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Association between baseline serum bicarbonate and the risk of postoperative delirium in patients undergoing cardiac surgery in the ICU: a retrospective study from the MIMIC-IV database

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Abstract

Background Although serum bicarbonate is a reliable predictor of various disease complications, its relationship with postoperative delirium (POD) remains unclear. Our research aimed to assess the effect of baseline serum bicarbonate levels on the incidence of POD in cardiac surgery patients.

Methods A retrospective analysis was conducted on cardiac surgery patients who met specific inclusion and exclusion criteria, using data from the Marketplace for Information in Critical Care Medicine (MIMIC-IV) database. Univariate and multivariate logistic regression models are employed to explore the correlation between serum bicarbonate levels and the risk of POD, and their predictive efficacy is assessed by means of restricted cubic spline regression models (RCS) and receiver operating characteristic curves (ROC). In addition, subgroup and sensitivity analyses are conducted to test the robustness of the results.

Results In this study, 5,422 patients were included, where the incidence of POD was 13.0%. For each 1 mmol/L increase in bicarbonate, a 13% reduction in the risk of POD was observed in the fully adjusted model (OR = 0.87, 95% CI: 0.83–0.91, $P < 0.001$). The RCS model demonstrated a linear negative correlation between the level of bicarbonate and the risk of POD (P for nonlinearity = 0.987). The ROC curve analysis demonstrated that the bicarbonate level had moderate predictive efficacy (AUC = 0.629). Both subgroup and sensitivity analyses reaffirmed the robustness of these results.

Conclusions Lower baseline serum bicarbonate levels in cardiac surgery patients are linked to a higher risk of POD. Monitoring and adjusting serum bicarbonate levels may help identify high-risk patients and potentially improve outcomes.

Keywords Cardiac surgery, Serum bicarbonate, MIMIC-IV database, Postoperative delirium

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Introduction

Delirium is an acute cerebral dysfunction characterized by confusion, diminished attention, a fluctuating course, and perceptual deficits [1]. The reported incidence of postoperative delirium (POD) in cardiac surgery patients ranges from 9–53.5% [2–4], with a notable prevalence in the intensive care unit (ICU) [5]. The occurrence of delirium is attributed to various complex and variable pathophysiological factors, including neurotransmitter imbalance, inflammatory response, electrolyte disturbances, metabolic issues, physiological stress, and genetic factors [6]. The occurrence of POD not only extends the length of hospitalization and deteriorates the quality of life for patients but also potentially increases the risk of death [7–10]. Consequently, exploring simple and practical indicators for predicting POD risk in cardiac surgery patients in the ICU is of utmost clinical importance.

As a critical indicator of acid-base balance in the body, abnormalities in serum bicarbonate typically signify respiratory or renal dysfunction [11]. In the ICU setting, due to the widespread use of blood gas analyzers, the bicarbonate level has become a readily accessible parameter for all patients. Early studies focused on the link between bicarbonate concentrations and mortality rates in individuals with kidney disease [12–14]. Recently, significant correlations have been found between bicarbonate levels and complications of cardiovascular disease and mortality [15, 16]. Furthermore, the associations between bicarbonate levels and mental health conditions, such as depression, brain dysfunction, and Alzheimer's disease, have received increasing attention [17–20]. While research has examined the link between bicarbonate concentrations and delirium rates among critically ill individuals [21, 22], these findings have been inconsistent, and investigations into a potential nonlinear relationship are limited. Consequently, the exact nature of the connection between bicarbonate concentrations and the risk of POD in ICU cardiac surgery patients remains unclear.

This study sought to clarify this connection through a retrospective analysis, utilizing data from the Medical Information Marketplace in Intensive Care (MIMIC-IV) database.

Methods

Data source

Information for this investigation was obtained from the publicly available database, MIMIC-IV (version: v2.2), documenting more than 50,000 ICU admissions at Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019 [23]. This database encompasses comprehensive demographic details, physiological monitoring metrics, laboratory results, and diagnoses according to the International Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) Editions. All personal information was deidentified to protect patient privacy; therefore, this study did not require informed consent from the patients and ethical review board approval. After completing web-based training and passing the Protecting Human Research Participants examination, One of the authors, Panxu Guo, was granted permission to extract data from the MIMIC-IV database (Record ID: 58462281). The study was conducted following the STROBE guidelines [24].

Participant selection

Patients meeting specific criteria were screened using the MIMIC-IV database (version 2.2) for this study. The study cohort comprised individuals aged 18 years and older who were first admitted to the hospital for a single cardiac procedure, including coronary artery bypass grafting (CABG), heart valve surgery, or aortic surgery. Diagnoses were determined based on the International Classification of Diseases (ICD) codes (see Supplementary Table 1). The exclusion criteria were as follows: (1) ICU stays of less than 24 h, (2) a diagnosis of schizophrenia or dementia, (3) absence of documented delirium assessment, (4) a diagnosis of delirium prior to surgery or within 24 h before ICU admission, and (5) bicarbonate levels not measured on the first day of ICU admission. Following the application of these criteria, a total of 5,422 patients were eligible for inclusion in the study. The patient screening process is illustrated in Fig. 1.

Data collection

Data were extracted from the MIMIC-IV database using PostgreSQL and Navicat 16.3.3 software. The collected information, recorded within 24 h of ICU admission, included patients' age, gender, body mass index (BMI), ethnicity, vital signs, laboratory results, co-morbidities, and disease severity scores. Additionally, the use of statins and benzodiazepines in the ICU, along with hospital and ICU stays. To reduce data bias, variables with over 10% missing values were excluded. For variables with less than 10% missing data, multiple imputation was performed using the random forest algorithm provided by the R package "missForest" [25], as detailed in Supplementary Fig. 1.

Exposure

The primary outcome variable analyzed in the study was serum bicarbonate level, which was assessed as a continuous variable. It was also divided into four quartile groups based on admission values from the MIMIC-IV database: Q1 (11–22 mmol/L), Q2 (22–23 mmol/L), Q3 (23–25 mmol/L), and Q4 (25–37 mmol/L). Baseline serum bicarbonate concentration was determined by the

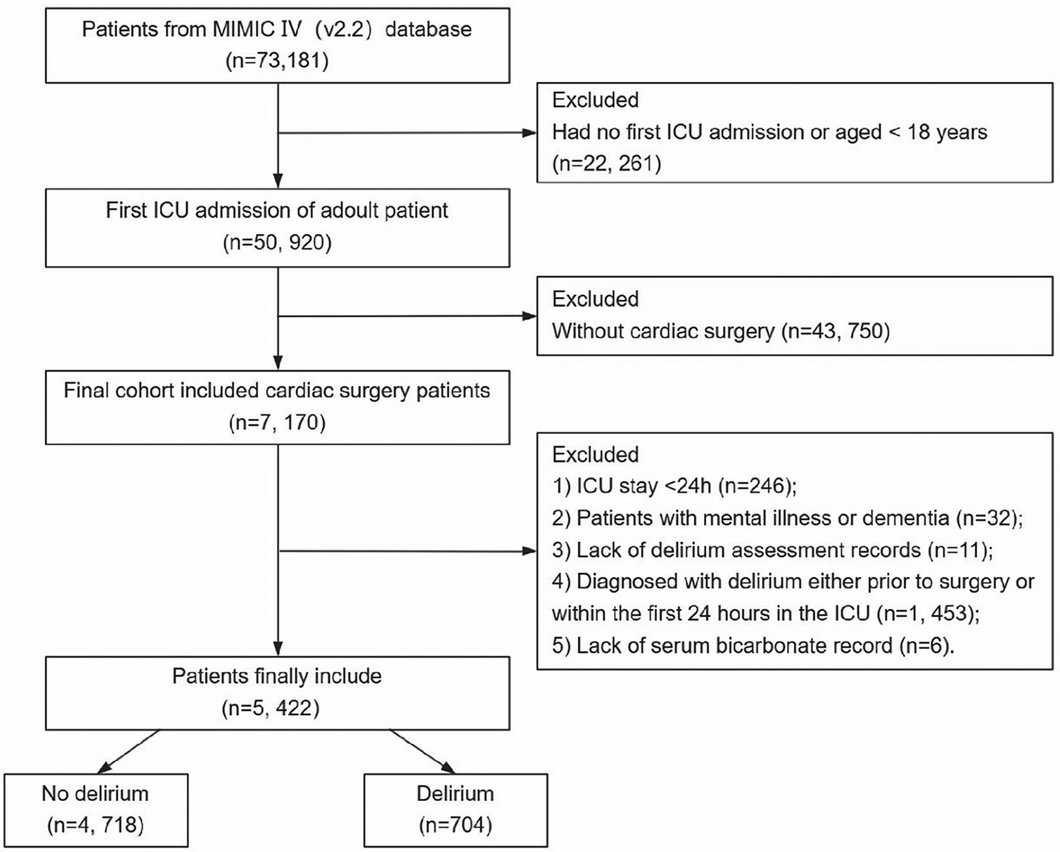


Fig. 1 The inclusion and exclusion criteria of study participants

initial measurement taken within 24 h of admission to the ICU.

Outcome

The primary outcome of this study involved determining the presence or absence of delirium during ICU hospitalization. The diagnosis of delirium was made using the CAM-ICU scoring tool, which includes four characteristics: (1) acute mental status changes or fluctuations; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. The medical staff meticulously documented these characteristics on the “chartevents” form. According to the CAM-ICU scale, a diagnosis of delirium (CAM-ICU-positive) is confirmed when the patient displays any combination of Characteristics 1 and 2, along with either 3 or 4.

Statistical analysis

Participants’ baseline characteristics are divided into two groups based on the presence or absence of delirium. Normally distributed continuous variables are presented as mean ± standard deviation, while skewed continuous variables are reported as median (interquartile range [IQR]), and categorical variables are shown as percentages (%). Continuous data between groups were compared using the Student’s t-test and the Wilcoxon rank-sum test, depending on the data distribution, while categorical data were compared using the chi-square test (χ^2).

Univariate and multivariate logistic regression analyses were employed to explore independent associations between baseline serum bicarbonate levels and the risk of developing POD. Confounders were selected based on clinical significance, prior scientific literature, and variables showing a $\geq$10% change in effect estimates. Serum bicarbonate concentration was evaluated as both a continuous and categorical variable across four adjusted models. The initial model included no adjustments for any covariates. In Model 1, adjustments were made for age, sex, BMI, and Ethnicity. Model 2 was further adjusted for comorbidities such as hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, renal disease, and liver disease. Model 3 included adjustments for respiratory rate (RR), anion gap (AG), creatinine, sodium, PH, partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO2), Benzodiazepine drugs, simplified acute physiology score II (SAPS II), sequential organ failure assessment (SOFA), and ICU length of stay. To prevent multicollinearity, variance inflation factors (VIF) were assessed, and variables with a VIF≥5 were subsequently excluded (see Supplementary Table 2).

The potential linear relationship between serum bicarbonate concentration and the risk of POD occurrence was investigated using restricted cubic spline (RCS) modeling. Receiver operating characteristic (ROC) curves assessing the predictive value of bicarbonate concentration on the incidence of POD. Additionally, subgroup analyses were conducted to examine the consistency of POD prediction across various subgroups. Subgroups were defined according to age (<65 years, ≥65 years), gender, ethnicity, surgical type, and comorbidities. Interactions between subgroup pairs were assessed using likelihood ratio tests.

To ensure the robustness of the study results, a series of sensitivity analyses were conducted. First, considering that cerebrovascular disease is a significant cause of delirium, patients with this condition were excluded to reduce potential confounding factors. Second, patients with renal disease were excluded to specifically examine the risk of postoperative delirium (POD) in cardiac surgery patients whose condition is not closely related to bicarbonate levels. Third, the analysis was performed using the original data set without applying multiple imputation to minimize potential biases introduced by the imputation process.

All statistical analyses were performed using R software (version 4.4.1). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 5,422 participants were enrolled in this study, with 3,873 (71.4%) being male and having a mean age of 66.9±11.6 years. POD developed in 704 patients, which represents an incidence rate of 13.0% among cardiac surgery patients. Compared with patients who did not develop delirium, those with delirium tended to be older and exhibited higher rates of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, renal disease, and liver disease. Additionally, these patients were more likely to undergo heart valve and aortic surgeries and exhibited higher rates of benzodiazepine use. Patients with delirium displayed significantly higher RR, AG, White blood cell count (WBC), creatinine, and lactate levels, along with elevated SAPS II, SOFA, and CCI scores, and prolonged hospital and ICU stays. In contrast, levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin, chloride, and PO_2 were significantly lower, as detailed in Table 1.

Incidence of POD in different groups

Figure 2A shows that the incidence of POD progressively decreases across quartiles of serum bicarbonate levels, with the highest incidence in the first quartile group (Q1) at 19.4% and the lowest in the fourth quartile group (Q4) at 8.0%. Figure 2B presents the incidence of POD stratified by age and gender, indicating a general trend of increasing POD incidence with advancing age. Notably, among patients older than 45 years, the incidence of POD is significantly higher in females than in males, while in patients over 75 years of age, the incidence of POD remained high in both males and females.

Relationship between baseline bicarbonate levels and the incidence of POD in cardiac surgery patients

This study explored the correlation between baseline bicarbonate levels and the risk of postoperative delirium (POD) in cardiac surgery patients. Utilizing univariate logistic regression analysis, a significant association was confirmed between bicarbonate level and the risk of POD. Additionally, factors including age, gender, race, and various clinical and surgical parameters were also found to be significantly associated with the risk of POD, as detailed in Supplementary Table 3.

Further multivariate analyses revealed that a significant negative correlation between bicarbonate levels and risk of POD persisted (see Table 2). In the fully adjusted model (Model 3), a 1 mmol/L increase in bicarbonate was associated with a 13% reduction in the risk of POD (OR=0.87, 95% CI: 0.83–0.91, $P<0.001$). The highest bicarbonate level group (Q4) demonstrated a 59% reduction in POD incidence compared to the lowest group (Q1) (OR=0.41, 95% CI: 0.29–0.59, $P<0.001$). Trend tests across all models yielded p-values below 0.001, underscoring the robust negative association between bicarbonate levels and POD risk.

Restricted cubic spline regression model

The relationship between serum bicarbonate levels and POD risk was elucidated using the RCS model. In the initial model (Fig. 3A) and subsequent adjustments in Model1 (Fig. 3B) and Model2 (Fig. 3C), a nonlinear relationship was observed between increasing serum bicarbonate levels and the risk of POD (P for nonlinearity<0.05). However, in Model3 (Fig. 3D), which was fully adjusted, the relationship between bicarbonate levels and POD risk transitioned to linear, revealing a significant linear trend of decreasing POD risk with increasing bicarbonate levels (P for nonlinearity=0.987).

Receiver operating characteristic curves

Through ROC curve analysis, the predictive performance of serum bicarbonate levels and severity of illness scores (SAPS II and SOFA) was assessed for the occurrence

Table 1 The baseline characteristics of participants

Variable	Overall	Non-delirium	Delirium	*P* value
Number	5,422	4,718	704	
Demographics				
Age, years	66.9 ± 11.6	66.6 ± 11.5	69.1 ± 12.1	< 0.001
Male, n (%)	3873 (71.4)	3404 (72.1)	469 (66.6)	0.003
BMI, kg/m^2	30.1 ± 5.8	30.1 ± 5.8	29.7 ± 6.0	0.091
Ethnicity, white (%)	3996 (73.7)	3508 (74.4)	488 (69.3)	0.005
Comorbidities, **n (%)**				
Hypertension	3257 (60.1)	2927 (62.0)	330 (46.9)	< 0.001
Myocardial infarct	1540 (28.4)	1314 (27.9)	226 (32.1)	0.022
Congestive heart failure	1434 (26.4)	1126 (23.9)	308 (43.8)	< 0.001
Peripheral vascular disease	923 (17.0)	753 (16.0)	170 (24.1)	< 0.001
Cerebrovascular disease	541 (10.0)	438 (9.3)	103 (14.6)	< 0.001
Chronic pulmonary disease	1197 (22.1)	1024 (21.7)	173 (24.6)	0.096
Diabetes	1847 (34.1)	1608 (34.1)	239 (33.9)	0.978
Renal disease	837 (15.4)	637 (13.5)	200 (28.4)	< 0.001
Liver disease	200 (3.7)	160 (3.4)	40 (5.7)	0.004
Surgery type, **n (%)**				< 0.001
CABG	3129 (57.7)	2775 (58.8)	354 (50.3)	
Heart valve surgery	2115 (39.0)	1830 (38.8)	285 (40.5)	
Aortic surgery	178 (3.3)	113 (2.4)	65 (9.2)	
Vital signs				
HR, beats/min	82.3 ± 9.5	82.2 ± 9.4	82.4 ± 10.5	0.668
RR, times/min	17.7 ± 2.7	17.6 ± 2.6	18.5 ± 3.2	< 0.001
SBP, mmHg	111.9 ± 8.4	112.1 ± 8.2	110.9 ± 9.6	0.001
DBP, mmHg	57.3 ± 6.8	57.5 ± 6.6	56.3 ± 7.9	< 0.001
SPO_2, %	97.8 ± 1.5	97.8 ± 1.4	97.7 ± 1.7	0.170
Laboratory events				
Bicarbonate, mmol/L	23.3 ± 2.4	23.4 ± 2.3	22.3 ± 2.7	< 0.001
AG, mmol/L	11.4 ± 2.9	11.2 ± 2.7	13.0 ± 3.5	< 0.001
WBC, k/uL	12.2 (9.1, 15.7)	12.2 (9.1, 15.6)	12.6 (9.1, 16.9)	0.018
Hemoglobin, g/dl	9.7 ± 1.9	9.8 ± 1.8	9.4 ± 2.0	< 0.001
Creatinine, mg/dl	0.9 (0.7, 1.1)	0.8 (0.7, 1.0)	1.0 (0.8, 1.3)	< 0.001
Lactate, mmol/L	2.1 (1.6, 2.8)	2.1 (1.6, 2.7)	2.2 (1.5, 3.0)	0.012
Sodium, mmol/L	139.0 ± 3.0	139.0 ± 2.9	139.3 ± 3.5	0.010
Potassium, mmol/L	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.6	0.817
Chloride, mmol/L	108.7 ± 4.2	108.9 ± 4.0	107.5 ± 4.9	< 0.001
PCO_2, mmHg	41.1 ± 6.6	41.2 ± 6.5	40.8 ± 6.8	0.106
PO_2, mmHg	314.3 ± 101.0	316.4 ± 100.0	300.5 ± 106.6	< 0.001
PH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	0.003
Drug, **n (%)**				
Statin drugs	4607 (85.0)	4024 (85.3)	583 (82.8)	0.097
Benzodiazepine drugs	1795 (33.1)	1487 (31.5)	308 (43.8)	< 0.001
Disease severity score				
SAPS II	38.1 ± 11.7	37.5 ± 11.5	41.9 ± 12.5	< 0.001
SOFA	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	4.0 (2.0, 5.0)	< 0.001
CCI	4.0 (3.0, 6.0)	4.0 (3.0, 5.0)	5.0 (4.0, 7.0)	< 0.001
Events				
Hospital length of stay, days	7.0 (5.3, 10.2)	6.8 (5.1, 9.8)	10.7 (7.1, 17.2)	< 0.001
ICU length of stay, days	2.0 (1.3, 3.2)	1.5 (1.2, 2.5)	4.9 (3.2, 8.5)	< 0.001

Abbreviations BMI: body mass index; CABG: coronary artery bypass grafting; HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; SPO_2: saturation of peripheral oxygen; AG: anion gap; WBC: white blood cell count; PCO_2: partial pressure of carbon dioxide; PO_2: partial pressure of oxygen; PH: potential of hydrogen; SAPS II: simplified acute physiology score II; SOFA: sequential organ failure assessment; CCI: charlson comorbidity index

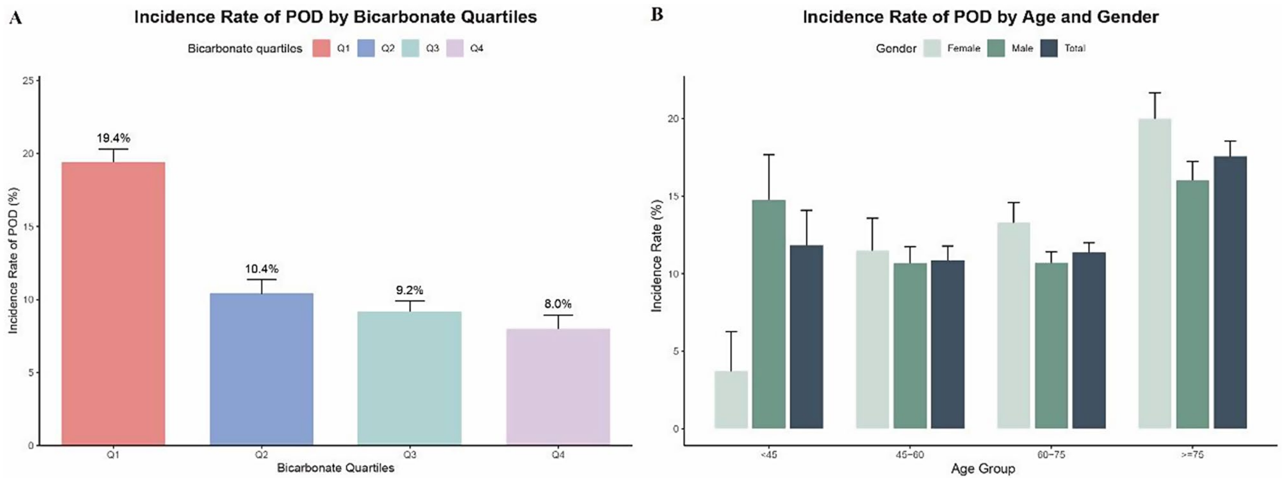


Fig. 2 **A**: Bar graph depicting the incidence of POD across different bicarbonate quartiles; **B**: Comparative graph illustrating POD incidence across age groups

Table 2 Relationships between bicarbonate concentrations and the risk of postoperative delirium according to the different models

variable	Crude model		Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Continuous	0.82 (0.79, 0.85)	< 0.001	0.83 (0.80, 0.86)	< 0.001	0.85 (0.82, 0.88)	< 0.001	0.87 (0.83, 0.91)	< 0.001
Quintiles								
Q1	1(ref)		1(ref)		1(ref)		1(ref)	
Q2	0.48 (0.38, 0.60)	< 0.001	0.50 (0.39, 0.63)	< 0.001	0.57 (0.44, 0.72)	< 0.001	0.70 (0.54, 0.91)	0.009
Q3	0.42 (0.34, 0.51)	< 0.001	0.44 (0.36, 0.54)	< 0.001	0.48 (0.39, 0.59)	< 0.001	0.62 (0.49, 0.79)	< 0.001
Q4	0.36 (0.27, 0.47)	< 0.001	0.39 (0.30, 0.52)	< 0.001	0.41 (0.31, 0.54)	< 0.001	0.41 (0.29, 0.59)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001		< 0.001

Bicarbonate index: Q1 (11–22), Q2 (22–23), Q3 (23–25), Q4 (25–37)

Crude model: adjusted for none

Model 1: adjusted for Age, Gender, BMI, and Ethnicity

Model 2: adjusted for Model 1 + Hypertension, Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Renal disease, Liver disease

Model 3: adjusted for Model 2 + RR, AG, Creatinine, Sodium, PH, PO2, PCO2, Benzodiazepine drugs, SAPS II, SOFA, ICU length of stay

of POD in patients after cardiac surgery. It was found that the serum bicarbonate levels (AUC = 0.629, 95% CI: 0.606–0.652) surpassed both SAPS II (AUC = 0.616, 95% CI: 0.594–0.639) and SOFA (AUC = 0.589, 95% CI: 0.564–0.611) in predicting POD, demonstrating moderate predictive accuracy. This observation underscores the potential of serum bicarbonate levels as a reliable predictor of POD in patients undergoing cardiac surgery. See Fig. 4 for details.

Sensitivity and subgroup analysis

To confirm the robustness of our main findings concerning the relationship between serum bicarbonate levels and the risk of postoperative delirium (POD), several sensitivity analyses were conducted. The results indicated that the significant association between serum bicarbonate levels and the risk of developing POD persisted across all analyses, as detailed in Supplementary Tables 4–6.

Furthermore, in conducting subgroup analyses, multiple variables were assessed, including age, gender, ethnicity, surgical type, and various comorbidities such as hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, renal disease, and liver disease. Analysis results demonstrated that no significant interactions were observed between these subgroups (P for interaction > 0.05), as illustrated in Fig. 5. This further confirms that the association between the risk of POD and bicarbonate levels remained consistent across subgroups.

Discussion

In this study, we retrospectively analyzed data from 5,422 patients who underwent cardiac surgery. Findings indicated that lower bicarbonate levels were significantly correlated with an increased risk of developing POD; the robustness of these results was further confirmed

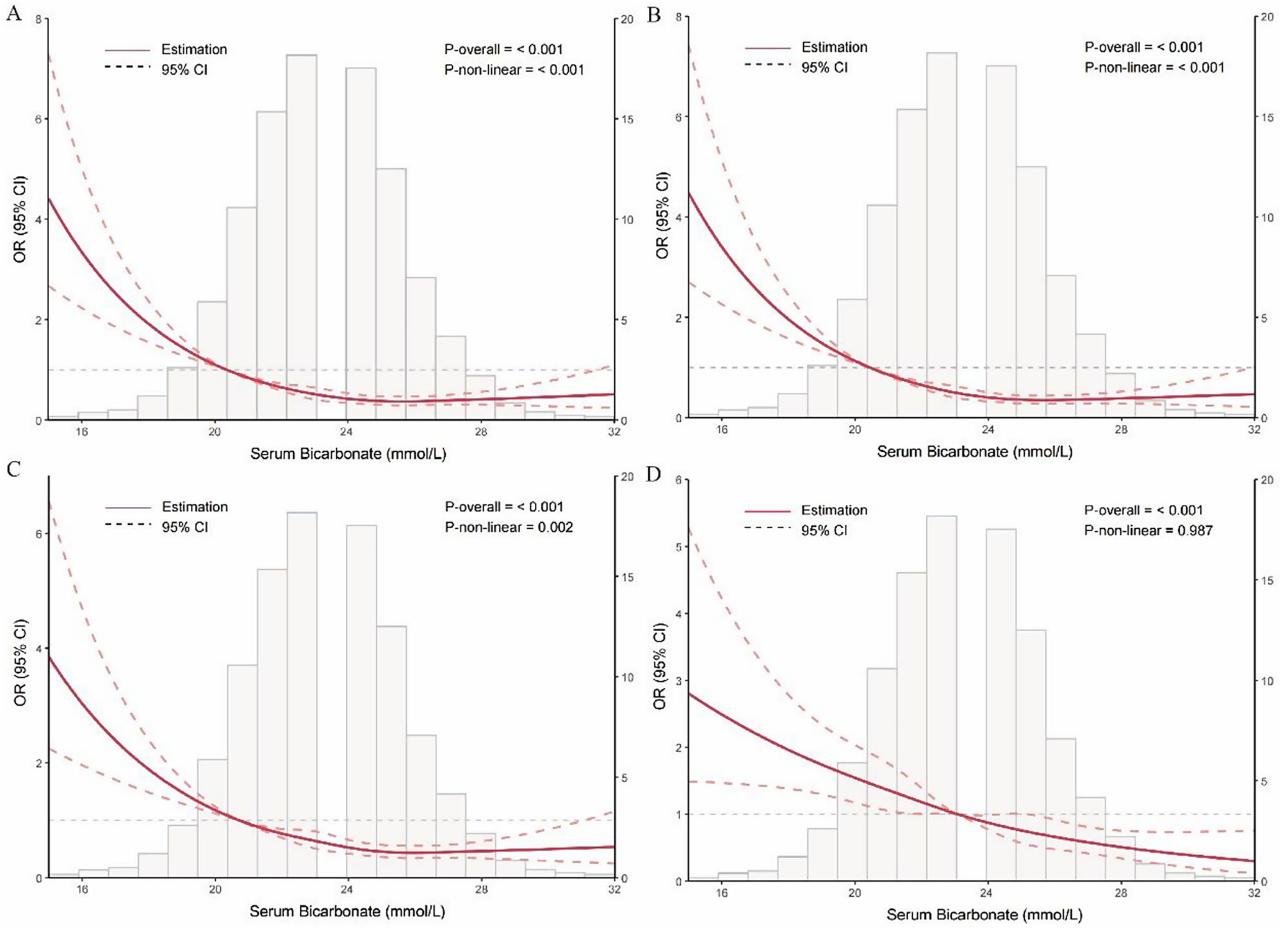


Fig. 3 Restricted cubic spline curves illustrating the relationship between serum bicarbonate levels and the risk of postoperative delirium. Panels **A**, **B**, **C**, and **D** represent the different multivariable adjustment models: Crude Model, Model 1, Model 2, and Model 3, respectively. Each model accounts for varying sets of confounding factors

through sensitivity and subgroup analyses. Additionally, ROC curve analysis revealed moderate predictive efficacy of bicarbonate for POD in cardiac surgery patients, highlighting its significance as a predictive tool in intensive care management.

The bicarbonate concentration is an essential indicator of the body's acid-base balance status. It is usually measured as part of routine biochemical tests to monitor renal diseases [26]. In recent years, several clinical studies have shown that bicarbonate levels are crucial not only for patients with kidney disease but also for patients with other diseases. For example, low bicarbonate concentrations are associated with increased mortality after aortic coarctation, whereas high concentrations may increase the risk of cardiovascular disease complications [27]. However, studies on the relationship between bicarbonate levels and the risk of delirium remain limited. One known randomized controlled study conducted in Thailand involving 62 surgical ICU patients revealed that patients with delirium had significantly lower bicarbonate levels than those without delirium [21], revealing for the first time a strong correlation between low bicarbonate levels and the occurrence of delirium. However, in a follow-up study, the group performed a generalized estimating equation (GEE) analysis on 65 elderly patients who underwent undergoing hip fracture surgery, and showed that bicarbonate levels were negatively correlated with psychomotor abnormalities (agitation or retardation), but were not definitively correlated a the direct diagnosis of delirium [22]. These inconsistencies might partly stem from the use of venous rather than arterial blood samples to assess acid- base status and blood gas markers. Although analyses of both venous and arterial blood gases have been shown to yield similar outcomes [28], venous blood data might not precisely mirror arterial blood criteria. Additionally, differences in study populations may also be responsible. The previous study included all surgical ICU patients, whereas the subsequent study was limited to elderly patients undergoing hip fracture surgery. Although prior studies indicated a correlation between postoperative bicarbonate concentrations and delirium in ICU patients, the conclusions

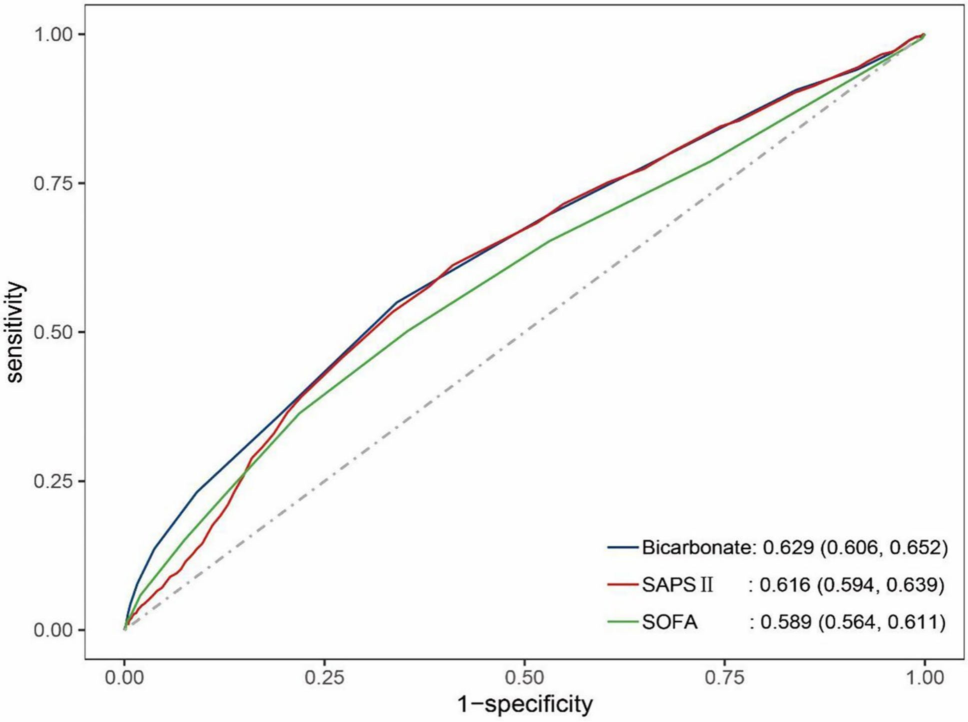
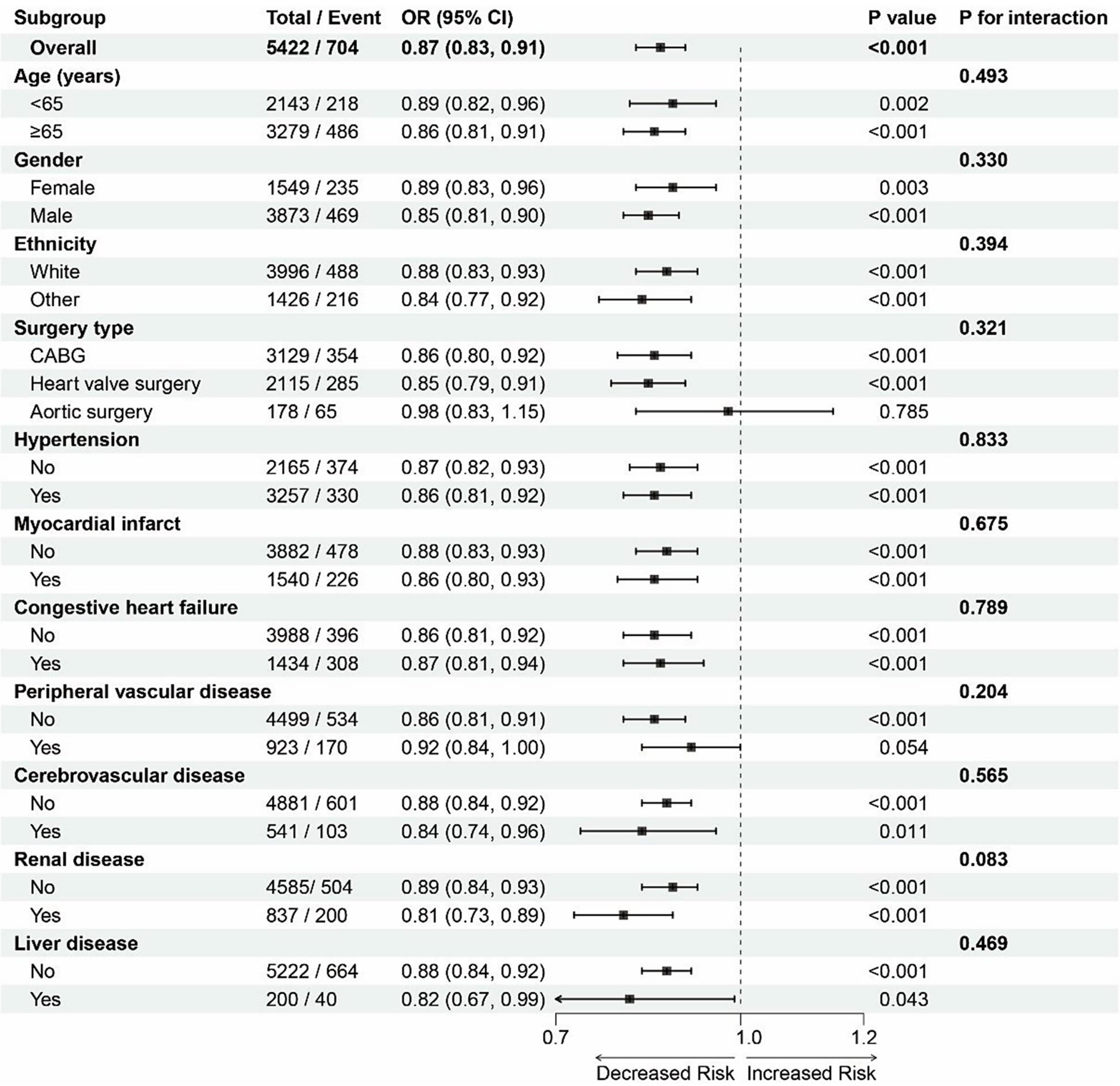


Fig. 4 ROC curves to assess the predictive power of bicarbonate levels on the incidence of postoperative delirium. Abbreviation: ROC, receiver operating characteristic

were limited by small sample sizes, hindering comprehensive adjustment for all confounders in multivariate analyses. Our present study analyzed the correlation between bicarbonate levels and the risk of POD in a continuous and categorical manner by including 5,422 patients who underwent undergoing cardiac surgery and adjusting for 22 potential variables.

Our study revealed that lower bicarbonate levels significantly increased the risk of POD development. The existence and stability of this relationship were further validated by sensitivity analyses of participants who did not experience in-hospital death and did not have cerebrovascular or renal disease. Despite the decrease in mortality among patients undergoing cardiac surgery [29], postoperative neurocognitive complications and delirium remain major clinical concerns due to their frequency. The pathophysiological underpinnings of delirium are not entirely understood; however, evidence indicates metabolic acidosis's association with delirium development, providing a potential physiological rationale for the lower bicarbonate levels in POD patients [30, 31], and offering a possible physiological explanation for the decreased bicarbonate levels in POD patients. Low bicarbonate levels, indicative of metabolic acidosis, might initiate a systemic inflammatory response [32–34], impairing brain function and enhancing blood- brain barrier permeability, thus increasing patient vulnerability to circulating delirium factors [35, 36]. Animal experiments have also shown that metabolic acidosis may affect the release and reuptake of neurotransmitters [37–39], such as dopamine and acetylcholine, and changes in these neurotransmitters have been associated with the development of delirium [40, 41]. In particular, sustained reductions in bicarbonate levels may lead to vascular endothelial dysfunction, affecting hemodynamics and brain oxygen supply, thereby impairing neurological function [42]. These findings emphasize the significance of assessing bicarbonate levels in cardiac surgery patients and suggest targeted treatments for those exhibiting low concentrations.

To date, no single medication has been shown to effectively prevent delirium. Consequently, understanding the diverse risk factors for delirium is essential for facilitating its early detection and prevention, highlighting the primary purpose and clinical significance of our research. Therefore, we initiated this study to examine the relationship between baseline bicarbonate levels and the incidence of POD in patients undergoing cardiac surgery. Our research has several strengths. First, to the best of our knowledge, this is the first study to investigate the correlation between baseline bicarbonate levels and the risk of postoperative delirium (POD) in cardiac surgery patients. Second, this study utilized a large dataset with ethnically diverse participants, enhancing the generalizability and applicability of the findings. Furthermore, incorporating a wide range of covariates in multivariate



Subgroup	Total / Event	OR (95% CI)	P value	P for interaction
Overall	**5422 / 704**	**0.87 (0.83, 0.91)**	**<0.001**	
Age (years)				**0.493**
<65	2143 / 218	0.89 (0.82, 0.96)	0.002	
≥65	3279 / 486	0.86 (0.81, 0.91)	<0.001	
Gender				**0.330**
Female	1549 / 235	0.89 (0.83, 0.96)	0.003	
Male	3873 / 469	0.85 (0.81, 0.90)	<0.001	
Ethnicity				**0.394**
White	3996 / 488	0.88 (0.83, 0.93)	<0.001	
Other	1426 / 216	0.84 (0.77, 0.92)	<0.001	
Surgery type				**0.321**
CABG	3129 / 354	0.86 (0.80, 0.92)	<0.001	
Heart valve surgery	2115 / 285	0.85 (0.79, 0.91)	<0.001	
Aortic surgery	178 / 65	0.98 (0.83, 1.15)	0.785	
Hypertension				**0.833**
No	2165 / 374	0.87 (0.82, 0.93)	<0.001	
Yes	3257 / 330	0.86 (0.81, 0.92)	<0.001	
Myocardial infarct				**0.675**
No	3882 / 478	0.88 (0.83, 0.93)	<0.001	
Yes	1540 / 226	0.86 (0.80, 0.93)	<0.001	
Congestive heart failure				**0.789**
No	3988 / 396	0.86 (0.81, 0.92)	<0.001	
Yes	1434 / 308	0.87 (0.81, 0.94)	<0.001	
Peripheral vascular disease				**0.204**
No	4499 / 534	0.86 (0.81, 0.91)	<0.001	
Yes	923 / 170	0.92 (0.84, 1.00)	0.054	
Cerebrovascular disease				**0.565**
No	4881 / 601	0.88 (0.84, 0.92)	<0.001	
Yes	541 / 103	0.84 (0.74, 0.96)	0.011	
Renal disease				**0.083**
No	4585/ 504	0.89 (0.84, 0.93)	<0.001	
Yes	837 / 200	0.81 (0.73, 0.89)	<0.001	
Liver disease				**0.469**
No	5222 / 664	0.88 (0.84, 0.92)	<0.001	
Yes	200 / 40	0.82 (0.67, 0.99)	0.043	

Fig. 5 Subgroup analyses of the relationship between bicarbonate and postoperative delirium. Bicarbonate was analyzed as a continuous variable. The above models were adjusted for the variables in model 3. In each case, the models were not adjusted for stratification variables

regression analyses reduced potential selection bias, thereby enhancing the accuracy of the findings. Our findings indicate that cardiac surgery patients with low bicarbonate levels at ICU admission face an increased risk of developing POD. This highlights the importance of monitoring bicarbonate levels in cardiac surgery patients to help physicians identify those at high risk for POD and develop tailored treatment strategies for patients with low bicarbonate levels. Finally, sensitivity analyses of patients who did not experience in-hospital death or who suffered from cerebrovascular or renal disease confirmed the stability and reliability of our findings.

This study also has several limitations. First, as a retrospective observational study, it unavoidably suffers from selection bias. Nonetheless, we established strict inclusion criteria to closely mirror real-world scenarios. Second, delirium can present in various subtypes, such as hyperactive, hypoactive, and mixed forms, our inability to differentiate between these subtypes. Third, the study's reliance on a single-center sample may restrict the generalizability of the findings. Finally, our data span from 2008 to 2019, a period marked by significant changes in delirium management. Due to data anonymization in the MIMIC-IV database, we could not evaluate the specific impact of these changes on postoperative delirium. Future studies could explore the effects of various stages of delirium management on patient outcomes.

Conclusion

Our study indicates that low serum bicarbonate levels constitute an independent risk factor for the increased incidence of POD following cardiac surgery. Being a simple, cost-effective, and readily accessible biomarker, serum bicarbonate offers potential clinical applications. To corroborate this finding and further investigate the underlying mechanisms of POD and its broader implications, further in-depth studies are essential.

Abbreviations

POD	Postoperative delirium
MIMIC-IV	Medical Information Mart for Intensive Care IV
ICU	Intensive Care Unit
CABG	Coronary artery bypass grafting
CPB	Cardiopulmonary bypass
BMI	Body Mass Index
AG	Anion Gap
WBC	White blood cell count
PO_2	Partial pressure of oxygen
PCO_2	Partial Pressure of Carbon Dioxide
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SpO_2	Oxygen Saturation
HR	Heart rate
RR	Respiratory rate
SAPS II	Simplified Acute Physiology Score II
CCI	Charlson Comorbidity Index
SOFA	Sequential Organ Failure Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02738-9.

Supplementary Material 1: Supplementary File: **Supplementary Fig. 1**. Graph of the percentage of missing variables for patients undergoing acute cardiac surgery in the MIMIC database. **Supplementary Table 1**. The ICD-9 and ICD-10 codes for identifying cardiac surgeries. **Supplementary Table 2**. The variance inflation factor for all covariates of the fully adjusted model. **Supplementary Table 3**. Univariate logistic regression analysis of postoperative delirium in cardiac surgery patients. **Supplementary Table 4**. The association between various bicarbonate groups and the risk of postoperative delirium in patients undergoing cardiac surgery after excluding patients with renal disease (n=4, 585). **Supplementary Table 5**. The association between various bicarbonate groups and the risk of postoperative delirium in patients undergoing cardiac surgery after excluding patients with cerebrovascular disease (n=4, 881). **Supplementary Table 6**. Relationship between different bicarbonate groups and risk of postoperative delirium in patients undergoing cardiac surgery in the original data before multiple interpolation (n=4, 810).

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Author contributions

PG, YM, and PW formulated the research questions and designed the study. PG extracted clinical data from the MIMIC-IV database. DX, XL, and KW conducted the data analysis. PG and YM drafted the manuscript. PW and WS critically reviewed, edited, and approved the manuscript. PG and YM finalized the manuscript based on all the authors' comments. All authors provided comments and approved the final manuscript.

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Data availability

Publicly available datasets were analyzed in this study. These datasets can be found at https://physionet.org/content/mimiciv/2.2/. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The database was approved for research use by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Studies using the database were granted a waiver of informed consent, and all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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