

Association Between the Admission Serum Bicarbonate and Short-Term and Long-Term Mortality in Acute Aortic Dissection Patients Admitted to the Intensive Care Unit

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Objective: Serum bicarbonate (HCO_3^-) level is strongly related to multiple cardiovascular complications. Currently, there is no study evaluating the prognostic ability of serum HCO_3^- level in intensive care unit (ICU) patients with acute aortic dissection (AAD). Hence, this study was to assess the relationship between admission serum HCO_3^- level and clinical outcomes in patients with AAD.

Design, Settings and Participants: Clinical data were extracted from the MIMIC-III database. Cox proportional hazards models and Kaplan–Meier (KM) survival curve were used to evaluate the association between serum HCO_3^- levels and short- and long-term mortality in ICU patients with AAD. The subgroup analysis and the receiver operating characteristic (ROC) curve analysis and further KM survival curve based on best cut-off value were applied to assessment of the performance of HCO_3^- in predicting the mortality in each period (30 days, 90 days, 1 year and 5 years).

Main Results: Firstly, 336 eligible patients were trisected to low- HCO_3^- level group (<22 mmol/L), mid- HCO_3^- level group (22–24 mmol/L) and high- HCO_3^- level group (>24 mmol/L). Then, in multivariate analysis, the serum HCO_3^- of low levels (<22 mmol/L) was a significant risk predictor of all-cause mortality in 30 days, 90 days, 1 year and 5 years. Subgroup analyses indicated that there is no interaction in most strata. Finally, areas under ROC curve ranged from 0.60 to 0.69.

Conclusion: The low HCO_3^- serum level measured at ICU admission significantly predicts short-term and long-term mortality in AAD patients.

Keywords: serum bicarbonate, intensive care unit, acute aortic dissection, all-cause mortality

Introduction

Acute aortic dissection (AAD) is a devastating disease that needs emergent aortic replacement or repair surgery for survival. Due to its acute onset, rapid progression and high incidence of rupture of aorta, a majority of patients with AAD admitted to hospital had a loss of operation opportunity.¹ Clinical data indicated that the mortality rate in patients with AAD within 48 hours of admission to the intensive care unit (ICU) ranged from 36% to 72%, with an increase of 1–2% per hour.² Hence, identification of simple biomarkers for evaluating the prognosis of AAD plays a vital role in risk stratification in this kind of patient. Previous studies have

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shown that lymphocyte-to-monocyte ratio (LMR),³ hypotensive systolic blood pressure,⁴ N-terminal pro-brain natriuretic peptide,⁵ C-reactive protein,⁶ cardiac troponin⁷ and serum fibrinogen level⁸ were associated with the prognosis of patients with AAD; however, the studies above mainly used in-hospital mortality as outcomes. Effective variables to predict the prognosis of AAD are still lacking in clinical practice. Thus, more new risk factors should be explored and longer follow-up time to be validated in future study of AAD.

Serum bicarbonate (HCO_3^-) is a biomarker of the homeostasis of acid–base. Abnormal serum HCO_3^- is mainly caused by respiratory disorder or kidney dysfunction. Previous studies mainly focused on the relationship between mortality of renal disease and serum HCO_3^- level.⁹ Recently, serum HCO_3^- level was reported to be strongly related to multiple complications and mortality of cardiovascular diseases like stroke and myocardial infarction.¹⁰ In a large cohort of US adults, the hazard for cardiovascular mortality was increased by 8% for every 1 mEq/L increase in serum HCO_3^- level above 26 mEq/L.¹¹ However, the relationship between serum HCO_3^- level and clinical outcomes in AAD patients is still unknown. This study was instigated to assess the association between serum HCO_3^- levels on admission

and short-term and long-term mortality in AAD patients in ICU.

Methods

Database Source

We acquired clinical data from the MIMIC-III database which contains comprehensive information on ICU admissions for over 60,000 patients from 2001 to 2012.¹² The data include general information, treatment process and survival data. This study on human participants obtained the approval of the Massachusetts Institute of Technology (MIT) ethics committee. Author Tan completed the National Institutes of Health web-based training course “Protecting Human Research Participants” and gained access to the database (Certification Number: 35950815).

Study Population Criteria

According to the ninth revision of the International Classification of Diseases (ICD9) adopted in the MIMIC III database, we selected adult patients with Stanford A and B types of AAD. Patients were excluded as follows: 1) patients with multiple admission records; 2) no serum HCO_3^- data; 3) missing more than 5% individual data. Complete selection process is indicated in Figure 1.

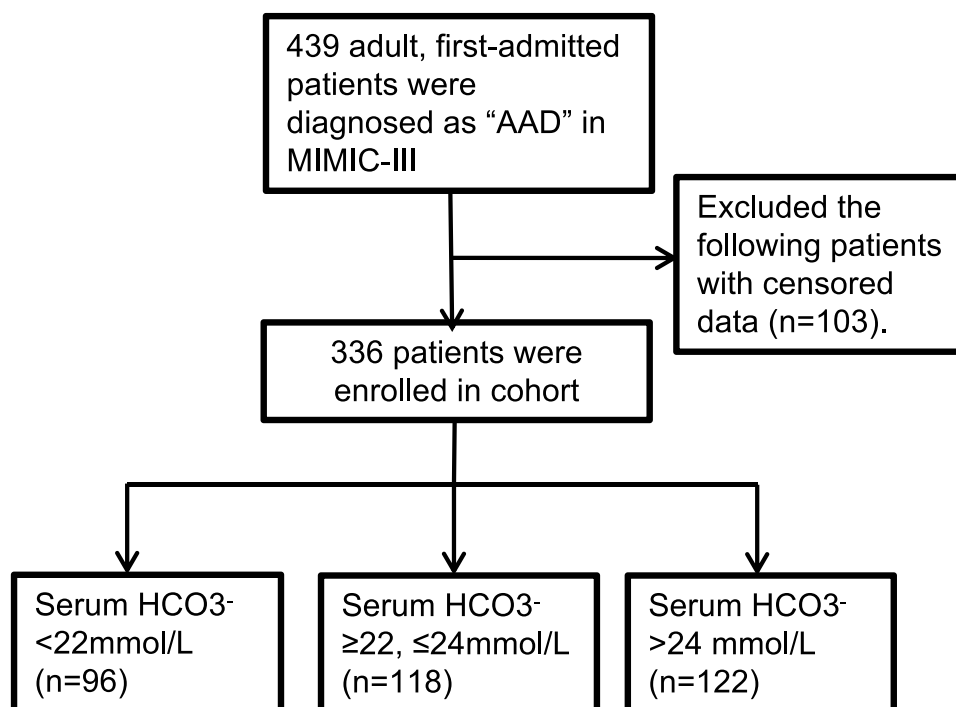


Figure 1 The flow chart describing the procedure used for patients selection.

Table I Characteristics of Subjects

Characteristics	Total (n=336)	Serum HCO ₃ ⁻ Levels (mmol/L)			P value
		<22 (n=96)	22–24 (n=118)	>24 (n=122)	
Gender					0.764
Male	213 (63.39%)	61 (63.54%)	72 (61.02%)	80 (65.57%)	
Female	123 (36.61%)	35 (36.46%)	46 (38.98%)	42 (34.43%)	
Age, years	69.00 (56.00–78.00)	67.00 (54.75–78.00)	70.50 (59.00–80.00)	71.00 (57.25–77.00)	0.347
Insurance					0.55
Government	20 (5.95%)	5 (5.21%)	7 (5.93%)	8 (6.56%)	
Medicaid	17 (5.06%)	7 (7.29%)	3 (2.54%)	7 (5.74%)	
Medicare	176 (52.38%)	46 (47.92%)	63 (53.39%)	67 (54.92%)	
Private	118 (35.12%)	38 (39.58%)	43 (36.44%)	37 (30.33%)	
Selfpay	5 (1.49%)	0 (0.00%)	2 (1.69%)	3 (2.46%)	
Ethnicity					0.261
White	233 (69.35%)	69 (71.88%)	88 (74.58%)	76 (62.30%)	
Black	44 (13.19%)	11 (11.46%)	15 (12.71%)	18 (14.75%)	
Hispanic	13 (3.87%)	5 (5.21%)	4 (3.39%)	4 (3.28%)	
Others	46 (13.69%)	11 (11.46%)	11 (9.32%)	24 (19.67%)	
Stanford type					0.003
A type	230 (68.45%)	68 (70.83%)	75 (63.56%)	87 (71.31%)	
B type	106 (31.55%)	28 (29.17%)	43 (36.44%)	35 (28.69%)	
Dissection site					0.392
Thoracic	187 (55.65%)	56 (58.33%)	68 (57.63%)	63 (51.64%)	
Abdominal	62 (18.45%)	21 (21.88%)	21 (17.80%)	21 (17.21%)	
Thoracoabdominal	87 (25.89%)	19 (19.79%)	30 (25.42%)	38 (31.15%)	
Aorta replacement	198 (58.93%)	57 (59.38%)	72 (61.02%)	69 (56.56%)	0.777
ICU MV	170 (50.60%)	69 (71.88%)	60 (50.85%)	79 (64.75%)	0.005
Comorbidities					
Hypertension	44 (13.1%)	46 (47.92%)	80 (67.80%)	73 (59.83%)	0.013
Diabetes	30 (8.93%)	11 (11.46%)	10 (8.47%)	9 (7.38%)	0.564
HC	53 (15.77%)	16 (16.67%)	20 (16.95%)	17 (13.93%)	0.782
Valvular disease	33 (9.82%)	9 (9.38%)	11 (9.32%)	13 (10.66%)	0.927
Malignancy	11 (3.27%)	3 (3.13%)	4 (3.39%)	4 (3.28%)	0.994
Stroke	26 (7.74%)	9 (9.38%)	8 (6.78%)	9 (7.38%)	0.765
CAD	60 (17.86%)	25 (26.04%)	17 (14.41%)	18 (14.75%)	0.046
CHF	31 (9.23%)	10 (10.42%)	11 (9.32%)	10 (8.20%)	0.853
Atrial fibrillation	57 (16.96%)	16 (16.67%)	20 (16.95%)	21 (36.84%)	0.994
Renal disease	45 (13.39%)	15 (15.63%)	15 (12.71%)	15 (12.30%)	0.745
Liver disease	10 (2.98%)	2 (2.08%)	4 (3.39%)	4 (3.28%)	0.83
Respiratory disease	64 (19.05%)	12 (12.50%)	17 (14.41%)	35 (28.69%)	0.003
AKI	135 (40.18%)	50 (52.08%)	43 (36.44%)	42 (34.43%)	0.018
RRT	29 (8.63%)	13 (13.54%)	8 (6.78%)	8 (6.56%)	0.127
Laboratory variables					
WBC, 10 ³ /μL	8.80 (6.20–11.00)	9.05 (5.90–12.43)	9.00 (6.85–10.80)	8.45 (6.05–10.38)	0.192
RBC, 10 ³ /μL	3.66 (2.26–4.16)	3.52 (3.22–3.92)	3.64 (3.29–4.11)	3.82 (3.29–4.33)	0.03
PLT, 10 ³ /μL	164 (119–228)	139 (93.75–193.50)	159 (123–224.75)	185.5 (128.5–273.75)	<0.001
RDW, %	14.40 (13.60–15.30)	14.50 (13.60–15.30)	14.35 (13.50–15.30)	14.40 (13.73–15.50)	0.85
Hematocrit, %	28.95 (23.00–33.80)	26.65 (21.98–30.78)	28.75 (23.75–33.95)	30.55 (23.68–34.20)	0.02
Hb, g/dL	9.75 (7.80–11.60)	9.10 (7.38–10.53)	9.85 (7.93–11.60)	10.25 (8.15–11.70)	0.023

(Continued)

Table I (Continued).

Characteristics	Total (n=336)	Serum HCO ₃ ⁻ Levels (mmol/L)			P value
		<22 (n=96)	22–24 (n=118)	>24 (n=122)	
Anion gap, mmol/L	12.50 (10.00–14.00)	14.00 (11.00–16.00)	13.00 (10.00–14.00)	12.00 (10.00–13.00)	<0.001
Lactate, mmol/L	3.20 (1.70–5.85)	4.10 (2.20–6.88)	3.60 (1.70–5.80)	2.00 (1.30–3.75)	<0.001
pH value	7.39 (7.33–7.43)	7.37 (7.27–7.42)	7.39 (7.34–7.44)	7.41 (7.36–7.44)	<0.001
BUN, mg/dL	16.00 (12.00–22.00)	18.00 (13.00–26.00)	16.50 (12.00–20.75)	16.00 (11.00–20.75)	0.037
Creatinine, mg/dL	1.05 (0.80–1.53)	1.20 (0.90–1.90)	1.00 (0.80–1.40)	0.95 (0.73–1.30)	<0.001
Chloride, mmol/L	103 (100–105)	104 (101.75–106)	103 (101–105)	101 (99–104)	<0.001
Glucose, mg/dL	103 (89.00–119.25)	101 (86–119)	104 (88–118)	102 (93–121.75)	0.541
APTT, s	28.15 (25.20–32.63)	28.70 (25.50–36.20)	27.35 (24.50–31.38)	28.75 (25.50–32.00)	0.47
PT, s	13.40 (12.50–14.40)	13.50 (12.40–14.53)	13.35 (12.70–14.10)	13.30 (12.50–14.60)	0.932
INR	1.20 (1.10–1.30)	1.20 (1.10–1.30)	1.20 (1.10–1.30)	1.20 (1.10–1.30)	0.836
Sodium, mmol/L	137 (134–139)	135.50 (133–138)	136 (134–139)	137.50 (135–139)	0.001
Potassium, mmol/L	3.60 (3.30–3.90)	3.60 (3.30–3.90)	3.70 (3.40–4.00)	3.60 (3.30–3.90)	0.264
Total Ca, mg/dL	8.50 (8.10–9.00)	8.50 (7.90–8.83)	8.50 (8.10–9.00)	8.60 (8.30–9.10)	0.02
Magnesium, mg/dL	2.00 (1.90–2.30)	2.10 (1.90–2.40)	2.00 (1.90–2.30)	2.00 (1.90–2.20)	0.439
Vital signs					
SBP, mmHg	151 (136–165)	149.50 (134–168)	151 (136–167.50)	150.50 (136–162)	0.526
DBP, mmHg	81.00 (72.00–91.00)	81.00 (72.00–94.00)	81.00 (72.00–94.00)	85.50 (72.25–87.00)	0.604
MBP, mmHg	102 (93–113)	101.50 (95–114.25)	103 (92.25–117.50)	101 (91.75–109.75)	0.193
HR, beats/min	90 (80–102.25)	95.00 (84.00–112.00)	90.50 (79.25–99.75)	87.50 (78.00–101.00)	0.015
RR, times/min	25.00 (22.00–29.00)	26.00 (23.00–30.00)	24.00 (22.00–29.00)	26.00 (22.00–29.00)	0.201
Temperature, °C	37.28 (36.78–37.83)	37.30 (36.72–38.01)	37.31 (36.78–37.89)	37.22 (36.89–37.70)	0.942
SPO ₂ , %	92.00 (90.00–94.00)	92.00 (91.00–94.00)	92.00 (91.00–94.00)	92.00 (90.00–94.00)	0.365
Severity score					
SAPSII	35.00 (28.00–43.00)	43.00 (33.75–53.50)	34.00 (28.25–39.00)	31.00 (25.00–39.00)	<0.001
OASIS	32.00 (26.75–39.00)	37.00 (32.00–42.25)	31.00 (26.00–37.00)	29.50 (25.00–34.00)	<0.001
SOFA	4.00 (2.00–6.00)	6.00 (3.75–9.00)	3.00 (2.00–5.00)	3.00 (1.00–5.00)	<0.001
SIRS	3.00 (2.00–3.00)	3.00 (2.00–4.00)	3.00 (2.00–3.00)	2.00 (1.00–3.00)	<0.001

Abbreviations: ICU MV, intensive care unit mechanical ventilation; HC, hypercholesterolemia; CAD, coronary artery disease; CHF, congestive heart failure; AKI, acute kidney injury; RRT, renal replacement therapy; WBC, white blood cell; RBC, red blood cell; PLT, platelet; RDW, red cell distribution width; BUN, blood urea nitrogen; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; Total Ca, total calcium; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; RR, respiratory rate; SAPS II, simplified acute physiology score; OASIS, Oxford acute severity of illness score; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.

Data Stratification

Similar to previous studies, we used Structured Query Language (SQL) with PostgreSQL 9.6 to extract data. Since some patients had multiple results of HCO₃⁻ measurement, we selected their first result after ICU admission. Other data, including demographics, vital signs and laboratory tests, were also extracted. Vital signs included heart rate (HR), respiratory rate (RR), temperature, SPO₂, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP); the laboratory variables included venous serum HCO₃⁻, lactate, anion gap, pH value, etc. Comorbidities were also collected, including hypertension, diabetes, malignancy, renal

disease, etc. Severity of illness was captured by severity scores such as simplified acute physiology score (SAPSII), Oxford acute severity of illness score (OASIS), sequential organ failure assessment (SOFA) and systemic inflammatory response syndrome (SIRS) score. Others included age, gender, Stanford type, dissection site, surgery of aorta replacement, ICU mechanical ventilation (MV) and survival time.

Statistical Analysis

Baseline characteristics of AAD patients were stratified to tertiles including low-HCO₃⁻, mid-HCO₃⁻ and high-HCO₃⁻. Normally distributed continuous variables were

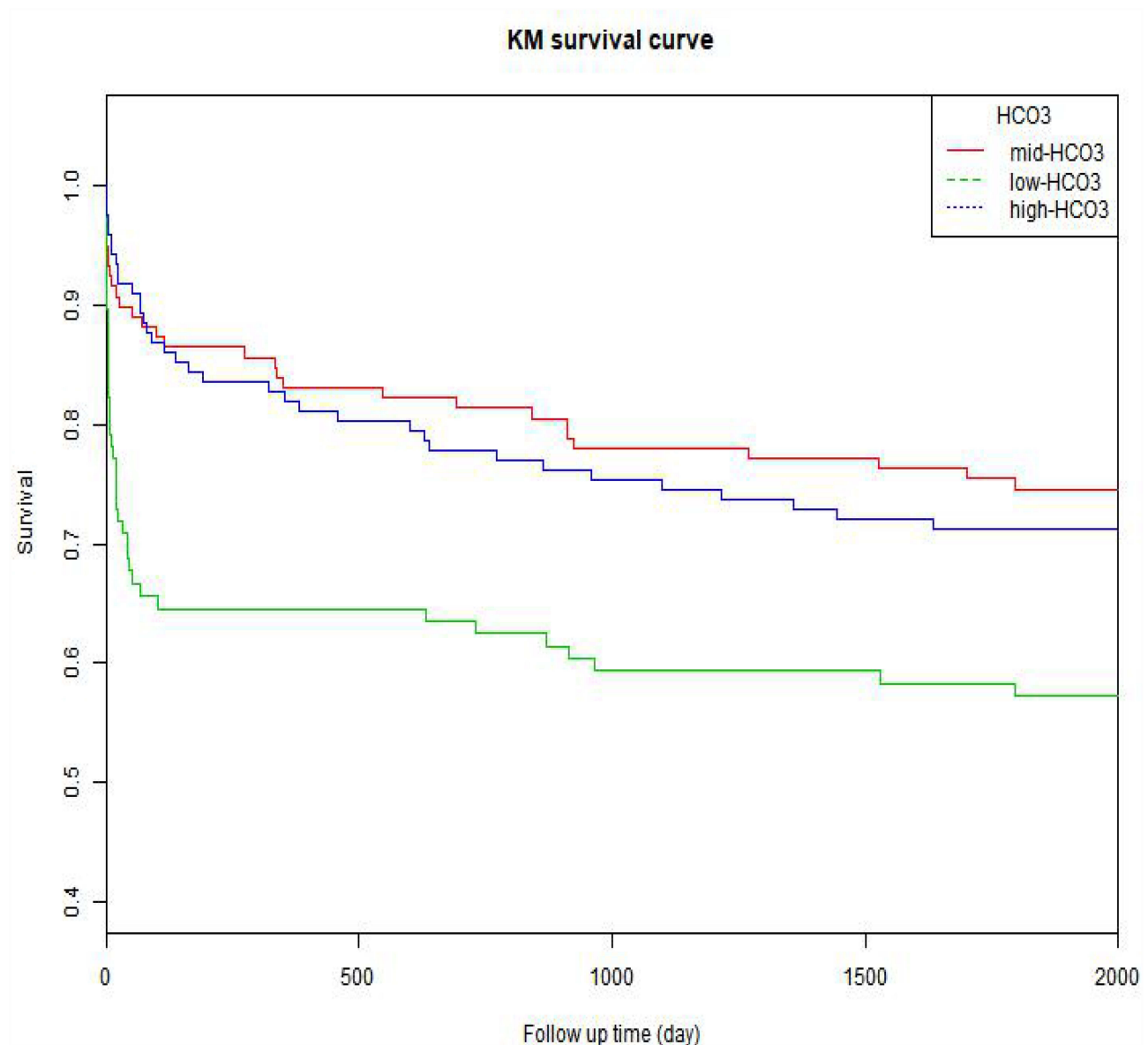


Figure 2 The KM survival curve of low-HCO₃⁻, mid-HCO₃⁻ and high-HCO₃⁻ groups.

presented as the means \pm SD, while other continuous variables were reported as the median and interquartile range (IQR). Categorical data were presented as total number and percentages, which were compared by the chi-square test to determine differences among the tertiles. Then, covariate selection and multi-collinearity check analysis were conducted. Multifactorial Cox regression models were performed to evaluate the predictive value of serum HCO₃⁻ in each period's mortality (30 days, 90 days, 1 year and 5 years) with hazard ratios (HRs) and 95% confidence intervals (CIs). In multivariate analysis, we used 2 adjusted multivariate models, and covariates were adjusted to age, gender, ethnicity, insurance, Stanford type,

dissection site, surgery of aorta replacement, ICU MV, etc. Besides, we used the log rank tests to compare the survival rates in low-HCO₃⁻, mid-HCO₃⁻ and high-HCO₃⁻ groups and report the results with Kaplan–Meier curves. Subgroup analyses were conducted to evaluate the relationship between the HCO₃⁻ level and 30-day mortality among the different subgroups, including age, gender, ethnicity, insurance, Stanford type, dissection site, surgery of aorta replacement, ICU MV, etc. Finally, we used ROC curve and calculated the value of AUC and best cut-off value according to the Youden index to test the effectiveness of HCO₃⁻ in predicting short-term and long-term mortality. The KM survival curve based on the best cut-

Table 2 HRs (95% CIs) for Mortality Across Groups of Serum HCO₃⁻

Serum HCO ₃ ⁻ Level	Non-Adjusted		Model 1		Model 2	
	HR (95% CIs)	P value	HR (95% CIs)	P value	HR (95% CIs)	P value
30-day mortality HCO ₃ ⁻ , mmol/L						
<22 mmol/L	3.54 (1.67, 7.49)	<0.001	3.54 (1.67, 7.49)	0.001	5.11 (1.41, 18.46)	0.013
22–24 mmol/L	1.0 (ref)	/	1.0 (ref)	/	1.0 (ref)	/
>24 mmol/L	0.77 (0.32, 1.87)	0.567	0.74 (0.30, 1.82)	0.507	0.75 (0.20, 2.78)	0.663
90-day mortality HCO ₃ ⁻ , mmol/L						
<22 mmol/L	3.95 (1.96, 7.98)	<0.001	3.95 (1.93, 8.08)	<0.001	5.58 (1.86, 16.77)	0.002
22–24 mmol/L	1.0 (ref)	/	1.0 (ref)	/	1.0 (ref)	/
>24 mmol/L	1.02 (0.47, 2.23)	0.951	0.98 (0.44, 2.19)	0.969	1.49 (0.49, 4.54)	0.486
1-year mortality HCO ₃ ⁻ , mmol/L						
<22 mmol/L	2.71 (1.43, 5.13)	0.002	2.67 (1.39, 5.13)	0.003	3.30 (1.24, 8.78)	0.016
22–24 mmol/L	1.0 (ref)	/	1.0 (ref)	/	1.0 (ref)	/
>24 mmol/L	1.06 (0.54, 2.07)	0.864	1.06 (0.53, 2.10)	0.877	1.51 (0.57, 3.98)	0.402
5-year mortality HCO ₃ ⁻ , mmol/L						
<22 mmol/L	2.19 (1.23, 3.91)	0.008	2.13 (1.18, 3.83)	0.012	4.08 (1.70, 9.78)	0.002
22–24 mmol/L	1.0 (ref)	/	1.0 (ref)	/	1.0 (ref)	/
>24 mmol/L	1.18 (0.67, 2.09)	0.574	1.14 (0.63, 2.04)	0.668	1.67 (0.75, 3.72)	0.209

Notes: Models were derived from Cox proportional hazards regression models. Non-adjusted model adjusted for: none. Model 1 adjusted for: gender; age; ethnicity and insurance. Model 2 adjusted for: age; gender; ethnicity; insurance; Stanford type; dissection site; ICU MV; therapy type; hypertension; diabetes; hypercholesterolemia; valvular disease; malignancy; stroke; CAD; CHF; atrial fibrillation; renal disease; liver disease; respiratory disease; AKI; WBC; RDW; RBC; Hb; PLT; BUN; creatinine; chloride; glucose; APTT; INR; sodium; potassium; total Ca; magnesium; anion gap; pH value; SBP; DBP; MBP; HR; RR; temperature and SPO₂.

off value was generated. Finally, the KM survival curve based on the best cut-off value was generated, and the comparison within HCO₃⁻, anion gap and lactate was conducted. All statistical analyses were conducted using the EmpowerStats ver 2.17.8 and R software version 3.42, and *P* value <0.05 was considered statistically significant.

Results

Characteristics of the Subjects

Overall, 336 eligible AAD patients were included in the study. Figure 1 is a flow chart describing the procedure of patient selection. Table 1 lists the baseline characteristics of the patients. Based on the value of serum HCO₃⁻, patients were categorized in trisected groups including low-HCO₃⁻ group, mid-HCO₃⁻ group and high-HCO₃⁻ group (<22 mmol/L; 22–24 mmol/L; >24 mmol/L). Patients with a high serum HCO₃⁻ level were more likely to have lower platelet (PLT), hematocrit, hemoglobin (Hb), creatinine, sodium, chloride; and higher red blood cell (RBC), lactate, anion gap, pH value, blood urea

nitrogen (BUN), total calcium. In addition, patients with low HCO₃⁻ level had less hypertension and higher severity scores.

Low-HCO₃⁻ Is Directly Related to the Short-Term and Long-Term Mortality of AAD

During the 5 years of follow-up, 106 (31.55%) patients died. The number of all-cause fatalities in the low (*n*=96), mid (*n*=118) and high (*n*=122) HCO₃⁻ groups were 41 (42.71%), 30 (25.42%) and 35 (28.69%), respectively. Figure 2 shows the Kaplan–Meier curve for patients in the low, mid and high HCO₃⁻ groups. The survival rate of the low-HCO₃⁻ group is lower than the other two groups.

To explore the relationship between serum HCO₃⁻ level and short-term and long-term mortality, multivariate Cox regression analysis was conducted and listed in Table 2. First of all, according to the results of covariates selection and multi-collinearity check analysis,

Table 3 Subgroup Analysis of the Associations Between Serum HCO₃⁻ and 30-Day All-Cause Mortality

	No. of Patients	Serum HCO ₃ ⁻ Levels (mmol/L)			P for Interaction
		<22	22–24	>24	
Gender					0.828
Male	213	2.96 (1.29, 6.80)	ref	0.66 (0.23, 1.89)	
Female	123	3.25 (1.00, 10.56)	ref	1.09 (0.27, 4.38)	
Age, years					0.924
<69	165	3.18 (1.26, 8.01)	ref	0.92 (0.30, 2.85)	
≥69	171	2.66 (0.95, 7.48)	ref	0.651 (0.18, 2.31)	
Insurance					/
Government	20	/	ref	/	
Medicaid	17	/	ref	/	
Medicare	176	2.32 (0.90, 5.99)	ref	0.39 (0.10, 1.53)	
Private	118	3.66 (1.32, 10.16)	ref	0.91 (0.24, 3.37)	
Selfpay	5	/	ref	1.00 (1.00, 1.00)	
Ethnicity					0.89
White	233	3.18 (1.38, 7.33)	ref	0.87 (0.30, 2.49)	
Black	44	1.38 (0.28, 6.84)	ref	0.49 (0.08, 2.94)	
Hispanic	13	/	ref	/	
Others	46	5.88 (0.69, 50.40)	ref	0.91 (0.08, 10.01)	
Stanford type					0.387
A type	230	8.50 (1.05, 16.26)	ref	0.95 (0.06, 16.29)	
B type	106	2.27 (1.17, 5.94)	ref	0.65 (0.20, 2.09)	
Aorta replacement					0.768
No	138	5.27 (1.44, 8.94)	ref	0.64 (0.72, 3.16)	
Yes	198	2.75 (0.98, 7.13)	ref	0.54 (0.17, 2.83)	
ICU MV					0.753
No	166	3.57 (2.26, 5.23)	ref	0.79 (0.33, 2.54)	
Yes	170	4.92 (1.67, 9.91)	ref	0.88 (0.12, 4.58)	
Hypertension					0.179
No	137	1.77 (0.72, 4.35)	ref	0.32 (0.08, 1.22)	
Yes	199	4.64 (1.63, 13.17)	ref	1.53 (0.48, 4.81)	
Diabetes					0.091
No	306	2.572 (1.27, 5.20)	ref	0.78 (0.34, 1.81)	
Yes	30	/	ref	/	
Hypercholesterolemia					0.156
No	283	3.56 (1.64, 7.69)	ref	1.04 (0.42, 2.55)	
Yes	53	1.597 (0.36, 7.14)	ref	/	
Valvular disease					0.668
No	303	3.00 (1.42, 6.33)	ref	0.87 (0.36, 2.15)	
Yes	33	3.36 (0.65, 17.39)	ref	0.38 (0.03, 4.19)	
Malignancy					0.478
No	325	2.93 (1.48, 5.81)	ref	0.79 (0.34, 1.83)	
Yes	11	/	ref	/	
Stroke					0.891
No	310	3.22 (1.47, 7.02)	ref	0.85 (0.33, 2.21)	

(Continued)

Table 3 (Continued).

	No. of Patients	Serum HCO ₃ ⁻ Levels (mmol/L)			P for Interaction
		<22	22–24	>24	
Yes	26	2.27 (0.56, 9.18)	ref	0.54 (0.09, 3.23)	
CAD					0.16
No	276	4.25 (1.88, 9.59)	ref	1.09 (0.42, 2.81)	
Yes	60	1.00 (0.28, 3.54)	ref	0.21 (0.02, 1.90)	
CHF					0.307
No	305	3.29 (1.57, 6.88)	ref	0.94 (0.39, 2.25)	
Yes	31	1.91 (0.32, 11.43)	ref	/	
Atrial fibrillation					0.735
No	279	3.49 (1.62, 7.55)	ref	0.84 (0.32, 2.18)	
Yes	57	1.80 (0.40, 8.03)	ref	0.64 (0.11, 3.83)	
Renal disease					0.094
No	291	3.16 (1.44, 6.94)	ref	1.07 (0.43, 2.62)	
Yes	45	2.35 (0.61, 9.13)	ref	/	
Liver disease					0.049
No	326	2.77 (1.39, 5.51)	ref	0.79 (0.34, 1.83)	
Yes	10	/	ref	/	
Respiratory disease					0.727
No	272	3.51 (1.55, 7.92)	ref	0.87 (0.30, 2.50)	
Yes	64	2.21 (0.62, 7.86)	ref	0.42 (0.11, 1.69)	
AKI					0.507
No	201	3.10 (1.22, 7.87)	ref	1.06 (0.39, 2.93)	
Yes	135	2.83 (1.03, 7.80)	ref	0.40 (0.08, 2.03)	
RRT					0.418
No	307	2.94 (1.43, 6.06)	ref	0.86 (0.37, 2.03)	
Yes	29	3.31 (0.39, 28.38)	ref	/	
WBC, 10 ³ /μL					0.84
<8.8	167	2.47 (0.85, 7.26)	ref	0.63 (0.17, 2.35)	
≥8.8	169	3.58 (1.49, 8.64)	ref	0.99 (0.33, 2.94)	
RDW, %					0.873
<14.4	159	3.58 (1.26, 10.17)	ref	0.84 (0.23, 3.12)	
≥14.4	177	2.65 (1.08, 6.50)	ref	0.74 (0.25, 2.22)	
Hematocrit, %					0.985
<28.9	167	2.91 (1.21, 7.01)	ref	0.80 (0.25, 2.51)	
≥28.9	169	3.16 (1.08, 9.26)	ref	0.83 (0.24, 2.85)	
Hb, g/dL					0.895
<9.7	163	2.75 (1.15, 6.60)	ref	0.65 (0.19, 2.23)	
≥9.7	173	3.25 (1.09, 9.71)	ref	0.99 (0.30, 3.23)	
RBC, 10 ³ /μL					0.254
<3.66	167	5.46 (1.9, 16.06)	ref	1.30 (0.33, 5.21)	
≥3.66	169	1.67 (0.63, 4.46)	ref	0.55 (0.19, 1.58)	

(Continued)

Table 3 (Continued).

	No. of Patients	Serum HCO ₃ ⁻ Levels (mmol/L)			P for Interaction
		<22	22–24	>24	
Platelet, 10 ³ /μL					
<164	165	4.06 (1.50, 11.00)	ref	1.29 (0.37, 4.45)	0.561
≥164	171	2.29 (0.87, 6.03)	ref	0.53 (0.17, 1.67)	
Anion gap, mmol/L					
<12	126	1.42 (0.41, 4.91)	ref	0.63 (0.18, 2.18)	0.313
≥12	210	4.18 (1.79, 9.80)	ref	0.89 (0.28, 2.81)	
pH value					
<7.39	167	6.19 (2.15, 10.74)	ref	0.68 (0.58, 3.20)	0.072
≥7.39	169	2.63 (1.39, 6.18)	ref	0.87 (0.31, 2.01)	
Lactate, mmol/L					
<4.1	166	5.13 (1.27, 8.84)	ref	1.12 (0.32, 3.84)	0.311
≥4.1	170	3.11 (1.33, 5.26)	ref	0.91 (0.33, 2.50)	
BUN, mg/dL					
<16	153	3.19 (0.80, 12.74)	ref	0.92 (0.19, 4.57)	0.979
≥16	183	2.83 (1.29, 6.18)	ref	0.76 (0.28, 2.04)	
Creatinine, mg/dL					
<1	132	4.12 (1.24, 13.70)	ref	1.12 (0.32, 3.95)	0.735
≥1	204	2.65 (1.16, 6.04)	ref	0.58 (0.17, 1.91)	
Chloride, mmol/L					
<103	167	2.36 (0.90, 6.19)	ref	0.69 (0.24, 1.97)	0.719
≥103	169	4.00 (1.47, 10.84)	ref	0.82 (0.20, 3.45)	
Glucose, mg/dL					
<103	167	3.29 (1.05, 10.34)	ref	0.65 (0.15, 2.90)	0.876
≥103	169	3.10 (1.33, 7.26)	ref	0.91 (0.33, 2.50)	
APTT, s					
<28.1	167	2.82 (1.11, 7.16)	ref	1.03 (0.35, 3.06)	0.59
≥28.1	169	3.33 (1.21, 9.17)	ref	0.60 (0.16, 2.22)	
INR					
<1.2	152	3.61 (1.39, 9.41)	ref	0.63 (0.18, 2.22)	0.628
≥1.2	184	2.69 (1.02, 7.06)	ref	0.96 (0.31, 2.96)	
PT, s					
<13.4	165	3.19 (1.21, 8.40)	ref	0.62 (0.18, 2.20)	0.775
≥13.4	171	2.96 (1.14, 7.69)	ref	0.97 (0.31, 3.01)	
Sodium, mmol/L					
<137	166	3.22 (1.26, 8.23)	ref	1.03 (0.32, 3.38)	0.831
≥137	170	2.92 (1.08, 7.91)	ref	0.63 (0.19, 2.08)	
Potassium, mmol/L					
<3.6	143	4.40 (1.23, 15.77)	ref	0.81 (0.16, 4.03)	0.726
≥3.6	193	2.65 (1.17, 6.00)	ref	0.83 (0.31, 2.22)	
Total calcium, mg/dL					
<8.5	152	6.16 (1.75, 21.63)	ref	1.46 (0.33, 6.51)	0.332

(Continued)

Table 3 (Continued).

	No. of Patients	Serum HCO ₃ ⁻ Levels (mmol/L)			P for Interaction
		<22	22–24	>24	
≥8.5	184	2.06 (0.89, 4.756)	ref	0.57 (0.20, 1.59)	
Magnesium, mg/dL					0.521
<2	119	2.20 (0.82, 5.91)	ref	0.48 (0.12, 1.84)	
≥2	217	4.32 (1.60, 11.64)	ref	1.21 (0.38, 3.82)	
SBP, mmHg					0.728
<151	166	3.27 (1.17, 9.18)	ref	1.09 (0.33, 3.57)	
≥151	170	2.96 (1.19, 7.32)	ref	0.56 (0.17, 1.93)	
DBP, mmHg					0.561
<81	162	2.92 (1.00, 8.55)	ref	1.13 (0.34, 3.69)	
≥81	174	3.10 (1.28, 7.48)	ref	0.55 (0.16, 1.87)	
MBP, mmHg					0.102
<102	162	2.57 (0.79, 8.35)	ref	1.46 (0.43, 4.98)	
≥102	174	3.62 (1.57, 8.34)	ref	0.40 (0.11, 1.50)	
HR, beats/min					0.914
<90	162	3.59 (1.12, 11.44)	ref	0.83 (0.21, 3.30)	
≥90	174	2.76 (1.19, 6.40)	ref	0.82 (0.29, 2.37)	
RR, times/min					0.599
<25	155	3.17 (0.79, 12.68)	ref	0.35 (0.04, 3.40)	
≥25	181	2.76 (1.26, 6.03)	ref	0.86 (0.34, 2.15)	
Temperature, °C					0.293
<37.28	166	2.22 (0.97, 5.07)	ref	0.79 (0.30, 2.04)	
≥37.28	170	5.59 (1.58, 19.82)	ref	0.67 (0.11, 4.03)	
SPO ₂ , %					0.853
<92	135	2.41 (0.98, 5.92)	ref	0.65 (0.22, 1.93)	
≥92	201	3.63 (1.28, 10.31)	ref	0.87 (0.23, 3.24)	

variables PT and hematocrit were eliminated in further analysis. Then Cox regression analysis was conducted. In model 1, after adjusting for age, gender, ethnicity and insurance, compared with the reference group (mid-HCO₃⁻: 22–24 mmol/L), low HCO₃⁻ level was a significant predictor of 30-day, 90-day, 1-year and 5-year mortality in AAD patients (HR, 95% CI: 3.03, 1.53–6.03; 3.26, 1.74–6.13; 2.44, 1.40–4.25; 1.99, 1.24–3.20). In model 2, after adjusting for age, gender, ethnicity, insurance, Stanford type, treatment strategy, ICU MV; hypertension; diabetes; hypercholesterolemia; valvular disease; malignancy; stroke; coronary artery disease (CAD); congestive heart failure (CHF); atrial fibrillation; renal disease; liver disease; respiratory disease;

congestive heart failure (AKI); white blood cell (WBC); Hb; RBC; PLT; BUN; creatinine; chloride; glucose; activated partial thromboplastin time (APTT); international normalized ratio (INR); sodium; potassium; total Ca; magnesium; anion gap; lactate; pH value; SBP; DBP; MBP; HR; RR; temperature and SPO₂, low HCO₃⁻ level remained a significant predictor of 30-day, 90-day, 1-year and 5-year mortality (HR, 95% CI: 5.11, 1.41–18.46; 5.58, 1.86–16.77; 3.30, 1.24–8.78; 4.08, 1.70–9.78). We additionally analyzed type A and B AAD separately, and the results are listed in [Supplemental Table 1](#). The results showed that the HR were significant in both type A and type B AAD, and HR of HCO₃⁻ in type A AAD group were higher.

Table 4 Area Under Receiver Operating Characteristic Curve of HCO₃⁻ and Severity Scores

Terms	AUC
30-day mortality	
HCO ₃ ⁻	0.69
SAPSII	0.68
OASIS	0.71
SOFA	0.58
SIRS	0.57
90-day mortality	
HCO ₃ ⁻	0.68
SAPSII	0.70
OASIS	0.74
SOFA	0.60
SIRS	0.55
1-year mortality	
HCO ₃ ⁻	0.68
SAPSII	0.71
OASIS	0.72
SOFA	0.64
SIRS	0.56
5-year mortality	
HCO ₃ ⁻	0.60
SAPSII	0.65
OASIS	0.65
SOFA	0.58
SIRS	0.57

Note: P value <0.05.

Abbreviation: AUC, area under curve.

Serum HCO₃⁻ Is an Effective Predictor of Short-Term and Long-Term Mortality of AAD

The results from subgroup analysis indicated that most strata had no interaction (*P* for interaction=0.09–0.98). Only patients with liver disease had a higher risk with a low-HCO₃⁻ (HR 2.01, 95% CI 1.24–3.27) (Table 3). In addition, the AUC of HCO₃⁻ level in predicting mortality in each period (30 days, 90 days, 1 year and 5 years) ranged from 0.60 to 0.68, which revealed a similar performance to SAPSII, OASIS and a better performance than SOFA and SIRS (Table 4). Moreover, ROC curve analysis and accordingly Kaplan–Meier curves with corresponding HCO₃⁻ cut-off value were performed respectively (Supplemental Figure 1: A and B: 30-day, C and D: 90-day, E and F: 1-year and G and H: 5-year). Anion gap and

lactate were also identified as a biomarkers of the homeostasis of acid–base and had a contribution to the outcome of AAD (Supplemental Table 2). But HCO₃⁻ had the highest AUC (0.683 versus 0.607 and 0.606 in Supplemental Figure 2).

Discussion

AAD is a severe cardiovascular disorder characterized by acute onset, rapid progression as well as high rates of complications and mortality.¹² Especially when AAD patients were transferred into ICU of the hospital, the mortality rate was increased hourly, which makes AAD a challenge in both internal medicine intervention and surgical repair. Currently, simple and effective biomarkers for evaluating risk of complications and mortality of AAD remain lacking. Therefore, the exploration of new indicators is crucial for the death-risk stratification of AAD patients in ICU. In our study, we found that serum HCO₃⁻ level measured at ICU admission is an independent predictor of short-term and long-term mortality in patients with AAD.

Serum HCO₃⁻ level reflects the acid–base homeostasis in the human body and is typically included in routine biochemical tests, especially when renal disease progresses. However, some clinical researches indicated a possible role of serum HCO₃⁻ level, which could be used to predict mortality from diseases other than progressive renal disease. For example, a low HCO₃⁻ level was associated with malignancy-related mortality, whereas a high HCO₃⁻ level was related to mortality and complications with cardiovascular diseases.¹¹ So far, there has been no research regarding the relationship between serum HCO₃⁻ level and clinical outcomes of AAD patients. Hence, we evaluated the associations between serum HCO₃⁻ and all-cause mortality of patients with AAD. Our results indicated that low HCO₃⁻ levels were related to high all-cause mortality (both short-term and long-term). Moreover, subgroup analysis proved excellent in predicting 30-day, 90-day, 1-year and 5-year mortality, and AUC analysis revealed a similar performance to SAPSII and OASIS and a better performance than SOFA, SIRS score, anion gap and lactate.

We hold that our study is distinct and meaningful, although some previous studies have reported better value ROC compared to HCO₃⁻ in our study.^{3,4,13} In these studies, the outcomes were in-hospital mortality and hospital complications such as aortic rupture, mechanical ventilation, renal dysfunction and visceral

hemorrhage. In contrast, survival time and longer-term mortality (30 days, 90 days, 1 year and 5 years) were set as our outcomes in this study.

Moreover, low serum HCO_3^- is a kind of index of acidosis. It has been proved that acidosis could decrease myocardial contraction and alter systemic vascular resistance promoting to aggravation of circulatory shock, leading to progressive cellular hypoxia and tissue malperfusion, and eventually causing end-organ failure including acute kidney injury. Therefore, it could be the main reason of poor prognosis in critically ill patients of AAD.

Our study is the first to prove the potential value of HCO_3^- levels in predicting short-term and long-term outcomes in AAD patients. We also provided the evidence of the application of a routinely measured serum HCO_3^- as a prognostic indicator, which could improve the adjustment of therapy and potentially reduce mortality rate. Recently, many indicators were proved to be closely associated to the short-term and long-term outcomes of AAD, including C-reactive protein (CRP),¹⁴ metalloproteinase (MMPs)¹⁵ and serum amyloid A protein.¹⁶ Moreover, many risk assessment models to AAD were constructed.^{17,18} The exploration and confirmation of the association between the mortality and serum HCO_3^- could provide a meaningful candidate of future composite prediction models of mortality of AAD. However, several limitations in our study exist. Firstly, the population size was relatively small due to the limited population source from a single-center database. Moreover, because the serum HCO_3^- levels were shown as integers (as is common laboratory practice), it limited the ability to define precise trisection boundaries. Thirdly, some kinds of data were censored in the MIMIC database, such as the time from onset to admission. Furthermore, we should carry out more in-depth mechanism research in our future work.

Conclusion

The low admission serum HCO_3^- level is an independent index to predict the short-term and long-term mortality in ICU patients with AAD.

Data Sharing Statement

Limited access in MIMIC III database.

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Disclosure

The authors report no conflicts of interest in this work.

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