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RESEARCH ARTICLE

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The association between serum anion gap and all-cause mortality of unselected adult patients: A retrospective cohort study of >20,000 patients

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Abstract

Background: Even though the serum anion gap (AG) is frequently measured in clinical practice, there is not much research that has examined long-term mortality in unselected adult patients. Our study's objective was to investigate how serum anion gap levels could be used to predict death in unselected participants.

Methods: The relationship between baseline serum AG levels and short-, intermediate-, and long-term all-cause mortality in unselected adult patients is examined using the Cox proportional risk analysis, smoothed curve fitting, subgroup analysis, and Kaplan–Meier survival curves.

Results: After screening the database using the appropriate method, a total of 26,270 patients were enrolled in our study for the final data analysis. Our study used smoothed curve fit plots and COX proportional risk regression models incorporating cubic spline functions to evaluate the association between AG levels and all-cause mortality in a non-selected population, and the results indicated a non-linear relationship. In the fully adjusted model, we found that AG levels were positively associated with 30-day, 90-day, 365-day, and 4-year all-cause mortality in unselected adult patients with HRs of 1.08 95% CIs (1.06, 1.09); 1.08 95% CIs (1.06, 1.09); 1.08 95% CIs (1.07, 1.08); 1.07 95% CIs (1.06, 1.07).

Conclusion: Serum anion gap levels were positively correlated with all-cause mortality in unselected adult patients, with increasing levels of serum anion gap increasing patient mortality.

KEYWORDS
all-cause mortality, cox proportional hazards regression, serum anion gap, unselected adult patients

1 | INTRODUCTION

The anion gap (AG) represents the sum of unmeasured negatively charged substances in the serum and includes mainly inorganic acids (e.g. phosphoric acid) and organic acids (e.g. acetoacetic acid, lactic acid, pyruvic acid, etc.). In clinical practice, the standard anion gap method is more commonly used than physicochemical methods to diagnose and guide common critical illnesses. High-anion gap

metabolic acidosis is particularly common in clinical practice, and elevated standard anion gaps are frequently observed in clinical practice.[1]

Acid–base disorders are common in critically ill patients. It is well known that persistent acid–base imbalances can reflect the severity of diseases and are associated with a poor prognosis.[2] Serum AG is one of the most commonly used biomarkers and provides important clues for the diagnosis and prognosis of various diseases.[3] Pulmonary and renal dysfunction, especially during cardiac and respiratory arrests and cardiopulmonary resuscitation, can be easily complicated by arterial blood gas abnormalities and acid–base disorders, which in turn can affect the function of vital organs. This can be a direct cause of death in critically ill patients.[4,5]

In recent years, serum anion gap (AG) has been of clinical value in acute kidney injury, cerebral infarction, acute pancreatitis, cardiogenic shock, diffuse intravascular coagulation, coronary artery disease, acute myocardial infarction, etc.[6–14] Numerous researchers have found that the higher the serum AG value, the higher the mortality rate and the worse the prognosis of patients.[6–14] Further studies have found that serum AG is of good clinical value in the identification of critical illnesses and the assessment of prognosis.[15,16] However, there are few studies on the prognosis of unselected adult patients and even fewer studies on the serum anion gap and long-term mortality. This study aims to investigate the relationship between serum AG and short-, medium-, and long-term all-cause mortality in unselected adult patients through a retrospective cohort study, to guide clinical application.

2 | MATERIALS AND METHOD

2.1 | Data source

The Massachusetts Institute of Technology, Beth Israel Deaconess Medical Center's Institutional Review Boards, and Philips Healthcare collaborated to create the Critical Care III Version 1.4 database. The Medical Information Intensive Care Center (MIMIC-III) database was used to compile the necessary information (version 1.4).[17,18] The MIMIC-III intensive care database contains clinical data on more than 60,000 ICU patient admissions in critical care, including 38,645 adults and 7875 newborns. This data includes basic information, symptoms, laboratory testing, and treatments. The most recent version of MIMIC III was updated in 2016.[17] All researchers who intend to utilize this database must first pass the requisite ethics exams before being granted access to it by the US National Institutional Review Board, which has approved the database. This study has been given CITI designation and approval (Record ID: 40171761).

2.2 | Study design

Our retrospective cohort study involved 26,270 unselected adult patients. Based on knowledge from multicenter clinical studies, the clinical data from these individuals was typical of regional critical care. Baseline serum anion gap levels were used as independent target variables to investigate the association between serum anion gap levels and short-, medium-, and long-term all-cause mortality in unselected adult patients.

2.3 | Study sample

Our study population was made up of unselected adult patients. Patients who met the inclusion criteria in the MIMIC-III database were used as study subjects. Patients must meet the following inclusion criteria: (1) be older than 18; (2) be included in the MIMIC-III database (which has information on more than 50,000 patients); and (3) have a record of serum anion gap upon admission.

We excluded (1) patients with missing baseline serum anion gap values at ICU entry, (2) patients under the age of 18, and (3) patients with Dbsource = metavision (Figure 1).

2.4 | Variables

All data in this study was extracted by structured query language (SQL), including general information (gender, age, admission and discharge time, time of death, etc.), comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease (COPD), etc.), laboratory tests (hemoglobin, WBC, PLT, APTT, etc.), criticality scores, and the number of patients in the study. Our study variable was the serum anion gap level at admission, and the primary outcome indicator in this study were the 30-day, 90-day, 365-day, and 4-year all-cause mortality rates.

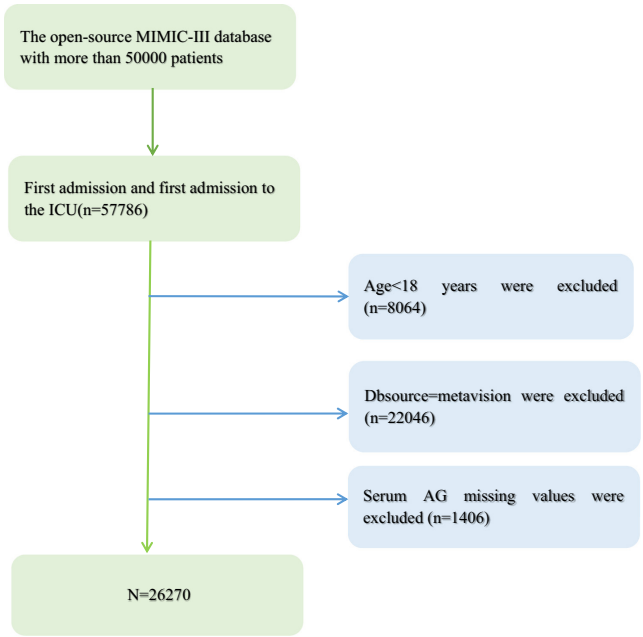

FIGURE 1 Flowchart of patient selection.

2.5 | Statistical analysis

We split the patients into two groups based on whether they survived or not, determined the contributing factors, and analyzed the outcomes. We performed correlation analyses to determine whether serum anion gap levels were associated with all-cause mortality after reporting and controlling covariates for these independent risk factors.

While continuous variables are provided as mean, standard deviation (SD), or median (range), categorical variables are shown as numbers and percentages (skewed distribution).[19] The $\chi 2$ test (for categorical variables), one-way ANOVA test (for normal distribution), or Kruskal-Wallis H test (for skewed distribution) were used to determine differences between various serum anion gaps (quartiles). To examine the relationship between serum anion gap and all-cause mortality, three different models were developed using univariate and multivariate Cox proportional hazards regression models, including unadjusted models (no adjustment for covariates), minimally adjusted models (adjusting for sociodemographic variables only), and fully adjusted models (adjusting for covariates in Table 1). The effect sizes and 95% confidence intervals were recorded.

Because methods based on Cox proportional hazards regression models are widely criticized for failing to handle non-linear models, curvilinear model selection and smoothed curve fitting were utilized to address the non-linearity between serum anion gap and all-cause mortality (penalized spline method).

If non-linearity was discovered, the inflection point was first identified using a recursive method, and then two-piece Cox proportional hazards regression models were constructed on either side of the inflection point. All analyses were conducted using the statistical software programs R (http://www.r-project.org, R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). A two-sided p-value of less than 0.05 was utilized to determine statistical significance.[20]

3 | RESULTS

3.1 | Baseline characteristics

In accordance with the inclusion and exclusion criteria, a total of 26,270 patients were included in the study, with 14,768 (56.2%) males and 11,502 (43.8%) females. The patients' mean age is 74.5 years. The baseline characteristics of these chosen people, including population characteristics, vital signs, laboratory results, physiological scores, and co-morbidities, are objectively displayed in Table 1. The procedure we followed to choose the patients is depicted in the flow chart. Groups were arranged according to quartile spacing as Q1 (AG < 12 mmol /L, $n = 5385$), Q2 (12 mmol /L ≤ AG < 14 mmol /L, $n = 6871$), Q3 (14 mmol /L ≤ AG < 16 mmol /L, $n = 6374$) and Q4 (AG≥16 mmol /L, $n = 7640$). After comparing the baseline data of the four groups of patients, the results of the study showed statistically significant differences in all indicators between the different AG groups. ($p < 0.05$).

Participants with the highest group of serum anion gap(mmol/L) (serum AG≥16 mmol /L) showed higher values for age, heart rate, respiratory rate, creatinine, glucose, hematocrit, platelet, potassium, Bun, WBC, RDW, SOFA, SAPS II, EVCI, and lower values for SPO2, bicarbonate. Congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation, hypertension, uncomplicated diabetes, complicated diabetes, renal failure, liver disease, coagulopathy, and deficiency anemias were more common in this group of individuals in contrast with those in the other subgroups.

3.2 | Results of the cox proportional hazard models

Multiple regression analysis (Table 2) was performed based on the independent variables having variability in all-cause mortality at 30 days, 90 days, 365 days, and 4 years, taking into account the actual situation of the patients. We examined the independent impact of serum AG levels on all-cause mortality in unselected adult patients using three different models. Table 2 presents the findings as effect sizes (HRs for the risk ratios) and 95% confidence intervals.

The crude model's (unadjusted model) HRs for 30-day all-cause mortality had a value of 1.14 (1.14, 95% CIs (1.14, 1.15)), implying an increased risk of 30-day all-cause mortality of 14%, ceteris paribus, a risk increase of 13% for 90-day all-cause mortality, an increased risk of 11% for 365-day all-cause mortality, and a 9% increased risk of 4-year all-cause mortality.

Model 1 (minimally-adjusted model) was defined by the relationship between serum AG levels and mortality risk in the minimally-adjusted model, where the HRs for 30-day all-cause mortality was 1.15 (1.15, 95% CIs (1.14, 1.16)), implying a 15% increase in the risk of 30-day all-cause mortality, ceteris paribus, a 13% increase in the risk of 90-day all-cause mortality, an 11% increase in the risk of 365-day all-cause mortality, and a 9% increase in the risk of 4-year all-cause mortality.

Model 2 (fully adjusted model) is characterized by the association between the serum AG levels linked with mortality risk in the fully adjusted model. The HRs for 30-day all-cause mortality is 1.08 (1.08, 95% CIs (1.06, 1.09)), reflecting an 8% increase in risk for 30-day all-cause mortality. The risk of 90-day all-cause mortality increased by 8%, the risk of 365-day all-cause mortality increased by 8%, and the risk of 4-year all-cause mortality increased by 7% as a result.

Using the G1 group as the reference group, in the fully adjusted model, the HRs for G2, G3, and G4 increased from 1.18 to 1.85 for 30-day mortality, from 1.13 to 1.69 for 90-day mortality, from 1.15 to 1.70 for 365-day mortality, and from 1.13 to 1.58 for 4-year mortality.

We conducted sensitivity analyses for mortality at 30 days, 90 days, 365 days, and 4 years, treating AG levels as categorical variables divided into four groups. We found that the results

TABLE 1 Participant's Baseline Characteristics ($N = 26,270$).

Anion gap (mmol/L) groups	Total	G1(<12)	G2(> = 12, <14)	G3(> = 14, <16)	G4(> = 16)	*p*-Value
Number, *n*	26,270	5385	6871	6374	7640	
Age (years)	74.5 (54.9) 65.7 (52.0–77.8)	70.9 (47.8) 64.6 (52.1–76.8)	74.0 (54.2) 65.5 (51.9–77.7)	75.5 (56.0) 66.2 (52.4–78.2)	76.6 (58.9) 66.3 (51.7–78.4)	<0.001
Gender, *n* (%)						
Male	14,768 (56.2%)	3108 (57.7%)	3914 (57.0%)	3572 (56.0%)	4174 (54.6%)	0.002
Female	11,502 (43.8%)	2277 (42.3%)	2957 (43.0%)	2802 (44.0%)	3466 (45.4%)	
Admission type, *n* (%)						
Emergency	20,557 (78.3%)	3679 (68.3%)	5229 (76.1%)	5124 (80.4%)	6525 (85.4%)	<0.001
Elective	5027 (19.1%)	1564 (29.0%)	1472 (21.4%)	1083 (17.0%)	908 (11.9%)	
Urgent	686 (2.6%)	142 (2.6%)	170 (2.5%)	167 (2.6%)	207 (2.7%)	
Insurance, *n* (%)						
Medicare	8472 (32.2%)	1941 (36.0%)	2406 (35.0%)	2042 (32.0%)	2083 (27.3%)	<0.001
Private	2123 (8.1%)	431 (8.0%)	526 (7.7%)	505 (7.9%)	661 (8.7%)	
Medicaid	14,687 (55.9%)	2828 (52.5%)	3680 (53.6%)	3575 (56.1%)	4604 (60.3%)	
Government	658 (2.5%)	126 (2.3%)	180 (2.6%)	163 (2.6%)	189 (2.5%)	
Self Pay	330 (1.3%)	59 (1.1%)	79 (1.1%)	89 (1.4%)	103 (1.3%)	
Vital signs						
Heart rate (bpm)	85.5 ± 15.7	84.5 ± 14.6	84.0 ± 15.1	85.1 ± 15.9	88.0 ± 16.7	<0.001
SBP (mmHg)	119.3 ± 17.4	117.5 ± 15.4	119.7 ± 16.5	120.6 ± 17.2	119.2 ± 19.6	<0.001
DBP (mmHg)	59.4 ± 10.8	58.6 ± 9.6	59.4 ± 10.0	60.1 ± 10.9	59.5 ± 12.0	<0.001
respiratory rate (bpm)	18.8 ± 4.1	17.9 ± 3.7	18.4 ± 3.9	18.8 ± 4.0	19.6 ± 4.4	<0.001
Temperature (°C)	36.9 ± 0.6	36.9 ± 0.6	36.9 ± 0.6	36.9 ± 0.6	36.8 ± 0.7	<0.001
SPO_2 (%)	97.3 ± 2.7	97.6 ± 1.9	97.5 ± 1.9	97.3 ± 2.2	96.8 ± 3.9	<0.001
Laboratory parameters						
Anion gap (mmol/L)	14.4 ± 3.6	10.3 ± 1.2	12.7 ± 0.6	14.7 ± 0.6	18.7 ± 3.1	<0.001
Bicarbonate (mmol/L)	23.7 ± 4.5	26.5 ± 4.6	24.7 ± 3.6	23.6 ± 3.6	21.0 ± 4.4	<0.001
Creatinine (mEq/L)	1.4 ± 1.6	0.9 ± 0.4	1.0 ± 0.6	1.2 ± 0.9	2.4 ± 2.4	<0.001
Glucose (mg/dl)	145.1 ± 55.4	131.9 ± 36.5	136.8 ± 42.7	145.0 ± 49.0	162.0 ± 74.3	<0.001
Hematocrit (%)	32.6 ± 5.2	31.3 ± 4.6	32.3 ± 4.9	33.3 ± 5.3	33.3 ± 5.7	<0.001
Hemoglobin (g/dl)	11.0 ± 1.9	10.6 ± 1.6	11.0 ± 1.8	11.3 ± 1.9	11.2 ± 2.1	<0.001
Platelet (10^9/L)	225.0 ± 112.4	202.6 ± 101.4	216.5 ± 102.1	235.6 ± 114.4	239.6 ± 123.4	<0.001
Potassium (mmol/L)	4.2 ± 0.6	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	4.3 ± 0.7	<0.001
Sodium(mmol/L)	138.6 ± 4.3	138.4 ± 4.1	138.6 ± 3.9	138.6 ± 4.2	138.5 ± 4.8	0.003
Bun (mg/dl)	26.0 ± 21.3	17.9 ± 11.0	20.3 ± 13.1	24.1 ± 17.1	38.5 ± 28.9	<0.001
WBC (10^9/L)	12.3 ± 9.4	11.3 ± 11.1	11.6 ± 9.6	12.3 ± 7.0	13.7 ± 9.6	<0.001
RDW (%)	15.0 ± 2.1	14.7 ± 1.9	14.7 ± 2.0	14.9 ± 2.1	15.4 ± 2.3	<0.001
RBC (10^{12}/L)	3.7 ± 0.6	3.5 ± 0.6	3.6 ± 0.6	3.8 ± 0.6	3.7 ± 0.7	<0.001
Scoring systems						
SOFA	4.0 ± 3.0	3.5 ± 2.4	3.5 ± 2.6	3.7 ± 2.7	5.3 ± 3.6	<0.001
SAPSII	34.5 ± 14.2	30.9 ± 11.7	31.8 ± 12.6	33.5 ± 13.2	40.3 ± 16.2	<0.001
EVCI	5.3 ± 6.7	4.4 ± 6.4	4.4 ± 6.3	5.0 ± 6.7	6.9 ± 7.0	<0.001
Comorbidities, *n* (%)						
Congestive heart failure	4652 (17.7%)	747 (13.9%)	982 (14.3%)	1128 (17.7%)	1795 (23.5%)	<0.001
Cardiac arrhythmias	4405 (16.8%)	755 (14.0%)	1088 (15.8%)	1085 (17.0%)	1477 (19.3%)	<0.001
Valvular disease	1565 (6.0%)	251 (4.7%)	397 (5.8%)	390 (6.1%)	527 (6.9%)	<0.001
Pulmonary circulation	758 (2.9%)	147 (2.7%)	178 (2.6%)	167 (2.6%)	266 (3.5%)	0.003

TABLE 1 (Continued)

Anion gap (mmol/L) groups	Total	G1(<12)	G2(> = 12, <14)	G3(> = 14, <16)	G4(> = 16)	*p*-Value
Peripheral vascular	2010 (7.7%)	443 (8.2%)	517 (7.5%)	440 (6.9%)	610 (8.0%)	0.03
Hypertension	2379 (9.1%)	198 (3.7%)	351 (5.1%)	519 (8.1%)	1311 (17.2%)	<0.001
Chronic pulmonary	4675 (17.8%)	1148 (21.3%)	1213 (17.7%)	1067 (16.7%)	1247 (16.3%)	<0.001
Diabetes uncomplicated	5019 (19.1%)	955 (17.7%)	1238 (18.0%)	1264 (19.8%)	1562 (20.4%)	<0.001
Diabetes complicated	1674 (6.4%)	225 (4.2%)	325 (4.7%)	337 (5.3%)	787 (10.3%)	<0.001
Hypothyroidism	2259 (8.6%)	435 (8.1%)	611 (8.9%)	542 (8.5%)	671 (8.8%)	0.389
Renal failure	3168 (12.1%)	273 (5.1%)	503 (7.3%)	695 (10.9%)	1697 (22.2%)	<0.001
Liver disease	3168 (12.1%)	273 (5.1%)	503 (7.3%)	695 (10.9%)	1697 (22.2%)	0.002
Coagulopathy	2565 (9.8%)	475 (8.8%)	583 (8.5%)	531 (8.3%)	976 (12.8%)	<0.001
Blood loss anemia	632 (2.4%)	152 (2.8%)	176 (2.6%)	138 (2.2%)	166 (2.2%)	0.045
Deficiency anemias	4125 (15.7%)	801 (14.9%)	935 (13.6%)	1003 (15.7%)	1386 (18.1%)	<0.001
30-day mortality	3751 (14.3%)	438 (8.1%)	688 (10.0%)	830 (13.0%)	1795 (23.5%)	<0.001
90-day mortality	5206 (19.8%)	704 (13.1%)	1018 (14.8%)	1185 (18.6%)	2299 (30.1%)	<0.001
365-day mortality	7573 (28.8%)	1116 (20.7%)	1585 (23.1%)	1757 (27.6%)	3115 (40.8%)	<0.001
4-year mortality	11,325 (43.1%)	1837 (34.1%)	2538 (36.9%)	2723 (42.7%)	4227 (55.3%)	<0.001

Abbreviations: SBP, systolic blood pressure; RBC, red blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; WBC, white blood cell; PT, prothrombin time; RDW, Red Blood Cell Distribution Width; DBP, diastolic blood pressure; SAPSII, simplified acute physiology score II; EVCI, Elixhauser-van Walraven Comorbidity Index; SOFA, sequential organ failure assessment.

were consistent with AG as a continuous variable, and all of the p-values were less than 0.05, making the differences statistically significant.

3.3 | Subgroup analysis

To explore differences in outcomes due to associated factors and diseases, we conducted a subgroup analysis, with mortality as the dependent variable. Our subgroup analysis's findings for diseases in all major organs demonstrate a high degree of consistency and dependability. In all systems, the patient's short-, medium-, and long-term mortality is positively correlated with the serum anion gap value: the greater the serum AG value, the higher the patient's short-, medium-, and long-term mortality. (Attached table-Table 3).

We used age (years), gender, admission type, insurance type, SBP (mmHg), heart rate (bpm), DBP (mmHg), respiratory rate (bpm), SPO_2 (%), anion gap (mmol/L), temperature (°C), bicarbonate level (mmol/L), creatinine level (mEq/L), glucose level (mg/dl), hemoglobin level (g/dl), hematocrit level (%), platelet level (10^9/L), potassium level (mmol/L), sodium level (mmol/L), Bun level (mg/dL), WBC count (10^9/L), RBC count (10^{12}/L), SOFA score, SAPS II score, EVCI score, cardiac arrhythmias, blood loss anemia, valvular disease, peripheral vascular disease, hypertension, chronic pulmonary disease, uncomplicated diabetes, congestive heart failure, complicated diabetes, hypothyroidism, renal failure, coagulopathy, blood loss anemia, pulmonary circulation, liver disease, and deficiency anemias were used as a stratification parameter to analyze the distribution of their effect sizes (Table 3). Our findings are quite credible and consistent when compared between subgroups and across all subgroups. This study shows significant effect values and 95 percent confidence intervals, the stratified analysis's findings for each subgroup all point in the same direction.

3.4 | The results of the non-linearity of serum anion gap and all-cause mortality

By using smoothed curve fit plots and COX proportional risk regression models that integrate cubic spline functions, our study investigated the relationship between serum AG levels and all-cause mortality in a non-selected population (Figures 2,3,4,5). The results showed that serum AG levels had a non-linear relationship with short-, medium-, and long-term all-cause mortality in a non-selected population.

The fully adjusted model displayed a non-linear positive correlation, and we adjusted for the following covariates: age; systolic blood pressure (SBP); pulse oxygen saturation (SPO_2); diastolic blood pressure (DBP); heart rate; respiratory rate; temperature; anion gap; albumin level; blood urea nitrogen (Bun) level; Platelet level; sodium level; hemoglobin level; hematocrit level; glucose level; potassium level; creatinine level; bicarbonate level; Phosphate level; Magnesium level; Serum calcium level; the Sequential Organ Failure Assessment (SOFA) score; the Elixhauser-van Walraven Comorbidity Index (EVCI); the Simplified Acute Physiology Score II (SAPS II); red blood cell distribution width (RDW) level; white blood cells (WBC) count; red blood cell (RBC) count; gender; insurance; admission type;pulmonary circulation; congestive heart failure; peripheral vascular; chronic pulmonary; diabetes uncomplicated; valvular disease; diabetes complicated; hypothyroidism; renal failure; liver disease;

TABLE 2 Association of Serum Anion Gap with Mortality.

Variable	Crude model HR (95% CIs) *p*-Value	Model I HR (95% CIs) *p*-Value	Model II HR (95% CIs) *p*-Value
30-day mortality			
Anion gap (mmol/L)	1.14 (1.14, 1.15) <0.0001	1.15 (1.14, 1.16) <0.0001	1.08 (1.06, 1.09) <0.0001
Anion gap (mmol/L) groups			
<12	Ref	Ref	Ref
> = 12, <14	1.25 (1.11, 1.41) 0.0003	1.22 (1.08, 1.38) 0.0011	1.18 (1.04, 1.33) 0.0096
> = 14, <16	1.65 (1.47, 1.85) <0.0001	1.60 (1.43, 1.80) <0.0001	1.41 (1.25, 1.60) <0.0001
> = 16	3.23 (2.91, 3.59) <0.0001	3.14 (2.82, 3.48) <0.0001	1.85 (1.63, 2.11) <0.0001
90-day mortality			
Anion gap (mmol/L)	1.13 (1.12, 1.13) <0.0001	1.13 (1.12, 1.14) <0.0001	1.08 (1.06, 1.09) <0.0001
Anion gap (mmol/L) groups			
<12	Ref	Ref	Ref
> = 12, <14	1.15 (1.05, 1.27) 0.0041	1.13 (1.02, 1.24) 0.0146	1.13 (1.02, 1.25) 0.0170
> = 14, <16	1.48 (1.35, 1.62) <0.0001	1.44 (1.31, 1.58) <0.0001	1.34 (1.21, 1.48) <0.0001
> = 16	2.64 (2.43, 2.87) <0.0001	2.57 (2.36, 2.79) <0.0001	1.69 (1.52, 1.88) <0.0001
365-day mortality			
Anion gap (mmol/L)	1.11 (1.10, 1.12) <0.0001	1.11 (1.10, 1.12) <0.0001	1.08 (1.07, 1.08) <0.0001
Anion gap (mmol/L) groups			
<12	Ref	Ref	Ref
> = 12, <14	1.13 (1.05, 1.22) 0.0013	1.11 (1.03, 1.20) 0.0076	1.15 (1.07, 1.25) 0.0004
> = 14, <16	1.40 (1.30, 1.51) <0.0001	1.37 (1.27, 1.47) <0.0001	1.34 (1.24, 1.46) <0.0001
> = 16	2.34 (2.19, 2.51) <0.0001	2.28 (2.13, 2.44) <0.0001	1.70 (1.56, 1.86) <0.0001
4-year mortality			
Anion gap (mmol/L)	1.09 (1.09, 1.10) <0.0001	1.09 (1.09, 1.10) <0.0001	1.07 (1.06, 1.07) <0.0001
Anion gap (mmol/L) groups			
<12	Ref	Ref	Ref
> = 12, <14	1.11 (1.04, 1.18) 0.0009	1.08 (1.02, 1.15) 0.0087	1.13 (1.06, 1.20) 0.0001
> = 14, <16	1.35 (1.27, 1.43) <0.0001	1.32 (1.24, 1.40) <0.0001	1.31 (1.23, 1.40) <0.0001
> = 16	2.04 (1.93, 2.15) <0.0001	2.00 (1.89, 2.11) <0.0001	1.58 (1.47, 1.69) <0.0001

Note: Models 1 and 2 were derived from Cox proportional hazards regression models: model 1 covariates were adjusted for age and sex; model 2 covariates were adjusted for age; systolic blood pressure (SBP); pulse oxygen saturation (SPO2); diastolic blood pressure (DBP); heart rate; respiratory rate; temperature; anion gap; albumin level; blood urea nitrogen (Bun) level; Platelet level; sodium level; hemoglobin level; hematocrit level; glucose level; potassium level; creatinine level; bicarbonate level; Phosphate level, Magnesium level, Serum calcium level, the Sequential Organ Failure Assessment (SOFA) score; and the Elixhauser-van Walraven Comorbidity Index (EVCI); the Simplified Acute Physiology Score II (SAPS II); red blood cell distribution width (RDW) level; white blood cells (WBC) count; red blood cell (RBC) count; gender; insurance; admission type;pulmonary circulation; congestive heart failure; peripheral vascular; chronic pulmonary; diabetes uncomplicated; valvular disease; diabetes complicated; hypothyroidism; renal failure; liver disease; coagulopathy; blood loss anemia; deficiency anemias; cardiac arrhythmias; hypertension.

coagulopathy; blood loss anemia; deficiency anemias; cardiac arrhythmias; hypertension.

To match this association, we used a Cox proportional risk model with two segments and a Cox proportional risk model without segments. The p-values from the log-likelihood ratio test were used to determine which model was the best.

3.5 | Survival status of the patients with different admission serum AG levels

We performed Kaplan–Meier survival curves based on serum AG groupings, with all-cause mortality as the dependent variable for the primary outcome indicator, and showed that as the serum AG levels increased, patient survival decreased, and patients in each serum AG group had survival time values of G1 > G2 > G3 > G4 at any point throughout the 4 years ($p < 0.0001$) (Figure 6).

4 | DISCUSSION

This study, which is the first to examine the relationship between serum anion gap levels and short-, medium-, and long-term all-cause mortality in unselected adult patients, supports the findings of our study, which found that high serum anion levels were predictive of high mortality in our patient population over the 30-day, 90-day,

TABLE 3 Each Subgroup's Serum Anion Gap Effect Size on Mortality in Prespecified and Exploratory Subgroups.

Characteristic		30-day mortality, *n* (%)		90-day mortality, *n* (%)		365-day mortality, *n* (%)		4-year mortality, *n* (%)	
	N	HR (95% CI)	P for interaction	HR (95% CI)	P for interaction	HR (95% CI)	P for interaction	HR (95% CI)	P for interaction
Age (years) groups			0.6654		0.5599		0.9666		0.4333
<60	10,293	1.16 (1.14, 1.17)		1.14 (1.13, 1.15)		1.12 (1.10, 1.13)		1.10 (1.09, 1.11)	
> = 60, <80	10,760	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.12 (1.11, 1.13)		1.10 (1.10, 1.11)	
> = 80	5217	1.15 (1.13, 1.16)		1.13 (1.12, 1.14)		1.12 (1.10, 1.13)		1.09 (1.08, 1.10)	
Gender, *n* (%)									
Male	14,768	1.15 (1.14, 1.16)	0.1008	1.13 (1.12, 1.14)	0.0379	1.12 (1.11, 1.13)	0.0009	1.10 (1.09, 1.11)	0.0002
Female	11,502	1.14 (1.12, 1.15)		1.12 (1.11, 1.13)		1.10 (1.09, 1.11)		1.08 (1.07, 1.09)	
Admission type, *n* (%)									
Emergency	20,557	1.13 (1.12, 1.14)	<0.0001	1.11 (1.10, 1.12)	<0.0001	1.09 (1.09, 1.10)	<0.0001	1.08 (1.07, 1.09)	<0.0001
Elective	5027	1.20 (1.17, 1.23)		1.17 (1.15, 1.20)		1.16 (1.14, 1.18)		1.13 (1.12, 1.15)	
Urgent	686	1.16 (1.12, 1.20)		1.14 (1.10, 1.18)		1.12 (1.09, 1.16)		1.11 (1.08, 1.14)	
Insurance, *n* (%)									
Private	8472	1.18 (1.16, 1.20)	<0.0001	1.17 (1.15, 1.18)	<0.0001	1.15 (1.13, 1.16)	<0.0001	1.12 (1.11, 1.14)	<0.0001
Medicaid	2123	1.16 (1.13, 1.19)		1.12 (1.09, 1.15)		1.09 (1.06, 1.11)		1.07 (1.05, 1.09)	
Medicare	14,687	1.13 (1.12, 1.14)		1.11 (1.10, 1.12)		1.10 (1.09, 1.10)		1.08 (1.08, 1.09)	
Government	658	1.14 (1.08, 1.19)		1.11 (1.06, 1.17)		1.09 (1.04, 1.13)		1.07 (1.03, 1.11)	
Self Pay	330	1.09 (1.03, 1.16)		1.09 (1.03, 1.16)		1.09 (1.02, 1.15)		1.07 (1.01, 1.14)	
Heart rate (bpm) groups									
<60	964	1.14 (1.09, 1.19)	0.0995	1.13 (1.08, 1.17)	0.1803	1.11 (1.08, 1.15)	0.1504	1.10 (1.07, 1.13)	0.4766
> = 60, <90	15,499	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.11 (1.10, 1.12)		1.10 (1.09, 1.10)	
> = 90	9437	1.13 (1.12, 1.14)		1.11 (1.10, 1.12)		1.10 (1.09, 1.11)		1.09 (1.08, 1.09)	
SBP (mmHg) groups									
<90	483	1.10 (1.08, 1.12)	<0.0001	1.09 (1.07, 1.11)	<0.0001	1.08 (1.06, 1.10)	<0.0001	1.07 (1.05, 1.09)	<0.0001
> = 90, <140	22,094	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.12 (1.11, 1.12)		1.10 (1.09, 1.10)	
> = 140	3322	1.05 (1.03, 1.08)		1.04 (1.02, 1.07)		1.05 (1.03, 1.06)		1.04 (1.03, 1.06)	
DBP (mmHg) groups									
<60	14,509	1.15 (1.14, 1.16)	0.0056	1.13 (1.13, 1.14)	0.0044	1.12 (1.11, 1.13)	0.001	1.10 (1.10, 1.11)	0.0004
> = 60, <90	11,151	1.13 (1.11, 1.14)		1.11 (1.10, 1.12)		1.09 (1.08, 1.11)		1.08 (1.07, 1.09)	
> = 90	239	1.08 (0.98, 1.20)		1.06 (0.96, 1.17)		1.08 (1.00, 1.16)		1.06 (1.00, 1.11)	

(Continues)

TABLE 3 (Continued)

Characteristic		30-day mortality, *n* (%)		90-day mortality, *n* (%)		365-day mortality, *n* (%)		4-year mortality, *n* (%)	
Respiratory rate (bpm) groups									
<12	377	1.16 (1.08, 1.25)	0.0722	1.11 (1.04, 1.18)	0.0925	1.10 (1.04, 1.16)	0.0271	1.08 (1.04, 1.13)	0.0256
> = 12, <20	17,139	1.14 (1.13, 1.16)		1.12 (1.11, 1.14)		1.11 (1.10, 1.12)		1.09 (1.09, 1.10)	
> = 20	8330	1.12 (1.11, 1.13)		1.11 (1.10, 1.12)		1.09 (1.08, 1.10)		1.08 (1.07, 1.08)	
Temperature (°C) groups									
<36.3	3963	1.11 (1.10, 1.13)	<0.0001	1.10 (1.09, 1.11)	<0.0001	1.09 (1.08, 1.10)	<0.0001	1.07 (1.06, 1.08)	<0.0001
> = 36.3, <37.2	14,654	1.13 (1.12, 1.15)		1.11 (1.10, 1.12)		1.10 (1.09, 1.11)		1.09 (1.08, 1.09)	
> = 37.2	7202	1.16 (1.15, 1.18)		1.14 (1.13, 1.16)		1.13 (1.11, 1.14)		1.11 (1.10, 1.12)	
SPO_2 (%) groups									
<95	2572	1.12 (1.11, 1.14)	0.7308	1.11 (1.10, 1.13)	0.4075	1.10 (1.08, 1.11)	0.763	1.07 (1.06, 1.09)	0.0907
> = 95	23,297	1.14 (1.13, 1.15)		1.12 (1.11, 1.13)		1.11 (1.10, 1.11)		1.09 (1.09, 1.10)	
Bicarbonate (mmol/L) groups									
<22	7616	1.12 (1.11, 1.13)	<0.0001	1.11 (1.10, 1.12)	<0.0001	1.09 (1.08, 1.10)	<0.0001	1.08 (1.07, 1.09)	<0.0001
> = 22, <27	13,297	1.16 (1.14, 1.18)		1.15 (1.13, 1.16)		1.15 (1.13, 1.16)		1.13 (1.12, 1.14)	
> = 27	5357	1.07 (1.04, 1.10)		1.06 (1.04, 1.08)		1.06 (1.04, 1.07)		1.06 (1.05, 1.08)	
Creatinine (mEq/L) groups									
<0.5	956	1.07 (1.01, 1.14)	0.0075	1.05 (1.00, 1.10)	0.0155	1.04 (1.00, 1.08)	0.0652	1.02 (0.99, 1.06)	0.1463
> = 0.5, <1.2	16,308	1.14 (1.13, 1.16)		1.11 (1.10, 1.13)		1.08 (1.07, 1.10)		1.06 (1.05, 1.07)	
> = 1.2	9000	1.11 (1.10, 1.12)		1.09 (1.08, 1.10)		1.07 (1.07, 1.08)		1.06 (1.05, 1.06)	
Glucose (mg/dl) groups									
<70	192	1.15 (1.10, 1.20)	0.304	1.14 (1.10, 1.19)	0.007	1.12 (1.07, 1.16)	0.0006	1.10 (1.06, 1.14)	<0.0001
> = 70, <110	5554	1.13 (1.12, 1.15)		1.11 (1.09, 1.12)		1.09 (1.07, 1.10)		1.07 (1.06, 1.08)	
> = 110	20,512	1.15 (1.14, 1.15)		1.13 (1.12, 1.14)		1.11 (1.11, 1.12)		1.10 (1.09, 1.10)	
Hematocrit (%) groups									
<37	20,851	1.15 (1.14, 1.15)	0.1419	1.13 (1.12, 1.14)	0.0765	1.11 (1.11, 1.12)	0.0698	1.10 (1.09, 1.10)	0.3496
> = 37, <50	5320	1.15 (1.13, 1.17)		1.13 (1.11, 1.15)		1.11 (1.09, 1.12)		1.09 (1.08, 1.10)	
> = 50	51	1.28 (1.11, 1.48)		1.28 (1.12, 1.47)		1.25 (1.10, 1.41)		1.15 (1.04, 1.27)	
Hemoglobin (g/dl) groups									
<11	13,863	1.14 (1.13, 1.15)	0.0728	1.12 (1.12, 1.13)	0.0246	1.11 (1.10, 1.12)	0.0159	1.10 (1.09, 1.10)	0.0584
> = 11, <16.5	12,193	1.15 (1.14, 1.17)		1.13 (1.12, 1.15)		1.12 (1.10, 1.13)		1.09 (1.09, 1.10)	
> = 16.5	100	1.24 (1.12, 1.39)		1.24 (1.12, 1.38)		1.24 (1.13, 1.37)		1.20 (1.10, 1.31)	

TABLE 3 (Continued)

Characteristic		30-day mortality, *n* (%)		90-day mortality, *n* (%)		365-day mortality, *n* (%)		4-year mortality, *n* (%)	
Platelet (109/L) groups									
<100	2137	1.12 (1.11, 1.14)	<0.0001	1.11 (1.09, 1.12)	<0.0001	1.09 (1.08, 1.11)	<0.0001	1.08 (1.06, 1.09)	<0.0001
> = 100, <300	19,114	1.16 (1.15, 1.17)		1.14 (1.13, 1.15)		1.12 (1.11, 1.13)		1.10 (1.10, 1.11)	
> = 300	4894	1.09 (1.08, 1.11)		1.08 (1.06, 1.10)		1.05 (1.04, 1.07)		1.04 (1.03, 1.05)	
Potassium (mmol/L) groups									
<3.5	1889	1.12 (1.09, 1.16)	0.0133	1.10 (1.07, 1.13)	0.0028	1.06 (1.04, 1.09)	<0.0001	1.04 (1.02, 1.06)	<0.0001
> = 3.5, <5.5	23,625	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.11 (1.11, 1.12)		1.10 (1.09, 1.10)	
> = 5.5	756	1.10 (1.07, 1.13)		1.08 (1.06, 1.11)		1.06 (1.04, 1.08)		1.04 (1.02, 1.06)	
Sodium(mmol/L) groups									
<135	3842	1.13 (1.11, 1.15)	<0.0001	1.11 (1.09, 1.12)	<0.0001	1.09 (1.08, 1.10)	<0.0001	1.07 (1.06, 1.08)	<0.0001
> = 135, <145	21,066	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.11 (1.11, 1.12) <0.0001		1.10 (1.09, 1.10) <0.0001	
> = 145	1362	1.08 (1.06, 1.11)		1.07 (1.04, 1.09)		1.05 (1.03, 1.07)		1.03 (1.02, 1.05)	
Bun (mg/dl) groups									
<9	2091	1.14 (1.09, 1.20)	<0.0001	1.11 (1.06, 1.16)	<0.0001	1.07 (1.03, 1.10)	0.0053	1.04 (1.01, 1.07)	0.3781
> = 9, <20	11,785	1.17 (1.15, 1.19)		1.13 (1.12, 1.15)		1.09 (1.08, 1.11)		1.06 (1.05, 1.07)	
> = 20	12,388	1.10 (1.09, 1.11)		1.08 (1.07, 1.09)		1.07 (1.06, 1.07)		1.05 (1.05, 1.06)	
WBC (109/L) groups									
<4	841	1.12 (1.09, 1.16)	0.0638	1.08 (1.06, 1.11)	0.0004	1.06 (1.03, 1.08)	<0.0001	1.04 (1.02, 1.06)	<0.0001
> = 4, <10	9733	1.13 (1.11, 1.15)		1.11 (1.10, 1.13)		1.09 (1.08, 1.10)		1.08 (1.07, 1.09)	
> = 10	15,543	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.12 (1.11, 1.13)		1.10 (1.10, 1.11)	
RDW (%) groups									
> = 11, <15	15,847	1.17 (1.15, 1.18)	<0.0001	1.15 (1.14, 1.16)	<0.0001	1.12 (1.11, 1.13)	<0.0001	1.10 (1.09, 1.11)	<0.0001
> = 15	10,171	1.11 (1.10, 1.12)		1.09 (1.08, 1.10)		1.07 (1.06, 1.08)		1.06 (1.05, 1.07)	
RBC (1012/L) groups									
<3.5	11,287	1.14 (1.13, 1.15)	0.1591	1.12 (1.11, 1.13)	0.1597	1.11 (1.10, 1.12)	0.686	1.10 (1.09, 1.11)	0.7053
> = 3.5, <5.5	14,624	1.15 (1.14, 1.16)		1.13 (1.12, 1.14)		1.11 (1.10, 1.12)		1.09 (1.09, 1.10)	
> = 5.5	147	1.21 (1.10, 1.34)		1.19 (1.08, 1.30)		1.13 (1.03, 1.23)		1.08 (1.00, 1.17)	
SOFA 分组									
<5	16,678	1.11 (1.09, 1.13)	0.5693	1.09 (1.07, 1.10)	0.1025	1.07 (1.06, 1.09)	0.0171	1.06 (1.05, 1.07)	<0.0001
> = 5	9592	1.11 (1.10, 1.12)		1.10 (1.09, 1.11)		1.09 (1.08, 1.10)		1.08 (1.07, 1.08)	

(Continues)

TABLE 3 (Continued)

Characteristic		30-day mortality, *n* (%)		90-day mortality, *n* (%)		365-day mortality, *n* (%)		4-year mortality, *n* (%)	
SAPSII 分组									
<39	17,224	1.09 (1.07, 1.11)	0.5436	1.07 (1.06, 1.09)	0.3825	1.06 (1.05, 1.07)	0.1454	1.05 (1.04, 1.06)	0.2415
> = 39	9046	1.09 (1.08, 1.10)		1.08 (1.07, 1.09)		1.07 (1.06, 1.07)		1.06 (1.05, 1.06) <0.0001	
EVCI 分组									
<8	18,035	1.16 (1.15, 1.17)	<0.0001	1.15 (1.13, 1.16)	<0.0001	1.12 (1.11, 1.13)	<0.0001	1.10 (1.09, 1.11)	<0.0001
> = 8	8235	1.10 (1.09, 1.11)		1.08 (1.07, 1.09)		1.06 (1.05, 1.07)		1.05 (1.04, 1.05)	
Congestive heart failure									
No	21,618	1.16 (1.15, 1.17)	<0.0001	1.14 (1.13, 1.15)	<0.0001	1.12 (1.12, 1.13)	<0.0001	1.10 (1.10, 1.11)	<0.0001
Yes	4652	1.07 (1.06, 1.09)		1.06 (1.04, 1.07)		1.04 (1.03, 1.05)		1.03 (1.02, 1.04)	
Cardiac arrhythmias									
No	21,865	1.15 (1.15, 1.16)	<0.0001	1.14 (1.13, 1.15)	<0.0001	1.12 (1.11, 1.13)	<0.0001	1.10 (1.09, 1.11)	<0.0001
Yes	4405	1.10 (1.09, 1.12)		1.08 (1.07, 1.09)		1.06 (1.05, 1.07)		1.05 (1.04, 1.06)	
Valvular disease									
No	24,705	1.15 (1.14, 1.16)	0.0009	1.13 (1.12, 1.14)	<0.0001	1.11 (1.11, 1.12)	0.0002	1.09 (1.09, 1.10)	<0.0001
Yes	1565	1.09 (1.06, 1.13)		1.08 (1.05, 1.10)		1.07 (1.05, 1.09)		1.06 (1.04, 1.07)	
Pulmonary circulation									
No	25,512	1.15 (1.14, 1.16)	0.0002	1.13 (1.12, 1.14)	<0.0001	1.11 (1.11, 1.12)	<0.0001	1.09 (1.09, 1.10) <0.0001	<0.0001
Yes	758	1.08 (1.05, 1.12)		1.07 (1.04, 1.10)		1.05 (1.03, 1.08)		1.04 (1.01, 1.06)	
Peripheral vascular									
No	24,260	1.14 (1.14, 1.15)	0.9898	1.13 (1.12, 1.13)	0.5122	1.11 (1.10, 1.11)	0.0244	1.09 (1.08, 1.09)	0.0003
Yes	2010	1.14 (1.12, 1.17)		1.13 (1.11, 1.16)		1.13 (1.11, 1.15)		1.13 (1.11, 1.14)	
Hypertension									
No	23,891	1.15 (1.15, 1.16)	<0.0001	1.13 (1.13, 1.14)	<0.0001	1.11 (1.11, 1.12)	<0.0001	1.09 (1.09, 1.10)	<0.0001
Yes	2379	1.10 (1.07, 1.12)		1.07 (1.05, 1.09)		1.05 (1.03, 1.06)		1.04 (1.03, 1.06)	
Chronic pulmonary									
No	21,595	1.15 (1.14, 1.16)	0.0009	1.13 (1.12, 1.14)	0.0002	1.12 (1.11, 1.12)	<0.0001	1.10 (1.10, 1.11)	<0.0001
Yes	4675	1.11 (1.09, 1.14)		1.10 (1.08, 1.11)		1.08 (1.07, 1.10)		1.07 (1.05, 1.08)	
Diabetes uncomplicated									
No	21,251	1.14 (1.13, 1.15)	0.0022	1.12 (1.11, 1.13)	0.0251	1.11 (1.10, 1.11)	0.3112	1.09 (1.08, 1.10)	0.255
Yes	5019	1.17 (1.15, 1.19)		1.14 (1.13, 1.16)		1.12 (1.10, 1.13)		1.10 (1.09, 1.11)	

TABLE 3 (Continued)

Characteristic		30-day mortality, *n* (%)		90-day mortality, *n* (%)		365-day mortality, *n* (%)		4-year mortality, *n* (%)	
Diabetes complicated									
No	24,596	1.15 (1.14, 1.16)	<0.0001	1.13 (1.12, 1.14)	<0.0001	1.11 (1.11, 1.12)	0.0005	1.09 (1.09, 1.10)	0.0266
Yes	1674	1.08 (1.05, 1.11)		1.08 (1.05, 1.10)		1.08 (1.06, 1.10)		1.08 (1.06, 1.09)	
Hypothyroidism									
No	24,011	1.15 (1.14, 1.15)	0.6802	1.13 (1.12, 1.13)	0.2554	1.11 (1.10, 1.12)	0.0994	1.09 (1.09, 1.10)	0.0603
Yes	2259	1.14 (1.11, 1.16)		1.11 (1.09, 1.14)		1.09 (1.07, 1.11)		1.08 (1.06, 1.09)	
Renal failure									
No	23,102	1.16 (1.15, 1.17)	<0.0001	1.14 (1.13, 1.14)	<0.0001	1.11 (1.11, 1.12)	<0.0001	1.09 (1.08, 1.10)	<0.0001
Yes	3168	1.09 (1.07, 1.11)		1.07 (1.05, 1.08)		1.05 (1.04, 1.06)		1.04 (1.03, 1.06)	
Liver disease									
No	24,842	1.14 (1.14, 1.15)	0.688	1.12 (1.12, 1.13)	0.8994	1.11 (1.10, 1.12)	0.5348	1.09 (1.09, 1.10)	0.1833
Yes	1428	1.15 (1.12, 1.17)		1.13 (1.11, 1.15)		1.11 (1.09, 1.13)		1.08 (1.06, 1.10)	
Coagulopathy									
No	23,705	1.14 (1.14, 1.15)	0.0006	1.12 (1.12, 1.13)	0.0028	1.11 (1.10, 1.11)	0.0246	1.09 (1.09, 1.10)	0.0203
Yes	2565	1.12 (1.10, 1.13)		1.10 (1.09, 1.12)		1.09 (1.08, 1.10)		1.08 (1.06, 1.09)	
Blood loss anemia									
No	25,638	1.15 (1.14, 1.15)	0.0169	1.13 (1.12, 1.13)	0.2257	1.11 (1.10, 1.12)	0.7061	1.09 (1.09, 1.10)	0.8519
Yes	632	1.09 (1.04, 1.14)		1.10 (1.06, 1.15)		1.11 (1.07, 1.14)		1.09 (1.07, 1.12)	
Deficiency anemias									
No	22,145	1.15 (1.15, 1.16)	<0.0001	1.14 (1.13, 1.14)	<0.0001	1.12 (1.11, 1.13)	<0.0001	1.10 (1.10, 1.11)	<0.0001
Yes	4125	1.09 (1.07, 1.11)		1.07 (1.06, 1.09)		1.06 (1.04, 1.07)		1.05 (1.04, 1.06)	

Abbreviations: BUN, blood urea nitrogen; DBP, Diastolic blood pressure; HR, Hazard Ratio; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; RDW, Red Blood Cell Distribution Width; EVCI, Elixhauser-van Walraven Comorbidity Index; SAPSII, simplified acute physiology score II; SBP, Systolic blood pressure; SOFA, sequential organ failure assessment.WBC, white blood cell.

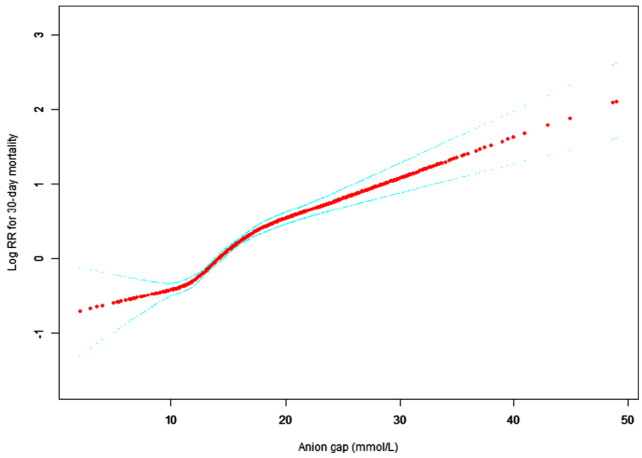

FIGURE 2 Association between serum AG and 30-day all-cause mortality. (After adjustment for other covariates) A generalized additive model (GAM) revealed a threshold, nonlinear relationship between serum anion gap levels and 30-day mortality. Positive relationship was observed after adjustment for other covariates by spline smoothing plot. The smooth curve fit between variables is shown by a solid rad line. The 95% confidence interval from the fit is represented by imaginary blue line.

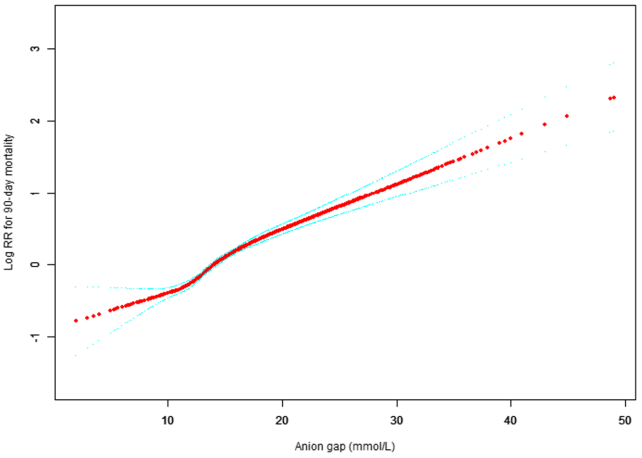

FIGURE 3 Association between serum AG and 90-day all-cause mortality. (After adjustment for other covariates) A generalized additive model (GAM) revealed a threshold, nonlinear relationship between serum anion gap levels and 90-day mortality. Positive relationship was observed after adjustment for other covariates by spline smoothing plot. The smooth curve fit between variables is shown by a solid rad line. The 95% confidence interval from the fit is represented by imaginary blue line.

365-day, and 4-year time periods. According to this study's analysis of 26,270 unselected adult patients from the MIMIC-III database, serum anion gap levels were higher in deceased patients at their first ICU admission than in survivors, and elevated serum anion gap levels were associated with all-cause mortality at 30 days, 90 days, 365 days, and 4 years, respectively.

Although some researchers have in the past shown a connection between serum anion gap and mortality in patients with critical illnesses, the outcomes of these studies have not always been consistent. For instance, base excess, unmeasured anion-induced base excess, and anion gap are excellent predictors of hyperlactatemia (>5 mmol/L). No matter how they are calculated, acid–base variables are not reliable indicators of hospital mortality in critically ill patients.[21] In contrast, the study by Cuhaci B claims that, after careful computation, the serum cation gap is a reliable indicator of hospital mortality in critically ill patients.[22] Patient survival at 28 days was tracked by Cusack RJ et al.[23] They discovered a significant difference in the mean AG of survivors and non-survivors ($p = 0.007$). The mean SIG did not significantly differ between survivors and non-survivors ($p = 0.088$). They concluded that the serum anion gap has prognostic value for such individuals, whereas the strong ion gap has no predictive value for critically ill patients in mixed medical and surgical adult intensive care units. Furthermore, the evidence at this time points to directly measured lactate having a better ability to predict mortality than albumin-corrected anion gap and strong ion gap without lactate.[24]

The relationship between elevated serum AG levels and the prognosis of associated disorders has recently been supported by numerous studies.[6–14] High serum AG levels were discovered to be an independent risk factor for death at 30 d and 90 d in patients with congestive heart failure in a recent study by Tang Y et al.[25] utilizing data from the MIMIC-III database. Similar results were reported in a study by Gong Y et al.[26] who discovered a non-linear, U-shaped relationship between AG levels and 30-day all-cause mortality in AKI patients. After taking into account potential confounders, higher AG was found to be a significant predictor of all-cause death at 30, 90, and 365 days in multivariate analyses compared to lower AG. A study by Braun AB et al.[15] found that the anionic gap was equally moderate in its ability to discriminate between 30-day mortality compared to standard base excess and strong ionic gaps. In this study, Patel KP et al.[27] analyzed the anion gap in 94 patients with acute age-related obstruction, and in this study they found that regardless of gender, anion gap abnormalities were found in >50% of patients, and in elderly patients, a high serum anion gap is normal and may be related to antibiotics or diuretics taken before admission altering the value of the anion gap. Abramowitz MK et al.[28] found that lower serum bicarbonate and a higher anion gap were associated with reduced cardiopulmonary adaptations in younger people.

The mechanisms by which the serum anion gap correlates with patient morbidity and mortality are not yet well understood. The main cause of the increased serum anion gap is metabolic acidosis, for which the rise in lactate levels is the most crucial component.[29] According to the research, excessive synthesis of organic acids and/or decreased anion excretion are the primary causes of the high serum anion gap.[30] The primary reasons are increased organic acids (lactate, pyruvate) brought on by stress, hypoxia, etc.[24,31] Acid–base abnormalities, particularly metabolic acidosis, may have a deleterious impact on the prognosis of critically ill patients. The most common cause and the one that most affects prognosis is lactic acidosis.

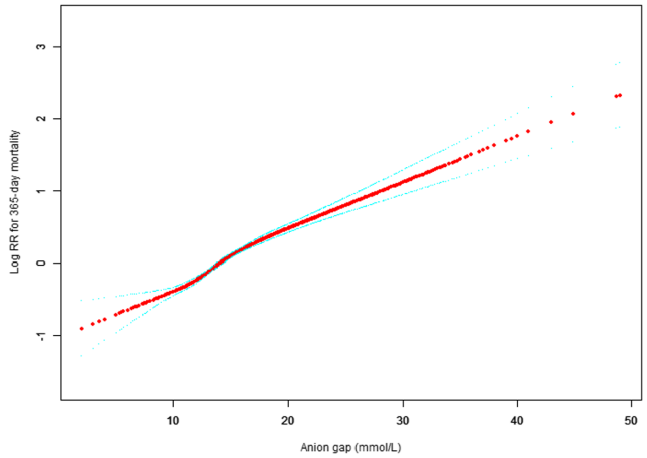

FIGURE 4 Association between serum AG and 365-day all-cause mortality. (After adjustment for other covariates) A generalized additive model (GAM) revealed a threshold, nonlinear relationship between serum anion gap levels and 365-day mortality. Positive relationship was observed after adjustment for other covariates by spline smoothing plot. The smooth curve fit between variables is shown by a solid rad line. The 95% confidence interval from the fit is represented by imaginary blue line.

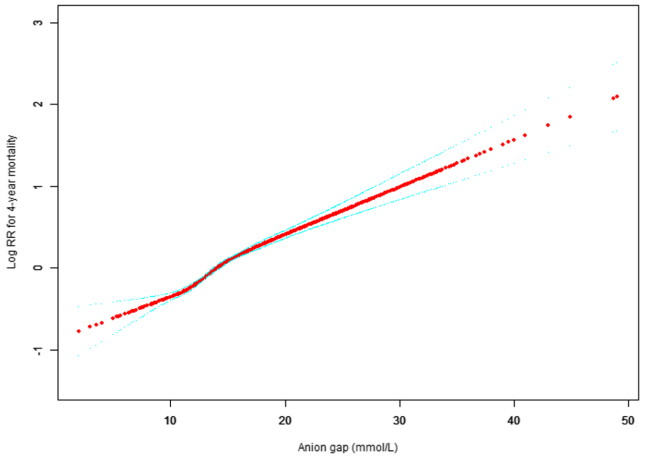

FIGURE 5 Association between serum AG and 4-year all-cause mortality. (After adjustment for other covariates) A generalized additive model (GAM) revealed a threshold, nonlinear relationship between serum anion gap levels and 4-year mortality. Positive relationship was observed after adjustment for other covariates by spline smoothing plot. The smooth curve fit between variables is shown by a solid rad line. The 95% confidence interval from the fit is represented by imaginary blue line.

As lactate measurement may not always be available at the bedside, it is considered one of the unmeasured anions.[24] On the one hand, patients who have higher lactate levels may die sooner.[32] On the other hand, metabolic acidosis can cause a drop in extracellular pH, which can lead to the emergence of an inflammatory response that involves neutrophil and complement system activation.[33]

Furthermore, due to the fact that renal insufficiency can raise the serum anion gap due to its lower ability to excrete unmeasured anions, some researchers have discovered that renal insufficiency is also an independent risk factor for patient death, renal insufficiency also carries a separate risk of patient death.[6] Reduced anion excretion in renal insufficiency, which is a common occurrence in the ICU, was similarly associated with higher blood levels of AG, according to a study by Kajimoto S et al.[34] As a result, clinical management should take into account the fact that critically ill patients tend to have high serum AG levels.

According to a preliminary examination of all study populations, the initial serum AG of patients who passed away while receiving hospital care was higher than that of survivors, raising the possibility that there may be a link between hospital death and AG. A logistic regression model was built to evaluate this association, and the results revealed that as initial serum AG increased, so did the chance of in-hospital death. After accounting for a number of variables that could have an impact on a patient's prognosis, the association between baseline serum AG and the likelihood of hospital death persisted. Serum anion gap on admission correlates with short-, medium-, and long-term prognosis, and as a result, serum anion gap can be utilized as a marker of mortality for prognosis in critically sick patients. Our study used many statistical approaches to explain this overall trend in in-hospital mortality.

Our research has the following advantages: (1) This study is more trustworthy than other retrospective studies because it used a large sample size, which increases the representativeness of the relevant values in retrospective analysis. (2) The database contains precise prognostic and follow-up data, making it simpler to evaluate prognostic markers in patients with short-, medium-, and long-term conditions. (3) We used various statistical techniques to show that our findings were reliable. Four clinically significant outcomes that were ascertained from hospital medical records were evaluated. (4) We have enough patients in our trial to have made sure that our estimates of mortality are trustworthy, and the complete cohort was followed up for a full 4 years.

Limitations: (1) Because this study is a retrospective cohort study, inevitable biases could taint the validity of the conclusions. (2) Remaining covariaties may exist even after comprehensive adjustment for measurable variables. Blood salt, hemoglobin, and physiological scores are examples of confounding factors that affect patient prognoses; however, there may be additional unidentified possible covariaties in this study. The association between serum anion gap and all-cause mortality in non-selected adult individuals must thus be confirmed in prospective cohort research that accounts for additional confounding variables.

5 | CONCLUSION

After considering the results, it can be concluded that serum anion gap levels were positively correlated with all-cause mortality in unselected adult patients at 30 days, 90 days, 365 days, and 4 years. Serum anion gap levels can be used as a reference indicator for

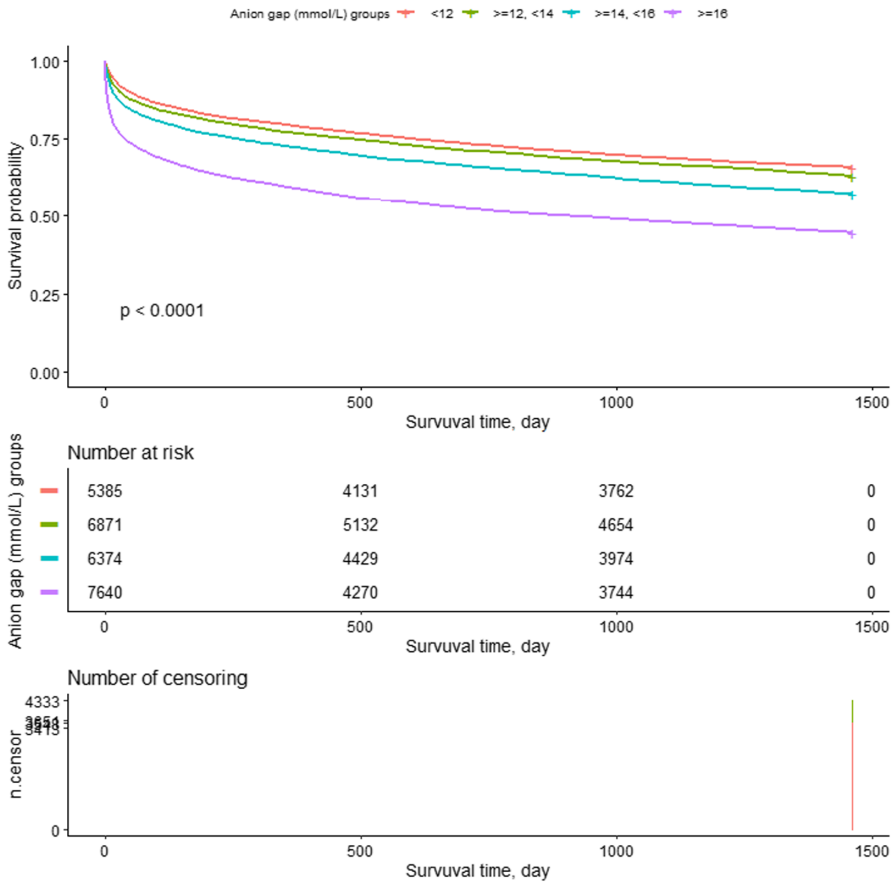

FIGURE 6 Kaplan–Meier survival curves demonstrating differences in overall survival (years).

long-term patient survival and early intervention to lower patient mortality.

AUTHOR CONTRIBUTIONS

Xuan Ji was in charge of the research's overall execution and manuscript writing, while Shixuan Peng was in charge of analyzing the data. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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CONFLICT OF INTEREST

There are no competing interests declared by the authors.

DATA AVAILABILITY STATEMENT

The datasets used in this investigation may be found in the MIMIC-III database (https://archive.physionet.org/works/MIMICIIIClinicalDatabase/files/).

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