pressure; SAPSII: The Simplified Acute Physiology Score II; AB: actual bicarbonate; BE: base excess; Hct: hematocrit; Hb: hemoglobin; AKI: acute kidney injury; RRT: renal replacement therapy.
|                | SB (N = 332) | Non-SB (N = 332) | P-value |
|----------------|--------------|------------------|---------|
| Hct (%)        | 27 (22, 32)  | 28 (24, 32)      | 0.162   |
| Hb (g/dL)      | 9.0 (7.2, 10.7) | 9.3 (8.1, 10.5) | 0.183   |

Note: Baseline characteristics were extracted within 6 hours of ICU admission or before SBT if it was initiated earlier. SB: Sodium bicarbonate; SBT: Sodium bicarbonate therapy; PSM: propensity score matching; SOFA: Sequential Organ Failure Assessment; MAP: mean arterial pressure; SAPSII: The Simplified Acute Physiology Score II; AB: actual bicarbonate; BE: base excess; Hct: hematocrit; Hb: hemoglobin; AKI: acute kidney injury; RRT: renal replacement therapy.

Association between SB therapy and newly d/eOD

The median (IQR) volume of SB administered within 48 hours after ICU admission was 60 (30, 150) ml (Table 1), which was initiated at 8.9 (4.45, 18.88) hours after ICU admission, as shown in Figure S1.

As shown in Fig. 2, the incidence of newly d/eOD within 7 days of ICU admission was significantly increased in the SB group compared with the non-SB group (54.8% vs 44.6%, p < 0.05), comprising central nervous system (CNS) dysfunction (29.1% vs 21.2%, p < 0.05), coagulopathy (13.0% vs 4.8%, p < 0.001) and circulation (10.1% vs 5.4%, p < 0.05). A significant difference was not found in the incidence of respiratory, liver or renal dysfunction between the two groups.

Using univariable logistic regression, it was demonstrated that there was a composite of newly d/eOD within 7 days after ICU admission in 173/316 (54.8%) patients in the SB group versus 141/316 (44.6%) patients in the non-SB group [OR (95% CI): 1.50 (1.10–2.06), p = 0.011, Table S3]. Multivariable logistic regression revealed that the adjusted OR of SBT for this composite outcome was no longer significant [OR (95% CI): 1.39 (0.9, 1.85); p = 0.164, Fig. 3]. The log-adjusted OR of SBT-associated newly d/eOD was also not significant in each quintile stratified by pH level (Figure S2A).

Borderline significance of an SBT-associated increase in risk potential for newly d/eOD was found in a subgroup of patients with AG ≥ 15 (adjusted OR (95% CI): 1.52 (0.97, 2.37), p = 0.067) and with AKI stage ≥ 2 (adjusted OR (95% CI): 1.51 (0.99, 2.33), p = 0.058, Fig. 3). This effect was neutral in the subgroup of patients with AG < 15 [adjusted OR (95% CI): 0.95 (0.5, 1.8), p = 0.882] and AKI stage ≥ 2 [adjusted OR (95% CI): 1.08 (0.52, 2.28), p = 0.828, Fig. 3]. Significantly, SBT was associated with a composite of newly d/eOD in the subgroup of patients with worsening hemodynamics [adjusted OR (95% CI): 3.6 (1.84, 7.22), p < 0.001, Fig. 3]. However, this association was not found in the subgroup of patients with either improving hemodynamics or unchanged hemodynamics (Fig. 3). In addition, there was no significant difference in the incidence of newly d/eOD between the SB group and the non-SB group among patients who were allocated into each sepsis subgroup, whether or not they received CPR (Fig. 3).

Impact of hemodynamic status on the risk potential for SBT-associated newly d/eOD
The risk potential for SBT-associated newly d/eOD was further compared among subgroups of patients who received SBT but were characterized by different hemodynamic statuses. The subgroup of improving hemodynamics served as a reference for a multivariable logistic regression analysis. The results demonstrated that the risk potential for SBT-associated newly d/eOD within 7 days after ICU admission was significantly increased in the subgroup of patients characterized by both worsening hemodynamics [adjusted OR (95% CI): 2.91 (1.54, 5.47), p < 0.001] and unchanged hemodynamics [adjusted OR (95% CI): 1.94 (1.01, 3.72), p = 0.046, Fig. 4].

SBT-associated 28-day mortality

It was observed that there was an increased mortality in the SBT group compared with the control group (37.35% vs 29.52%) in this study. Moreover, the multivariable-adjusted hazard ratios (HRs) of 28-day mortality associated with SBT were not significant in acute critically ill patients who had metabolic acidosis [adjusted HR (95% CI): 0.83 (0.62–1.11), p = 0.205], as shown in Fig. 5. Moreover, subgroup analysis failed to show a significantly increased hazard ratio (95% CI) of SBT for 28-day mortality. In addition, the log-adjusted OR of SBT for mortality was not significant in any quintile of patients stratified by pH (Figure S2B).

Discussion

In this study, it was observed that the incidence of a composite of newly d/eOD within 7 days of ICU admission was significantly higher in patients receiving SBT than in those not receiving SBT within 48 hours of ICU admission who had metabolic acidosis (Fig. 2). In addition, the adjusted odds ratio of this composite outcome associated with SBT was significantly increased in patients characterized by worsening hemodynamic status during initial resuscitation (within 6 hours of ICU admission or before SBT if SB was given earlier), although it was not observed in the mixed overall patient population (Fig. 3). Moreover, compared with patients who had improved hemodynamic status, patients with either worsening or unchanged hemodynamic status during initial resuscitation had a significantly higher risk potential for newly d/eOD subsequent to SBT (Fig. 4). These findings suggested that SBT for metabolic acidosis is associated with an increased risk potential for subsequent development or exacerbation of organ dysfunction, while the hemodynamic status remained unstable during the acute phase of critical illness.

Metabolic acidosis is common and associated with worse outcomes in critically ill patients [1, 27]. Causal treatment is the best option but often differs according to the primary disease and is actually difficult in the acute phase of critical illness. Therefore, SBT is thought to counterbalance the negative effects of severe acidemia on organ function in clinical practice [8, 11]. However, this approach has never been supported by prospective studies. For instance, two RCTs conducted by Mathieu D and Cooper DJ concluded that administration of sodium bicarbonate did not have a more favorable effect than saline solution on hemodynamics in critically ill patients who had lactic acidosis [14, 15]. In this study, although hemodynamic changes immediately following SBT were not traced due to too many missing records in
this database, it was found that the percentage of newly developed/exacerbated circulatory dysfunction (a net increase in SOFA score ≥ 2 in circulation within 7 days after admission) was markedly increased in the SBT group in comparison with the propensity score-matched control group (Fig. 2). In addition, our results did not demonstrate a significantly beneficial effect of SBT on reducing the incidence of newly d/eOD in patients with metabolic acidosis, even in a subgroup of patients with improved hemodynamics during initial resuscitation (Fig. 3). Moreover, the log of adjusted odds ratios of this composite outcome subsequent to SBT did not change significantly with any quintile of either pH (Figure S2A). These results support the recommendations of the updated guidelines against using SB at pH greater than 7.15 in septic patients or 7.20 in intensive care patients complicated with moderate-to-severe acute renal insufficiency [19, 20]. The rationale for SB infusion remains questionable for increasing clinical tolerance to severe acidemia or compensating for extra alkalinity loss beyond hemodynamic optimization in acute critically ill patients with metabolic acidosis.

Significantly, our study provided clinical evidence that SBT for metabolic acidosis raised the risk potential for subsequent organ dysfunction or exacerbation in acute critically ill patients who were characterized by an unstable hemodynamic status during initial resuscitation. Previously, the threat to organ function from the side effects of SB was mainly based on the results of the potential for paradoxical intracellular acidosis in some in vitro experiments or animal studies [4, 28, 29]. In theory, the administered bicarbonate reacted with acids to form water and CO₂, which readily diffused across cell membranes. The high CO₂ concentration could drive this same equation in reverse and generate intracellular H⁺. Additionally, administration of sodium bicarbonate significantly lowered plasma ionized calcium, which induced cell injury. In fact, the PaCO₂ was found to increase by approximately 5 mmHg at 15 minutes following 2 mmol/kg bicarbonate infusion in patients with severe acidosis [14]. However, no difference was detected with respect to organ dysfunction between the SBT group and the control group in these trials [14, 15], except for the data from animal studies [30]. Although the percentage of patients with newly d/eOD was increased in the SBT group compared with the control group (54.8% vs 44.6%), this side effect associated with SBT was neutral in all patients in this study (Fig. 3). Interestingly, our results revealed that the adjusted odds ratio of SBT resulting in subsequent organ dysfunction was significantly increased in the subgroup of patients with worsening hemodynamics during initial resuscitation (Fig. 3). In addition, this side effect was borderline significant in subgroups of patients with either AG values remaining ≥ 15 or severe AKI (fulfilling the KDIGO criteria for stage 2 and stage 3, Fig. 3), who might benefit from further hemodynamic optimization in the acute phase of critical illness [4, 31]. Although the mechanism remains under investigation, our findings issued a warning against decision making for SBT before adequate hemodynamic optimization in acute critically ill patients with metabolic acidosis.

Similar to previous results [1, 9, 13, 16], our data suggested that SBT for metabolic acidosis within 48 hours of ICU admission did not increase the adjusted odds ratio of 28-day mortality in critically ill patients (Fig. 4). This impact of SBT was also not significant in any quintile stratified by plasma pH (Figure S2B) and did not vary in patients with different hemodynamic statuses during initial resuscitation (Fig. 5). However, it was observed that there was an increased mortality rate in the SBT group compared with the
control group (37.35% vs 29.52%) in this study. Although there were multiple factors, the limited number of recruited patients could be one of the reasons for these negative results. Further prospective research is needed to investigate the SBT-associated outcomes in critically ill patients with severe metabolic acidosis, especially for SBT given to patients with unstable hemodynamics during initial resuscitation.

There were several limitations in this study. First, this study was based on electronic healthcare records of routine clinical practice. Missing data was found for almost all variables. For instance, measurements regarding hemodynamic status, plasma electrolytes and blood gas analysis 1 hour after initiating SBT were unavailable in most of the enrolled patients, which limited the mechanistic analysis of the effect of SB therapy for metabolic acidosis on organ dysfunction and mortality. Second, this is a retrospective study. The potential sources of bias might impair the reproducibility of the results. Although we used PSM to balance important confounding factors, the association between SBT for metabolic acidosis and threatened organ function and mortality in patients who experienced hemodynamic worsening during initial resuscitation needs to be validated in a prospective trial. Third, the results of the relationship between pH and BE levels and organ function or mortality should be interpreted with caution owing to the small sample size. Thus, a well-designed prospective trial is needed to further investigate the place of SBT for metabolic acidosis in acute critically ill patients.

**Conclusions**

The results of this study demonstrated that SBT for metabolic acidosis was associated with a composite of newly developed or exacerbated organ dysfunction within 7 days of ICU admission in acute critically ill patients who were characterized by hemodynamic worsening in initial resuscitation, despite a neutral effect in all patients. Notably, the worsening as well as the unchanged hemodynamic status was found to significantly increase the adjusted risk potential for organ dysfunction subsequent to SBT. These findings suggest that hemodynamic optimization is necessary before considering SBT for metabolic acidosis in the acute phase of critical illness.

**Abbreviations**

ICU: intensive care unit; SB: sodium bicarbonate; SBT: sodium bicarbonate therapy; d/eOD: newly developed or exacerbated organ dysfunction; AKI: acute kidney injury; MIMIC-III: Medical Information Mart for Intensive Care Database; RRT: renal replacement therapy; AG: anion gap; AB: actual bicarbonate; BE: base excess; Hct: hematocrit; Hb: hemoglobin; OR: odds ratio; aOR: adjusted odds ratio; HR: hazard ratio; aHR: adjusted hazard ratio; CPR: cardiac pulmonary resuscitation; SOFA: Sequential Organ Failure Assessment; MAP: mean arterial pressure; KDIGO: Kidney Disease: Improving Global Outcomes; SAPSII: The Simplified Acute Physiology Score II; PSM: Propensity score matching.

**Declarations**

*Ethics approval and consent to participate*
This study was based on the MIMIC-III database, which is a publicly anonymized database, and we did not collect any nominative, sensitive or personal data on patients, so institutional review board (IRB) approval from Peking University Third Hospital was exempted.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The data that support the findings of this study are available from the MIMIC-III Database.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

PLM, THW, LXY and THW designed the study protocol and interpreted the results. LZ, HZ, JJX and JHL were responsible for data cleaning and statistical analysis. THW and LXY were the major contributors in writing the manuscript. ZHZ helped to revise the manuscript. Peng-Lin Ma critically reviewed the manuscript and agreed with the final version and findings. All authors read and approved the final manuscript.

PLM is the corresponding author.

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**Figures**
Figure 1

Flowchart of patient selection.
Figure 2

Comparison of the incidences of newly d/eOD between the SB and non-SB group after PSM. The chi-square test was used to compare the percentages of d/eOD between the two groups. d/eOD: developed or exacerbated organ dysfunction; composite of newly d/eOD was defined as an increase in SOFA score $\geq$2 over the baseline (SOFA score in the first 24 hours) of one organ at least within 7 days of ICU admission. Resp: respiration; Coag: coagulation; Cir: circulation; CNS: central nervous system.
**Figure 3**

Multivariable-adjusted odds ratios of SBT for newly d/eOD. Multivariate Cox regression was used. We adjusted for variables including mechanical ventilation within 48 hours after ICU admission, sepsis diagnosis, ketoacidosis diagnosis, CPR, cumulative fluid balance within 48 hours after ICU admission, SOFA score during the first 24 hours after ICU admission and pH value. d/eOD: developed or exacerbated organ dysfunction; AKI: acute kidney injury; AG: anion gap; CPR: cardiopulmonary resuscitation.
| Outcomes                  | Risk factors                     | n/N (%)       | Adjusted OR (95%CI) | P-value |
|---------------------------|----------------------------------|---------------|---------------------|---------|
| **Newly d/eOD**           |                                  |               |                     |         |
| Hemodynamic improvement   | 36/87 (41.38)                    | 1             |                     |         |
| Hemodynamic worsening     | 86/124 (69.35)                   | 2.91 (1.54,5.47) | 0.001              |         |
| Unchanged hemodynamics    | 51/105 (48.57)                   | 1.94 (1.01,3.72) | 0.046              |         |
| **28-day mortality**      |                                  |               |                     |         |
| Hemodynamic improvement   | 29/91 (31.87)                    | 1             |                     |         |
| Hemodynamic worsening     | 62/129 (48.06)                   | 1.46 (0.75,2.86) | 0.267              |         |
| Unchanged hemodynamics    | 33/112 (29.46)                   | 1.10 (0.54,2.25) | 0.788              |         |

**Figure 4**

The adjusted OR for a composite of newly d/eOD and 28-day mortality in SB group. Multiple logistic regression was used. For the dependent variable of d/eOD and 28-day death, we adjusted variables including mechanical ventilation within 48 hours after ICU admission, sepsis diagnosis, ketoacidosis diagnosis, CPR, cumulative fluid balance within 48 hours after ICU admission, SOFA score during the first 24 hours after ICU admission and pH value. d/eOD: developed or exacerbated organ dysfunction.
Figure 5

Multivariable-adjusted hazard ratios (HRs) of SBT for 28-day mortality. Multivariate Cox regression was used. We adjusted variables including mechanical ventilation within 48 hours after ICU admission, sepsis diagnosis, ketoacidosis diagnosis, CPR, cumulative fluid balance within 48 hours after ICU admission, SOFA score during the first 24 hours after ICU admission and pH value. d/eOD: developed or exacerbated organ dysfunction; AKI: acute kidney injury; AG: anion gap; CPR: cardiopulmonary resuscitation.

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