

The Association Between Serum Anion Gap and All-Cause Mortality in Disseminated Intravascular Coagulation Patients: A Retrospective Analysis

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Purpose: Studies regarding death risk factors of disseminated intravascular coagulation (DIC) patients were limited. Therefore, we conducted this study to investigate whether the serum anion gap (AG) was independently related to all-cause mortality of DIC patients.

Methods: We used the data from Medical Information Mart for Intensive Care III version 1.4 (MIMIC-III v1.4). A total of 2,654 DIC patients were included. The main outcomes were in-hospital, 30-day, and 90-day all-cause mortality. The AG was measured upon ICU admission and its association with mortality was evaluated using the Cox proportional-hazards regression model. The generalized additive model and the smooth curve fitting were introduced to examine the non-linear association.

Results: After adjusting for potential covariates, the in-hospital, 30-day, and 90-day all-cause mortality were positively correlated with AG. The hazard ratio (HR), confidence intervals (CI), and *P* were 1.05 (1.04–1.07) <0.0001, 1.06 (1.04–1.07) <0.0001, and 1.05 (1.03–1.07) <0.0001, respectively. We did not find an obvious non-linear relationship between AG and in-hospital, 30-day, and 90-day mortality, which indicated that the association between AG and all-cause mortality of DIC patients was nearly linear.

Conclusion: Serum AG is positively related with all-cause mortality in DIC patients.

Keywords: anion gap, disseminated intravascular coagulation, all-cause mortality, MIMIC-III, retrospective study

Introduction

Disseminated intravascular coagulation (DIC) is a clinically severe syndrome characterized by uncontrolled and widespread activation of blood coagulation, which is caused by serious infections, trauma, malignancies, liver diseases, obstetric diseases, etc.¹ The pathophysiological mechanisms of DIC includes activation of tissue factor-related intravascular coagulation, a dysfunction of anticoagulant pathways and suppression of fibrinolysis caused by plasminogen activator inhibitor.² Together, these changes may result in micro-vascular thrombosis, multiple organ dysfunction, and severe bleeding tendency, which always lead to a significantly increased mortality.^{2,3} Mortality risks have been demonstrated to double in critically ill patients if DIC occurred.⁴ Because of the poor prognosis of DIC, it is necessary to identify its potential death risk factors. However, there are currently few clinical studies focusing on this field.

The development of DIC is closely related to acid-base imbalance.^{5,6} Acid-base imbalance is considered as one of the initiating factors resulting in DIC.^{5,6} Severe

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acidosis may injure the endothelial cell, which may further lead to the tissue factor release.⁷ The tissue factor–factor VII pathway is the principal initiator of thrombin generation in DIC.² Moreover, DIC is often associated with micro-vascular thrombosis and micro-circulatory dysfunction, which may further lead to or worsen metabolic acidosis.⁸ Metabolic acidosis is common in DIC patients and it may be a strong predictor of its prognosis.

The serum anion gap (AG), calculated by the formula $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$, reflects the concentration of unmeasured serum anions.^{9,10} AG is widely used in analysis of acid-base disorders and high values of AG always indicate metabolic acidosis.¹⁰ The level of serum AG is closely related to the severity of metabolic acidosis.¹¹

On the basis of the close pathophysiological relationship among DIC, metabolic acidosis, and AG, we speculate that AG might be one of the prognostic predictors of DIC patients. Furthermore, previous clinical research has demonstrated that high AG was an independent adverse prognostic factor in a variety of diseases,¹² such as coronary artery disease,¹³ acute kidney injury,¹⁴ and aortic aneurysm.¹⁵ Up to now, there is no clinical research focusing on the association between AG and DIC prognosis. We conducted this work to evaluate whether AG was independently related to all-cause mortality of DIC patients.

We used the data from the Medical Information Mart for Intensive Care III version 1.4 (MIMIC-III v1.4), which is a publicly available database enrolling 46,476 patients and 61,532 admissions to intensive care units (ICU).¹⁶ In total, 3,044 DIC patients were identified from MIMIC-III. We produced a series of clinical studies regarding mortality risk factors in DIC patients, and this paper is the first report of our studies.

Methods

Database

The MIMIC-III database is approved by the Massachusetts Institute of Technology and the Institutional Review Boards of Beth Israel Deaconess Medical Center.¹⁶ The authors, Bin Hu and Zuoan Qin, finished the Collaborative Institutional Training Initiative (CITI) program course named “Data or Specimens Only Research” and achieved access to the database (Record ID: 35942628 and 36208651).

Data Extraction

The Structure Query Language (SQL) with PostgreSQL (version 9.6) was introduced to extract the data from the

MIMIC-III database. The following information were collected: general information, causes of DIC, vital signs, scoring systems (sequential organ failure assessment (SOFA¹⁷) score, systemic inflammatory response syndrome (SIRS¹⁸) score, and simplified acute physiology score II (SAPSII¹⁹)), comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease (COPD), liver diseases, renal failure), laboratory data (AG, hemoglobin, hematocrit, red blood cell distribution (RDW), platelet, white blood cell (WBC), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), creatinine, urea nitrogen, glucose, potassium, sodium, bicarbonate, albumin, and lactate), and treatment (continuous renal replacement therapy (CRRT), vasopressor drugs and mechanical ventilation). It should be noted that all laboratory results we extracted were the first test results after admission to the ICU. The primary endpoint of this study was in-hospital, 30-day, and 90-day all-cause mortality from admission to the ICU.

Inclusion Criteria

The diagnosis of DIC was established using the scoring system recommended by the Japanese Association of Acute Medicine (JAAM).²⁰ We calculated patients' JAAM-DIC scores according to their SIRS scores, platelet count, fibrin degradation products (FDP) and, prothrombin time- international normalized ratio (PT-INR) within 24 hours of admission to the ICU. Patients were diagnosed as DIC if their JAAM-DIC scores were ≥ 4 .²⁰ Exclusion criteria were as follows:

- non-first admission to ICU;
- age <14 or >89 years old;
- a length of ICU stay less than 24 hours; and
- missing AG data at ICU admission.

Statistical Analysis

To examine the link between AG and the risk of all-cause mortality of DIC patients, we introduced three different models by univariate and multivariate Cox proportional-hazards regression model, including non-adjusted model (no covariates were adjusted), minimally-adjusted model (only sociodemographic variables were adjusted), and fully-adjusted model (all potential covariates were adjusted). Effect sizes with 95% confidence intervals were recorded. Accounting for the non-linear correlation between AG and all-cause mortality of DIC patients, we also used a generalized additive model and the smooth curve fitting

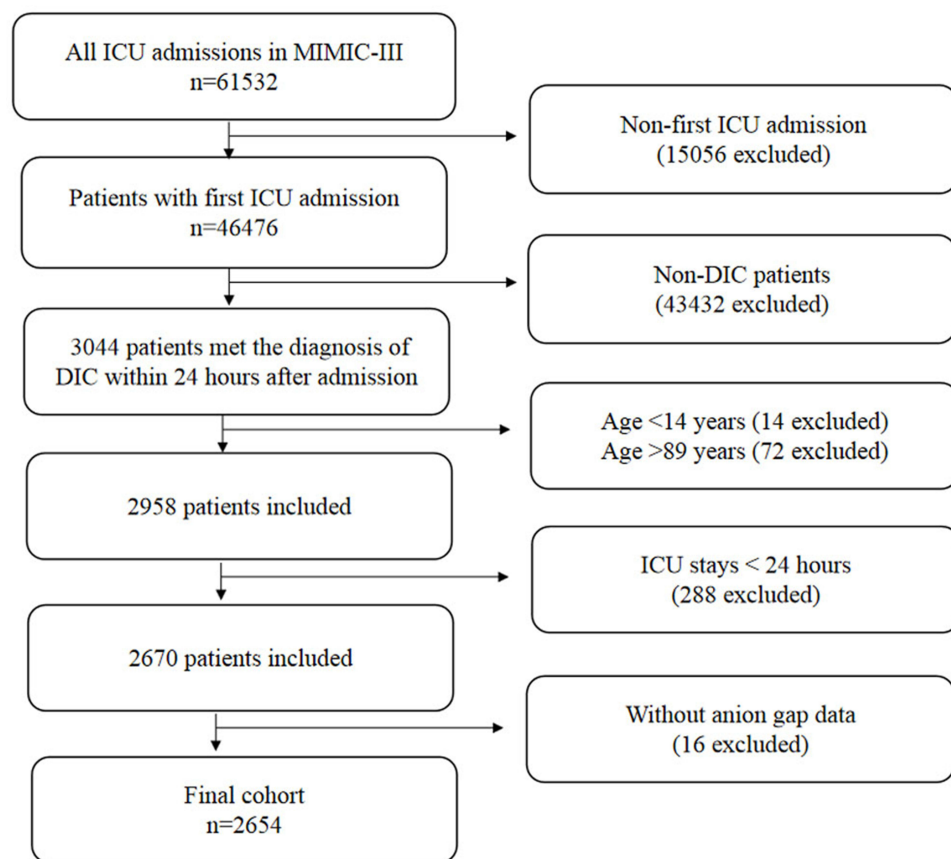


Figure 1 Flowchart of subject screening.

(penalized spline method) to address non-linearity. The subgroup analyses were conducted using a stratified Cox proportional-hazards regression model. To test the robustness of our results, we performed a sensitivity analysis. We converted AG into a categorical variable according to the bisected, and calculated the *P* for trend in order to verify the results of AG as the continuous variable. Modeling was performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). *P*-values less than 0.05 (two-sided) were considered statistically significant.

Results

Patients Characteristics

The detailed process of patients selection is shown in Figure 1. Initially, 46,476 patients with 61,532 admissions to the ICU were selected from the MIMIC-III database. In total, 3,044 patients fulfilled the diagnostic criteria of DIC. Of these, 2,654 patients fulfilled the inclusion criteria mentioned above and were enrolled in this study. Table 1 lists the

baseline characteristics of the included patients. Their average age was 60.55 ± 16.23 years old and 59.2% were male. The 2,654 patients were divided into four groups using the quartiles of AG level. There were 642 patients in the 4.00–11.00 mmol/L group, 540 patients in the 12.00–13.00 mmol/L group, 787 patients in the 14.00–17.00 mmol/L group, and 685 patients in the 18.00–48.00 mmol/L group.

The Association Between AG and All-Cause Mortality

Both univariate and multivariate Cox proportional-hazards regression models were introduced to evaluate the associations between AG and in-hospital, 30-day, and 90-day mortality of DIC patients (Table 2). Meanwhile, we show the non-adjusted and adjusted models in Table 2. We found that higher AG was associated with increased risk of in-hospital mortality (non-adjusted model: HR=1.08, 95% CI=1.07–1.10, $P<0.0001$; minimally-adjusted model: HR=1.09, 95% CI=1.07–1.10, $P<0.0001$; fully-adjusted model: HR=1.05, 95% CI=1.04–1.07, $P<0.0001$), 30-day mortality (non-adjusted model: HR=1.10, 95% CI=1.08–1.11,

Table 1 Baseline Characteristics of Participants

AG, mmol/L	Group 1 (4.00–11.00)	Group 2 (12.00–13.00)	Group 3 (14.00–17.00)	Group 4 (18.00–48.00)	P-value	P-value*
Number	642	540	787	685		
Age, mean (SD), years	61.03 (15.78)	61.51 (16.79)	60.50 (16.46)	59.42 (15.91)	0.123	0.073
Weight, mean (SD), kg	77.78 (18.99)	80.04 (19.95)	81.20 (21.17)	83.15 (23.38)	<0.001	0.001
Sex, n (%)						
Female	270 (42.06%)	214 (39.63%)	345 (43.84%)	253 (36.93%)	0.047	-
Male	372 (57.94%)	326 (60.37%)	442 (56.16%)	432 (63.07%)		
Ethnicity, n (%)						
White	451 (70.25%)	379 (70.19%)	532 (67.60%)	445 (64.96%)	0.002	-
Black	27 (4.21%)	52 (9.63%)	56 (7.12%)	53 (7.74%)		
Hispanic	38 (5.92%)	20 (3.70%)	28 (3.56%)	25 (3.65%)		
Asian	22 (3.43%)	17 (3.15%)	27 (3.43%)	22 (3.21%)		
Others	104 (16.20%)	72 (13.33%)	144 (18.30%)	140 (20.44%)		
Causes of DIC						
Sepsis	307 (47.82%)	275 (50.93%)	458 (58.20%)	467 (68.18%)	<0.001	-
Cardiovascular diseases	164 (25.55%)	106 (19.63%)	108 (13.72%)	57 (8.32%)		
Trauma	29 (4.52%)	33 (6.11%)	46 (5.84%)	35 (5.11%)		
Others	142 (22.12%)	126 (23.33%)	175 (22.24%)	126 (18.39%)		
Scoring systems, mean (SD)						
SOFA	6.57 (2.71)	6.90 (2.95)	7.88 (3.48)	10.26 (4.10)	<0.001	<0.001
SAPSII	37.83 (13.18)	39.26 (13.80)	42.87 (14.90)	52.37 (17.08)	<0.001	<0.001
JAAM-DIC	4.72 (0.74)	4.79 (0.79)	4.93 (0.94)	5.12 (1.04)	<0.001	<0.001
SIRS	2.92 (0.94)	3.04 (0.94)	3.15 (0.88)	3.30 (0.82)	<0.001	<0.001
Comorbidities, n (%)						
Hypertension	286 (44.55%)	230 (42.59%)	336 (42.69%)	270 (39.42%)	0.292	-
COPD	109 (16.98%)	77 (14.29%)	128 (16.26%)	80 (11.68%)	0.028	-
Diabetes	113 (17.60%)	119 (22.04%)	165 (20.97%)	176 (25.69%)	0.004	-
Renal failure	49 (7.63%)	57 (10.58%)	111 (14.10%)	120 (17.52%)	<0.001	-
Liver disease	203 (31.62%)	159 (29.50%)	282 (35.83%)	330 (48.18%)	<0.001	-
MBP, mean (SD), mmHg	76.68 (9.93)	77.61 (10.80)	77.90 (11.38)	76.93 (12.37)	0.145	0.097

Temperature, mean (SD), °C	36.87 (0.63)	36.97 (0.72)	36.90 (0.71)	36.71 (0.86)	<0.001	<0.001
SPO ₂ , mean (SD), %	97.61 (2.26)	97.56 (2.14)	97.19 (2.29)	96.39 (4.96)	<0.001	<0.001
Laboratory parameters, mean (SD)						
Hemoglobin, g/dL	9.51 (1.93)	9.91 (2.04)	9.95 (2.32)	10.31 (2.37)	<0.001	<0.001
Hematocrit, %	27.83 (5.68)	28.99 (5.89)	29.16 (6.96)	30.61 (7.09)	<0.001	<0.001
RDW, %	15.73 (2.38)	16.05 (2.68)	16.25 (2.70)	16.42 (2.79)	<0.001	<0.001
Platelet, 10 ⁹ /L	88.06 (70.73)	89.53 (71.87)	99.30 (96.94)	118.63 (139.91)	<0.001	<0.001
WBC, 10 ⁹ /L	10.05 (17.82)	9.65 (12.01)	12.72 (26.68)	13.60 (15.69)	<0.001	<0.001
APTT, seconds	45.05 (25.22)	42.89 (23.54)	44.11 (25.72)	50.58 (29.90)	<0.001	<0.001
PT, seconds	17.17 (4.52)	16.67 (3.97)	17.56 (6.96)	20.15 (10.49)	<0.001	<0.001
PT-INR	1.67 (0.62)	1.76 (3.08)	1.76 (0.94)	2.13 (1.36)	<0.001	<0.001
Creatinine, mEq/L	0.88 (0.52)	1.11 (1.00)	1.52 (1.22)	2.57 (2.33)	<0.001	<0.001
Urea nitrogen, mg/dL	19.98 (13.25)	22.94 (14.29)	30.36 (20.67)	46.72 (35.80)	<0.001	<0.001
Glucose, mg/dL	140.14 (63.39)	138.80 (54.79)	152.98 (71.68)	167.25 (97.83)	<0.001	<0.001
Potassium, mmol/L	4.15 (0.82)	4.05 (0.77)	4.12 (0.78)	4.39 (0.92)	<0.001	<0.001
Sodium, mmol/L	136.81 (5.34)	138.18 (4.93)	137.61 (5.43)	138.03 (6.26)	<0.001	<0.001
Bicarbonate, mg/dL	23.99 (3.80)	23.02 (3.75)	21.36 (4.22)	17.30 (4.90)	<0.001	<0.001
Treatments, n (%)						
CRRT	13 (2.02%)	19 (3.52%)	63 (8.01%)	131 (19.12%)	<0.001	-
Vasopressor drugs	315 (49.07%)	255 (47.22%)	369 (46.89%)	439 (64.09%)	<0.001	-
Mechanical ventilation	432 (67.29%)	358 (66.30%)	502 (63.79%)	509 (74.31%)	<0.001	-
In-hospital mortality, n (%)	91 (14.17%)	97 (17.96%)	174 (22.11%)	311 (45.40%)	<0.001	-
30-day mortality, n (%)	97 (15.11%)	98 (18.15%)	197 (25.03%)	314 (45.84%)	<0.001	-
90-day mortality, n (%)	138 (21.50%)	146 (27.04%)	251 (31.89%)	356 (51.97%)	<0.001	-

Note: P* indicated U-test.

Abbreviations: AG, anion gap; SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II; JAAMI, Japanese Association of Acute Medicine; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; COPD, chronic obstructive pulmonary disease; MBP, mean blood pressure; RDW, red blood cell distribution; WBC, white blood cell; APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; CRRT, continuous renal replacement therapy.

Table 2 Univariate and Multivariate Results by Cox Regression

Exposure	Non-Adjusted Model HR, 95% CI, P	Minimally-Adjusted Model HR, 95% CI, P	Fully-Adjusted Model HR, 95% CI, P
In-hospital mortality			
Anion gap	1.08 (1.07–1.10) <0.0001	1.09 (1.07–1.10) <0.0001	1.05 (1.04–1.07) <0.0001
Anion gap (quartiles)			
Q1	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Q2	1.19 (0.90–1.59) 0.2268	1.17 (0.88–1.56) 0.2719	1.07 (0.80–1.44) 0.6444
Q3	1.32 (1.02–1.70) 0.0336	1.32 (1.02–1.70) 0.0340	1.02 (0.78–1.33) 0.8943
Q4	2.92 (2.31–3.69) <0.0001	3.00 (2.37–3.79) <0.0001	1.83 (1.38–2.43) <0.0001
P for trend	1.47 (1.37–1.59) <0.0001	1.49 (1.38–1.61) <0.0001	1.22 (1.11–1.34) <0.0001
30-day mortality			
Anion gap	1.10 (1.08–1.11) <0.0001	1.10 (1.09–1.11) <0.0001	1.06 (1.04–1.07) <0.0001
Anion gap (quartiles)			
Q1	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Q2	1.22 (0.92–1.62) 0.1586	1.22 (0.92–1.62) 0.1635	1.06 (0.79–1.41) 0.6963
Q3	1.74 (1.37–2.22) <0.0001	1.76 (1.38–2.24) <0.0001	1.23 (0.95–1.59) 0.1122
Q4	3.92 (3.12–4.92) <0.0001	4.04 (3.22–5.08) <0.0001	1.97 (1.49–2.60) <0.0001
P for trend	1.64 (1.52–1.77) <0.0001	1.66 (1.54–1.79) <0.0001	1.26 (1.15–1.39) <0.0001
90-day mortality			
Anion gap	1.09 (1.08–1.10) <0.0001	1.09 (1.08–1.10) <0.0001	1.05 (1.03–1.07) <0.0001
Anion gap (quartiles)			
Q1	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Q2	1.29 (1.02–1.63) 0.0306	1.29 (1.02–1.63) 0.0320	1.15 (0.91–1.46) 0.2496
Q3	1.59 (1.29–1.96) <0.0001	1.61 (1.31–1.98) <0.0001	1.15 (0.92–1.43) 0.2170
Q4	3.27 (2.69–3.99) <0.0001	3.39 (2.78–4.13) <0.0001	1.73 (1.35–2.20) <0.0001
P for trend	1.50 (1.41–1.60) <0.0001	1.52 (1.43–1.62) <0.0001	1.18 (1.09–1.28) <0.0001

Notes: Non-adjusted model: no covariates were adjusted for. Minimally-adjusted model: we only adjusted for age and sex. Fully-adjusted model: we adjusted for age, sex, ethnicity, causes of DIC, SOFA score, SAPSII score, renal failure, CRRT, vasopressor drugs, mechanical ventilation, APTT, PT-INR, bicarbonate, creatinine, potassium, urea nitrogen, and RDW.

Abbreviations: CI, confidence interval; Ref, reference.

$P < 0.0001$; minimally-adjusted model: HR=1.10, 95% CI=1.09–1.11, $P < 0.0001$; fully-adjusted model: HR=1.06, 95% CI=1.04–1.07, $P < 0.0001$), and 90-day mortality (non-adjusted model: HR=1.09, 95% CI=1.08–1.10, $P < 0.0001$; minimally-adjusted model: HR=1.09, 95% CI=1.08–1.10, $P < 0.0001$; fully-adjusted model: HR=1.05, 95% CI=1.03–1.07, $P < 0.0001$). For the purpose of sensitivity analysis, we also handled AG as a categorical variable (quartile), and found the same trend (Table 2).

The Results of the Non-Linear Relationship

We did not find an obvious non-linear relationship between AG and in-hospital mortality (Figure 2A), 30-day mortality (Figure 2B), or 90-day mortality (Figure 2C) using the generalized additive model and the smooth curve fitting. The

association between AG and all-cause mortality of DIC patients was nearly linear.

Subgroup Analyses

Table 3 displays the results of subgroup analyses regarding the outcome of 30-day mortality. The tests for interactions were not statistically significant for sex, age, care unit, causes of DIC, COPD, diabetes, CRRT use, vasopressor drugs use, or mechanical ventilation use (P for interaction=0.7543, 0.2294, 0.4727, 0.1526, 0.3802, 0.2487, 0.7379, 0.9986, and 0.2795). The test for interactions were significant for renal failure (P for interaction=0.0310). The positive association between AG and 30-day mortality was more obvious in DIC patients with renal failure (HR=1.10, 95% CI=1.06–1.14, $P < 0.0001$) than those without renal failure (HR=1.05, 95% CI=1.03–1.07, $P < 0.0001$).

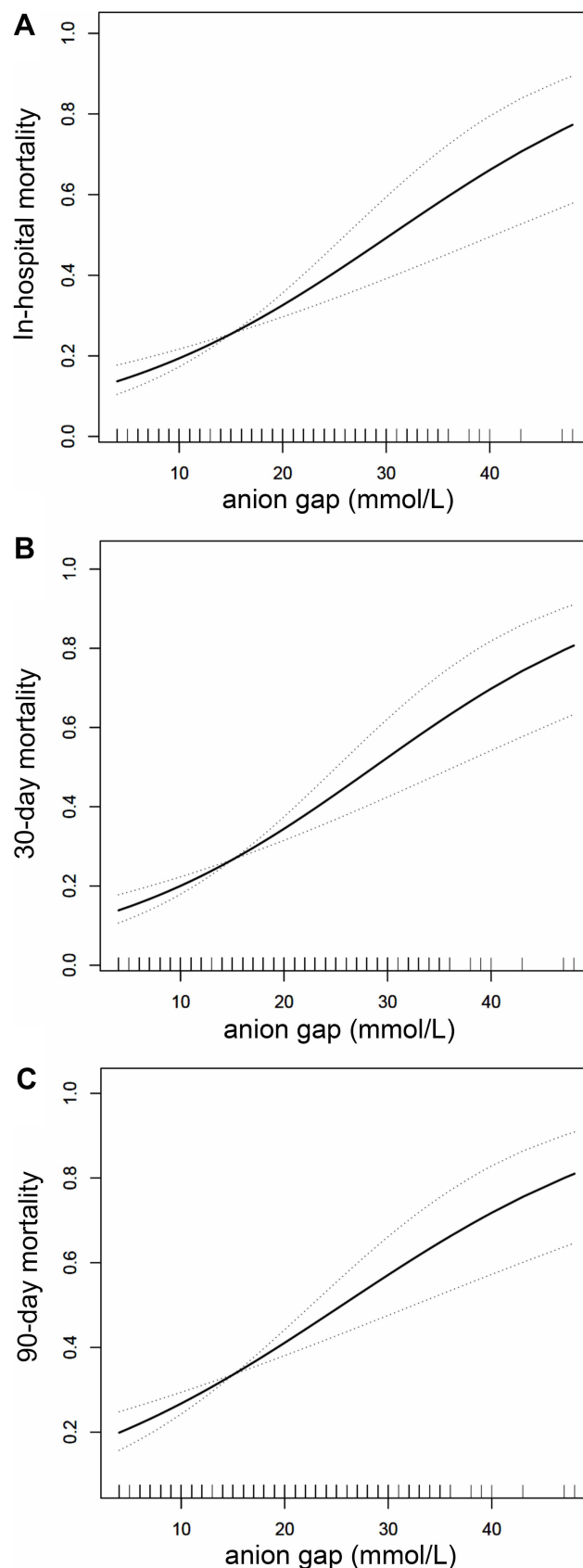


Figure 2 Non-linear relationship between AG and in-hospital mortality (A), 30-day mortality (B), and 90-day mortality (C) of DIC patients.

Discussion

DIC is a critical illness which always results in short-term mortality. So, we introduced the in-hospital and 30-day mortality as our outcomes. Moreover, we also introduced the 90-day mortality, a middle-long outcome in this paper, which can more comprehensively evaluate the relationship between AG and all-cause mortality in DIC patients. This study demonstrated that in-hospital, 30-day, and 90-day mortality of DIC patients was positively correlated with AG level. This indicates that high AG is an independent-death risk factor of DIC patients, which means down-regulating AG may be of benefit to DIC. This may provide an important theoretical basis for the treatment of DIC.

AG represents the concentration of unmeasured anions in serum, which is calculated by the formula $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$.¹⁰ AG is an easily available laboratory indicator and is not influenced by acute respiratory changes. Serum AG can find subtle changes in serum electrolytes and the degree of metabolic acidosis and is a more sensitive indicator of metabolic acidosis.¹¹ Many serious diseases are most commonly accompanied with metabolic acidosis and an elevated AG level.^{10,11} Several clinical studies have evaluated the association between serum AG and the clinical outcomes in various diseases.^{21,22} Cheng et al²¹ demonstrated that increased AG values were associated with elevated risk of all-cause mortality in critically ill patients with acute kidney injury. Sahu et al²² assessed the relationship between AG and in-hospital outcomes among consecutive acute myocardial infarction patients. They found that the presence of an initial anion gap acidosis was associated with the risk of death (odds ratio=4.2, 95% confidence interval=2.3–7.5, $P<0.001$), independent of other data available at the time of admission.²² Our study further confirmed the positive relationship between a high AG level and increased all-cause mortality in DIC patients.

In order to prove the usefulness of AG for prognosis in DIC patients, we also evaluated the association between the AG and mortality in non-DIC patients. In total, 36,619 patients of the MIMIC-III database were enrolled in the non-DIC cohort. The in-hospital, 30-day, and 90-day all-cause mortality were positively correlated with AG in the non-DIC patients also. Detailed data is displayed in [Supplementary Table 1](#). The results were similar to the DIC cohort. There did not exist a more obvious positive relationship between AG and all-cause mortality in DIC patients than in non-DIC patients. This indicated that AG

Table 3 Subgroup Analysis of the Relationship Between AG and 30-Day Mortality

Characteristic	Number of Patients	HR (95% CI)	P-value	P for Interaction
Sex				
Female	1,050	1.05 (1.03–1.08)	<0.0001	0.7543
Male	1,530	1.06 (1.04–1.08)	<0.0001	
Age (years)				
<60	1,226	1.06 (1.04–1.09)	<0.0001	0.2294
≥60	1,354	1.04 (1.02–1.07)	0.0005	
Care unit				
CCU	196	1.02 (0.93–1.11)	0.7084	0.4727
CSRU	476	1.14 (1.03–1.25)	0.0084	
MICU	1,268	1.05 (1.02–1.07)	0.0004	
SICU	386	1.05 (1.00–1.10)	0.0469	
TSICU	263	1.07 (1.00–1.13)	0.0505	
Causes of DIC				
Sepsis	1,465	1.04 (1.02–1.06)	0.0003	0.1526
Cardiovascular diseases	424	1.11 (1.02–1.21)	0.0126	
Trauma	140	1.09 (1.00–1.19)	0.0582	
Others	551	1.09 (1.04–1.15)	0.0004	
COPD				
No	2,193	1.05 (1.03–1.07)	<0.0001	0.3802
Yes	387	1.08 (1.03–1.13)	0.0028	
Diabetes				
No	2,091	1.05 (1.03–1.07)	<0.0001	0.2487
Yes	561	1.08 (1.04–1.12)	0.0003	
Renal failure				
No	2,254	1.05 (1.03–1.07)	<0.0001	0.0310
Yes	326	1.10 (1.06, 1.14)	<0.0001	
CRRT use				
No	2,359	1.06 (1.03–1.08)	<0.0001	0.7379
Yes	221	1.05 (1.01–1.08)	0.0053	
Vasopressor drugs use				
No	1,229	1.05 (1.02–1.09)	0.0023	0.9986
Yes	1,351	1.05 (1.03–1.08)	<0.0001	
Mechanical ventilation use				
No	810	1.07 (1.04– 1.11)	0.0001	0.2795
Yes	1,770	1.05 (1.03–1.07)	<0.0001	

Abbreviations: CCU, Coronary Care Unit; CSRU, Cardiac Surgery Recovery Unit; MICU, Medical Intensive Care Unit; SICU, Surgical Intensive Care Unit; TSICU, Trauma/Surgical Intensive Care Unit; DIC, disseminated intravascular coagulation; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy.

is positively related with all-cause mortality of nearly all of the critically ill patients. Further research is needed to clarify this phenomenon.

Subgroup analysis is extremely important for a scientific study.²³ In the present study, we conducted detailed subgroup analyses using sex, age, care unit, causes of DIC, COPD, diabetes, renal failure, CRRT use, vasopressor drugs use and mechanical ventilation use as

stratification variables. The positive association between AG and 30-day mortality was more obvious in DIC patients with renal failure than without renal failure. The possible reason is DIC patients with renal failure are more likely to complicate with metabolic acidosis and higher AG.

It should be noted that, regarding the diagnosis of DIC, there exists three main criteria recommend by different

associations, including the Scientific and Standardization Committee (SSC)/International Society of Thrombosis and Haemostasis (ISTH), JAAM, and Japanese Ministry Health, Labour and Welfare (JMHLW).²⁴ A previous study compared the different diagnostic criteria, and found the JAAM scoring system was the most sensitive one.²⁵ So, we introduced the JAAM scoring system in this study. However, despite the JAAM scoring system having a high sensitivity in the diagnosis for DIC patients, its specificity was relatively low and it was useful mainly for sepsis.²⁶ So, we have enrolled non-DIC patients in our study.

In 2015, Kury et al²⁷ sought to reproduce, as a computational retrospective study in the MIMIC-II database, a large prospective clinical study.²⁸ They identified 2,257 eligible patients in MIMIC-II and found their results remarkably agreed with the original prospective study. This further demonstrated that the results drawn from a retrospective study regarding DIC in the MIMIC database were reliable.

Our work has a number of strengths. First, our studies were the first research series regarding the mortality risk factors of DIC patients. This study focused on AG and was the first to investigate the relationship between AG and the mortality in DIC patients. Second, this study enrolled 2,654 patients, which is a very large sample size for the clinical study of DIC. Third, we explored both the linear and non-linear relationship. Fourth, we analyzed the exposure variable (AG) as not only a continuous variable but also a categorical variable, and calculated the hazard ratio using binary logistic regression models. Such a method can minimize the incidence of contingency in statistical analysis, and enhance the reliability of the final results.

There are some limitations to our study. First, some variables, including FDP, D-dimer, C-reactive protein, lactate, pH, thrombin, antithrombin, thrombin-antithrombin complex, plasmin-alpha 2-antiplasmin complex, procalcitonin, and the severity of the causes of DIC, may also be related to the prognosis of DIC patients. However, because of a high percentage of missing data or unable obtaining for these variables, we could not include these variables in our data analyses. Second, regarding treatment, we only analyzed CRRT, mechanical ventilation, and vasopressor. The prognosis of DIC patients may also be influenced by other therapeutic measures, such as plasma transfusion, cryoprecipitation transfusion, and platelet transfusion. However, we could not obtain these data from the MIMIC-III database. Thirdly, as a single-center retrospective study,

selection bias was inevitable; therefore, multicenter registry, prospective studies are needed to confirm this findings.

Conclusion

Serum AG is positively related with all-cause mortality in DIC patients.

Data Sharing Statement

The datasets are publicly available in the <https://mimic.physionet.org/>.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

References

1. Squizzato A, Hunt BJ, Kinasevitz GT, et al. Supportive management strategies for disseminated intravascular coagulation. An international consensus. *Thromb Haemost.* 2016;115(5):896–904.
2. Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. *Nat Rev Dis Prim.* 2016;2:16037.
3. Iba T, Levy JH, Warkentin TE. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. *J Thromb Haemost.* 2019;17(11):1989–1994.
4. Costello RA, Nehring SM. Disseminated Intravascular Coagulation. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing LLC.; 2020.
5. Gando S, Otomo Y. Local hemostasis, immunothrombosis, and systemic disseminated intravascular coagulation in trauma and traumatic shock. *Crit Care.* 2015;19(1):72.
6. Shirahata A, Shirakawa Y. [New approach to the diagnosis of disseminated intravascular coagulation in childhood]. *Nihon Rinsho.* 1993;51(1):61–66. [Japanese]
7. Crimi E, Taccone FS, Infante T, Scolletta S, Crudele V, Napoli C. Effects of intracellular acidosis on endothelial function: an overview. *J Crit Care.* 2012;27(2):108–118.
8. Iba T, Levi M, Levy JH. Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. *Semin Thromb Hemost.* 2020;46(1):89–95.
9. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol.* 2007;2(1):162–174.
10. Jones BJ, Twomey PJ. The anion gap revisited. *Int J Clin Pract.* 2009;63(10):1409–1412.
11. Brubaker RH, Vashisht R, Meseha M. High Anion Gap Metabolic Acidosis. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing LLC.; 2020.
12. Glasmacher SA, Stones W. Anion gap as a prognostic tool for risk stratification in critically ill patients - a systematic review and meta-analysis. *BMC Anesthesiol.* 2016;16(1):68.
13. Yang SW, Zhou YJ, Zhao YX, et al. The serum anion gap is associated with disease severity and all-cause mortality in coronary artery disease. *J Geriatr Cardiol.* 2017;14(6):392–400.

14. Abramowitz MK, Hostetter TH, Melamed ML. The serum anion gap is altered in early kidney disease and associates with mortality. *Kidney Int.* **2012**;82(6):701–709.
15. Chen Q, Chen Q, Li L, et al. Serum anion gap on admission predicts intensive care unit mortality in patients with aortic aneurysm. *Exp Ther Med.* **2018**;16(3):1766–1777.
16. Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data.* **2016**;3:160035.
17. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. *Crit Care.* **2019**;23(1):374.
18. Jacome T, Tatum D. Systemic Inflammatory Response Syndrome (SIRS) score independently predicts poor outcome in isolated traumatic brain injury. *Neurocrit Care.* **2018**;28(1):110–116.
19. Capuzzo M, Moreno RP, Le Gall JR. Outcome prediction in critical care: the simplified acute physiology score models. *Curr Opin Crit Care.* **2008**;14(5):485–490.
20. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med.* **2006**;34(3):625–631.
21. Cheng B, Li D, Gong Y. Serum anion gap predicts all-cause mortality in critically ill patients with acute kidney injury: analysis of the mimic-iii database. *Dis Mark.* **2020**;2020:6501272.
22. Sahu A, Cooper HA, Panza JA. The initial anion gap is a predictor of mortality in acute myocardial infarction. *Coron Artery Dis.* **2006**;17(5):409–412.
23. Vandembroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med.* **2007**;4(10):e297.
24. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *J Intensive Care.* **2014**;2(1):15.
25. Kury FS, Cimino JJ. Computationally comparing and analyzing all published scoring systems for diagnosis of disseminated intravascular coagulation. *Stud Health Technol Inform.* **2015**;216:956.
26. Gando S, Wada H, Asakura H, et al. Evaluation of new Japanese diagnostic criteria for disseminated intravascular coagulation in critically ill patients. *Clin Appl Thromb Hemost.* **2005**;11(1):71–76.
27. Kury FS, Huser V, Cimino JJ. Reproducing a prospective clinical study as a computational retrospective study in MIMIC-II. *AMIA Annu Symp Proc.* **2015**;2015:804–813.
28. Gando S, Saitoh D, Ogura H, et al. A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis. *Crit Care.* **2013**;17(3):R111.

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