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ORIGINAL

Effectiveness of sodium bicarbonate infusion on mortality in septic patients with metabolic acidosis

Zhongheng Zhang[1*], Carlie Zhu[2], Lei Mo[3] and Yucai Hong[1]

Abstract

Objective: Although sodium bicarbonate (SB) solution has been widely used in clinical practice, its effect on mortality when administered to a large population of patients with acidosis is not known. The study aimed to investigate the effectiveness of SB infusion in septic patients with metabolic acidosis.

Methods: Septic patients with metabolic acidosis were identified from the Medical Information Mart for Intensive Care (MIMIC)-III database. Propensity score (PS) was used to account for the baseline differences in the probability to receive SB or not. The marginal structural Cox model (MSCM) was employed to adjust for both baseline and time-varying confounding factors.

Main results: A total of 1718 septic patients with metabolic acidosis were enrolled in the study, including 500 in the SB group and 1218 in the non-SB group. Both pH [7.16 (standard deviation (SD): 0.10) vs. 7.22 (SD: 0.07); $p < 0.001$] and bicarbonate concentration (BC) [11.84 (SD: 3.63) vs. 14.88 (SD: 3.36) mmol/l; $p < 0.001$] were significantly lower in the SB than that in the non-SB group. While there was no significant mortality effect in the overall population [hazard ratio (HR): 1.04; 95% CI 0.86–1.26; $p = 0.67$], SB was observed to be beneficial in patients with acute kidney injury (AKI) stage 2 or 3 and pH < 7.2 (HR 0.74; 95% CI 0.51–0.86; $p = 0.021$). Similar results were replicated with the MSCM.

Conclusion: Our study observed that SB infusion was not associated with improved outcome in septic patients with metabolic acidosis, but it was associated with improved survival in septic patients with AKI stage 2 or 3 and severe acidosis. The results need to be verified in randomized controlled trials.

Keywords: Sodium bicarbonate, Critical care, Sepsis, Mortality, Marginal structural Cox, Model

Introduction

Sepsis is a leading cause of morbidity and mortality in the intensive care unit (ICU). It has been reported that the short-term mortality rate ranges from 30 to 50%, depending on illness severity [1, 2]. Fluid resuscitation was of vital importance in the resuscitation phase. Sodium bicarbonate solution (SB) can be used for fluid resuscitation and to correct acid–base derangements. Multiple organ failure and metabolic acidosis resulting from tissue hypoperfusion are among the most important factors associated with mortality. While multiple organ failure has been extensively investigated for its association with mortality [3, 4], metabolic acidosis has been less well investigated. Pathophysiologically, metabolic acidosis can have negative impact on cardiac contractility, sensitivity of adrenergic receptors, adenosine triphosphate generation and immune response [5–7], leading to circulatory failure and decreased survival [8–10]. Extracellular alkalinization may help to correct these disorders. Survey

*Correspondence: zh_zhang1984@zju.edu.cn
[1] Department of Emergency Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, No. 3, East Qingchun Road, 310016 Hangzhou, Zhejiang, China
Full author information is available at the end of the article

studies show that most critical care physicians would consider SB to treat severe metabolic acidosis [11, 12]. However, its effect on mortality when administered to a large population of patients with acidosis is not known. A recent multicenter randomized controlled trial (RCT) did not observed the anticipated results that SB was beneficial for patients with severe acidosis [13]. However, this study focused on a heterogeneous study population, and a definitive conclusion cannot be drawn. Furthermore, the treatment with SB is a time-dependent variable, depending on the pH and bicarbonate concentration (BC). Thus, pH and BC are both the causes and results of SB treatment. In this context, the present study aimed to investigate the effectiveness of SB infusion in septic patients with metabolic acidosis. The marginal structural cox model (MSCM) was employed to account for baseline and time-dependent covariates and past history of SB infusion [14]. The aim of the study was to investigate the effect of SB in overall septic population with metabolic acidosis and in subgroups with severe metabolic acidosis and acute kidney injury (AKI). We hypothesized that SB infusion was not associated with improved hospital mortality in overall septic population with metabolic acidosis, contrary to the patients with severe metabolic acidosis and AKI.

Materials and methods

Setting

A large US-based critical care database named Medical Information Mart for Intensive Care (MIMIC-III) was employed for this study. The description of MIMIC-III is available elsewhere [15]. Briefly, the MIMIC-III database integrated de-identified, comprehensive clinical data of the patients admitted to the ICUs of Beth Israel Deaconess Medical Center in Boston, Massachusetts, from June 1st, 2001 to October 31st, 2012 (single center). There were 53,423 distinct hospital admissions for adult patients (aged 16 years or above) admitted to ICUs during the study period. Since the study was an analysis of the third party anonymized publicly available database with pre-existing institutional review board (IRB) approval, IRB approval from our institution was exempted. The study was reported according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement [16].

Participants

Inclusion criteria were patients (1) with sepsis; (2) had metabolic acidosis with pH < 7.3 and BC < 20 mmol/l; and (3) in the absence of respiratory acidosis ($PaCO_2$ < 50 mmHg). The inclusion criteria of BC, pH and $PaCO_2$ were measured within 48 h after ICU entry. If there were multiple measurements, the minimum values of pH and BC, and the maximum value of $PaCO_2$ were used. The third sepsis definition defined sepsis as a condition with life-threatening organ dysfunction caused by a dysregulated host response to infection [17]. In this study, we screened patients with documented or suspected infection, plus an acute change in total SOFA score $\geq$ 2 points [17]. Infection was identified from ICD-9 code in the MIMIC-III database. Patients with cardiac arrest, and those who stayed in ICU for over 100 days were excluded. For patients who had multiple admissions to ICU, only the first ICU admission was included for analysis.

Demographical and laboratory variables

The following variables were extracted from the MIMIC-III database for the first day of ICU admission: age at the time of hospital admission, gender, admission type, urine output, sequential organ failure assessment (SOFA) score, each component of SOFA score, qSOFA, Simplified Acute Physiology Score II (SAPSII), use of vasopressors and renal replacement therapy (RRT). SOFA score was calculated within the first 24 h after the ICU admission. If a variable was measured more than once in the first 24 h, the value associated with the greatest severity of illness was used. For example, the lowest value of mean BP and GCS reported in the first 24 h were used in the study. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [18]. Both urine output and creatinine during the first 48 h after ICU entry were used to define AKI stages. Patients with conditions of diarrhea and/or vomiting were identified on day 1 for potential digestive loss of bicarbonate. Daily fluid input and the use of balanced solution (acetate or lactate) for the first day were also included for analysis, because they might influence the acid–base status.

Laboratory variables of pH, $PaCO_2$ and bicarbonate concentration (BC) were measured during the entire ICU stay. The chart time of measurement and physiological values were extracted from the database. For patients with multiple measurements, the lowest daily value of pH and BC, and highest daily value of $PaCO_2$ were included for analysis. The median (IQR) number of measurements per patient-day were 2 (1–4), 1 (1–1) and 2 (1–4) for $PaCO_2$, BC and pH, respectively.

The primary endpoint was the hospital mortality, which was defined as the status of patient survival at the time of hospital discharge.

All screening variables contained less than 25% missing values (Table S1). Single imputation was performed for variables with missing values of less than 25% [19], which included lactate, urine output, pH, BC and $PaCO_2$.

Statistical analysis

The study population was categorized into the BS (intervention) and non-BS (control) groups according to BS treating status within 48 h after ICU entry. Categorical variables were expressed as the number of percentage. They were compared between BS and non-BS groups with Chi-square or Fisher's exact test as appropriate. Continuous variables were expressed as mean (standard deviation) or median [interquartile range (IQR)] as appropriate [20, 21].

Propensity score (PS) was used to account for the baseline differences in the probability to receive or not SB [22]. The PS measures the probability of a patient being assigned to SB treatment. In PS analysis, the SB-group received SB infusion within 48 h after ICU entry. Patients in the treatment group were matched to those with untreated patients by nearest neighbor matching. Standardized mean difference (SMD) was calculated before and after matching to examine whether the PSM reduced the differences in pretreatment covariates between treatment and control groups. Finally, Cox regression model was used to adjust for residual imbalance by including parameters with $p < 0.05$ and potential confounders judged by clinical expertise.

SB treatment during ICU stay was considered as time-dependent variable in MSCM. Potential baseline confounders such as age, gender, use of mechanical ventilation, RRT, vasopressor, urine output, SOFA, qSOFA and SAPSII were obtained on day 1 after ICU admission. BC, PaO_2 and pH during entire ICU stay were included in the model as time-varying confounding factors. The parameters of MSCM could be estimated using inverse probability weighting (IPW) to correct both for confounding and for forms of selection bias such as informative censoring [14]. By weighting each patient by IPW, two pseudo-populations are created, similar with regards to baseline and time-dependent confounding factors, and different in SB exposure. Details of IPW and R code for the performance of MSCM can be found at electronic supplemental material (ESM) S1. The ipw package (version 1.0–11) was used for estimating inverse probability weights [23].

Several prespecified subgroup analyses were performed by restricting to (1) patients with severe metabolic acidosis (pH < 7.2) and AKI stages 2 or 3; (2) patients with digestive loss of SB and severe acidosis (pH < 7.2); (3) patients receiving balanced solution and (4) patients with lactic acidosis (pH < 7.2 and lactate > 2.2 mmol/l). These

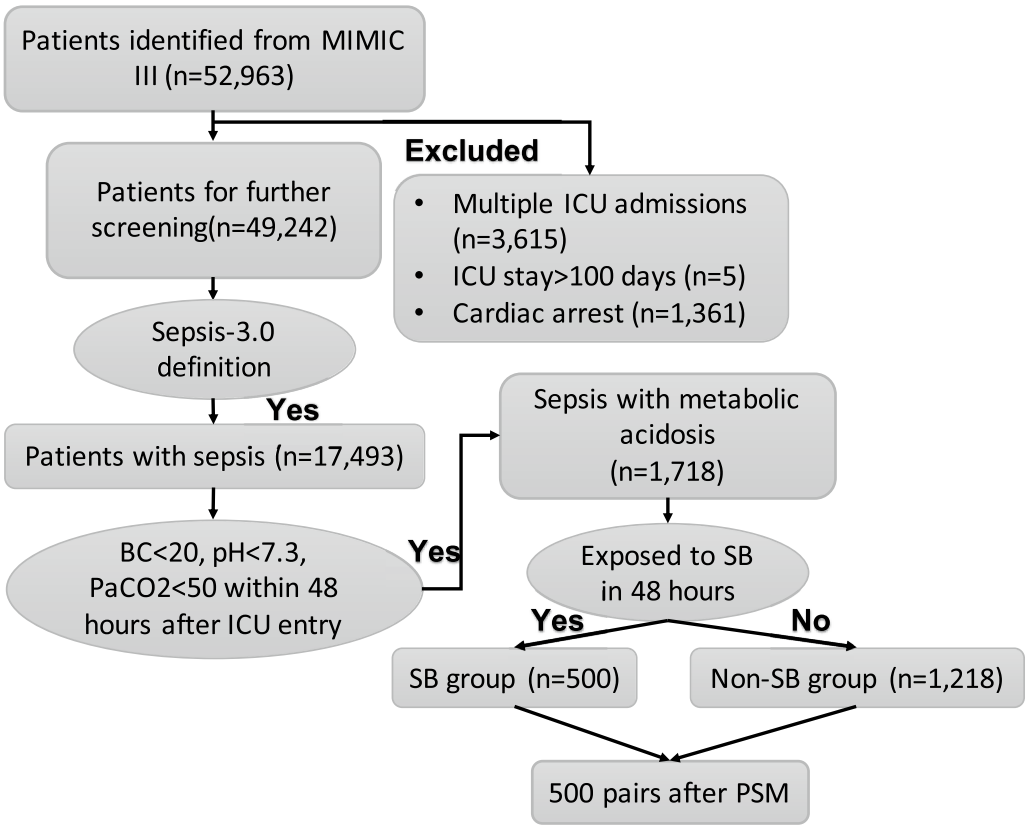

Fig. 1 Flowchart of patient selection

Table 1 Baseline differences between groups before matching

Variables	Non-SB group ($n=1218$)	SB group ($n=500$)	*P*	SMD
Gender, male (%)	593 (48.7)	235 (47.0)	0.560	0.034
Age [mean (SD)]	65.88 (16.71)	64.09 (16.41)	0.043	0.108
Admission type (%)			0.238	0.093
Elective	62 (5.1)	19 (3.8)		
Emergency	1116 (91.6)	470 (94.0)		
Urgent	40 (3.3)	11 (2.2)		
SOFA [median (IQR)]	7.00 [5.00, 10.00]	9.00 [7.00, 12.00]	< 0.001	0.556
qSOFA [median (IQR)]	2.00 [2.00, 2.00]	2.00 [2.00, 2.00]	0.017	0.138
SAPSII [median (IQR)]	48 [39, 58]	57 [47, 68]	< 0.001	0.522
Vasopressor, *n* (%)	608 (49.9)	300 (60.0)	< 0.001	0.204
Urine output [median (IQR)]	1135 [572, 1986]	709 [249, 1486]	< 0.001	0.290
RRT, *n* (%)	98 (8.0)	62 (12.4)	0.006	0.144
Elective surgery, *n* (%)	49 (4.0)	16 (3.2)	0.501	0.044
Mechanical ventilation, *n* (%)	684 (56.2)	344 (68.8)	< 0.001	0.263
Minimum pH [mean (SD)][a]	7.22 (0.07)	7.16 (0.10)	< 0.001	0.609
Minimum BC [mean (SD)][a]	14.88 (3.36)	11.84 (3.63)	< 0.001	0.866
AKI, *n* (%)	571 (46.9)	238 (47.6)	0.827	0.014
AKI stage, *n* (%)			< 0.001	0.237
0	647 (53.1)	262 (52.4)		
1	110 (9.0)	26 (5.2)		
2	245 (20.1)	84 (16.8)		
3	216 (17.7)	128 (25.6)		
Diarrhea or vomiting, *n* (%)	181 (14.9)	84 (16.8)	0.348	0.053
Lactate [mean (SD)]	4.33 (3.42)	5.42 (4.51)	< 0.001	0.273
Maximum PaCO2 [mean (SD)][a]	41.57 (6.12)	39.82 (6.56)	< 0.001	0.276
Fluid input day 1 [median (IQR)]	1661 [711, 4000]	2361 [956, 5731]	< 0.001	0.255
Balanced solution, *n* (%)[b]	310 (25.5)	64 (12.8)	< 0.001	0.326
Admission period, *n* (%)			< 0.001	0.494
Before 2008	812 (66.7)	215 (43.0)		
2008–2012	406 (33.3)	285 (57.0)		

RRT renal replacement therapy, *LOS* length of stay, *ICU* intensive care unit, *IQR* interquartile range, *SOFA* sequential organ failure assessment, *SAPSII* Simplified Acute Physiology Score II, *SMD* standardized mean difference, *AKI* acute kidney injury, BC bicarbonate concentration, *SB* sodium bicarbonate

[a] Minimum values were calculated based on values obtained during the first 48 h after ICU admission. [b]Balanced fluid included lactate and acetate solutions

subgroup analyses were performed in both PS analysis and MSCM.

Dose–response relationship between SB infusion and mortality was also explored by categorizing SB into subclasses by daily dose (non-SB, < 200 ml, 200–400 ml, 400–800 ml, and > 800 ml of equivalent volume of 8.4% SB solution). The analysis was restricted to patients with AKI stage 2 or 3 and pH < 7.2 as a post hoc analysis.

All statistical analyses were performed using R package (version 3.4.3). A p value less than 0.05 was considered to be statistically significant.

Results

The initial search identified 52,963 ICU admissions from the MIMIC-III database. A total of 17,493 patients fulfilled the definition of sepsis and 1718 had metabolic acidosis within 48 h after ICU admission. Of the study cohort, 500 patients were exposed to SB infusion in the first 48 h after ICU entry, and the remaining 1218 patients did not receive SB infusion (Fig. 1).

Table 1 shows the baseline characteristics for SB and non-SB groups. In general, patients in the SB group were more critically ill than the non-SB group [SOFA 9 (IQR 7–12) vs. 7 (IQR 5–10); $p < 0.001$]. On day 1 after ICU entry, SB group showed less urine output [709 (IQR 249–1486) vs. 1135 (IQR 572–1986) ml/24 h; $p < 0.001$], was more likely to use vasopressor (60.0% vs. 49.9%; $p < 0.001$), mechanical ventilation (68.8% vs. 56.2%; $p < 0.001$) and RRT (12.4% vs. 8.0%; $p = 0.006$) than the non-SB group. The admission type was not significantly

Table 2 Association of SB use and mortality outcome in the overall and subgroups by using propensity score analysis

Overall and subgroups	HR	Lower.95	Upper.95	*p*
Overall population ($n=1718$)	1.04	0.86	1.26	0.673
AKI stage ≥ 2 and pH < 7.2 ($n=251$)	0.74	0.51	0.86	0.021
pH < 7.2 and digestive loss ($n=90$)	1.12	0.67	1.87	0.664
Use of balanced solution ($n=374$)	0.84	0.52	1.36	0.476
pH < 7.2 and lactate > 2.2 ($n=474$)	0.91	0.70	1.20	0.518

AKI acute kidney injury, *HR* hazard ratio, *SB* sodium bicarbonate

Table 3 Cox regression model after propensity score matching in patients with AKI stage 2 or 3 and pH < 7.2

Variables	HR	Lower.95	Upper.95	*p*
Use of SB	0.74	0.51	0.86	0.021
SAPSII	1.01	0.99	1.02	0.524
SOFA	1.19	1.02	1.35	0.044
Age	1.01	1.00	1.03	0.029
Minimum pH	0.83	0.63	1.09	0.181
Minimum BC	0.97	0.90	1.04	0.346
Maximum $PaCO_2$	0.99	0.95	1.02	0.375
Urine output	1.00	1.00	1.00	< 0.001
Lactate	1.08	1.04	1.13	< 0.001
Fluid input day 1	1.09	1.05	1.13	< 0.001
Balanced solution	0.82	0.55	1.21	0.310

AKI acute kidney injury, *SOFA* sequential organ failure assessment, *SAPSII* simplified acute physiology score II, *BC* bicarbonate concentration, *HR* hazard ratio

different between the two groups. Both pH [7.16 (SD 0.10) vs. 7.22 (SD 0.07); $p<0.001$] and BC [11.84 (SD 3.63) vs. 14.88 (SD 3.36) mmol/l; $p<0.001$] were significantly lower in the SB than that in the non-SB group. The use of balanced solution was significantly higher in the non-SB group and more fluid input was observed for the SB group [2361 (IQR 956–5731) vs. 1661 (IQR 711–4000) ml for day 1; $p<0.001$]. Patients in the SB group were more likely to be enrolled during 2008–2012 (57.0% vs. 33.3%; $p<0.001$). Patients with multiple admissions were balanced between the two groups. There were 126 patients with multiple admissions with 40 (8%) in the SB group and 86 (7%) in the control group ($p=0.56$ for Pearson's Chi-squared test).

Propensity score analysis

The 500 patients who received SB were matched to 500 patients who did not received SB by PSM. The imbalance between SB and non-SB groups were significantly reduced after PSM (Figure S1, ESM table S2). Since there were still residual imbalances between SB and non-SB groups, Cox proportional hazard model was used. The results showed that SB was not associated with improved mortality in overall population (HR 1.07, 95% CI 0.95–1.19; $p=0.264$) (Table 2). However, the SB was associated with improved outcome in patients with severe acidosis (pH < 7.2) and AKI stage 2 or 3 (HR 0.74, 95% CI 0.51–0.86; $p=0.021$). The mortality effects on other subgroups were not statistically significant (Table 3). Variable importance with respect to mortality is shown in ESM figure S2.

Marginal structural cox model

Time-varying confounding and SB treatment were included in the MSCM. The distribution of IPW is shown in figure S3. As expected, pH (OR for each 0.1 increase 0.88; 95% CI 0.79–0.98; $p<0.001$) and BC (OR for each 5 mmol/l increase 0.40; 95% CI 0.35–0.47; $p<0.001$) were the most important predictors of BS infusion (ESM table S3).

MSCM results showed that SB infusion was not associated with significantly improved mortality (HR 0.69; 95% CI 0.38–1.26; $p=0.228$) in the overall sepsis population with metabolic acidosis. Similarly, the study did not identify significant beneficial effect of SB treatment on hospital mortality in the subgroup with pH < 7.2 and possible digestive loss of bicarbonate (HR 0.99; 95% CI 0.20–4.99; $p=0.989$), those with lactic acidosis (HR 0.38; 95% CI 0.14–1.08; $p=0.068$) and those with use of balanced solution (HR 1.02; 95% CI 0.59–1.75; $p=0.946$). Interestingly, SB treatment was associated with reduced mortality risk in patients with KIDGO AKI stage 2 or 3 and pH < 7.2 (HR 0.22; 95% CI 0.05–0.88; $p=0.032$) (Fig. 2, Table S4).

By considering daily SB volumes, the results showed that receiving 200–400 ml was associated with reduced risk of mortality as compared with the non-SB group (HR 0.55; 95% CI 0.18–0.85; $p=0.029$). Beneficial effect was not observed in the small (daily dose < 200 ml) and large volume (daily dose > 800 ml) groups (ESM table S5).

Discussion

Our study observed that although SB infusion was not associated with improved survival in overall sepsis patients with metabolic acidosis (pH < 7.3, BC < 20 mmol/l and $PaCO_2$ < 50 mmHg). A significant beneficial effect was observed in patients with AKI stage 2 or 3 and severe metabolic acidosis (pH < 7.2). Pathophysiologically, SB provides weak base and is able to correct acidosis by adding the bicarbonate base. Since acidosis is associated with multiple physiological derangements such as a decrease in myocardial contractility, fall in BP,

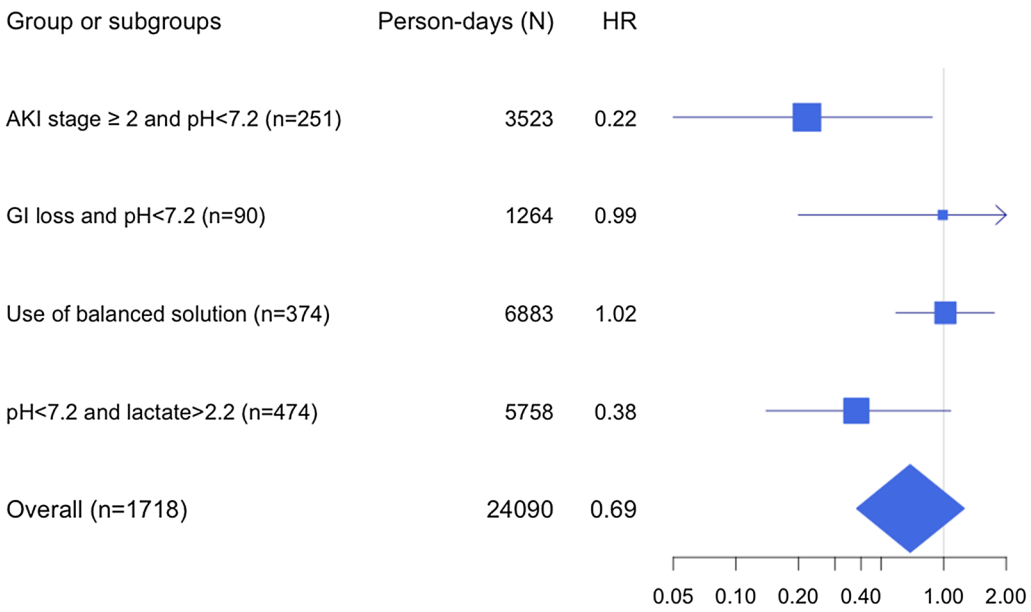

Fig. 2 Forest plot showing the effect of sodium bicarbonate treatment on mortality in overall sepsis population with metabolic acidosis and subgroups. The hazard ratios were estimated using the marginal structural Cox model. Person-days were the days of ICU length of stay. The *x*-axis tick marks follow a logarithmic scale. *AKI* acute kidney injury, *GI* gastrointestinal, *HR* hazard ratio

decreases in the binding of norepinephrine to its receptors and the shifts the oxyhemoglobin curve to the right, allowing more O_2 to be released, the correction of acidosis is thought to be beneficial in specific circumstances [9]. As expected, pH and BC were the most important predictors of BS infusion. Mechanical ventilation was also associated with use of SB, which was probability attributable to the fact that MV was associated with more illness severity, and it was reasonable that SB was more likely to be used in patients with more severe illness. The fact that SB use was neither associated with higher mortality, in overall population and in subgroups, is also an argument for using it.

The strength of the study was the use of MSCM, accounting for both baseline and time-varying confounders. The healthcare process of SB infusion is time-varying, depending on prior measurements of pH, $PaCO_2$ and BC, and the SB infusion would influence subsequent pH, PaO_2 and BC. This created a complex and dynamic relationships between SB infusion, pH and BC, and the mortality. With the MSCM method, Dupuis C and colleagues investigated the effect of red blood cell (RBC) transfusion on mortality in critically ill septic patients. The clinical scenario is quite similar to our study that RBC transfusion is determined by previous hemoglobulin and will influence subsequent hemoglobulin levels [24]. The MSCM model has also been successfully employed in other situations of time-dependent interventions [25, 26].

Although SB has been widely used for patients with acidosis in critical care setting, the evidence supporting its usefulness has not been well established. A recent multicenter randomized controlled trial (BICAR-ICU) showed that SB was ineffective in improving primary outcome of 28-mortality and organ dysfunction in patients with severe metabolic acidosis [13]. Consistent with our study, the BICAR-ICU study showed that SB infusion was associated with improved 28-day mortality in patients with AKI stage 2 or 3. In other small RCTs, SB infusion resulted in increased pH and BC, but the mortality effect was conflicting [27–30]. The 2016 surviving sepsis guideline suggested against the use of SB for patients with pH > 7.15 [31], but there is a lack of evidence for patients with AKI. Our study is timely in this regard to provide evidence that giving SB is potentially beneficial for patients with pH < 7.2 and AKI stage 2 or 3. Although our study failed to observe a linkage between SB and improved mortality in the subpopulation with GI loss, SB infusion can still be used because it is a standard of care.

A number of limitations must be acknowledged in the present study. First, the study was based on electronic healthcare records (EHR) whose data were generated during routine clinical practice. Thus, it is possible that the cohort selection is not exactly consistent with the definition of sepsis from guidelines. However, we have tried to identify septic patients that were consistent with the third definition of sepsis (e.g. infection plus an acute change in total SOFA score $\geq$ 2 points). Second,

the retrospective design of the study made it subject to confounding by indication (e.g. the selection criteria for the treating physicians to use bicarbonate infusion). Although SB may be used as a crystalloid, using it as a way to increase the plasma pH and/or bicarbonate concentration is very different than using it for fluid loading. We used PSM and MSCM to balance important confounding factors, but residual confounding cannot be fully excluded. Third, we did not fully explore the acid–base effect of fluid resuscitation and of using balanced solution. With a balanced solution, if the liver can metabolize the weak acids (lactate, acetate or malate) contained in the solution then it will have an alkalizing effect. On the other hand sodium chloride increases the risk of acidosis through hyperchloremia. We explored the amount of fluid input and the use of balanced solutions. These variables were included in multivariable model to eliminate their potential impact on the effect of SB solution. Forth, the database spanned more than 10 years and clinical practice for the management of sepsis was changed during the study period. The results may not be generalizable to current practice. However, we have accounted for the study period (2008–2012 vs. before 2008) in our model, and the results were adjusted for the study period. Fifth, the study performed multiple subgroup analyses, which may result in false positive findings. However, both PS analysis and MSCM showed the same result, which added to the robustness of the finding. Finally, the adverse events of SB were not reported in our study. While it is difficult to extract information on adverse events by using EHR, this can be explored in prospective trials.

In conclusion, in concordance with one randomized clinical trial performed in septic and non-septic population, the current study observed that SB infusion was associated with improved survival outcome in septic patients with AKI stage 2 or 3 and pH < 7.2. Further large randomized controlled trials are needed to confirm these results.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5379-2) contains supplementary material, which is available to authorized users.

Author details
[1] Department of Emergency Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, No. 3, East Qingchun Road, 310016 Hangzhou, Zhejiang, China. [2] Department of Clinical Statistics, 3M China Research and Development Center, Shanghai, China. [3] Department of Biostatistics, Lejiu Healthcare Technology Co., Ltd, Shanghai, China.

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Compliance with ethical standards

Conflicts of interest
There is no conflict of interest.

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