

Therapeutic effectiveness of sodium bicarbonate in diabetic ketoacidosis

A retrospective cohort analysis using the marginal structural Cox model

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Abstract

The treatment effect of sodium bicarbonate in diabetic ketoacidosis (DKA) remains controversial, as clinical guidelines recommend its use only in extreme acidemia (pH < 6.9) owing to inconsistent evidence and concerns over potential risks such as paradoxical central nervous system acidosis, delayed ketone clearance, and electrolyte imbalance. This study aimed to evaluate the real-world effectiveness and safety of sodium bicarbonate therapy in critically ill patients with DKA in a large clinical database. This is a retrospective cohort study following the STROBE guidelines on the MIMIC-IV database. The propensity score matching was used to balance the baseline difference. The primary outcome was the risk of multiple organ dysfunction syndrome (MODS). Secondary outcomes were the risk of renal function worsening, and neurological worsening. Adverse events included mortality, hospital readmission, and the occurrence of posttreatment supplementation of potassium or calcium. The Cox regression along with the marginal structural Cox model was employed to analyze the internal time-varying covariates. A total of 482 patients after propensity score matching was included. The Cox regression reveals that sodium bicarbonate (NaHCO₃) use was associated with a lower risk of MODS, renal worsening, and neural worsening, while marginal structural Cox model also proved a lower risk in the creatinine exceeding (hazards ratio: 0.36, 95% confidence interval: 0.25–0.52, $P < .05$) and Glasgow Coma Scale worsening (hazards ratio: 0.36, 95% confidence interval: 0.18–0.75, $P < .05$). No statistically significant association was found between NaHCO₃ use and mortality, readmission, or posttreatment of potassium or calcium, but potential adverse effect of NaHCO₃ use on MODS or readmission was detected in the severe subgroups. Sodium bicarbonate showed a potential protective association with MODS, neurological function protection, and was associated with modest protection in renal function among patients with DKA. Its use did not appear to significantly increase the risk of mortality, readmission, or posttreatment electrolyte supplementation. However, a possible adverse association with MODS and readmission was observed in the most severe subgroups. In all, NaHCO₃ in DKA patients still need cautious patient selection and close monitoring of fluid and biochemical status during therapy.

Abbreviations: AG = anion gap, AKI = acute kidney injury, CI = confidence interval, DKA = diabetic ketoacidosis, HR = hazards ratio, ICU = intensive care unit, KNN = K-nearest neighbors, MODS = multiple organ dysfunction syndrome, MSCM = marginal structural Cox model, NaHCO₃ = sodium bicarbonate, OR = odds ratio, PSM = propensity score matching, SAPS II = Simplified Acute Physiology Score II, SIRS = systemic inflammatory response syndrome, SMD = standardized mean differences, SOFA = Sequential Organization Failure Assessment.

Keywords: diabetes, DKA, intensive care, marginal structural Cox model, sodium bicarbonate, time-varying confounders

1. Introduction

Diabetic ketoacidosis (DKA) arises from an absolute or relative deficiency of insulin coupled with elevated levels of counter-regulatory hormones, including glucagon, catecholamines, cortisol, and growth hormone.^[1] This hormonal imbalance

triggers uncontrolled hepatic gluconeogenesis and glycogenolysis, resulting in marked hyperglycemia. Concurrently, enhanced lipolysis leads to the excessive release of free fatty acids, which are converted into ketone bodies, namely acetoacetate and β -hydroxybutyrate, within the liver. The accumulation of

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was an analysis of the third-party anonymized databases with preexisting IRB approval, and XW have finished the CITI program and own the certification of the MIMIC-IV database (No. 54756232). MIMIC-IV database is a broad-consent, de-identified database, which have been reviewed and approved by the Institutional Review Boards of BIDMC and MIT, with a waiver of informed consent.

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these organic acids overwhelms the buffering capacity of the body, culminating in high anion gap (AG) metabolic acidosis. Additionally, DKA induces a state of systemic inflammation and oxidative stress, with increased secretion of cytokines such as IL-6 and TNF- α , contributing to endothelial dysfunction and potential tissue injury. Electrolyte disturbances, notably potassium and phosphate shifts, further complicate the metabolic derangements. In severe cases, these pathophysiological changes can impair organ perfusion and predispose to complications such as cerebral edema and acute kidney injury (AKI), highlighting the urgency of timely and effective therapeutic intervention.^[2,3]

In current clinical guidelines, standard treatments for DKA, such as fluid resuscitation, insulin infusion, and electrolyte correction, are well defined. However, the use of sodium bicarbonate remains controversial, particularly regarding the appropriate threshold for its initiation and whether it should be used at all in moderate acidosis.^[4]

In contrast, recent clinical trials have demonstrated moderate benefits of sodium bicarbonate therapy in other types of metabolic acidosis. For instance, in patients with AKI or sepsis-induced acidosis, sodium bicarbonate administration has been associated with reduced mortality in certain well-defined subgroups,^[4,5] and a randomized controlled trial reported notably favorable outcomes in cases of severe renal acidosis, suggesting that bicarbonate therapy may confer a survival advantage under specific clinical conditions.^[6]

The use of sodium bicarbonate remains a topic of controversy, especially on the risk to induce edema, renal disorder, abnormal hypokalemia, or any other complication.^[1,7] Existing literature comprises primarily physiological studies and small-scale clinical trials. However, most of them lack clear prognostic implications, and the experimental studies did not obtain any promising outcome.^[2,8] The use of sodium bicarbonate and the optimal timing for its administration in DKA patients remain subjects of ongoing discussion among researchers and clinical institutions, with no full consensus yet established.^[5,6] In spite of this, part of clinicians prefer sodium bicarbonate in DKA management by experience.^[8]

Taken together, researching the impact of sodium bicarbonate administration in DKA patients is of importance. This study objected to comprehensively assessing sodium bicarbonate (NaHCO₃) on organ function and related adverse impacts, aiming to provide more evidence in managing DKA patients.

2. Methods

2.1. Study design and participants

This is a retrospective cohort study, following the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guideline. It was based on the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.2), a large, freely available critical care database developed by the MIT Laboratory for Computational Physiology. The database includes de-identified health-related data of patients admitted to Beth Israel Deaconess Medical Center (Boston) from 2008 to 2019. Data access was approved after completing the required credentialing (Certification Number 54756232 to XW).^[9,10]

2.2. Data collection

Patients who met the following criteria were encompassed: diagnosed with diabetic ketoacidosis by any causes; one's first hospital and intensive care unit (ICU) admission; and at least one of the time-varying endpoints (Glasgow coma score, Sequential Organization Failure Assessment [SOFA] score, creatinine)

reported. Patients would be divided into NaHCO₃ group if they received any sort of sodium bicarbonate during the hospital stay.

Variables were extracted from 2 aspects: time-fixed variables, such as age, gender, and past histories of the characteristics, and time-varying variables such as AG, glucose, pH, potassium, and chloride, which reflected the most serious indicators of the patients. Detailed information of the extraction standard was given in Table S1, Supplemental digital content, <https://links.lww.com/MD/R297>, with the definition of the variables in Table S2, Supplemental digital content, <https://links.lww.com/MD/R297>.

2.3. Outcomes

The treatment effect evaluation of sodium bicarbonate on DKA is separated into primary outcome, secondary outcomes, and adverse events. The primary outcome was defined as the risk of multiple organ dysfunction syndrome (MODS). Secondary outcomes were the risk of renal function worsening and neural worsening, recorded as survival endpoints. These endpoints were identified and constructed based on deterioration in corresponding clinical scores or serum creatinine levels. Once the deterioration reached a prespecified threshold compared with baseline, it was recorded as an "endpoint event." Adverse events were including the posttreatment administration of potassium and calcium during the ICU stay, in-hospital mortality, and readmission. The definition was detailed in Table S3, Supplemental digital content, <https://links.lww.com/MD/R297>.

2.4. Statistical analysis

We used sequential K-nearest neighbors (KNN) imputation to handle the continue values for matching and marginal structural Cox regression. A variable would be excluded from our analysis if the missing rate was over 30%, and the patients without any survival endpoint would be exclusive as well. For continuous variables with a missing rate below 30%, we performed imputation using a sequential KNN algorithm. Variables with higher missing rates were generally excluded from the analysis. However, due to the clinical importance of arterial pH in the assessment of acid-base balance and severity stratification in DKA, we retained the pH variable and still applied KNN-based imputation despite its missing rate being ~39%. To minimize potential confounding arising from baseline differences, propensity score matching (PSM) was performed. Given the limited number of patients in the exposure group, a 1:5 nearest-neighbor matching without replacement was applied to maximize statistical power while maintaining comparability. Propensity scores were estimated using a multivariable logistic regression model including clinically relevant covariates (e.g., age, sex, comorbidities, laboratory indices, and disease severity). Covariate balance between matched groups was evaluated using standardized mean differences (SMD), with SMD values < 0.1 indicating adequate balance. We also used the love plot to compare the SMD before and after match. The detailed information for PSM is in Supplementary Method 1, Supplemental digital content, <https://links.lww.com/MD/R303>. Hypothesis testing was implied to check the difference of the baseline in the 2 groups before and after the PSM.

Correlation analysis was first conducted to assist in the selection of covariates for subsequent Cox regression and to provide reference for subgroup stratification.

To handle time-varying confounders derived from repeated measurements, monitoring data were segmented at a daily interval. From these time slices, the values within intervals most associated with the outcome were selected to construct a time-structured cohort. Subsequently, an inverse probability

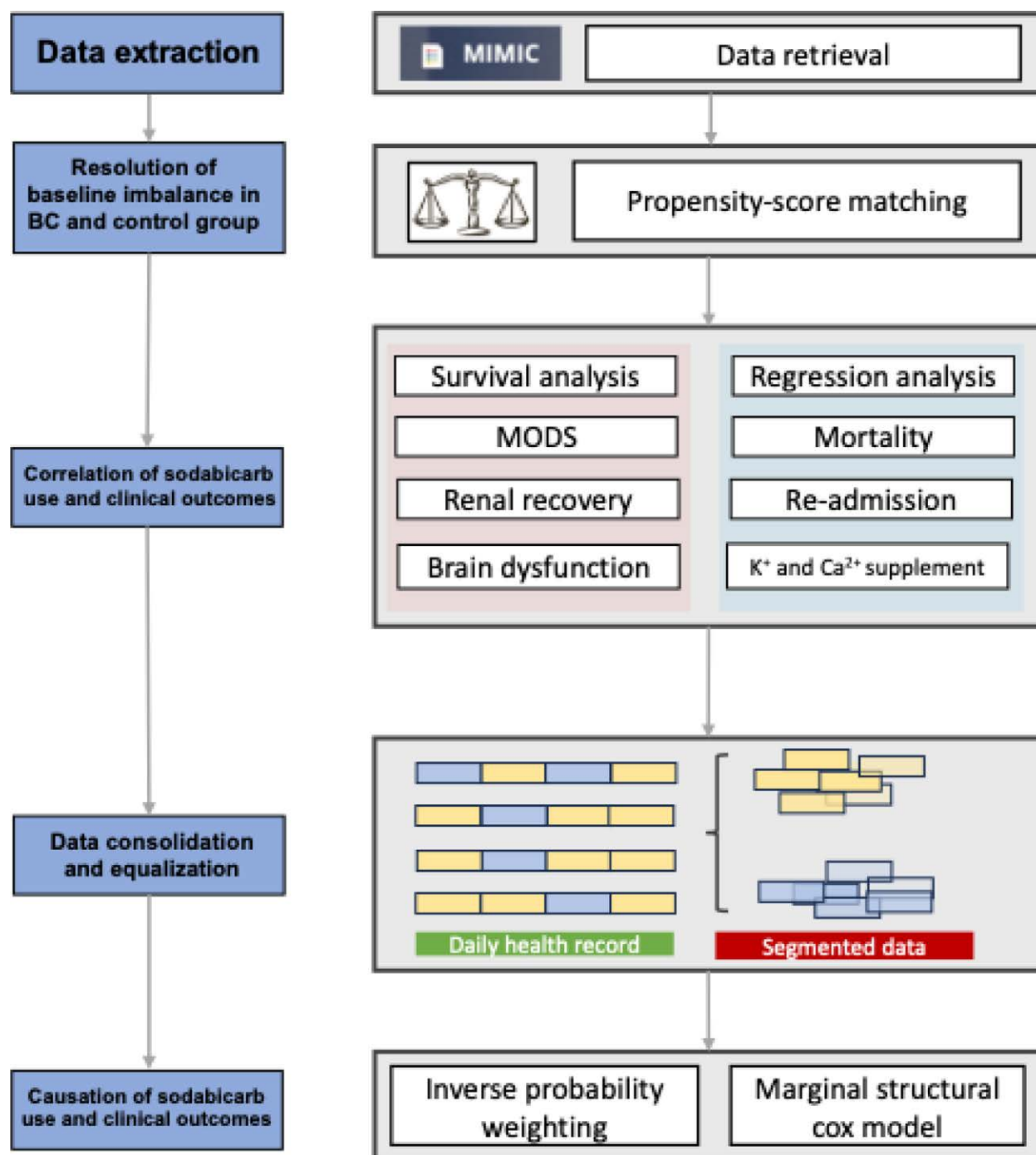


Figure 1. Research diagram of this study. MODS = multiple organ dysfunction syndrome.

weighting with marginal structural Cox model (MSCM) was applied to assess the causal relationship between NaHCO₃ exposure and mortality risk under time-varying conditions.^[11,12] The detailed information is in Supplementary Method 2, Supplemental digital content, <https://links.lww.com/MD/R303>. We employed generalized linear models to examine the association between sodium bicarbonate use and secondary adverse outcomes. Subgroup analyses were conducted based on key blood gas and electrolyte parameters, with clinically relevant cutoff values used to stratify patients. The analytical approach in these subgroups was consistent with that of the primary and secondary outcome analysis. R

(Version 4.3.2) was implied in our study to conduct all of the analysis process.

3. Results

3.1. Baseline of the characteristics

A flow chart of the design of this study was summarized in Figure 1, and the selection process of patients was presented on Figure 2. An initial cohort of 2011 patients diagnosed with DKA was identified from the MIMIC-IV database. Following predefined criteria, 991 patients were excluded due

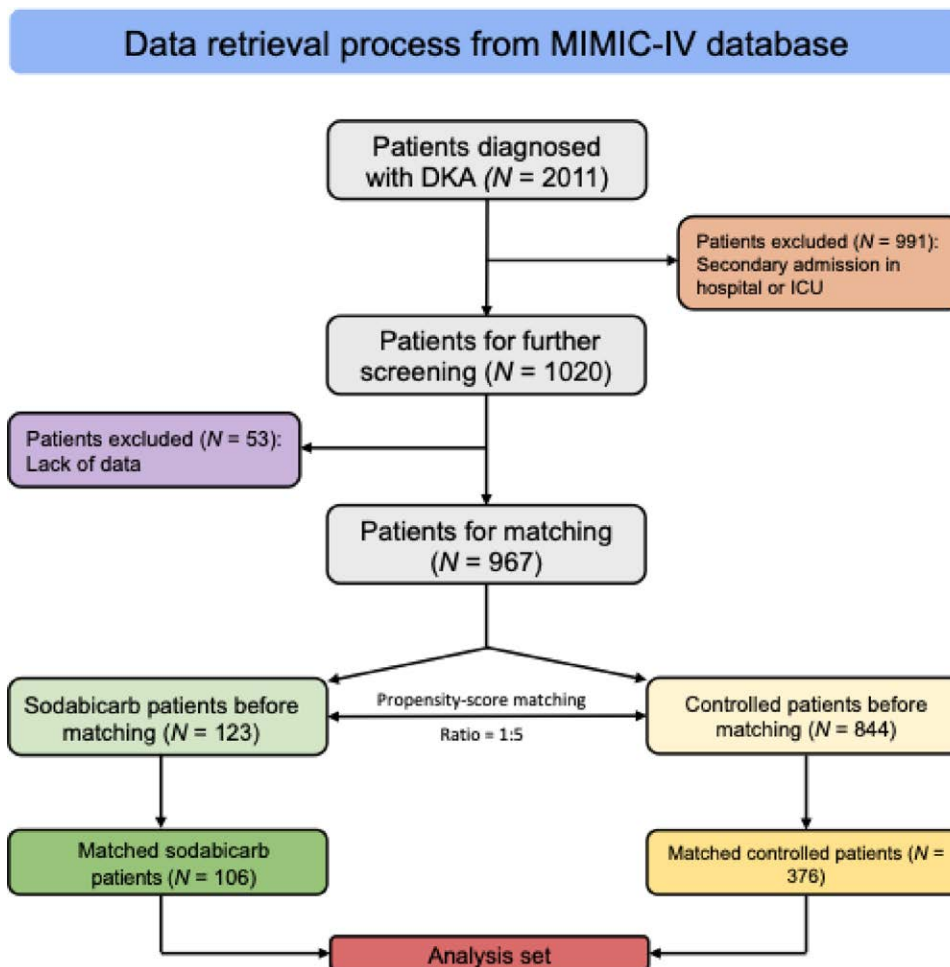


Figure 2. Flow chart for the selection of the patients. DKA = diabetic ketoacidosis, ICU = intensive care unit.

to secondary hospital or ICU admissions, and the rest of 1020 patients who met the basic eligibility for further screening. Among them, 123 patients had received sodium bicarbonate therapy, and 844 served as controls. After excluding 53 patients due to insufficient data, 967 patients remained for PSM, which was conducted at a 1:5 ratio to ensure baseline comparability. Finally, a sum of 482 patients was enrolled in our analysis, in which 106 patients received sodium bicarbonate therapy. The baseline of the characteristics was presented in Table 1. There was a relatively large difference in the baseline characteristics; however, after the PSM process, most of the variables had a lower standard mean difference (Table S4, Supplemental digital content, <https://links.lww.com/MD/R297>). The love plot (Fig. S1, Supplemental digital content, <https://links.lww.com/MD/R297>) showed a decrease of SMD after the PSM process. The correlation of some variables was presented in Figure S2, Supplemental digital content, <https://links.lww.com/MD/R297>.

3.2. Primary and secondary outcomes

Regarding the primary outcome, the forest plot (Fig. 3) presented that NaHCO_3 lowered the risk for MODS (hazards ratio [HR]: 0.63, 95% confidence interval [CI]: 0.48–0.83, $P < .05$), which could be also found in the Kaplan–Meier plot (Fig. 4A and B).

In the secondary outcomes, patients who received NaHCO_3 therapy had a lower risk of an increase in renal SOFA score (HR: 0.50, 95% CI: 0.37–0.70, $P < .05$) and creatinine (HR 0.45,

95% CI: 0.35–0.57, $P < .05$). MSCM analysis also revealed that NaHCO_3 use had a lower risk of creatinine exceeding (HR: 0.36, 95% CI: 0.25–0.52, $P < .05$). NaHCO_3 did not trigger a worsening in neural function (HR: 0.50, 95% CI: 0.36–0.70, $P < .05$), which can be also found in the MSCM model (HR: 0.36, 95% CI: 0.18–0.75, $P < .05$). All of these outcomes could also be also found in the Kaplan–Meier plot (Fig. 4C–H).

3.3. Adverse events

No statistical significance was detected between NaHCO_3 for the posttreatment supplementation of potassium (odds ratio [OR]: 0.52, 95% CI: 0.19–1.69, $P = .279$) and posttreatment supplementation of calcium (OR: 2.83, 95% CI: 0.57–13.93, $P = .203$). There was also no statistical significance in the association of NaHCO_3 use on mortality (OR: 1.03, 95% CI: 0.98–1.08, $P = .215$) and readmission (OR: 1.05, 95% CI: 0.99–1.10, $P = .104$), which was presented in Table 2.

3.4. Subgroup and multivariate analysis

Subgroup analyses were presented on Table 3. NaHCO_3 treatment have no statistically significant association of the MODS risk when the bicarbonate concentrate was below 11 mg/dL (HR: 0.83, 95% CI: 0.45–1.51, $P = .539$), the pH below 7.15 (HR: 1.01, 95% CI: 0.50–2.03, $P = .988$), the potassium was ≥ 5 mmol/L (HR: 1.11, 95% CI: 0.62–1.97, $P = .727$), or glucose was ≥ 250 mg/dL (HR: 0.77, 95% CI: 0.54–1.09, $P = .143$). NaHCO_3 therapy has high risk to acquire

Table 1**Baseline characteristics of study population (after propensity score matching).**

Variables	Control group (n = 376)	NaHCO ₃ group (n = 106)	P-value	SMD
Age (yr)	52.88 (18.45)	52.59 (17.32)	.885	0.016
Gender (male, %)	199 (52.9)	62 (58.5)	.365	0.112
Type of diabetes (%)			.016	0.328
Type 1	164 (43.6)	49 (46.2)		
Type 2	116 (30.9)	19 (17.9)		
Others	96 (25.5)	38 (35.8)		
Dialysis (%)	11 (2.9)	14 (13.2)	<.001	0.384
Oasis (mean [SD])	28.80 (8.80)	32.27 (11.33)	.001	0.343
Elective surgery (%)	1 (0.3)	1 (0.9)	.918	0.087
Myocardial infarct (%)	68 (18.1)	26 (24.5)	.18	0.158
Congestive heart failure (%)	67 (17.8)	23 (21.7)	.445	0.098
Chronic pulmonary disease (%)	50 (13.3)	18 (17.0)	.421	0.103
Mild liver disease (%)	34 (9.0)	11 (10.4)	.819	0.045
Severe liver disease (%)	5 (1.3)	5 (4.7)	.076	0.199
Renal disease (%)	78 (20.7)	48 (45.3)	<.001	0.541
Malignant cancer (%)	21 (5.6)	4 (3.8)	.621	0.086
SAPS II (mean [SD])	32.34 (13.52)	37.31 (16.25)	.001	0.333
SIRS (mean [SD])	2.83 (0.82)	2.99 (0.75)	.066	0.208
Vasopressor (%)	17 (4.5)	14 (13.2)	.003	0.309
Ventilator (%)	176 (46.8)	65 (61.3)	.011	0.294
AG (mean [SD])	20.48 (6.46)	21.61 (7.21)	.122	0.165
PH (mean [SD])	7.27 (0.11)	7.24 (0.15)	.085	0.175
Glucose (mean [SD])	308.68 (208.74)	303.87 (180.47)	.829	0.025
Sodium (mean [SD])	137.75 (5.79)	137.22 (5.45)	.394	0.095
Potassium (mean [SD])	4.32 (0.88)	4.47 (1.04)	.165	0.146
Chloride (mean [SD])	104.75 (7.53)	105.11 (8.93)	.677	0.044
Calcium (mean [SD])	8.22 (0.96)	7.98 (1.10)	.029	0.231
Bicarbonate (mean [SD])	15.52 (6.10)	14.50 (6.21)	.129	0.166
Bun (mean [SD])	27.78 (19.43)	45.45 (35.15)	<.001	0.622
Creatinine (mean [SD])	1.54 (1.48)	2.89 (2.70)	<.001	0.619
GCS (mean [SD])	14.53 (1.53)	14.57 (1.70)	.819	0.024
SOFA (mean [SD])	1.21 (1.81)	2.37 (2.63)	<.001	0.514
SOFA (renal, mean [SD])	0.40 (0.83)	0.92 (1.24)	<.001	0.485
KDIGO (mean [SD])	0.04 (0.21)	0.08 (0.37)	.106	0.15
Hospital days (mean [SD])	7.92 (8.27)	11.31 (11.73)	.001	0.334
ICU days (mean [SD])	3.09 (3.44)	4.69 (5.96)	<.001	0.33

AG = anion gap, GCS = Glasgow Coma Scale, ICU = intensive care unit, SAPS II = Simplified Acute Physiology Score II, SIRS = systemic inflammatory response syndrome, SMD = standardized mean differences, SOFA = Sequential Organization Failure Assessment.

secondary admission when the bicarbonate concentrate was below 11 mg/dL (OR: 1.08, 95% CI: 1.01–1.15, $P < .05$), the pH below 7.15 (OR: 1.12, 95% CI: 1.03–1.22, $P < .05$), the potassium was ≥ 5 mmol/L (OR: 1.15, 95% CI: 1.02–1.30, $P < .05$) or glucose was equal or ≥ 250 mg/dL (OR: 1.07, 95% CI: 1.00–1.15, $P = .05$). Apart from these subgroups, we also carried out multiple variables regression with MSCM (Table S5, Supplemental digital content, <https://links.lww.com/MD/R297>).

4. Discussion

4.1. Interpretation of our findings

This is a prospective, cohort study exploring the effects of bicarbonate therapy on patients with DKA. We carried out an analysis of internal time-varying covariates and presenting a patient cohort with relatively balanced characteristics. The use of sodium bicarbonate showed a potential protection in the risk of MODS. However, this effect was only observed in traditional Cox regression and within a subgroup of more severe patients, while it was not evident in the overall MSCM analysis. Our results showed that sodium bicarbonate administration was associated with a lower risk of increase in serum creatinine levels and renal SOFA scores compared with the control group. This finding is in line with the established theory that sodium bicarbonate may help flush the renal tubules, reducing local

acidosis within the proximal tubular cells. This buffering effect helps mitigate pro-inflammatory and pro-fibrotic responses triggered by low bicarbonate concentrations, thereby slowing the maladaptive progression of tubular injury.^[13,14]

Although our threshold for defining renal function deterioration was relatively permissive – set as either an increase in serum creatinine by more than 0.1 mg/dL or a rise in the SOFA renal score by more than 1 point within 1 week – it was applied consistently across all groups to maintain comparability. Even under this broader criterion, the use of sodium bicarbonate appeared to confer at least modest renal protection in patients with DKA.^[15] We did not observe an elevated risk of neurological worsening. In routine clinical guidelines, neurological complications are typically associated with cerebral edema and increased intracranial pressure, especially in pediatric or severe DKA cases. Moreover, although current guidelines tend to recommend sodium bicarbonate for patients with more severe acidosis, our findings suggest that certain adverse outcomes were more frequently observed in the subgroup with severe acidosis, partially challenging the conventional practice.

We further analyzed the posttreatment use of potassium and calcium supplementation, which served as indirect indicators of potential hypokalemia and hypocalcemia following sodium bicarbonate administration. The subgroup results suggest that caution may still be necessary during bicarbonate therapy.

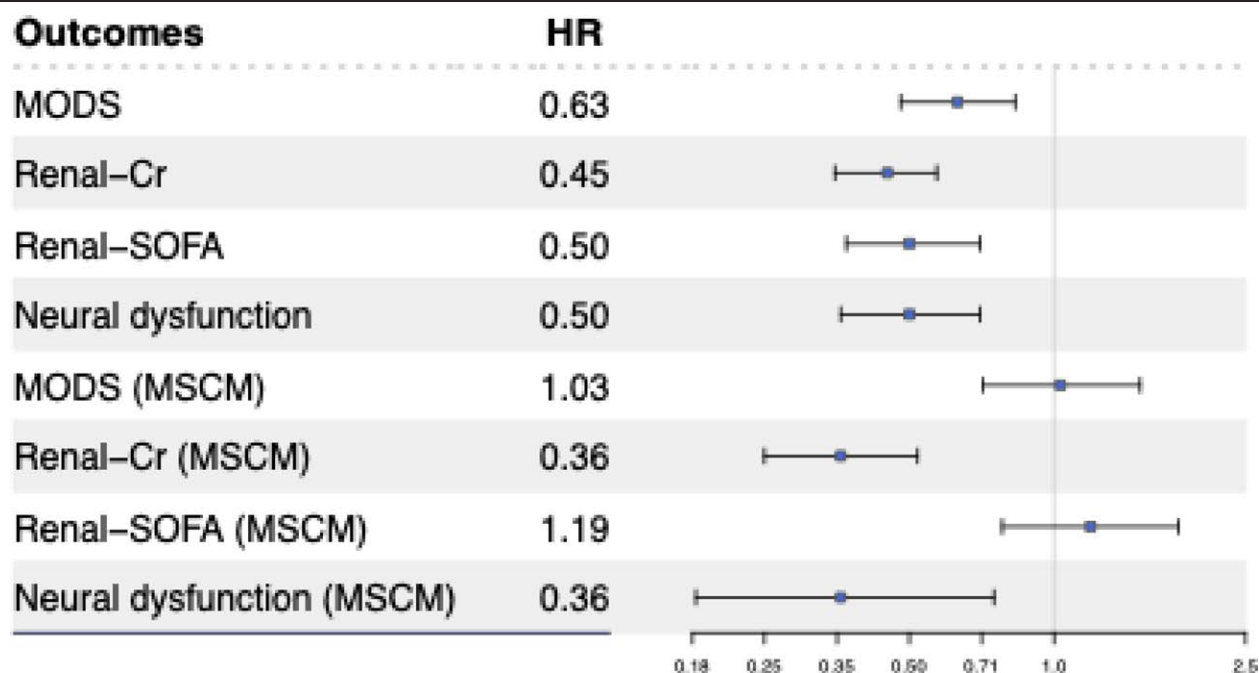


Figure 3. Forest plot of Cox and the MSCM model about the impact of NaHCO_3 use on the renal, neural, and organ function after propensity score matching or inverse probability weighting. MODS = multiple organ dysfunction syndrome, MSCM = marginal structural Cox model, SOFA = Sequential Organization Failure Assessment.

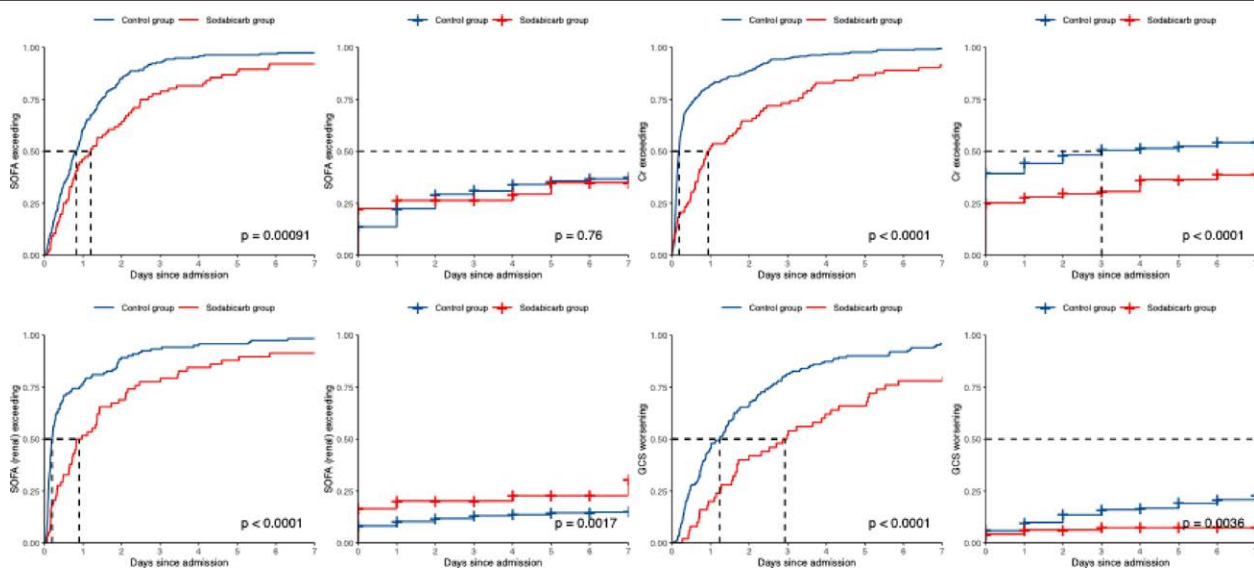


Figure 4. Kaplan-Meier plots of NaHCO_3 versus control on cohort after PSM and the MSCM cohort. (A) The SOFA score exceeding rate after PSM. (B) The SOFA score exceeding rate after MSCM and IPW. (C) The Cr exceeding rate after PSM. (D) The Cr exceeding rate after MSCM and IPW. (E) The renal SOFA score exceeding rate after PSM. (F) The renal SOFA score exceeding rate after MSCM and IPW. (G) The GCS score worsening rate after PSM. (H) The GCS score worsening rate after MSCM and IPW. Cr = Creatinine, GCS = Glasgow Coma Scale, MSCM = marginal structural Cox model, PSM = propensity score matching, SOFA = Sequential Organization Failure Assessment.

Recent perspectives suggest the assessment of DKA severity should not rely solely on pH value. Instead, it could be estimated by blood gas index such as AG or the synthesis of potassium, chloride, and bicarbonate levels.^[16] Our study carried out several subgroup analyses, but most did not yield statistically significant differences. In some cases, a potential increase in risk was even observed. These findings may be partially attributed to the limited sample size within each subgroup, which could have reduced the statistical power to detect meaningful differences.

4.2. Merits

Several factors may have contributed to the inconclusive findings in previous early trials. First, many earlier studies involved relatively small sample sizes, which may not have provided adequate power for ratio-based comparisons and could have introduced sampling bias. In addition, sodium bicarbonate is typically used as a temporary intervention rather than a 1-time definitive treatment, given its short-acting nature in real-world clinical settings. These characteristics may limit the applicability of rigid randomized or

Table 2**Association between NaHCO₃ use and potassium supplements, calcium supplements, mortality, and readmission.**

Adverse events	OR (95% CI)	P-value
Potassium supply	0.52 (0.16–1.69)	.279
Calcium supply	2.83 (0.57–13.93)	.203
Mortality	1.03 (0.98–1.08)	.215
Readmission	1.05 (0.99–1.10)	.104

Potassium supplements and calcium supplements refer to any the “supplements” in this table refer specifically to the posttreatment administration of potassium and calcium during the ICU stay.
CI = confidence interval, ICU = intensive care unit, OR = odds ratio.

Table 3**Association of NaHCO₃ use and all the outcomes in the subgroups (point estimate, 95% confidence interval, and P-value).**

Subgroups	MODS	Renal-Cr	Renal SOFA	Neural dysfunction	Potassium supply	Calcium supply	Mortality	Readmission
Bicarbonate < 11 mg/dL	0.83 (0.45–1.51, P = .539)	0.37 (0.22–0.61, P < .001)	0.46 (0.21–1.04, P = .061)	0.19 (0.07–0.52, P = .001)	0.47 (0.10–2.25, P = .346)	1.51 (0.89–2.55, P = .128)	1.08 (1.01–1.15, P = .029)	1.08 (1.01–1.15, P = .029)
AG ≥ 28mmol/L	0.63 (0.48–0.83, P = .001)	0.45 (0.35–0.57, P < .001)	0.50 (0.37–0.70, P < .001)	0.50 (0.36–0.70, P < .001)	0.52 (0.16–1.69, P = .279)	2.83 (0.57–13.93, P = .203)	1.03 (0.98–1.08, P = .215)	1.05 (0.99–1.10, P = .104)
PH < 7.15	1.01 (0.50–2.03, P = .988)	0.32 (0.18–0.57, P < .001)	0.31 (0.10–0.95, P = .040)	0.34 (0.15–0.76, P = .009)	0.65 (0.10–4.38, P = .662)	1.98 (0.80–4.90, P = .141)	1.06 (0.97–1.15, P = .217)	1.12 (1.03–1.22, P = .012)
Potassium ≥ 3.5 mmol/L	0.64 (0.48–0.86, P = .003)	0.45 (0.34–0.59, P < .001)	0.51 (0.36–0.71, P < .001)	0.47 (0.33–0.69, P < .001)	0.54 (0.18–1.65, P = .282)	2.32 (0.40–13.52, P = .351)	1.03 (0.98–1.08, P = .300)	1.03 (0.98–1.10, P = .257)
Potassium ≥ 5 mmol/L	1.11 (0.62–1.97, P = .727)	0.62 (0.38–1.02, P = .059)	0.66 (0.34–1.31, P = .238)	0.79 (0.36–1.70, P = .540)	0.30 (0.04–2.17, P = .237)	3.04 (0.08–111.53, P = .547)	1.10 (0.95–1.27, P = .215)	1.15 (1.02–1.30, P = .022)
Glucose ≥ 250mg/dL	0.77 (0.54–1.09, P = .143)	0.44 (0.31–0.63, P < .001)	0.47 (0.31–0.70, P < .001)	0.46 (0.30–0.70, P < .001)	0.45 (0.10–2.10, P = .311)	2.19 (0.18–27.13, P = .543)	1.01 (0.94–1.09, P = .746)	1.07 (1.00–1.15, P = .050)

AG = anion gap, Cr = creatinine, MODS = multiple organ dysfunction syndrome.

observational trial designs and partly explain the heterogeneity in reported outcomes.

Second, the observation windows in some of these studies were relatively short, potentially missing longer-term effects on organ function or patient prognosis during the subsequent ICU or hospital stay.^[17–19] Moreover, many trials lacked granular monitoring of time-dependent variables, making it difficult to adjust for real-time changes in physiological parameters or laboratory indicators. This limitation may have affected the accuracy of outcome assessments and hindered adequate confounder control. In contrast, our study was based on the MIMIC-IV database, which offers detailed temporal information on biochemical and vital sign measurements, along with records of repeated sodium bicarbonate administration. This allowed us to incorporate more dynamic modeling of patient trajectories. Using a Cox regression model, we evaluated the association between sodium bicarbonate use and clinical outcomes. Furthermore, the application of inverse probability weighting and the marginal structural Cox model (MSCM) enabled us to simulate a pseudo-population that accounts for time-varying confounders and multiple interventions, providing a closer approximation to real-world clinical decision-making and strengthening the causal interpretability of our findings.

The recent qualified trials investigated the causal association between NaHCO₃ use and acidosis in some aspects.^[20,21] Zhang et al^[4] firstly introduced the marginal structural model and the inverse weighting for the imbalance, exploring the NaHCO₃ infusion had a positive outcome on sepsis-induced acidosis and then found a similar efficacy on patients with AKI. Jaber et al^[6] in their randomized controlled trial also detected a protective effect of sodium bicarbonate on AKI and death. However, DKA was notably absent from these cohorts. By integrating a complex, hierarchical definition of DKA with progressive modeling strategies, our study extends this body of evidence, providing a complementary and much-needed contribution to

the broader understanding of bicarbonate therapy across acidosis subtypes.

4.3. Limitations

There are several important limitations to be acknowledged in this study. First, the pH value, although clinically critical, had a substantial proportion of missing data. While we attempted to address this through sequential KNN imputation, the incompleteness may introduce bias, particularly in the subgroup analysis and regression modeling. Second, the outcome definitions, especially for renal recovery, deviate from standardized criteria such as KDIGO. For instance, we defined renal recovery as an increase in serum creatinine of more than 0.1 mg/dL, whereas the KDIGO criterion is 0.3 mg/dL. This concession was made to increase sensitivity and maintain model stability in the time-series analysis, but it may limit generalizability and clinical comparability. Third, despite propensity score matching and adjustment with marginal structural models, residual imbalance remained: patients in the sodium bicarbonate group had slightly greater baseline severity. This may introduce unmeasured confounding and affect the interpretation of treatment effects. Finally, given the retrospective design and reliance on a single-center public database, causality cannot be inferred. Future multicenter prospective studies with standardized endpoints and richer biochemical datasets are warranted to validate our findings.

5. Conclusion

Sodium bicarbonate showed a potential protective association with MODS protection, as reflected by SOFA scores, and was associated with modest protection in renal function and neural worsening among patients with DKA. Its use did not appear to significantly increase the risk of MODS, mortality, readmission,

or posttreatment electrolyte supplementation. However, a possible adverse association with MODS and readmission was observed in the most severe subgroups. In all, NaHCO_3 in DKA patients still need cautious patient selection and close monitoring of fluid and biochemical status during therapy.

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Author contributions

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