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Association between serum anion gap and all-cause mortality in patients with acute myocardial infarction: A retrospective study based on MIMIC-IV database

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ABSTRACT

Background: Although previous studies have reported that many biomarkers can determine the prognosis of patients with acute myocardial infarction (AMI), serum anion gap (AG) has not been well studied. We aimed to investigate the association between serum AG and mortality in patients with AMI.

Methods: Adult patients first admitted to the ICU and diagnosed with AMI from 2008 to 2019 in the MIMIC-IV database were included. Patients were divided into the survival and non-survival groups based on 30-day and 90-day outcomes. According to the AG value (15.12 mmol/L) with a hazard ratio of 1 in the restricted cubic spline (RCS) analysis, patients were further divided into high and low AG groups. The Kaplan-Meier survival curve was plotted, and all-cause mortality was compared between the high and low groups using the log-rank test. Multivariate Cox regression analysis and RCS analysis were constructed to assess the relationship between AG and recent all-cause mortality in patients with AMI.

Results: 4446 patients were enrolled. The 30-day and 90-day mortality rates in the high AG group (25.53%, 31.75%) were higher than that in the low AG group (9.73%, 14.01%, $P < 0.001$) independently. The Kaplan-Meier curve showed that the 30-day and 90-day cumulative survival rates were lower in the high AG group than that in the low AG group ($P < 0.001$). RCS analysis showed that there was a non-linear relationship between AG and the risk of 90-day all-cause mortality in patients with AMI ($\chi 2 = 18.680$ $P < 0.001$). When AG was 15.12 mmol/L, its HR was about 1. Multivariable Cox regression analysis confirmed that increased AG was associated with higher 30-day and 90-day mortality.

Conclusion: Elevated serum AG ($\geq$15.12 mmol/L) is an independent predictor for short-term mortality in patients with AMI, and it may provide a basis for clinicians to identify patients with poor prognosis as early as possible.

1. Introduction

Acute myocardial infarction (AMI), is a common cardiovascular disease, and the leading cause of death worldwide [1]. Cardiogenic

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shock in AMI remains a major cause of morbidity and mortality [2]. Recognizing and understanding the risk factors for death after AMI provides clinicians with important information for determining prognosis and guiding treatment. However, the early and accurately determination of patients' outcomes is full of challenges and often biased by unavoidable factors.

Many indicators for determining the prognosis of patients with AMI have been discovered, such as brain natriuretic peptide, troponin, high-sensitivity C-reactive protein, miRNAs, and neutrophil-to-lymphocyte ratio; however, their specificity and sensitivity remain questionable [3]. Therefore, identifying a simple but efficient marker is particularly imperative.

Serum anion gap (AG) is widely used in acid-base balance analysis, usually by calculating the difference between unmeasured anions and unmeasured cations, with abnormal and high values suggesting metabolic acidosis [4]. So, AG can evaluate acid-base disorders and identify the cause of metabolic acidosis [5]. Additionally, serum AG levels are closely associated with metabolic acidosis severity. Recently, AG has been commonly used as a significant indicator for disease diagnosis or prognosis in clinical practice. Serum AG of adult patients in the intensive care unit (ICU) has been reported to be an excellent tool with good sensitivity and specificity for predicting prognosis or death. Some studies have established a connection between high serum AG levels and poor prognoses in patients with acute pancreatitis [6], sepsis [7], acute pesticide poisoning [8] and so on. Furthermore, it has been used to predict mortality in ICU children [9]. However, there is still no research on the relationship between serum AG and the prognosis in adult patients with AMI, so we analyzed the association between serum AG levels and recent all-cause mortality in order to assess the predictive value of AG in adult patients with AMI. We presented the following article according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist.

2. Methods

2.1. Sources of data

The study data were obtained from a large and publicly available critical care database (Medical Information Mart for Intensive Care IV [MIMIC-IV]). One author (Lei Zhong) who has passed the "Protecting Human Research Participants" examination, could access the database and was responsible for data extraction (Record ID: 36142713).

The data abstracted from the MIMIC-IV database using a structured query language were stored in PostgreSQL. Baseline characteristics included age, sex, comorbidities, the sequential organ failure assessment (SOFA) score, simplified acute physiology score II (SAPS II), acute physiology score (APS III), length of ICU stay, length of hospital stay for patients with AMI. Comorbidities such as hypertension, diabetes, cardiac arrest (CA), congestive heart failure, cardiogenic shock, atrial fibrillation (AF), acute kidney injury (AKI), chronic kidney disease (CKD), chronic pulmonary disease and malignant cancer were counted. Also, data on the therapy of defibrillation, norepinephrine, intra-aortic balloon counterpulsation (IABP), continuous renal replacement therapy (CRRT), and transthoracic echocardiography were also collected. In addition, we collected data from blood tests including serum AG, bicarbonate, white blood cell (WBC) count, hemoglobin, platelet, red blood cell distribution width (RDW), creatinine, blood urea nitrogen (BUN), mean corpuscular volume (MCV), prothrombin time (PT), glucose, potassium, magnesium, chlorine and sodium. The first laboratory test results were obtained after ICU admission.

2.2. Population selection criteria

In MIMIC-IV, the diagnoses of patients were defined according to the International Classification of Diseases, Clinical Modification. We retrospectively collected data of ICU patients from 2008 to 2019, according to the ICD-9 and ICD-10 codes of 410%, 121% and 122%. Adult patients first admitted to the ICU and diagnosed with AMI were included in the study.

The exclusion criteria were as followings:

(1) ICU length of stay (LOS) $<$ 24 h or death within 24 h
(2) Repeated ICU admissions
(3) Missing key data.

2.3. Groups and primary endpoints

According to the 30-day follow-up outcomes, the enrolled patients were divided into the survival group (n = 3673) and the non-survival group (n = 773). Based on the90-day follow-up outcomes, patients were divided into the survival group (n = 3441) and the non-survival group (n = 1005). In addition, the patients were further divided into high AG group (n = 2292) and low AG group (n = 2154) based on the AG value (15.12 mmol/L) with a hazard ratio (HR) of 1 in the restricted cubic spline (RCS) analysis, which was described later in this study.

The primary endpoint was 90-day all-cause mortality and the secondary endpoint was 30-day all-cause mortality.

2.4. Statistical analysis

Continuous variables were first tested for normality. Continuous variables conformed to normal distribution are expressed as mean ± standard deviation [SD] and were analyzed using the *t*-test method. While continuous variables that did not conform to a normal distribution are presented as median (interquartile range) and were analyzed using a nonparametric method (Mann-Whitney *U* test).

Categorical data are presented as frequencies and percentages and were analyzed by the chi-square method.

Kaplan-Meier curves were plotted, and the log-rank test was used to compare the cumulative survival rate between the high and low AG groups.

After the 24 factors of $P < 0.1$ between the survival and non-survival group in the basic data were adjusted, including age, sex, SOFA score, hemoglobin, MCV, RDW, creatinine, BUN, glucose, prothrombin time, WBC, the incidence of hypertension, CA, congestive heart failure, cardiogenic shock, AF, AKI, CKD, chronic pulmonary disease , malignant cancer, the number of receiving norepinephrine, defibrillation, transthoracic echocardiography and CRRT. RCS analysis were performed to investigate the relevance between AG and 90-day all-cause mortality risk in patients with AMI.

Univariate and multivariate Cox regression analysis was applied to determine whether increased serum AG was independently associated with higher 30-day and 90-day all-cause mortality in patients with AMI, and the results are expressed as HR with 95% confidence intervals (CI). In model I, there were no adjustments for covariates. In model II, the following covariates were adjusted: age, sex, SOFA score, hemoglobin, MCV, RDW, creatinine, BUN, glucose, prothrombin time and WBC. On the basis of model II, model III adjusted for the incidence of hypertension, CA, congestive heart failure, cardiogenic shock, AF, AKI, CKD, chronic pulmonary disease, malignant cancer, the therapy of norepinephrine, defibrillation, transthoracic echocardiography and CRRT.

We analyzed the data using Stata version 14.0 and R programming language version 4.2.0. Statistical significance was defined as a two-tailed *P*-value of <0.05.

3. Results

3.1. Subject characteristics

Finally, 4446 adult ICU patients were screened in this study (Fig. 1). The average age of the participants was 71.38 ± 13.02 years, and the average SOFA score was 5. As shown in Table 1, compared to the survival group, age, SOFA score, SAPS II, APS III, serum AG, WBC count, RDW, creatinine, BUN, MCV, PT, glucose, potassium, the incidence of CA, congestive heart failure, cardiogenic shock, AF, AKI, CKD, chronic pulmonary disease, malignant cancer, the proportion of receiving CRRT, defibrillation, norepinephrine, transthoracic echocardiography, ICU LOS and the proportion of women in the non-survival group were higher ($P < 0.05$). However, bicarbonate, hemoglobin, chlorine, the incidence of hypertension, and length of hospital stay in the non-survival group were lower ($P < 0.05$).

3.2. All-cause mortality

The 30-day and 90-day all-cause mortality rates of the included patients were 17.39% and 22.60% independently. The 30-day mortality rate in the high AG group (25.53%) was significantly higher than that in the low AG group (9.73%, $\chi 2 = 193.101$; $P < 0.001$). While, the 90-day mortality rate in the high AG group (31.75%) was also higher than that in the low AG group (14.01%, $\chi 2 = 199.967$; $P < 0.001$), as shown in Table 2.

3.3. Kaplan-Meier survival curve analysis

The Kaplan-Meier curve showed that the 30-day and 90-day cumulative survival rates were lower in the high AG group than that in the low AG group (log-rank test, $\chi_1^2 = 194.950$, $P < 0.001$; $\chi_2^2 = 207.240$, $P < 0.001$) (Figs. 2 and 3).

3.4. Correlation between AG and all-cause mortality

After adjusting the confounding factors, RCS showed that there was a non-linear relationship between AG and the risk of 90-day all-cause mortality in patients with AMI ($\chi 2 = 18.680$, $P < 0.001$). With the increase of AG, the risk of 90-day all-cause mortality in

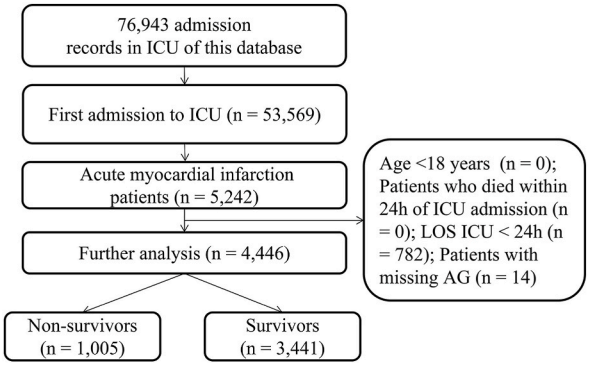

Fig. 1. Flowchart of the patient flow diagram.

Table 1
Baseline data of patents with AMI in the two groups based on 90-day all-cause mortality.

Variables	All participants (n = 4446)	Survival group (n = 3441)	Non-survival group (n = 1005)	*t/Z/χ2*	*P*- value
Age	71.38 ± 13.02	69.91 ± 12.82	76.42 ± 12.42	−14.257	<0.001
Sex, female, n (%)	1640 (36.89)	1220 (35.45)	420 (41.79)	13.414	<0.001
SOFA score	5.00 (3.00 , 8.00)	4.00 (2.00, 7.00)	8.00 (5.00, 11.00)	−20.992	<0.001
SAPS II	50.21 ± 24.80	44.54 ± 20.66	69.61 ± 27.81	−31.483	<0.001
APS III	39.15 ± 13.79	36.41 ± 12.44	48.50 ± 12.44	−26.267	<0.001
AG (mmol/L)	16.04 ± 4.99	15.36 ± 4.70	18.38 ± 5.25	−17.397	<0.001
Bicarbonate (mmol/L)	22.26 ± 4.62	22.64 ± 4.30	20.94 ± 5.38	10.406	<0.001
WBC ($\times 10^9$/L)	11.40 (8.40, 15.50)	11.10 (8.30, 14.90)	12.80 (9.20, 17.60)	−7.538	<0.001
Hemoglobin (g/L)	111.26 ± 24.98	112.28 ± 25.17	107.75 ± 23.96	5.083	<0.001
Platelet ($\times 10^9$/L)	204.00 (153.00, 266.00)	204.00 (154.00, 263.00)	209.00 (151.00, 282.00)	−0.861	0.389
RDW (%)	14.61 ± 2.04	13.35 ± 1.86	15.49 ± 2.35	−15.926	<0.001
Creatinine (umol/L)	97.24 (79.56, 150.28)	97.24 (70.72, 132.60)	132.60 (97.24, 203.32)	−15.567	<0.001
Blood urea nitrogen (mmol/L)	22.00 (16.00, 37.00)	21.00 (15.00, 32.00)	33.00 (21.00, 52.00)	−18.424	<0.001
Mean corpuscular volume (fL)	91.48 ± 6.74	91.12 ± 6.41	92.70 ± 7.62	−6.577	<0.001
Prothrombin time (s)	13.60 (12.2, 15.9)	13.60 (12.10, 15.50)	14.20 (12.70, 17.80)	−8.836	<0.001
Glucose (mmol/L)	7.72 (6.28, 10.38)	7.50 (6.17, 9.94)	8.61 (6.67, 11.94)	−8.680	<0.001
Blood potassium (mmol/L)	4.40 ± 0.83	4.36 ± 0.77	4.55 ± 0.89	−6.667	<0.001
Blood magnesium (mmol/L)	0.85 ± 0.17	0.85 ± 0.18	0.85 ± 0.16	−0.279	0.780
Blood chlorine (mmol/L)	102.96 ± 6.23	103.30 ± 5.86	101.83 ± 7.24	6.593	<0.001
Blood sodium (mmol/L)	137.98 ± 4.77	137.93 ± 4.29	138.15 ± 6.13	−1.288	0.198
Comorbidities, n (%)					
Hypertension	1864 (41.93)	1555 (45.19)	309 (30.75)	66.650	<0.001
Diabetes	1868 (42.02)	1447 (42.05)	421 (41.89)	0.008	0.927
Cardiac arrest	283 (6.37)	131 (3.81)	152 (15.12)	167.154	<0.001
Congestive heart failure	2318 (52.14)	1687 (49.03)	631 (62.79)	59.013	<0.001
Cardiogenic shock	658 (14.80)	372 (10.81)	286 (28.46)	192.097	<0.001
Atrial fibrillation	1579 (35.52)	1147 (33.33)	432 (42.99)	31.639	<0.001
Acute kidney injury	3060 (68.83)	2242 (65.16)	818 (81.39)	95.582	<0.001
Chronic kidney disease	1296 (29.15)	901 (26.18)	395 (39.30)	64.822	<0.001
Chronic pulmonary disease	1136 (25.55)	815 (23.68)	321 (31.94)	27.867	<0.001
Malignant cancer	376 (8.46)	207 (6.02)	169 (16.82)	117.194	<0.001
IABP, n (%)	475 (10.68)	358 (10.40)	117 (11.64)	1.249	0.264
CRRT, n (%)	249 (5.60)	113 (3.28)	136 (13.53)	154.524	<0.001
Defibrillation, n (%)	165 (3.71)	94 (2.73)	71 (7.06)	40.865	<0.001
Norepinephrine, n (%)	1237 (27.82)	710 (20.63)	527 (52.44)	391.789	<0.001
Transthoracic echocardiography, n (%)	1292 (29.06)	925 (26.88)	367 (36.52)	35.032	<0.001
ICU LOS (d)	2.64 (1.57, 4.71)	2.33 (1.47, 4.06)	3.76 (1.99, 6.91)	−13.351	<0.001
Length of hospital stay (d)	8.08 (4.96, 12.96)	8.13 (5.17, 12.75)	7.75 (3.96, 14.58)	2.141	0.032

Abbreviations: AMI acute myocardial infarction, SOFA sequential organ failure estimate, SAPS II Simplified Acute Physiology Score II, APSIII Acute Physiology Score, AG anion gap; WBC white blood cell; RDW red blood cell distribution width, IABP intraaortic balloon counterpulsation, CRRT continuous renal replacement therapy, ICU intensive care unit, LOS length of stay.

Table 2
30-day and 90-day all-cause mortality in patients with AMI between the two groups.

	30-day		χ2	*P*- value	90-day		χ2	*P*- value
Group	Survivors (n = 3673)	Non-survivors (n = 773)			Survivors (n = 3441)	Non-survivors (n = 1005)		
Low AG	2069 (90.27)	223 (9.73)	193.101	<0.001	1971 (85.99)	321 (14.01)	199.967	<0.001
High AG	1604 (74.47)	550 (25.53)			1470 (68.25)	684 (31.75)		

AG, anion gap.

patients with AMI also increased. When AG was 15.12 mmol/L, its HR was 1 (Fig. 4).

Univariate Cox regression showed that high AG (≥15.12 mmol/L) was associated with 30-day and 90-day all-cause mortality (HR 2.869, 95%CI 2.456–3.352, $P < 0.001$ and HR 2.550, 95%CI 2.233–2.912, $P < 0.001$, respectively). In model II, after adjusting for age, sex, SOFA score, hemoglobin, MCV, RDW, creatinine, BUN, glucose, prothrombin time and WBC, high AG (≥15.12 mmol/L) also positively associated with 30-day and 90-day mortalities. In addition to adjusting for the covariates in model II, model III also adjusted for the incidence of hypertension, CA, congestive heart failure, cardiogenic shock, AF, AKI, CKD, chronic pulmonary disease, malignant cancer, the therapy of norepinephrine, defibrillation, transthoracic echocardiography and CRRT. The results showed that the high AG group had a higher 30-day (HR, 1.593, 95%CI 1.338–1.897, $P < 0.001$) and 90-day (HR, 1.498, 95 %CI 1.289–1.739, $P < 0.001$) all-cause mortality than the low AG group, indicating that increased AG (≥15.12 mmol/L) was an independent risk indicator for recent poor outcomes in patients with AMI (Table 3).

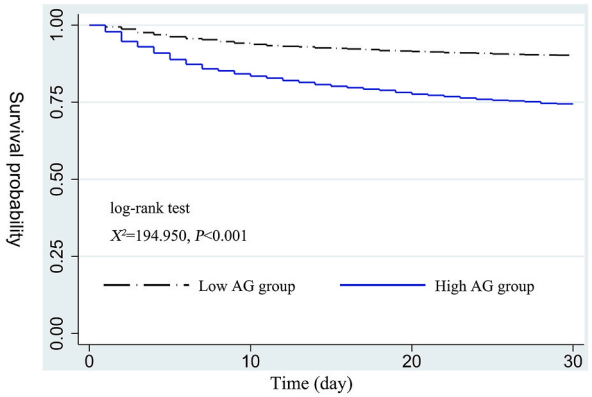

Fig. 2. Kaplan-Meier survival curve of 30-day cumulative survival rate for low and high AG groups.

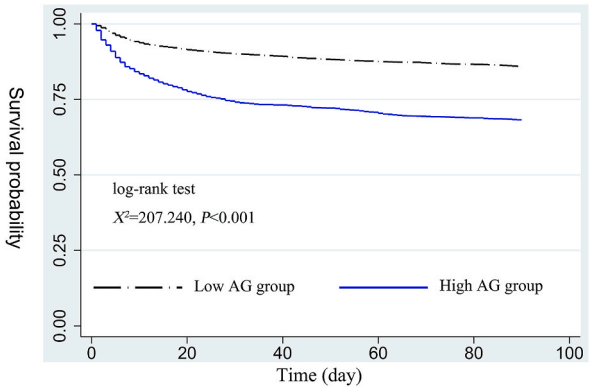

Fig. 3. Kaplan-Meier survival curve of 90-day cumulative survival rate for low and high AG groups.

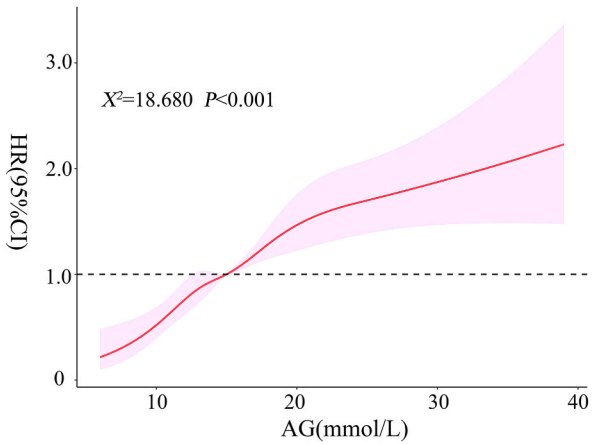

Fig. 4. The association between serum AG and 90-day all-cause mortality risk in patients with AMI.

4. Discussion

In this article, we aimed to investigate the relationship between serum AG levels and recent all-cause mortality in patients with AMI. The results showed that the 30-day and 90-day mortality rates in the high AG group were significantly higher than that in the low AG group ($P < 0.001$). Kaplan-Meier survival curve analysis showed that the 30-day and 90-day cumulative survival rates were significantly lower in the high AG group than in the low AG group. After adjusting for covariates, the multivariate Cox regression and RCS analysis showed that high AG (≥15.12 mmol/L) was association with recent all-cause mortality in patients with AMI, indicating

Table 3
Cox regression analysis results of the two groups.

Variable	Model I			Model II			Model III		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value	HR	95%CI	*P*-value
30-day mortality									
Low AG group	1			1			1		
High AG group	2.869	2.456–3.352	<0.001	1.764	1.483–2.098	<0.001	1.593	1.338–1.897	<0.001
90-day mortality									
Low AG group	1			1			1		
High AG group	2.550	2.233–2.912	<0.001	1.657	1.428–1.922	<0.001	1.498	1.289–1.739	<0.001

Model I: no covariates were adjusted.
Model II: adjusted for age, sex, SOFA score, hemoglobin, MCV, RDW, creatinine, BUN, glucose, prothrombin time, and WBC.
Model III: based on model II, adjusted for the incidence of hypertension, CA, congestive heart failure, cardiogenic shock, AF, AKI, CKD, chronic pulmonary disease, malignant cancer, the therapy of norepinephrine, defibrillation, transthoracic echocardiography and CRRT.
Abbreviations: HR hazard ratio, 95% CI 95% confidence interval.

that high AG (≥15.12 mmol/L) was an independent factor to predict the poor outcomes in patients with AMI, which may provide a basis for early intervention in those patients.

Critically ill patients are more prone to electrolyte and acid-base disorders [10], and metabolic acidosis is the most common type of acid-base disturbance in this population [11]. Metabolic acidosis refers to a group of acid-base disorders in which the serum bicarbonate concentration is reduced, and can usually be divided into high AG normochloremic and normal AG hyperchloremic metabolic acidosis [12]. High AG metabolic acidosis is an important subtype of metabolic acidosis, and identifying the possible causes of this condition is beneficial to treatment strategies. Many studies have reported that metabolic acidosis is a risk factor for mortality in critically ill patients with chronic liver disease [13]and acute kidney injury [14]. Therefore, it is clinically significant to conduct research on patients with severe metabolic acidosis. In recent years, as a serological index, AG has attracted the attention of clinicians because it can be easily calculated. Zhao et al. found that AG (≥17.00) was an independent predictive factor for long-term all-cause mortality in patients following coronary artery bypass grafting, where a high AG value was associated with an increased mortality [15]. In addition, other studies have shown that elevated AG levels are associated with the severity and mortality of diseases such as chronic kidney disease [16] and aortic aneurysm [17].

As a common clinical emergency that is sometimes accompanied by serious complications such as cardiorespiratory arrest, shock, stroke, atrioventricular block, and respiratory failure [18]. There are a series of characteristics in patients with AMI, such as myocardial energy deficit, oxidative stress, ionic imbalance, cardiac cytotoxicity, and membrane injury [19]. Moreover, AMI is often accompanied by anaerobic cellular respiration and severe inflammatory response, while anaerobic respiration and the pentose phosphate pathway can increase the concentration of lactic acid and carbon dioxide in the body, resulting in acidosis [20]. As an indicator of acidosis, serum AG may be associated with AMI severity or prognosis; however, there are few studies on the relationship between different AG levels and poor clinical prognosis in AMI patients. In 2006, a retrospective clinical study of 773 AMI patients reported that metabolic acidosis with increased AG (>12 mmol/L) on admission was an independent risk factor for in-hospital mortality (odds ratio [OR] 4.2, 95%CI 2.3–7.5) [21]. However, in 2013, a clinical study of 63 patients with ST-segment elevation AMI reported the absence of a significant difference in AG between the survival and non-survival groups, but the sample size of this study was too small to draw conclusions [22]. Recently, a retrospective clinical study showed that the area under the curve for AG predicted AMI was 0.62 (0.59, 0.65) and the albumin-corrected AG was an independent risk factor for 30-day all-cause mortality (HR 1.75, 95% CI 1.24, 2.47) [23]. In contrast, the patients included in our study were AMI patients who were hospitalized in the ICU and the follow-up period was relatively longer in our study. We explored the clinical value of different serum AG levels while evaluating the predicting value of the short-term outcomes. Finally, we found that high serum AG (≥15.12 mmol/L) was an independent predictor for recent all-cause mortality in patients with AMI.

The advantage of our study is that it was a real-world clinical study with a large sample size (4446 adult patients with AMI) and a relatively long follow-up period of 90 days. Additionally, a cutoff value of serum AG was provided to guide the clinician to predict prognosis timely and accurately. Thus, serum AG should be monitored in patients with AMI to early value the outcomes and intervene in clinically in order to obtain a better prognosis. However, this study has some limitations. It was a retrospective single-center clinical study and did not provide specific information on the Killip classification in patients with AMI. Therefore, multicenter and prospective studies, with a longer follow-up and a larger sample size are needed to confirm our results.

5. Conclusion

In conclusion, elevated serum AG (≥15.12 mmol/L) is an independent risk factor for short-term mortality in adult patients with AMI, and it may provide a basis for clinicians to identify patients with poor prognosis as early as possible.

Ethics approval and consent participate

One author (Lei Zhong) who has passed the “Protecting Human Research Participants” examination, could access the database and was responsible for data extraction (Record ID: 36142713). MIMIC-IV database used in the present study was approved by the

Institutional Review Boards (IRB) of Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology and was given a waiver of informed consent.

Consent for publication

Not applicable.

Author contribution statement

Jianhong Lu: Designed the protocol, rite the manuscript, reviewed and edit he manuscript.
Lei Zhong: Collected and analyzed the data.
Meng Yuan: Reviewed and edited the paper.
Jie Min: Reviewed and edited the paper.
Yin Xu: Designed the protocol, write the manuscript, reviewed and edit he manuscript.

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Data availability statement

Date will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interests.

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None.

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