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Impact of anion gap on in-hospital mortality in trauma-induced coagulopathy patients: a MIMIC-IV study

Xin Zuo¹, Huan Zuo¹ and Pengyu Zhu^{2*}

Abstract

Objective This study aimed to investigate the association between anion gap (AG) and clinical outcomes in patients with trauma-induced coagulopathy (TIC), and to evaluate the predictive value of dynamic AG trajectories for 28-day mortality.

Methods A retrospective cohort study was conducted using the MIMIC-IV database, including 1,358 TIC patients (INR > 1.4 or PTT > 40 s). Demographics, laboratory data (including AG), vital signs, and severity scores within 24 h of ICU admission were collected. Latent class growth modeling was used to identify AG trajectories at 8, 16, and 24 h. The primary outcome was 28-day mortality, analyzed via Cox regression and Kaplan–Meier survival analysis.

Results Among 1,358 patients, the 28-day mortality rate was 19.9%. Non-survivors were older and had worse vital signs, higher AG, and lower platelet and bicarbonate levels ($P < 0.05$). Elevated AG was independently associated with increased mortality (HR = 2.615, $P < 0.001$), even after multivariate adjustment. Patients with AG > 14.5 mEq/L had significantly reduced 28-day survival ($P < 0.001$). Four distinct AG trajectories were identified; Class 4, with persistently rising AG, showed the highest mortality risk (HR = 2.46, $P = 0.033$).

Conclusion AG is an independent predictor of 28-day mortality in TIC patients. AG > 14.5 mEq/L and persistently elevated trajectories are associated with poor short-term outcomes, especially in those with renal dysfunction or myocardial infarction. Dynamic AG monitoring may help identify high-risk patients early and guide clinical management.

Keywords Anion gap, Trauma-induced coagulopathy, MIMIC, Prognosis

Introduction

Trauma-induced coagulopathy (TIC) is a critical condition that significantly impacts the outcomes of trauma patients, contributing to high morbidity and mortality rates [1]. It is characterized by a complex interaction of

coagulation abnormalities following severe trauma, with estimates suggesting that TIC occurs in up to 33.4% of trauma patients [2]. The pathophysiology of TIC involves both primary and secondary coagulation abnormalities, which can lead to increased bleeding, disseminated intravascular coagulation, and impaired hemostasis, ultimately complicating clinical management and increasing the risk of adverse outcomes [3, 4].

The anion gap (AG) is a commonly used clinical indicator that measures the difference between the measured cations and anions in the blood, typically calculated as the concentration of sodium minus the sum of chloride and bicarbonate levels. This metric serves as a useful tool in identifying metabolic acidosis and assessing the

*Correspondence:

Pengyu Zhu
13069870666@163.com

¹ Department of Acupuncture and Moxibustion, Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, China

² Department of Acupuncture and Moxibustion, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin 150001, China



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underlying etiology of acid–base imbalances [5]. The AG reflects the concentration of unmeasured anions in the blood, making it an important marker for detecting disturbances in metabolic processes, especially in critically ill patients [6].

The pathophysiology of TIC is complex, involving multiple pathways such as coagulation factor consumption, endothelial cell activation, platelet dysfunction, fibrinolytic system imbalance, and metabolic disturbances [7]. Among these pathogenic factors, acidosis is one of the important concomitant conditions of TIC, particularly metabolic acidosis, which can exacerbate bleeding by reducing coagulation factor activity, inhibiting platelet function, and accelerating fibrinogen consumption [3, 7]. Studies have shown that acidosis may also trigger excessive activation of anticoagulant pathways, such as the activated protein C system, further inhibiting coagulation responses and worsening the hypocoagulable state [3]. In TIC patients, an elevated AG often indicates the presence of tissue hypoperfusion, hypoxia, and the accumulation of metabolic byproducts. These factors are not only closely related to coagulation dysfunction, but may also create a vicious cycle, leading to further exacerbation of coagulopathy [8]. Beyond its role in diagnosing acid–base disorders, the AG has been investigated in a variety of clinical settings, including its association with sepsis, renal failure, and cardiovascular diseases [9–11]. Previous studies have found that when elevated AG coexists with TIC, the risk of multiple organ dysfunction syndrome and death in patients is significantly increased [8, 12]. Therefore, the anion gap is not only an important biochemical marker for assessing the severity of TIC, but also serves as a critical reference for early identification of high-risk patients, prognosis prediction, and guiding clinical interventions. Although metabolic disturbances often accompany trauma and coagulopathy, the potential association between AG values and trajectories and the prognosis of TIC patients has not yet been fully explored.

This study aims to utilize the large-scale clinical data from the Medical Information Mart for Intensive Care (MIMIC-IV) database to explore the relationship between AG and its trajectory changes with the prognosis of TIC patients [13].

Method

Data source

The MIMIC-IV (version 3.1) database is a publicly accessible large-scale critical care database that contains detailed clinical information on over 70,000 hospitalized patients, including demographics, laboratory tests, medication records, vital signs, and clinical outcomes [13]. Access to the database requires formal application and completion of training. In this study, one of the authors,

Huan Zuo (ID: 65378168), obtained data access certification and was responsible for data extraction, including anion gap and other relevant variables, to analyze their association with the prognosis of TIC patients. As this study is retrospective and based on publicly available data, informed consent was not required. The methodology and reporting of our study follow the principles outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14].

Study population

Association between anion gap and outcomes in TIC patients

We used standard coagulation tests to determine the incidence of TIC in the study cohort. TIC was defined using standard coagulation parameters according to the Berlin Definition of Polytrauma (BerDef), where $\text{INR} > 1.4$ or $\text{PTT} > 40$ s [15, 16]. Data were extracted from the MIMIC-IV database, and the initial cohort consisted of 10,474 patients who were admitted to the trauma ICU.

Exclusion criteria: age < 18 years or > 100 years ($n = 1$); two or more ICU admissions ($n = 1168$); ICU length of stay < 24 h ($n = 2309$); patients with missing INR or PTT data ($n = 1508$); patients without coagulopathy ($\text{INR} \leq 1.4$ or $\text{PTT} \leq 40$ s) ($n = 3533$); mild or severe liver disease ($n = 323$); missing AG values ($n = 4$).

After applying the exclusion criteria, a total of 1358 TIC patients were included in the analysis and stratified into groups based on their 28-day prognosis (Fig. 1a). Variables with $> 15\%$ missing data were excluded, and those with $\leq 15\%$ missing data were imputed using the Random Forest method implemented in the missForest R package. This process ensured homogeneity within the study population and improved the reliability of subsequent analyses.

Anion gap trajectory analysis

The trajectory analysis was conducted in TIC patients from the above cohort who had AG measurements available at all three predefined time points (8 h, 16 h, and 24 h) after ICU admission.

Additional exclusion criterion: missing AG measurement at any of the predefined time points (8 h, 16 h, 24 h) ($n = 919$). Consecutive AG measurements were analyzed using latent class trajectory analysis (LCTA) to identify distinct AG trajectory patterns. Patients were classified into different trajectory classes, and clinical outcomes were compared across these groups (Fig. 1b).

Data collection

Data for this study were extracted from the MIMIC-IV database using PostgreSQL software, focusing on TIC patients. The data used in this analysis were limited to those collected on the first day of hospitalization to

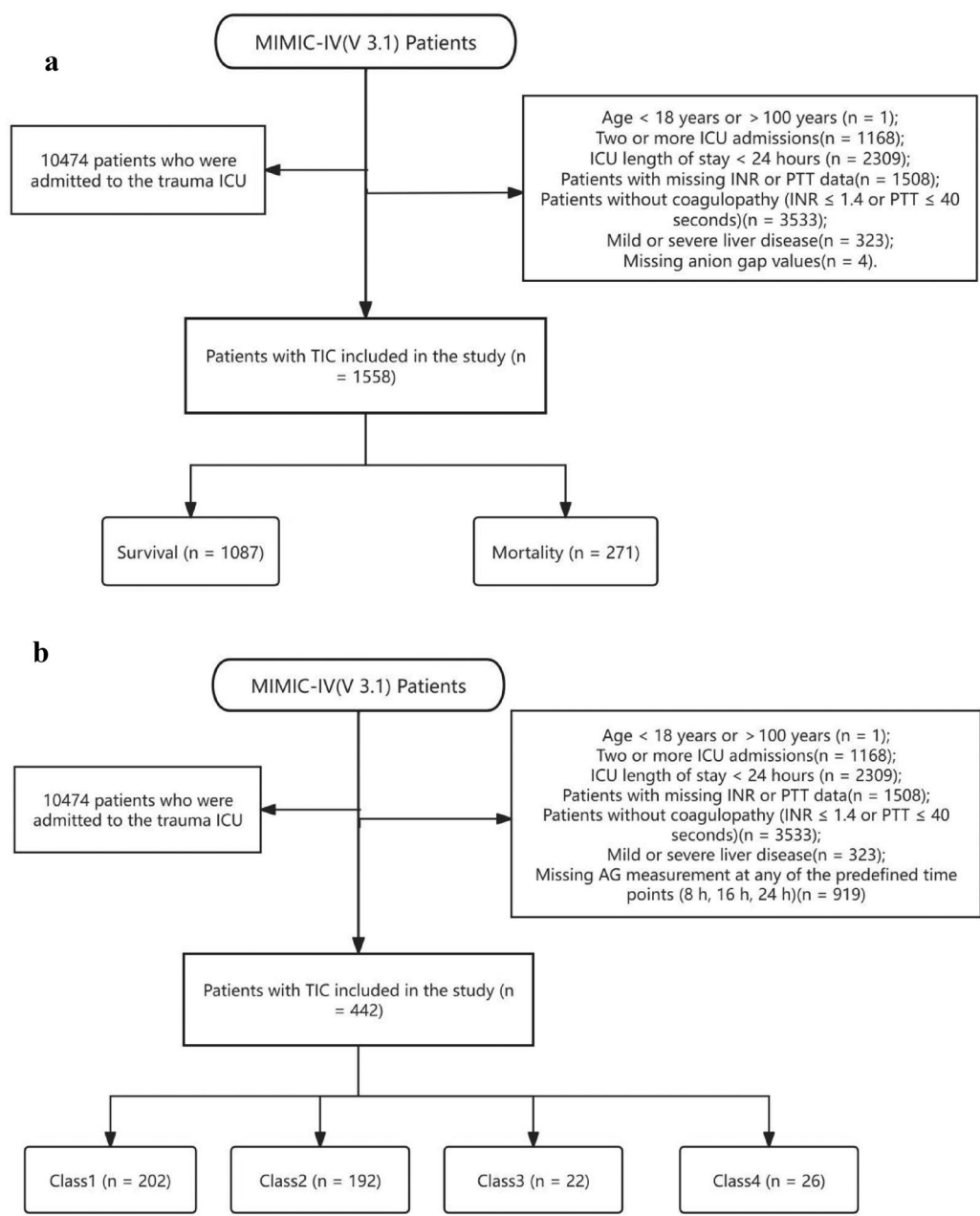


Fig. 1 a. Inclusion and exclusion criteria for the association between anion gap and outcomes in TIC patients. b. Inclusion and exclusion criteria for the anion gap trajectory analysis in TIC patients

standardize the study population and minimize confounding factors related to subsequent treatments or clinical changes. The collected variables included demographic information (age, gender, and race), laboratory test results [such as chloride, anion gap, bicarbonate, calcium, blood urea nitrogen (BUN), potassium, sodium, creatinine, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), white blood cell count (WBC), red cell distribution width

(RDW), red blood cell count (RBC), platelet, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), hemoglobin, hematocrit, and glucose], as well as vital signs (heart rate, blood pressure, oxygen saturation, respiratory rate, and temperature). Additionally, clinical scores such as the Charlson comorbidity index, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score II (SAPS II), and Glasgow Coma Scale (GCS) were recorded, alongside data on

comorbidities (including myocardial infarction, diabetes, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, acute kidney injury and renal disease). Treatment information, including the use of ventilator support and continuous renal replacement therapy (CRRT), was also collected. This comprehensive dataset, focused on the early clinical characteristics of patients, forms the basis for exploring the potential prognostic role of anion gap in TIC.

Latent growth mixture modeling

In the trajectory analysis, anion gap values were collected at 8, 16, and 24 h following ICU admission. To identify distinct AG trajectory patterns over the first 24 h, latent growth mixture modeling (LGMM) was applied using the *lcmm* package in R. This method assumes that the study population consists of unobserved (latent) subgroups, each following a unique time-based trajectory characterized by different patterns of change over time.

Quadratic growth models with one to seven latent classes were fitted to determine the optimal number of trajectory groups [17]. Model selection was based on a combination of statistical fit and clinical interpretability, with the following criteria:

Lower values of the Akaike information criterion (AIC), Bayesian information criterion (BIC), and sample-size-adjusted BIC; each class comprising at least 1% of the total sample; average posterior probabilities of class assignment $\geq 70\%$; Selection of the most parsimonious and clinically meaningful model. Patients missing AG measurements at any of the three predefined time points (8 h, 16 h, 24 h) were excluded from the trajectory analysis.

Outcomes

The primary outcome of the study was 28-day mortality, defined as patient survival within 28 days following hospital admission.

Statistical analysis

All analyses were performed using R software (version 4.2). Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed data were expressed as mean $\pm$ standard deviation (SD) and compared using the independent t-test or one-way ANOVA; non-normally distributed data were expressed as median (IQR) and compared using the Mann–Whitney U or Kruskal–Wallis test. Categorical variables were presented as counts and percentages and compared using the Chi-square or Fisher's exact test.

For AG level analysis, the optimal cutoff for predicting mortality was determined by ROC curve analysis with the Youden index, categorizing patients into low

and high AG groups. Kaplan–Meier curves with the log-rank test compared 28-day survival. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for in-hospital mortality, with multivariable adjustment for confounders ($P < 0.05$ in univariate analysis). Restricted cubic spline (RCS) analysis assessed nonlinear associations, and subgroup analyses evaluated interactions with age, sex, and comorbidities.

For AG trajectory analysis, LGMM was applied using the *lcmm* package in R, based on AG measurements at 8, 16, and 24 h after ICU admission. Quadratic growth models with one to seven classes were tested, with model selection guided by lower AIC, BIC, and sample-size-adjusted BIC, each class $\geq 1\%$ of the cohort, average posterior probability $\geq 70\%$, and clinical interpretability. Cox models assessed the association between trajectory groups and 28-day mortality using three models: Model 1 unadjusted; Model 2 adjusted for age, sex, and race; Model 3 additionally adjusted for significant variables in univariate analysis. Kaplan–Meier curves compared survival across trajectory groups, and subgroup analyses examined potential interactions. Two-sided $P < 0.05$ was considered statistically significant.

Result

Clinical and laboratory characteristics associated with mortality in trauma patients

This study included 1358 patients (1087 in the survival group and 271 in the mortality group). Compared with the survival group, the mortality group had older age, lower blood pressure, higher respiratory rate, and lower body temperature and oxygen saturation (all $P < 0.01$). Laboratory results showed higher INR, PT, RDW, MCV, anion gap, BUN, and creatinine, and lower RBC count, platelet count, and bicarbonate levels (all $P < 0.05$). SOFA, SAPS II, and Charlson comorbidity index scores were significantly higher (all $P < 0.001$), and renal disease, myocardial infarction, congestive heart failure, AKI, and CRRT use were more frequent (all $P < 0.05$). These factors may be associated with increased mortality risk (Table 1).

Association of anion gap with mortality across different models

Multivariate Cox regression identified lower DBP, SBP, MBP, SpO₂, temperature, RBC, platelet count, bicarbonate, and calcium, as well as higher respiratory rate, INR, PT, RDW, MCV, anion gap, BUN, creatinine, SOFA, SAPS II, and Charlson index as independent mortality risk factors (all $P < 0.05$). Black race was linked to lower risk, while “other” race, CRRT use, renal disease, myocardial infarction, and AKI were linked to higher risk (Table 2).

Table 1 Baseline characteristics of all participants according to survival status

Variables	Total (n = 1358)	Survival (n = 1087)	Mortality (n = 271)	P
Age(years)	70.00 (56.00, 81.00)	69.00 (54.00, 80.00)	76.00 (64.00, 86.00)	< 0.001
Gender, n (%)				0.098
Female	586 (43.15)	457 (42.04)	129 (47.60)	
Male	772 (56.85)	630 (57.96)	142 (52.40)	
Race, n(%)				< 0.001
White	916 (67.45)	742 (68.26)	174 (64.21)	
Black	114 (8.39)	102 (9.38)	12 (4.43)	
Others	328 (24.15)	243 (22.36)	85 (31.37)	
Vital signs				
Heart rate(beats/min)	73.00 (63.00, 85.00)	73.00 (63.00, 85.00)	73.00 (64.00, 86.00)	0.799
SBP(mmHg)	86.00 (77.00, 95.00)	87.00 (78.00, 96.50)	81.00 (70.00, 90.00)	< 0.001
DBP(mmHg)	44.00 (38.00, 50.00)	45.00 (39.00, 51.00)	41.00 (35.00, 48.00)	< 0.001
MBP(mmHg)	57.00 (51.00, 64.00)	58.00 (52.00, 65.00)	54.00 (45.00, 60.00)	< 0.001
Respiratory rate(breaths/min)	12.00 (10.00, 15.00)	12.00 (10.00, 14.00)	13.00 (10.50, 15.00)	< 0.001
SpO ₂ (%)	93.00 (90.00, 95.00)	93.00 (91.00, 95.00)	92.00 (87.00, 95.00)	0.007
Temperature(°C)	36.44 (36.00, 36.67)	36.44 (36.11, 36.67)	36.28 (35.26, 36.56)	< 0.001
Laboratory index				
Glucose(mg/dL)	107.00 (89.00, 127.00)	107.00 (90.00, 126.00)	109.00 (85.00, 129.00)	0.898
INR	1.60 (1.50, 2.00)	1.60 (1.50, 2.00)	1.70 (1.50, 2.05)	0.005
PT(s)	18.00 (16.10, 21.90)	17.80 (16.00, 21.80)	18.60 (16.50, 22.15)	0.006
PTT(s)	39.40 (32.20, 57.72)	38.90 (32.00, 58.20)	40.80 (34.00, 57.50)	0.063
WBC(K/uL)	9.70 (6.60, 13.70)	9.60 (6.60, 13.40)	10.10 (6.50, 14.55)	0.241
RBC(M/uL)	3.09 (2.64, 3.65)	3.12 (2.67, 3.70)	3.00 (2.59, 3.48)	0.011
RDW(%)	14.60 (13.70, 15.90)	14.50 (13.70, 15.70)	14.90 (14.00, 16.50)	< 0.001
Platelet(K/uL)	169.00 (110.00, 239.00)	174.00 (117.00, 243.50)	149.00 (94.00, 216.50)	< 0.001
MCV(fL)	89.00 (86.00, 94.00)	89.00 (85.00, 93.00)	91.00 (86.00, 95.00)	< 0.001
MCH(pg)	29.60 (28.20, 30.90)	29.50 (28.10, 30.90)	29.80 (28.70, 31.10)	0.063
Hemoglobin(%)	9.10 (7.80, 10.88)	9.20 (7.80, 11.00)	9.00 (7.80, 10.55)	0.092
Hematocrit(g/L)	27.80 (23.70, 32.80)	27.90 (23.80, 32.80)	27.40 (23.50, 32.00)	0.409
Anion gap(mEq/L)	12.00 (10.00, 14.00)	12.00 (10.00, 14.00)	13.00 (11.00, 16.00)	< 0.001
Chloride(mg/dL)	104.00 (100.00, 107.00)	104.00 (100.00, 107.00)	103.00 (98.50, 108.00)	0.947
Bicarbonate(mEq/L)	21.00 (18.00, 24.00)	21.00 (18.00, 24.00)	19.00 (15.00, 22.00)	< 0.001
Calcium(mg/dL)	7.80 (7.30, 8.30)	7.90 (7.40, 8.35)	7.70 (7.10, 8.30)	0.003
BUN(mg/dL)	18.00 (12.00, 29.00)	17.00 (11.00, 27.00)	23.00 (14.00, 35.50)	< 0.001
Potassium(mEq/L)	3.80 (3.50, 4.20)	3.80 (3.50, 4.20)	3.90 (3.50, 4.30)	0.508
Sodium(mEq/L)	137.00 (135.00, 140.00)	137.00 (135.00, 140.00)	138.00 (134.50, 141.00)	0.122
Creatinine(mg/dL)	0.90 (0.70, 1.40)	0.90 (0.70, 1.30)	1.10 (0.80, 1.70)	< 0.001
Score				
SOFA	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)	2.00 (1.00, 4.00)	< 0.001
SAPS II	38.00 (30.00, 49.00)	36.00 (28.00, 45.00)	50.00 (39.00, 60.00)	< 0.001
Charlson comorbidity index	5.00 (2.00, 7.00)	4.00 (2.00, 6.00)	6.00 (4.00, 8.00)	< 0.001
GCS	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)	0.706
Treatment				
Ventilator, n(%)				0.305
No	194 (14.29)	150 (13.80)	44 (16.24)	
Yes	1164 (85.71)	937 (86.20)	227 (83.76)	
CRRT, n(%)				< 0.001
No	1273 (93.74)	1048 (96.41)	225 (83.03)	
Yes	85 (6.26)	39 (3.59)	46 (16.97)	

Table 1 (continued)

Variables	Total (n = 1358)	Survival (n = 1087)	Mortality (n = 271)	P
Comorbidities				
Peptic ulcer disease, n(%)	47 (3.46)	37 (3.40)	10 (3.69)	0.818
Diabetes, n(%)	336 (24.74)	263 (24.20)	73 (26.94)	0.349
Renal disease, n(%)	267 (19.66)	201 (18.49)	66 (24.35)	0.030
Myocardial infarct, n(%)	168 (12.37)	124 (11.41)	44 (16.24)	0.031
Congestive heart failure, n(%)	350 (25.77)	256 (23.55)	94 (34.69)	< 0.001
Peripheral vascular disease, n(%)	213 (15.68)	166 (15.27)	47 (17.34)	0.401
Cerebrovascular disease, n(%)	167 (12.30)	131 (12.05)	36 (13.28)	0.580
Dementia, n(%)	59 (4.34)	47 (4.32)	12 (4.43)	0.940
Chronic pulmonary disease, n(%)	321 (23.64)	250 (23.00)	71 (26.20)	0.267
Rheumatic disease, n(%)	50 (3.68)	39 (3.59)	11 (4.06)	0.712
AKI, n(%)	1098 (80.85)	846 (77.83)	252 (92.99)	< 0.001

Values are expressed as the median (interquartile range) or n (%). *BUN* blood urea nitrogen, *INR* international normalized ratio; *PT* prothrombin time, *PTT* partial thromboplastin time, *WBC* white blood cell, *RDW* red blood cell volume distribution width; *RBC* red blood cell, *MCV* mean corpuscular volume; *MCH*, mean corpuscular hemoglobin, *SBP* systolic blood pressures, *DBP* diastolic blood pressures, *MBP* mean arterial pressures, *SpO₂* oxygen saturation, *SOFA* Sequential Organ Failure Assessment score, *GCS* Glasgow Coma Scale, *AKI* acute kidney injury, *CRRT* continuous renal replacement therapy

The hazard ratios for anion gap across different models are presented in Table 3. Across all models, a higher anion gap remained significantly associated with increased mortality. In the crude model and after adjusting for gender, race, and age, each unit increase in anion gap was linked to higher mortality hazard (all $P < 0.001$). This association persisted after further adjustment for vital signs, laboratory parameters, and severity scores ($P < 0.001$), and remained significant after additionally adjusting for CRRT use, renal disease, myocardial infarction, and AKI ($P = 0.002$).

Kaplan–Meier survival curve for anion gap and mortality in TIC

AG stratification was used to evaluate 28-day survival probability. Based on receiver operating characteristic (ROC) curve analysis, a threshold of 14.5 mEq/L was identified as the optimal cutoff for predicting 28-day mortality in patients with trauma-induced coagulopathy, and patients were divided into two groups accordingly. Kaplan–Meier survival analysis showed that patients with an AG > 14.5 mEq/L had a significantly lower 28-day survival probability compared to those with AG ≤ 14.5 mEq/L, with separation of the survival curves evident from the early follow-up period. The difference between the groups was statistically significant (log-rank $P < 0.001$), and a high AG was associated with a 2.615-fold increased risk of mortality (95% CI: 2.052–3.334) (Fig. 2).

Nonlinear association between anion gap and mortality risk

To further evaluate the relationship between AG and 28-day mortality risk, a restricted cubic spline (RCS)

model was applied. As shown in Fig. 3, AG exhibited a positive linear association with mortality risk (P for overall = 0.006), with no significant evidence of nonlinearity (P for nonlinear = 0.330). When the AG level was below approximately 12 mEq/L, the hazard ratio (HR) remained close to 1, indicating a low or baseline risk of mortality. However, as AG increased beyond 12 mEq/L, the HR rose progressively, demonstrating a consistent upward trend. Notably, when AG exceeded 20 mEq/L, the rate of increase in mortality risk became steeper, suggesting that elevated AG is strongly associated with higher risk of death in trauma-induced coagulopathy patients.

Subgroup analysis of anion gap and mortality risk

Subgroup analysis revealed that the association between anion gap and mortality risk remained significant across different subgroups. In all patients, higher anion gap was associated with a 7% increased risk of mortality (HR = 1.07, $P = 0.002$). Although younger patients, those without renal disease, and those without myocardial infarction appeared to exhibit a stronger association, no statistically significant interaction was observed for gender, age, renal disease, or myocardial infarction. No significant interaction was found between anion gap and other variables, such as peripheral vascular disease, cerebrovascular disease, and AKI (Fig. 4).

Model fit indices and AVEPP results for latent class analysis in trauma-induced coagulopathy

Latent class analysis was conducted with models ranging from one to seven classes. AIC and BIC values decreased as the number of classes increased, with the lowest AIC observed in the seven-class model (AIC = 7066.437).

Table 2 Univariate analysis of hospital mortality

Variables	P	HR (95%CI)
DBP	<0.001	0.97 (0.96~0.98)
SBP	<0.001	0.98 (0.97~0.98)
MBP	<0.001	0.98 (0.97~0.98)
Respiratory rate	<0.001	1.07 (1.04~1.11)
SpO ₂	<0.001	0.98 (0.97~0.98)
Temperature	<0.001	0.72 (0.67~0.78)
INR	0.011	1.12 (1.03~1.23)
PT	0.008	1.01 (1.01~1.02)
RBC	0.028	0.83 (0.70~0.98)
RDW	<0.001	1.11 (1.06~1.17)
Platelet	<0.001	0.99 (0.99~0.99)
MCV	<0.001	1.04 (1.02~1.06)
Anion gap	<0.001	1.14 (1.10~1.17)
Bicarbonate	<0.001	0.90 (0.88~0.93)
Calcium	0.014	0.85 (0.74~0.97)
BUN	<0.001	1.02 (1.01~1.02)
Creatinine	<0.001	1.19 (1.09~1.29)
SOFA	<0.001	1.14 (1.09~1.18)
SAPSII	<0.001	1.05 (1.04~1.06)
Charlson comorbidity index	<0.001	1.12 (1.08~1.16)
Race		
White		1.00 (Reference)
Black	0.032	0.53 (0.29~0.95)
Others	0.003	1.48 (1.14~1.92)
CRRT		
No		1.00 (Reference)
Yes	<0.001	3.87 (2.82~5.32)
Renal disease		
No		1.00 (Reference)
Yes	0.044	1.33 (1.01~1.75)
Myocardial infarct		
No		1.00 (Reference)
Yes	0.037	1.41 (1.02~1.95)
AKI		
No		1.00 (Reference)
Yes	<0.001	3.38 (2.12~5.39)

HR hazard ratio, CI confidence interval. BUN blood urea nitrogen, INR international normalized ratio, PT prothrombin time, RDW red blood cell volume distribution width, RBC red blood cell, MCV mean corpuscular volume, MCH mean corpuscular hemoglobin, SBP systolic blood pressures, DBP diastolic blood pressures, MBP mean arterial pressures, SpO₂ oxygen saturation, SOFA Sequential Organ Failure Assessment score, SAPSII Simplified Acute Physiology Score II, AKI acute kidney injury, CRRT continuous renal replacement therapy

AVEPP values were generally high (>0.7), except for the 5-class (Class 3: 0.645) and 6-class (Class 2: 0.683) models.

In the comparison of multiple candidate latent class models, we comprehensively evaluated the Bayesian information criterion (BIC), Akaike information criterion

(AIC), average posterior probability (AvePP), and class proportions. The results showed that the 4-class model (Class 4) had the lowest BIC value (7186.87) and a relatively low AIC value (7096.86) among all models. Additionally, the AvePP for each class was 0.761, 0.757, 0.846, and 0.917, all exceeding 0.70, indicating good classification accuracy. The class distribution in this model was relatively balanced, and the number of parameters was moderate, achieving a good balance between model fit and complexity. Based on these results, the 4-class model was chosen as the best-fitting model for subsequent analysis (Table 4).

The four AG trajectory patterns were: Class 1, baseline near the lower limit of normal (12–14 mmol/L) with a gradual decline; Class 2, baseline near the upper limit of normal ($\approx$ 15 mmol/L) with a slight initial rise followed by a decline; Class 3, markedly elevated baseline ($\approx$ 26 mmol/L) decreasing to $\approx$ 18 mmol/L before rising again; and Class 4, moderately elevated baseline ($\approx$ 19 mmol/L) rapidly increasing to $\approx$ 27 mmol/L, then gradually decreasing to $\approx$ 22 mmol/L. Overall, Class 1 and Class 2 had AG levels close to the normal range with small fluctuations, whereas Class 3 and Class 4 showed markedly elevated AG levels with large fluctuations—Class 3 demonstrated an initial improvement followed by rebound, and Class 4 showed acute worsening followed by gradual recovery (Fig. 5).

Association of anion gap trajectories with baseline characteristics, clinical risk factors, and 28-day mortality in trauma-induced coagulopathy

Trauma-induced coagulopathy patients were grouped by anion gap (Class1–Class4). Class4, with the highest anion gap, showed the oldest age, lowest vital signs, and the highest levels of INR, PT, BUN, and creatinine. It also had higher rates of diabetes, renal disease, and AKI, along with increased CRRT use and the lowest 28-day survival (all $P<0.05$). Higher anion gap was associated with worse clinical outcomes and increased mortality (Table 5).

This study compared baseline characteristics and identified key risk factors for 28-day mortality in trauma-induced coagulopathy patients. The mortality group was older and had worse vital signs, including lower SBP, DBP, MBP, SpO₂, and temperature (both $P<0.05$). Laboratory results showed higher INR, RDW, and lower platelet counts. The mortality group also had higher SOFA and SAPS II scores and more CRRT use (all $P<0.05$). AKI was more common in the mortality group ($P=0.008$) (Supplementary Table 1).

Cox regression analysis identified significant mortality risk factors, including older age, CRRT, AKI, and lower vital signs, specifically SBP, DBP, MBP, SpO₂, and

Table 3 Hazard ratios for anion gap across different models

Variables	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Anion gap	1.14 (1.10 ~ 1.17)	<0.001	1.14 (1.10 ~ 1.17)	<0.001	1.07 (1.03 ~ 1.12)	<0.001	1.07 (1.02 ~ 1.11)	0.002

HR hazard ratio, CI confidence interval

Model1: crude

Model2: adjust: gender, race, age

Model3:adjust: gender, race, age, SBP, DBP, MBP, respiratory_rate,SpO₂, temperature, INR,PT, RBC,RDW, platelet, MCV, bicarbonate, calcium, BUN, creatinine, SOFA, SAPSII, Charlson_comorbidity_index

Model4: adjust: gender, race, age, CRRT, renal_disease, myocardial_infarct, AKI, SBP, DBP, MBP, respiratory_rate, SpO₂, temperature, INR, PT, RBC, RDW, platelet, MCV, bicarbonate, calcium BUN, creatinine, SOFA, SAPSII, Charlson_comorbidity_index

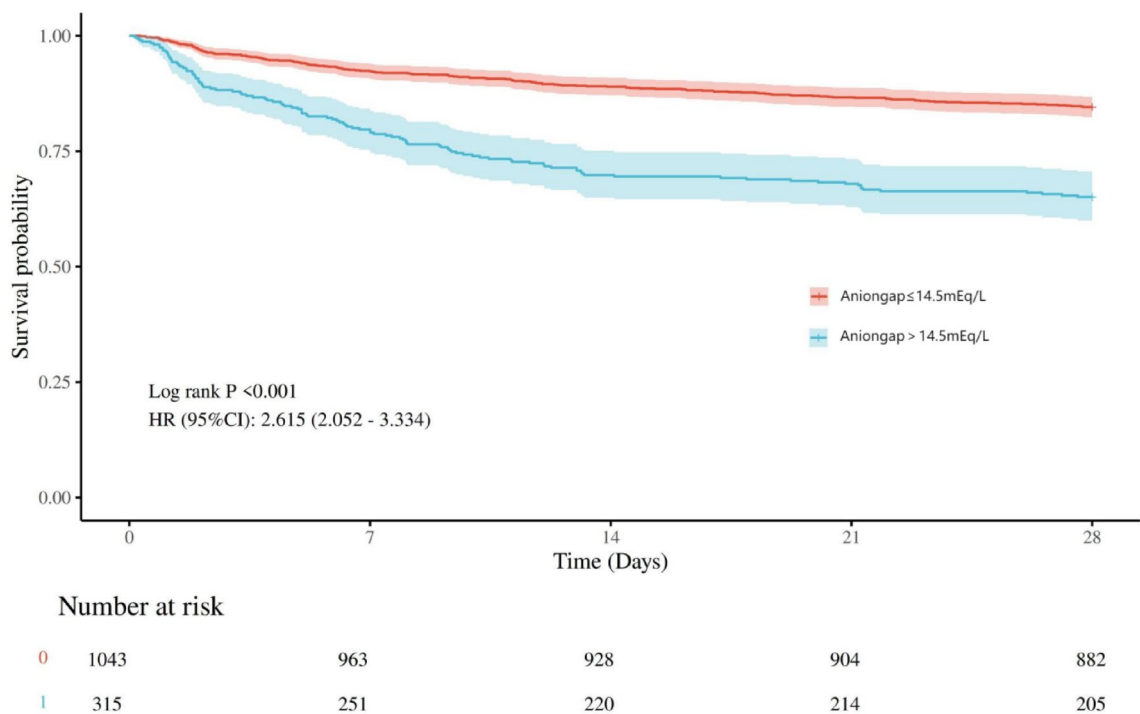


Fig. 2 Survival probability stratified by anion gap levels in TIC

temperature, were also associated with higher mortality risk. Laboratory and score data showed that higher INR, MCV, SOFA, and SAPS II scores were associated with increased mortality. Additionally, lower platelet count and lower bicarbonate levels were also significant risk factors (all $P<0.05$). These factors contribute to the higher mortality risk in this cohort (Supplementary Table 2).

Multivariate Cox regression analysis showed that, in the crude model (Model 1), compared with Class 1, mortality risk was significantly higher in Class 2 ($HR=2.13$, $P<0.001$),

Class 3 ($HR=3.03$, $P=0.003$), and Class 4 ($HR=6.22$, $P<0.001$). After adjusting for gender, age, and race (Model 2), the association remained significant for Class 2 ($HR=2.05$, $P=0.001$), Class 3 ($HR=3.33$, $P=0.001$), and Class 4 ($HR=6.24$, $P<0.001$). In the fully adjusted model (Model 3), which additionally accounted for vital signs, laboratory indices, SOFA, SAPS II, ventilator use, CRRT, and AKI, Class 2 ($HR=1.64$, $P=0.034$) and Class 4 ($HR=2.46$, $P=0.033$) remained significantly associated with increased mortality risk, while Class 3 showed no statistically significant association ($HR=2.02$, $P=0.096$) (Table 6).

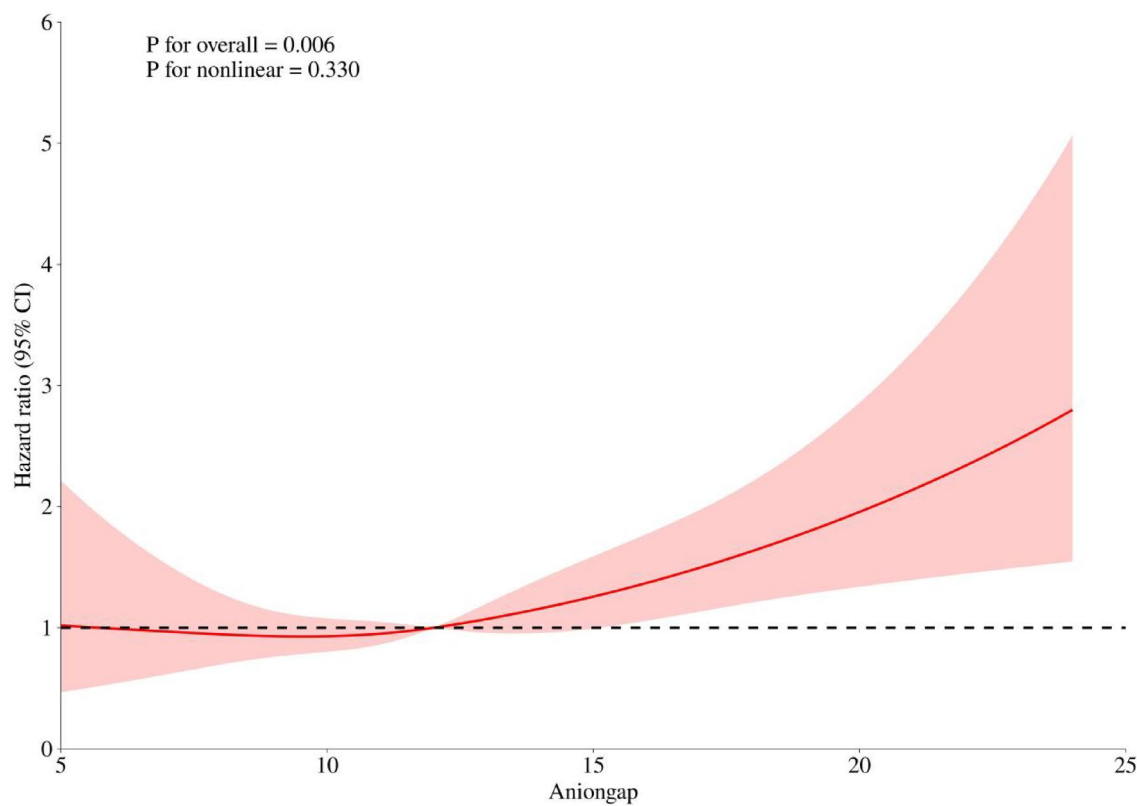


Fig. 3 Nonlinear relationship between anion gap and hazard ratio in TIC

Variables	n (%)	HR (95% CI)	P	P for interaction
All patients	1358 (100.00)	1.07 (1.02 ~ 1.11)	0.002	
Gender				0.829
Female	586 (43.15)	1.10 (1.04 ~ 1.17)	0.001	
Male	772 (56.85)	1.06 (1.00 ~ 1.13)	0.04	
Age Group				0.853
≤ 65	525 (38.66)	1.16 (1.07 ~ 1.25)	<.001	
>65	833 (61.34)	1.05 (1.00 ~ 1.11)	0.056	
Renal Disease				0.837
NO	1091 (80.34)	1.07 (1.02 ~ 1.12)	0.005	
YES	267 (19.66)	1.09 (1.01 ~ 1.18)	0.034	
Myocardial Infarct				0.923
NO	1190 (87.63)	1.07 (1.02 ~ 1.12)	0.003	
YES	168 (12.37)	1.08 (0.96 ~ 1.21)	0.19	
Peripheral Vascular Disease				0.721
NO	1145 (84.32)	1.08 (1.03 ~ 1.13)	0.002	
YES	213 (15.68)	1.15 (1.03 ~ 1.28)	0.015	
Cerebrovascular Disease				0.618
NO	1191 (87.70)	1.08 (1.03 ~ 1.12)	<.001	
YES	167 (12.30)	1.04 (0.90 ~ 1.20)	0.607	
AKI				0.113
NO	260 (19.15)	1.35 (1.02 ~ 1.78)	0.036	
YES	1098 (80.85)	1.07 (1.02 ~ 1.11)	0.003	

00.511.52

Worse better

Fig. 4 Subgroup analysis of hazard ratios for anion gap and prognosis in TIC

Table 4 Goodness-of-fit comparison of latent class analysis models (1–7 classes) in trauma-induced coagulopathy patients

Model	C1	C2	C3	C4	C5	C6	C7	AIC	BIC
1	1	NA	NA	NA	NA	NA	NA	7342.99	7371.628
2	0.938	0.892	NA	NA	NA	NA	NA	7156.383	7205.479
3	0.83	0.767	0.928	NA	NA	NA	NA	7139.389	7208.941
4	0.761	0.757	0.846	0.917	NA	NA	NA	7096.861	7186.87
5	0.772	0.8	0.645	0.868	0.894	NA	NA	7088.289	7198.754
6	0.796	0.683	0.702	0.825	0.878	0.893	NA	7081.006	7211.927
7	0.829	0.747	0.735	0.904	0.79	0.893	0.911	7066.437	7217.815

AIC Akaike information criterion, BIC Bayesian information criterion

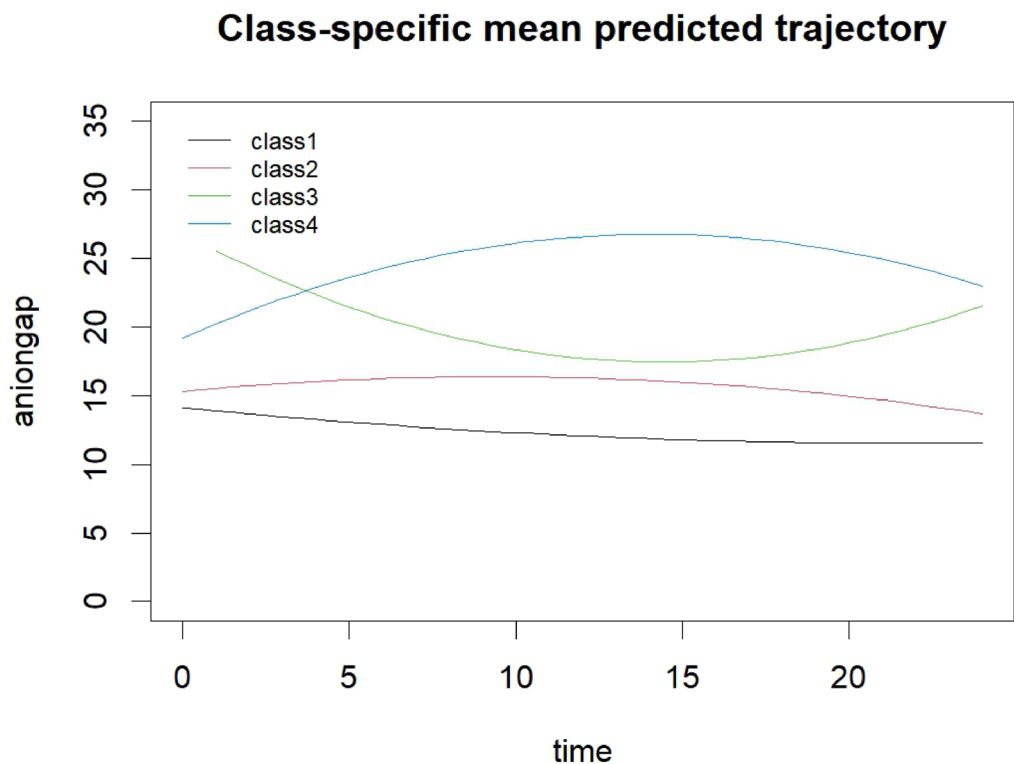


Fig. 5 Trajectories of anion gap across latent classes in TIC. Predicted mean trajectories of anion gap over time in 4 latent classes (class1–class4)

Survival analysis of anion gap trajectories in TIC patients

The results showed that patients in Class 4 (highest anion gap) had the lowest survival probability, followed by Class 3, while Class 1 had the highest survival rate. The log-rank test yielded $P < 0.001$, indicating statistically significant differences in survival curves among the groups. The decline in survival probability was most pronounced within the first 7 days, particularly in Classes 3 and 4, suggesting that a higher anion gap is associated with poorer short-term prognosis (Fig. 6).

Discussion

In this study, we demonstrated that a higher anion gap was strongly associated with adverse clinical profiles and increased mortality in TIC patients. Patients with

elevated anion gap exhibited more severe physiological derangements, including lower blood pressure, oxygen saturation, and temperature, as well as abnormal coagulation and metabolic parameters such as higher INR, PT, RDW, BUN, and creatinine, and lower bicarbonate and platelet counts. Survival analysis revealed that those in the highest anion gap trajectory (Class 4) had markedly poorer 28-day survival, with the steepest decline occurring within the first week. Multivariate Cox regression confirmed that this association persisted after adjusting for demographic factors, vital signs, laboratory indices, severity scores, and treatment variables, underscoring the independent prognostic value of anion gap in predicting short-term mortality in TIC.

Table 5 Comparison of baseline characteristics in TIC patients stratified by anion gap groups

Variables	Total (n = 442)	Class1 (n = 202)	Class2 (n = 192)	Class3 (n = 22)	Class4 (n = 26)	P
Age	69.00 (51.25, 78.00)	66.00 (47.25,77.00)	71.00 (54.75,80.00)	59.50 (42.25,72.75)	73.00 (63.50,78.00)	0.029
Gender, n(%)						0.872
Female	182 (41.18)	79 (39.11)	83 (43.23)	9 (40.91)	11 (42.31)	
Man	260 (58.82)	123 (60.89)	109 (56.77)	13 (59.09)	15 (57.69)	
Race, n(%)						0.195
White	276 (62.44)	125 (61.88)	123 (64.06)	11 (50.00)	17 (65.38)	
Black	33 (7.47)	15 (7.43)	10 (5.21)	4 (18.18)	4 (15.38)	
Others	133 (30.09)	62 (30.69)	59 (30.73)	7 (31.82)	5 (19.23)	
Vital signs						
Heart Rate(beats/min)	75.00 (63.00, 89.00)	73.00 (63.00,88.00)	75.00 (61.00,87.00)	77.00 (63.00,96.75)	85.00 (71.25,99.75)	0.093
SBP(mmHg)	80.00 (70.00, 90.00)	84.00 (75.00,94.00)	77.00 (68.50,87.00)	82.00 (72.00,88.00)	74.00 (63.50,81.75)	< 0.001
DBP(mmHg)	43.00 (36.00, 48.00)	44.00 (38.00,50.00)	41.00 (34.75,47.00)	43.50 (38.00,48.00)	38.00 (33.00,41.75)	0.001
MBP(mmHg)	55.50 (47.00, 61.00)	57.00 (51.25,62.75)	54.00 (44.00,59.25)	55.00 (37.88,58.75)	48.50 (32.25,51.00)	< 0.001
Respiratory rate(breaths/min)	12.00 (10.00, 15.00)	12.00 (9.00,14.00)	12.00 (10.00,15.00)	11.50 (10.00,15.00)	12.50 (10.25,14.75)	0.146
SpO ₂ (%)	93.00 (89.00, 96.00)	94.00 (91.00,96.00)	92.50 (87.00,95.25)	90.50 (85.25,95.00)	87.00 (79.00,93.75)	< 0.001
Temperature(°C)	36.39 (35.41, 36.61)	36.44 (35.62,36.61)	36.39 (35.56,36.61)	35.56 (34.26,36.44)	35.28 (33.47,36.21)	< 0.001
Laboratory index						
Glucose(mg/dL)	105.00 (84.25, 125.00)	104.50 (89.00,123.00)	106.00 (84.00,126.25)	110.00 (91.00,128.00)	72.00 (49.25,117.25)	0.029
INR	1.70 (1.50, 2.10)	1.70 (1.50,2.00)	1.70 (1.50,2.10)	1.65 (1.50,1.90)	2.25 (1.83,3.08)	< 0.001
PT(s)	18.70 (16.50, 22.60)	18.20 (16.30,21.20)	18.75 (16.58,22.60)	18.30 (16.12,20.85)	24.90 (19.88,33.88)	< 0.001
PTT(s)	41.10 (33.73, 64.15)	41.65 (33.70,72.62)	40.25 (32.98,61.73)	41.80 (33.05,55.48)	47.20 (38.23,70.75)	0.315
WBC(K/uL)	9.10 (5.20, 13.80)	8.75 (5.40,12.10)	10.45 (5.75,15.30)	7.10 (5.05,12.83)	7.10 (3.73,16.18)	0.139
RBC(M/uL)	2.90 (2.51, 3.44)	2.87 (2.51,3.36)	2.96 (2.58,3.54)	3.16 (2.40,4.62)	2.65 (2.24,3.22)	0.088
RDW(%)	14.30 (13.60, 15.30)	14.20 (13.50,15.17)	14.40 (13.70,15.50)	14.20 (13.38,14.93)	15.45 (14.20,17.20)	0.027
Platelet(K/uL)	138.50 (84.50, 195.75)	131.50 (87.25,192.00)	148.00 (93.25,206.25)	139.50 (58.25,194.00)	67.50 (51.75,145.75)	0.051
MCV(fL)	88.00 (85.00, 92.00)	88.00 (85.00,92.00)	88.00 (85.00,92.00)	87.00 (83.25,90.75)	91.50 (87.25,94.50)	0.059
MCH(pg)	29.60 (28.33, 30.80)	29.60 (28.33,30.90)	29.60 (28.40,30.72)	29.30 (27.48,30.15)	29.20 (28.33,30.28)	0.606
Hemoglobin(%)	8.70 (7.50, 10.30)	8.70 (7.50,10.00)	8.80 (7.60,10.60)	9.20 (7.00,12.97)	8.20 (6.45,9.23)	0.133
Hematocrit(g/L)	26.35 (22.40, 30.87)	26.15 (22.33,29.75)	26.60 (22.60,31.70)	28.40 (21.55,38.25)	25.95 (21.18,30.45)	0.285
Chloride(mg/dL)	103.00 (99.00, 107.00)	105.00 (102.00,108.00)	103.00 (99.00,107.00)	98.50 (94.00,104.75)	98.50 (95.25,101.75)	< 0.001
Bicarbonate(mEq/L)	18.00 (15.00, 21.00)	20.00 (17.00,22.00)	18.00 (15.00,20.00)	13.50 (10.00,15.75)	10.00 (8.00,13.00)	< 0.001
Calcium(mg/dL)	7.50 (7.00, 8.00)	7.50 (7.10,8.00)	7.40 (6.90,8.00)	7.45 (6.95,7.77)	7.25 (6.80,7.88)	0.392
BUN(mg/dL)	19.50 (13.00, 30.00)	16.00 (11.00,22.00)	23.00 (14.00,35.00)	22.00 (13.00,35.75)	27.50 (17.25,37.75)	< 0.001
Potassium(mEq/L)	3.80 (3.40, 4.20)	3.75 (3.40,4.10)	3.80 (3.48,4.20)	3.60 (3.23,3.98)	3.75 (3.32,4.07)	0.461
Sodium(mEq/L)	137.00 (134.00, 140.00)	137.00 (134.00,140.00)	136.00 (133.75,139.00)	137.50 (133.25,142.00)	137.00 (135.25,139.75)	0.164
Creatinine(mg/dL)	1.00 (0.70, 1.60)	0.90 (0.70,1.20)	1.20 (0.80,1.80)	1.40 (1.00,2.45)	1.80 (1.35,3.15)	< 0.001
Score						
SOFA	2.00 (1.00, 5.00)	2.00 (0.00,4.00)	3.00 (1.00,5.00)	3.50 (2.25,4.75)	5.00 (3.00,8.00)	< 0.001
SAPS II	45.00 (35.00, 57.00)	40.00 (31.00,49.75)	50.00 (37.00,61.00)	51.50 (33.00,58.75)	62.00 (57.00,72.00)	< 0.001
Charlson comorbidity index	4.00 (2.00, 6.00)	4.00 (1.00,6.00)	5.00 (2.00,7.00)	3.00 (2.00,5.75)	5.50 (4.00,7.00)	0.002
GCS	15.00 (15.00, 15.00)	15.00 (15.00,15.00)	15.00 (15.00,15.00)	15.00 (15.00,15.00)	15.00 (15.00,15.00)	0.152
Treatment						
Ventilator, n(%)						0.627
No	40 (9.05)	19 (9.41)	15 (7.81)	3 (13.64)	3 (11.54)	
Yes	402 (90.95)	183 (90.59)	177 (92.19)	19 (86.36)	23 (88.46)	
CRRT, n(%)						< 0.001
No	381 (86.20)	195 (96.53)	165 (85.94)	14 (63.64)	7 (26.92)	

Table 5 (continued)

Variables	Total (n = 442)	Class1 (n = 202)	Class2 (n = 192)	Class3 (n = 22)	Class4 (n = 26)	P
Yes	61 (13.80)	7 (3.47)	27 (14.06)	8 (36.36)	19 (73.08)	
Comorbidities						
Peptic ulcer disease, n(%)	14 (3.17)	8 (3.96)	5 (2.60)	0 (0.00)	1 (3.85)	0.709
Diabetes, n(%)	104 (23.53)	36 (17.82)	53 (27.60)	5 (22.73)	10 (38.46)	0.034
Renal disease, n(%)	80 (18.10)	26 (12.87)	40 (20.83)	6 (27.27)	8 (30.77)	0.025
Myocardial infarct, n(%)	63 (14.25)	23 (11.39)	29 (15.10)	7 (31.82)	4 (15.38)	0.080
Congestive heart failure, n(%)	114 (25.79)	41 (20.30)	55 (28.65)	6 (27.27)	12 (46.15)	0.022
Peripheral vascular disease, n(%)	71 (16.06)	33 (16.34)	28 (14.58)	2 (9.09)	8 (30.77)	0.182
Cerebrovascular disease, n(%)	36 (8.14)	17 (8.42)	18 (9.38)	0 (0.00)	1 (3.85)	0.546
Dementia, n(%)	16 (3.62)	7 (3.47)	5 (2.60)	0 (0.00)	4 (15.38)	0.038
Chronic pulmonary disease, n(%)	97 (21.95)	46 (22.77)	41 (21.35)	5 (22.73)	5 (19.23)	0.971
Rheumatic disease, n(%)	21 (4.75)	10 (4.95)	9 (4.69)	1 (4.55)	1 (3.85)	1.000
AKI, n(%)	401 (90.72)	173 (85.64)	182 (94.79)	20 (90.91)	26 (100.00)	0.005
Outcome						
Hosp time 28d	28.00 (20.91, 28.00)	28.00 (28.00,28.00)	28.00 (12.32,28.00)	28.00 (6.27,28.00)	10.40 (3.23,28.00)	< 0.001
Hosp outcome 28 d, n(%)						< 0.001
Survival	321 (72.62)	169 (83.66)	131 (68.23)	13 (59.09)	8 (30.77)	
Mortality	121 (27.38)	33 (16.34)	61 (31.77)	9 (40.91)	18 (69.23)	

Values are expressed as the median (interquartile range) or n (%). *BUN* blood urea nitrogen, *INR* international normalized ratio, *PT* prothrombin time, *PTT* partial thromboplastin time, *WBC* white blood cell, *RDW* red blood cell volume distribution width, *RBC* red blood cell, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *SBP* systolic blood pressures, *DBP* diastolic blood pressures, *MBP* mean arterial pressures, *SpO₂* oxygen saturation, *SOFA* Sequential Organ Failure Assessment score, *GCS* Glasgow Coma Scale, *AKI* acute kidney injury, *CRRT* continuous renal replacement therapy

Table 6 Multivariate Cox regression analysis of AG trajectories and 28-day mortality in TIC

Model	Class	HR (95% CI)	P
Model 1	Class1	Reference	–
	Class2	2.13(1.39, 3.25)	< 0.001
	Class3	3.03(1.45, 6.33)	0.003
	Class4	6.22(3.49, 11.07)	< 0.001
Model 2	Class1	Reference	–
	Class2	2.05(1.34, 3.14)	0.001
	Class3	3.33(1.59, 7.00)	0.001
	Class4	6.24(3.50, 11.13)	< 0.001
Model 3	Class1	Reference	–
	Class2	1.64(1.04, 2.59)	0.034
	Class3	2.02(0.88, 4.63)	0.096
	Class4	2.46(1.08, 5.60)	0.033

HR hazard ratio. CI confidence interval

Model1: crude

Model2: adjust: gender, age, race

Model3: adjust: gender, age, race, SBP, DBP, MBP, SpO₂, temperature, INR, platelet, MCV, bicarbonate, SOFA, SAPSII, ventilator, CRRT, AKI

TIC, occurs when patients transition from an initial hypocoagulable state to a hypercoagulable state after surviving the initial trauma, increasing the risk of thromboembolic complications. Early recognition and treatment are crucial [18]. Trauma induces a systemic inflammatory state, contributing to coagulation derangements and increased fibrinolysis. Approximately 25% of severely injured patients exhibit coagulopathy upon hospital admission, with higher rates in those with severe injuries [3]. TIC is a multifactorial condition involving endothelial injury, systemic inflammation, and coagulation factor consumption. Endothelial damage exposes subendothelial structures, activating platelets and initiating the coagulation cascade. However, this response is often coupled with a systemic inflammatory reaction, which depletes coagulation factors and platelets, leading to a hypocoagulable state [19]. Inflammatory mediators further impair platelet function and endothelial integrity, exacerbating coagulation abnormalities [19, 20].

Elevated AG is associated with poor outcomes in trauma patients [21]. AG is often elevated in the presence of metabolic acidosis, lactate accumulation—factors

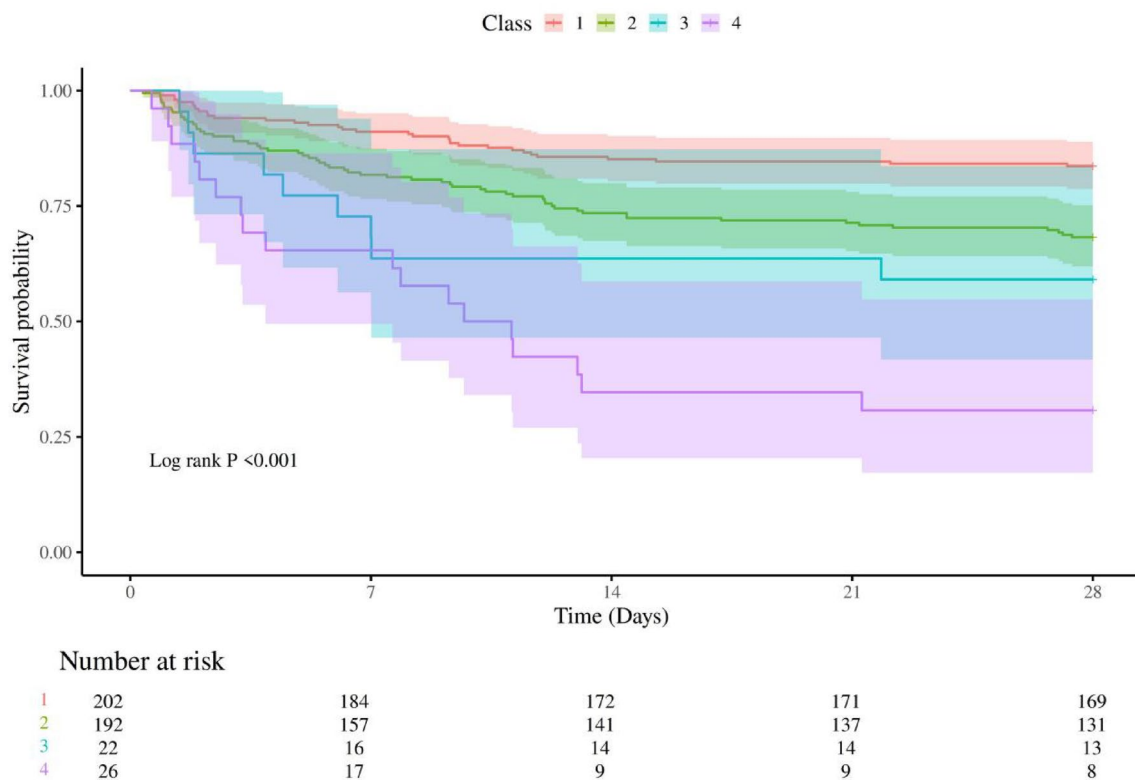


Fig. 6 Comparison of 28-day survival curves by anion gap groups in TIC. The log-rank test indicated statistically significant differences in survival rates among the four groups ($P < 0.001$). Patients in Class 4 showed significantly worse survival compared to other groups. The number at risk at each time point is presented in the table below

that exacerbate coagulopathy [22]. Lactate accumulation, caused by tissue hypoxia and impaired perfusion, leads to an acidotic environment that inhibits coagulation factors and platelet function, contributing to bleeding and coagulation dysfunction in TIC [23].

Studies have shown that in patients with mild trauma, an elevated AG may not immediately manifest as clinical symptoms, but it could reflect underlying metabolic imbalance and physiological disturbances, which can impact the patient's complication rate and mortality. An increase in AG is positively correlated with trauma severity and mortality, particularly when the AG exceeds 16, at which point the risk of death significantly increases [21]. Furthermore, Kaplan et al. noted that in the emergency setting of traumatic large vessel injury, an increase in the anion gap is closely associated with acid–base disturbances, particularly with lactate accumulation and standard base deficit. Together, these factors make AG a strong predictor of mortality. These studies suggest that an elevated anion gap reflects the metabolic acidosis and hypoperfusion states associated with TIC. Currently, no studies have explored the relationship between anion gap and prognosis in trauma-induced coagulopathy. Our

study fills this gap by providing novel insights into the prognosis of patients with trauma-induced coagulopathy [24].

In patients with TIC, an elevated AG is often regarded as a reflection of lactate accumulation; however, existing evidence suggests that lactate is not the sole contributor. Severe hemorrhagic shock can lead to systemic tissue hypoperfusion and reduced oxygen delivery, promoting anaerobic metabolism and lactate production, while also being accompanied by mitochondrial dysfunction and tricarboxylic acid cycle blockade, resulting in the generation and release of various non-lactate unmeasured anions [25]. In a standardized canine hemorrhagic shock model, although lactate concentration increased from 1.5 mEq/L to 5.5 mEq/L, it accounted for only about 36% of the AG elevation. The remaining portion was primarily attributable to unmeasured anions such as acetate (+2.2 mEq/L), citrate (+2.2 mEq/L), α -ketoglutarate, fumarate, and urate. Most of these acidic metabolites originate from impaired mitochondrial metabolism and nucleotide degradation processes [25]. In addition, clinical studies on sepsis have also found a limited correlation between elevated AG and lactate concentration,

suggesting that changes in AG may reflect a more complex process of metabolic acidosis [26]. These studies suggest that in TIC patients, elevated AG may not merely reflect lactate accumulation but rather result from systemic metabolic disturbances induced by shock. Therefore, the extent of AG elevation may be closely related to the severity of TIC and its associated metabolic alterations, making it an important marker for prognostic assessment. In fact, multiple studies have confirmed that elevated AG is strongly associated with clinical outcomes, particularly in trauma and critically ill patients. For TIC patients, an elevated AG may serve as an important warning sign of disease progression and increased mortality risk, indicating the presence of more severe metabolic derangements and acidosis.

In this study, trajectory analysis classified patients into four groups, revealing that dynamic changes in AG not only reflect heterogeneity in metabolic status but are also closely associated with prognosis. Class 1 and Class 2 had AG levels near the normal range with small fluctuations, suggesting relatively stable metabolic status. However, although Class 2 showed only mild elevation with a “rise-then-fall” pattern, its mortality risk remained significantly higher than that of Class 1 (HR=1.64), indicating that dynamic AG changes may better reveal underlying risk than static values. In contrast, Class 3 and Class 4 exhibited markedly elevated AG levels with large fluctuations, suggesting severe metabolic disturbances such as tissue hypoxia, renal dysfunction, or toxin accumulation. The “fall-then-rise” pattern of Class 3 may reflect metabolic deterioration after initial improvement, which, although not statistically significant, still warrants caution. The “rapid rise followed by gradual decline” seen in Class 4 aligns with an acute critical illness course; even after full adjustment, its mortality risk was 2.46 times that of Class 1, indicating that abrupt AG fluctuations are an independent predictor of poor prognosis [27, 28].

In the subgroup analysis of this study, elevated AG was significantly associated with increased mortality risk in most subgroups, and its prognostic value remained consistent across different clinical contexts, including sex, age, and the presence or absence of renal disease, myocardial infarction, cerebrovascular disease, and peripheral vascular disease (all interaction $P > 0.05$). Notably, among patients without AKI, the association between AG and mortality was the strongest (HR=1.35, 95% CI: 1.02–1.78, $P=0.036$), suggesting that in patients with relatively preserved renal function, AG may be a more sensitive marker of underlying metabolic abnormalities and tissue perfusion status [27]. However, the interaction between this subgroup and others did not reach statistical significance (P for interaction=0.113), indicating that AG has broad applicability across different clinical

subgroups. These findings highlight that AG, as a simple and readily available indicator, demonstrates robust risk prediction capability in diverse populations, supporting its potential for widespread use in the management of critically ill patients.

This study has several limitations. First, the data were derived from the MIMIC-IV database, a retrospective dataset from a single hospital, which may introduce selection bias and may not fully represent the clinical characteristics of all trauma patients. Trauma patients were identified based on ICU type codes (trauma ICU); however, the database did not provide detailed information on the primary injured organ systems for all patients, making it impossible to stratify or report patients by injury site. This limitation may affect the comprehensiveness and generalizability of the results. Second, the study only considered data from the first day of hospitalization, which may overlook dynamic changes during the hospital stay and limit the ability to assess long-term outcomes. In addition, although multiple factors were analyzed, other unmeasured variables—such as trauma type, injury severity, surgical interventions, and nutritional status—may also influence TIC and mortality risk. Furthermore, the MIMIC-IV database lacks systematic and complete pre-admission medication information, such as oral anticoagulants (e.g., warfarin, direct oral anticoagulants) or other drugs that could affect coagulation function. As a result, we could not accurately determine whether patients had used such medications before admission, which may have led to some cases of elevated INR not being entirely attributable to TIC but rather to drug-related effects. Although an elevated anion gap is associated with TIC, it is not specific to TIC. In trauma patients without TIC, hemorrhagic shock can also lead to increased anion gap. Shock-induced impairment of tissue perfusion and oxygen delivery can cause lactate accumulation, which in turn increases the anion gap. Therefore, part of the elevated anion gap may reflect metabolic disturbances caused by shock rather than TIC alone. Although adjustments were made for multiple clinical variables, lactate accumulation from acute hemorrhagic shock may still partially explain the association between high anion gap and increased mortality risk. Finally, although Cox regression models were used, their observational nature prevents establishing causality. Therefore, while an association between elevated anion gap and TIC was found, causality should be interpreted with caution. Moreover, the results are based on data from a large hospital in the United States, limiting their generalizability to trauma patient populations in other regions. Future studies should incorporate prospective, multicenter designs, along with more

clinical interventions and long-term follow-up, to further validate these findings and explore their applicability across different regions and populations.

Conclusion

This study systematically evaluated the association between anion gap (AG) and 28-day mortality in TIC patients. Elevated AG was significantly associated with increased mortality, as confirmed by multivariate Cox regression and Kaplan–Meier analysis, even after adjusting for confounders. Nonlinear analysis showed an approximately linear relationship between AG and mortality risk. Latent class analysis identified four AG trajectory patterns, with Classes 3 and 4—marked by elevated and fluctuating AG—exhibiting worse clinical profiles and the lowest survival rates. Class 4 had the highest adjusted mortality risk. Overall, AG is a simple yet powerful prognostic marker in TIC, and its dynamic changes may aid in early risk stratification and intervention.

Supplementary Information

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Supplementary file 1

Supplementary file 2

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Author contributions

Study concept and design by XZ and HZ; Acquisition, analysis, or interpretation of data by all authors; Drafting of the manuscript by HZ; Critical revision of the manuscript by HZ and XZ; Statistical analyses by PZ and XZ; Supervision of research by PZ. All authors contributed to the article and approved the submitted version.

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Data availability

This study analyzed publicly available datasets, accessible at: <https://physionet.org/content/mimiciv/2.0/>.

Declarations

Ethics approval and consent to participate

This study received approval from the Institutional Review Board (IRB) at Beth Israel Deaconess Medical Center under approval number 2001P-001699/14, with informed consent obtained from all study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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