International Journal of Emergency Medicine

RESEARCH

Open Access

The association between anion gap and prognosis in patients myocardial infarction with congestive heart failure: a retrospective analysis of the MIMIC-IV database

Muzheng Li[1†], Chenyang Li[2†], Jihua Wang[1] and Qinghua Yuan[1*]

Abstract

Background Elevated serum anion gap at hospital admission is often linked to a poor prognosis in critically ill patients, but there is insufficient data on this correlation in patients with acute myocardial infarction accompanied by heart failure. In this study, we aimed to determine the relationship between serum admission AG and all-cause mortality in patients with acute myocardial infarction accompanied by heart failure.

Methods We conducted a retrospective analysis of data within the MIMIC-IV database. Serum AG was collected at ICU admission, and all-cause mortality after discharge was analyzed. Multivariable Cox proportional hazards regression models and Kaplan-Meier survival curve analyses were used to assess the relationship between serum AG and myocardial infarction accompanied by heart failure as well as all-cause mortality.

Results A total of 943 patients with acute myocardial infarction complicated by heart failure were included in the study. The all-cause mortality rate after discharge was 24.7% and 18.9%. Multivariable analysis, adjusted for potential confounders, indicated that compared to low serum AG levels (< 12 mmol/L), high serum AG levels (> 17 mmol/L) were associated with an increased risk of all-cause mortality. Similarly, Kaplan-Meier survival curves also indicated that patients with higher serum AG levels had lower survival rates. Stratified analysis further showed that the association between higher serum AG levels and in-hospital all-cause mortality was observed across different subgroups based on stratification variables.

Conclusions In patients with acute myocardial infarction complicated by heart failure, elevated serum AG levels at ICU admission are associated with an increased risk of all-cause mortality.

Keywords Anion gap, Heart failure post myocardial infarction, Prognosis

†Muzheng Li and Chenyang Li contributed equally to this work.

*Correspondence:
Qinghua Yuan
yuanqinghua@sysush.com

[1]Department of Cardiology, the Seventh Affiliated Hospital of Sun Yat-sen University, Shenzhen 518000, Guangdong, China
[2]Department of Cardiovascular Medicine, the Second Affiliated Hospital, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, Zhejiang, China

Introduction

Myocardial infarction (MI) is characterized by localized ischemic necrosis of the heart tissue due to obstructed blood supply, leading to ischemia and hypoxia. MI has a rapid onset, with high rates of mortality and disability [1–3]. Despite improved outcomes from early reperfusion and medical interventions, congestive heart failure following MI (HFpMI) remains common, correlating with increased morbidity and mortality [4]. Given the severe risks of MI and HFpMI, there is an urgent need for quick, accessible, and cost-effective tests to identify those at higher risk, guiding more targeted management strategies.

In recent years, some studies have found that intermountain risk score (IMRS) have prognostic value in patients with critical status such as ST-elevation myocardial infarction or cardiogenic shock [5–6]. Anion gap (AG), which is very similar to the IMRS and determined by the difference between serum cations and anions, is a standard biochemical indicator for evaluating clinical acid-base balance. It has been linked to a variety of medical conditions [7–16], Assessing the anion gap helps determine disease severity and predict outcomes [12, 14, 16]. Evaluating base excess upon admission is beneficial for early risk stratification and mortality prediction [17, 18]. Metabolic acidosis, a common occurrence in critical care settings, is closely tied to patient prognosis [19]. Ischemia can induce metabolic disturbances, altering ion concentrations [20]. The systemic acid-base balance is sensitive to ischemic events [21], suggesting that the anion gap (AG) could be a potential biomarker for myocardial infarction (MI). However, the relationship between AG and heart failure post-MI (HFpMI) has not been fully elucidated. This analysis aims to investigate the link between serum AG levels and patient prognosis in HFpMI.

Methods

Study population and data extraction

We performed a retrospective cohort study on data extracted by the Structured Query Language (SQL) in the MIMIC-IV database (version 1) from 2008 to 2019, which was approved by the institutional review boards of Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) and the Massachusetts Institute of Technology. We followed the methods structure of Changli Zhong, et al. [22]. The extracted data included demographics, vital signs, laboratory tests, and comorbidities. We designed and conducted this study in accordance with the relevant guidelines and regulations (Declaration of Helsinki). Since all data were anonymized, informed consent was no needed.

These 1863 patients were admitted to the intensive care unit (ICU) for the first time between 2008 and 2019 with acute myocardial infarction. We excluded 901 patients not have congestive heart failure ($n = 901$), lack of data anion gap ($n = 19$); ultimately, 943 patients with CHF were included in the study.

Exclusion criteria include the following: (I) ICU stays less than 24 h, (II) repeat ICU admissions, and (III) missing key data such as anion gap (AG), (IV) loss to follow-up.

Clinical data encompassed age, race, gender, heart rate, blood pressure, respiratory rate, temperature, blood glucose, sodium, potassium, presence of diabetes, liver and renal diseases, and the Charlson Comorbidity Index.

Laboratory parameters were collected at time points aligned with the MIMIC database guidelines, which define the first ICU day as the period from 6 h before to 24 h after ICU admission. These data were based on the initial test results post-ICU admission. Notably, AG was specifically extracted from the MIMIC database to minimize confounding factors from different time points.

The definition of variable exposure and outcome events

The primary endpoint was all-cause hospital mortality, with ICU mortality as the secondary endpoint, assessed at hospital discharge. Continuous variables were reported as means ± standard deviation (SD) or medians with interquartile ranges (IQR), while categorical variables were expressed as percentages. Statistical differences among the four AG groups were analyzed using Fisher's exact test, Chi-square tests, or the Kruskal-Wallis test.

Restricted cubic spline (RCS) analysis was employed to delineate the linear relationship between serum AG levels and all-cause mortality in ICU and hospital settings for patients with HFpMI.

Multivariate Cox proportional hazard models were utilized to elucidate the association between AG and the risk of all-cause mortality at 30, 60, 90, and 365 days. Kaplan-Meier survival curves were plotted, and log-rank tests were applied to compare survival rates across different AG groups over these time frames.

Receiver operating characteristic (ROC) curves assessed the predictive value of AG for 30-day and 365-day mortality. Subgroup analyses were conducted to determine if the relationship between AG and mortality at 30 and 365 days was influenced by factors such as age (>70 vs. ≤50 years), sex, race, presence of diabetes, and renal disease.All analyses were performed with SPSS v. 24.0 and the R statistical software package (http://www.R-project.org, R Foundation) and the Fengrui statistical software version 1.9.2 were used for all analyses.

Results

Baseline characteristics of the participants

A total of 943 individuals were selected from 1863 patients with acute myocardial infarction combined

with congestive heart failure (Fig. 1). Among them, 614 were male and 329 were female, with an average age of 68.1 ± 14.3 years. As shown in Table 1, patients are assigned to four groups according to the quartile of AG value. It was found that patients with high serum AG levels (≥ 17 mmol/L) had higher heart rates and respiratory rates, but lower blood pressure and body temperature, indicating worse vital signs. Additionally, the proportion of patients with diabetes, mild liver disease, and kidney disease was higher, and the Charlson Comorbidity Index further confirmed these findings.

Cox regression of myocardial infarction with quartile of anion gap

Table 2 presents both unadjusted and adjusted analyses of serum AG levels and one-year all-cause mortality in patients with acute myocardial infarction and heart failure, using the Cox proportional hazards model. When serum AG was treated as a continuous variable, it was associated with an increased risk of one-year all-cause mortality [HR = 1.87 (95% CI: 1.63–2.14)]. When treated as a categorical variable, patients with lower serum AG levels (< 12 mmol/L) served as the reference group. In the crude model, higher serum AG levels were associated with an increased risk of one-year all-cause mortality, with this effect becoming more pronounced as AG levels increased. For instance, patients in the highest serum AG quartile (Q4) had a 514% increased risk of all-cause mortality compared to those in the lowest quartile (Q1) [HR = 6.14, 95% CI = 3.59–10.51, $p < 0.01$]. However, patients in the third quartile (Q3; 15 < AG ≤ 17) had only a 148% increased risk of all-cause mortality compared to those in Q1 [HR = 2.48, 95% CI = 1.38–4.43, $p < 0.01$]. This finding is consistent with the observed trend that one-year all-cause mortality increases as serum AG levels rise. After adjusting for confounding factors (age, heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, Charlson Comorbidity Index, and congestive heart failure), serum AG remained associated with an increased risk of one-year all-cause mortality, whether treated as a continuous or categorical variable.

Kaplan-Meier curves survival analysis

The Kaplan-Meier survival curves showed that, in 30 days-, 60 days-, 90 days- and 365 days- survival analysis, high serum AG levels at admission (≥ 17 mmol/L) were significantly associated with a lower survival rate ($p < 0.0001$), and this effect became more pronounced over time in the high AG group (Fig. 2).

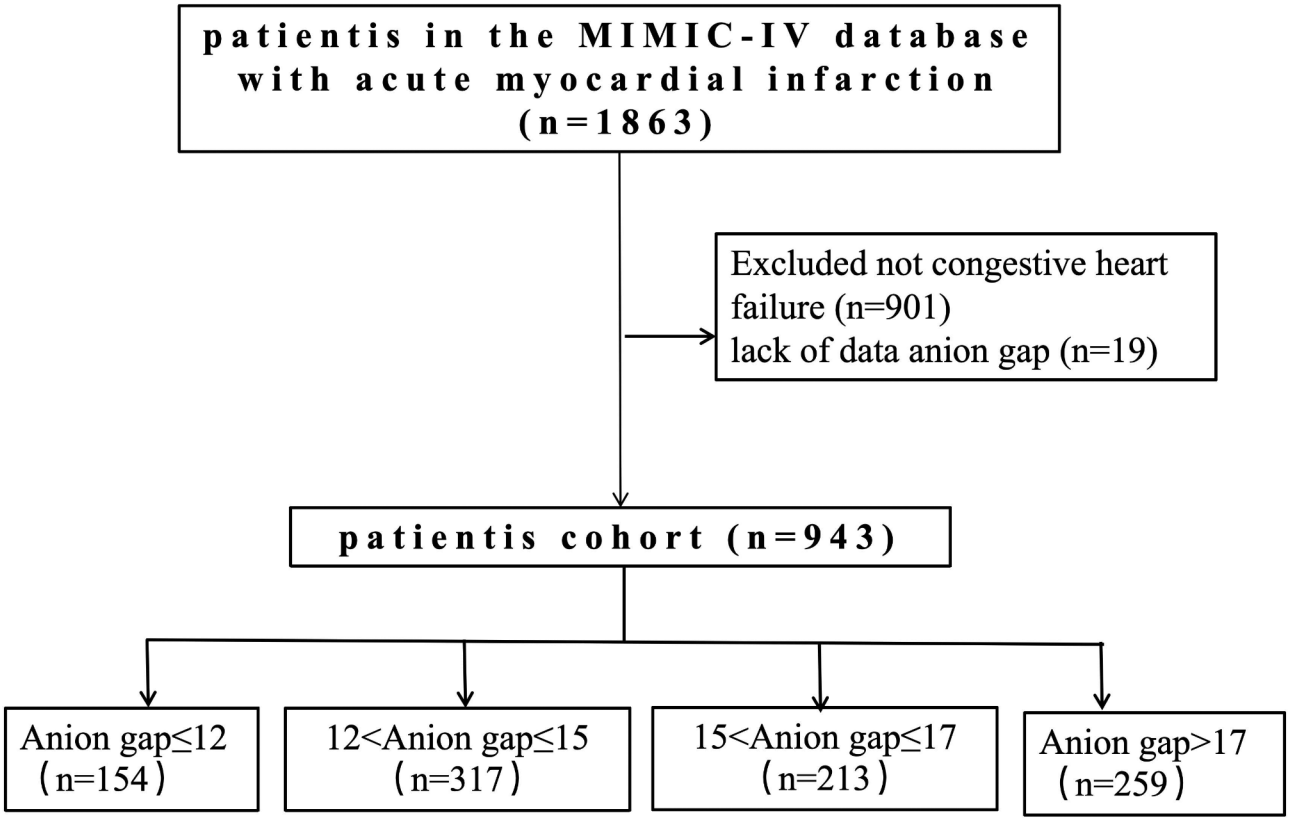

Fig. 1 Flowchart for the study population

Table 1 Basic characteristics of myocardial infarction with congestive heart failure according with quartile of anion gap

Variables	Total (*n* = 943)	Anion gap ≤ 12 (*n* = 154)	12 < Anion gap ≤ 15 (*n* = 317)	15 < Anion gap ≤ 17 (*n* = 213)	Anion gap > 17 (*n* = 259)	*p*	statistic
Admission age, Mean ± SD	68.1 ± 14.3	69.2 ± 12.6	67.9 ± 13.9	67.1 ± 15.0	68.5 ± 15.0	0.52	0.75
Race, *n* (%)						0.56	7.79
1	585 (62.0)	101 (65.6)	198 (62.5)	136 (63.8)	150 (57.9)		
2	58 (6.2)	8 (5.2)	15 (4.7)	13 (6.1)	22 (8.5)		
3	53 (5.6)	9 (5.8)	22 (6.9)	10 (4.7)	12 (4.6)		
4	247 (26.2)	36 (23.4)	82 (25.9)	54 (25.4)	75 (29)		
gender, *n* (%)						0.23	4.27
Female	329 (34.9)	45 (29.2)	118 (37.2)	69 (32.4)	97 (37.5)		
Male	614 (65.1)	109 (70.8)	199 (62.8)	144 (67.6)	162 (62.5)		
heart rate mean, Mean ± SD	80.2 ± 15.5	78.7 ± 13.5	76.5 ± 12.7	81.3 ± 16.0	84.7 ± 17.9	< 0.01	14.82
sbp mean, Mean ± SD	113.6 ± 15.1	112.7 ± 12.1	115.4 ± 14.0	115.3 ± 15.6	110.6 ± 17.0	< 0.01	5.93
dbp mean, Mean ± SD	64.2 ± 11.5	61.9 ± 9.9	65.0 ± 10.6	65.5 ± 12.8	63.5 ± 12.0	0.01	3.89
mbp mean, Mean ± SD	78.1 ± 10.6	75.8 ± 8.9	78.7 ± 10.3	79.7 ± 11.0	77.4 ± 11.4	< 0.01	4.95
resp rate mean, Mean ± SD	19.2 ± 3.3	18.2 ± 2.9	18.4 ± 2.9	19.4 ± 3.1	20.5 ± 3.8	< 0.01	27.29
temperature mean, Mean ± SD	36.7 ± 0.7	36.7 ± 0.4	36.7 ± 0.5	36.7 ± 0.6	36.5 ± 1.0	< 0.01	5.48
Glucose mean, Mean ± SD	155.6 ± 60.0	138.3 ± 38.7	141.9 ± 47.5	154.1 ± 54.6	183.9 ± 76.4	< 0.01	31.77
first sodium, Mean ± SD	137.7 ± 4.2	137.5 ± 4.8	137.8 ± 3.5	137.1 ± 3.3	138.2 ± 5.1	0.03	2.96
first potassium, Mean ± SD	4.2 ± 0.7	4.1 ± 0.6	4.1 ± 0.6	4.3 ± 0.6	4.4 ± 0.8	< 0.01	12.71
first creatinine, Mean ± SD	1.3 ± 1.0	0.9 ± 0.3	1.1 ± 0.7	1.1 ± 0.5	1.9 ± 1.6	< 0.01	45.69
diabetes, *n* (%)	288 (30.5)	42 (27.3)	83 (26.2)	58 (27.2)	105 (40.5)	< 0.01	16.92
mild liver disease, *n* (%)	68 (7.2)	7 (4.5)	10 (3.2)	12 (5.6)	39 (15.1)	< 0.01	34.06
renal disease, *n* (%)	166 (17.6)	18 (11.7)	41 (12.9)	36 (16.9)	71 (27.4)	< 0.01	25.74
charlson comorbidity index, Mean ± SD	6.0 ± 2.5	5.9 ± 2.4	5.7 ± 2.2	5.7 ± 2.6	6.6 ± 2.7	< 0.01	8.48

Table 2 One year cox regression of myocardial infarction with quartile of anion gap

Variable	*n*.total	*n*.event%	Followup.Time	crude.HR (95%CI)	crude.*P* value	adj.HR (95%CI)	adj.*P* value
Anion gap ≤ 12	154	15 (9.7)	51652.1	1(Ref)		1(Ref)	
12 < Anion gap ≤ 15	317	53 (16.7)	99399.5	1.76 (0.99 ~ 3.13)	0.05	2.09 (1.16 ~ 3.74)	0.01
15 < Anion gap ≤ 17	213	47 (22.1)	62666.5	2.48 (1.38 ~ 4.43)	< 0.01	2.57 (1.42 ~ 4.65)	< 0.01
Anion gap > 17	259	118 (45.6)	55101.9	6.14 (3.59 ~ 10.51)	< 0.01	3.96 (2.25 ~ 6.97)	< 0.01
Trend.test	943	233 (24.7)	271750.1	1.87 (1.63 ~ 2.14)	< 0.01	1.48 (1.28 ~ 1.72)	< 0.01

Adjust for: age, heart rate mean, sbp mean, dbp mean, resp rate mean, charlson comorbidity index, congestive heart failure

Restricted cubic spline regression model

Restricted cubic spline analysis visually demonstrated a nonlinear relationship between serum AG and one-year all-cause mortality in both myocardial infarction patients and those with myocardial infarction combined with heart failure ($p > 0.05$ for all data) (Fig. 3).

Subgroup mortality analysis

To evaluate the relationship between high serum AG levels and all-cause mortality, a subgroup analysis was conducted (Fig. 4). Across most subgroups (age, race, diabetes, and renal failure), higher serum AG levels were associated with 30-day and one-year in-hospital all-cause mortality, with no significant interaction between serum AG levels and the subgroup variables ($p > 0.05$ for all data). However, among female participants, an increase in serum AG levels was associated with a worse prognosis, including higher 30-day and one-year all-cause mortality (interaction $p \leq 0.05$).

Discussion

This study found that patients with high serum AG levels had lower survival rates and shorter survival times, and high serum AG levels at admission were identified as a significant risk factor for all-cause mortality in patients with acute myocardial infarction combined with heart failure. Additionally, this study observed that there was no interaction between serum AG levels and most subgroups in relation to in-hospital all-cause mortality, but female patients with increased serum AG levels had a noticeably worse prognosis.

In addition to its predictive advantages for adverse outcomes in cardiovascular, neurological, and urinary system diseases, serum AG is also easy to implement

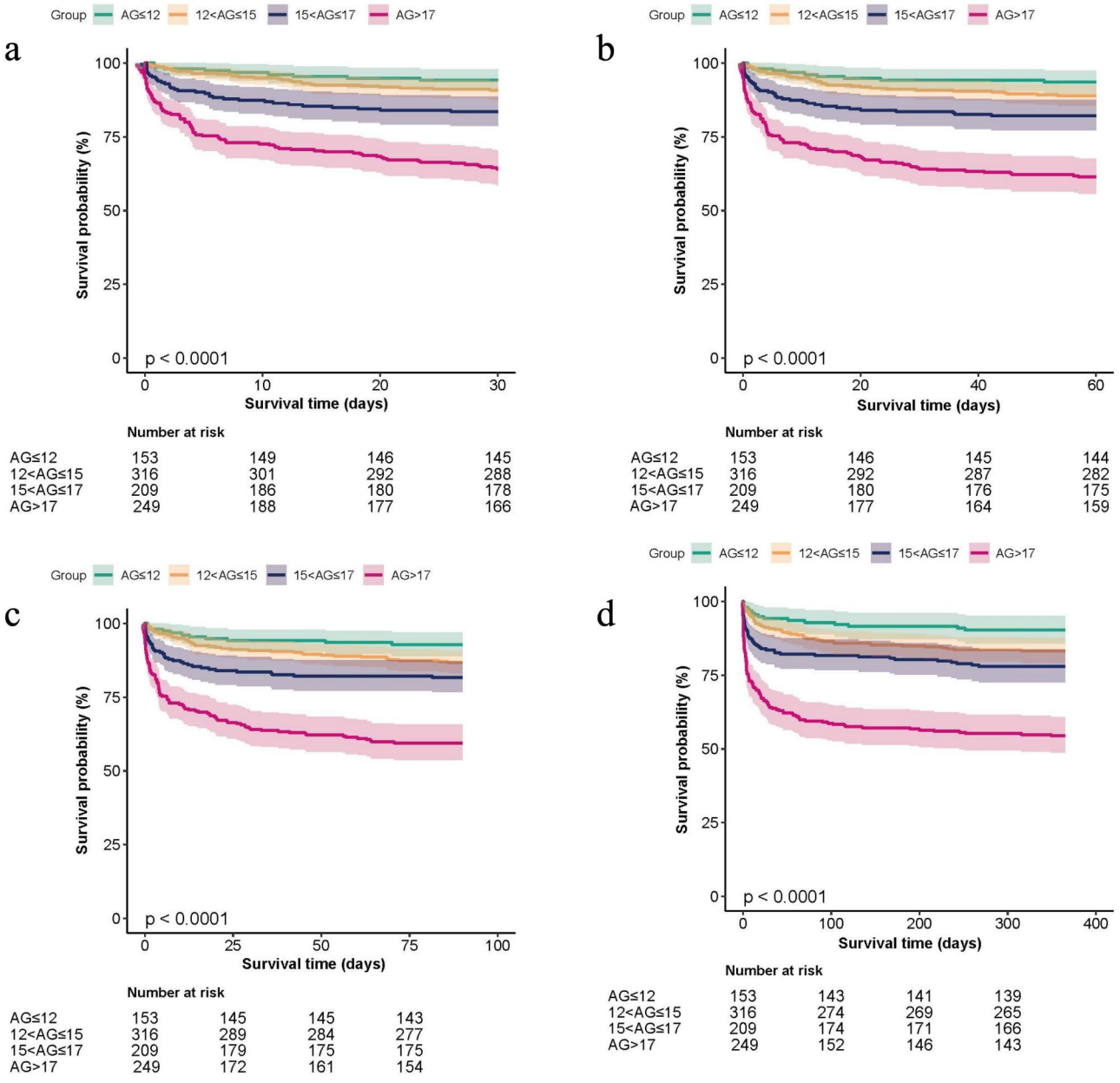

Fig. 2 Kaplan-Meier curves survival analysis of myocardial infarction with congestive heart failure according by quartile of anion gap. **a**: 30 days survival; **b**: 60 days survival; **c**: 90 days survival; d: 365 days survival

nationwide due to its simplicity, low cost, and significant impact on guiding treatment in impoverished and remote areas. Previous studies have shown that serum AG is associated with the occurrence of heart failure and cardiovascular death events in patients with acute myocardial infarction [23], which is consistent with our findings. After adjusting for confounding factors, patients with high serum AG levels (> 17 mmol/L) had a 2.96 times higher risk of all-cause mortality compared to those with low serum AG levels (≤ 12 mmol/L).

However, it is important to note that although the study by Zhao et al. demonstrated an independent association between increased serum AG levels and the risk of post-MI HF and cardiovascular mortality, it did not find an independent association with all-cause mortality [23]. This finding contrasts with several other studies [24–26]. The discrepancy may be due to the inclusion of too many confounding factors in their model, as suggested by their *p*-value of 0.062 when predicting all-cause mortality. In contrast, our study included a more streamlined and effective set of confounding factors, and the data were derived from the MIMIC-IV database, reducing potential selection bias associated with single-center sample data.

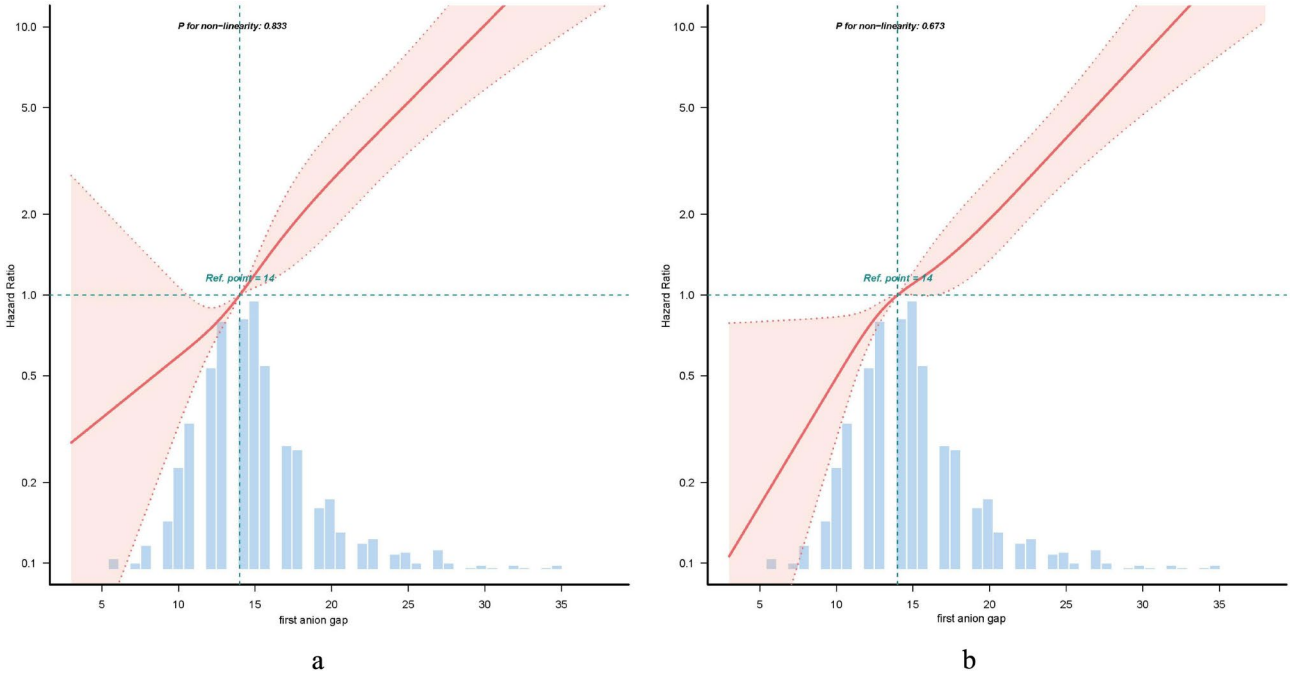

Fig. 3 The nonlinear relationship between anion gap and long-time mortality in myocardial infarction with congestive heart failure. **a**: myocardial infarction patients; **b**: myocardial infarction with congestive heart failure patients. Adjusted for all covariates as models

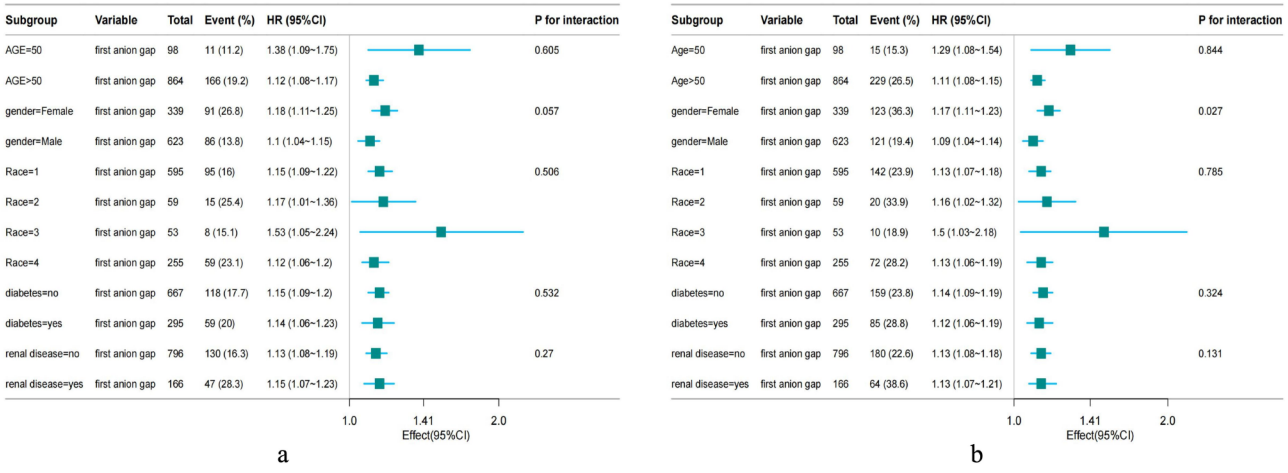

Fig. 4 Subgroup analysis mortality analysis with myocardial infarction with congestive heart failure according by quartile of anion gap. **a** 30 days mortality; **b** 365 days mortality

This study validated the relationship between serum AG levels and all-cause mortality at multiple time points. Significant differences in all-cause mortality rates among different serum AG groups were consistently observed on the KM curves at 30, 60, and 90 days, as well as at one year. This finding highlights the significant advantage of serum AG in predicting both early and late mortality events. An interesting observation from the subgroup analysis was that female patients with high serum AG levels had higher mortality rates compared to males. However, similar studies have shown that this result may not be consistent; for instance, Zhao et al. found that elevated serum AG levels in men were associated with an increased risk of out-of-hospital HF [23]. This discrepancy might be related to the sample population, and further research is needed to confirm this finding.

Serum AG is closely related to all-cause mortality in patients with acute myocardial infarction combined with heart failure, although the exact underlying mechanisms remain unclear. However, several possible explanations can be proposed. One explanation is that in patients with myocardial infarction combined with heart failure, decreased cardiac output leads to insufficient renal perfusion. The overactivation of the sympathetic nervous

system further causes renal vasoconstriction, leading to renal parenchymal ischemia and necrosis, which decreases the glomerular filtration rate (GFR). Studies have indicated that one-third of the mechanisms through which elevated serum AG leads to poor prognosis are due to a reduced GFR [23]. The reduced GFR leads to a significant decline in the kidney's ability to excrete acids, and the accumulation of various inorganic and organic acids in the body contributes to the elevation of serum AG. This partially explains why serum AG levels are elevated in patients with myocardial infarction combined with heart failure.In addition, diabetes may also affect serum AG. However, in our study, when subgroup analysis of eGFR, diabetes was conducted, serum AG was not affected by these factors, which may indicate that serum AG is an independent risk factor for patients with acute myocardial infarction complicated with heart failure.

Moreover, because the heart cannot supply blood normally, the body is in a state of ischemia and hypoxia, forcing the myocardium to rely on glycolysis for energy production. The resulting lactic acid is also an important source of elevated serum AG. Serum AG reflects the acid load in the body, in other words, the higher the serum AG, the more severe the metabolic acidosis. A study by Park et al. evaluated the prognostic value of arterial blood gases in high-risk acute heart failure, finding that compared to the group with the highest bicarbonate levels, the group with the lowest bicarbonate levels had a 1.46 times higher risk of all-cause mortality (HR = 1.46, 95% CI = 1.068–1.995) and a 2.647 times higher risk of cardiovascular mortality (HR = 2.647, 95% CI = 1.148–6.103). However, they did not clarify the relationship between the type of acidosis and poor prognosis [26]. Guo et al.'s study further elucidated that metabolic acidosis, in particular, is associated with worse survival rates [27].

The mechanisms through which severe metabolic acidosis leads to poor prognosis may originate from multiple factors. For example, to clear the excess acid load, the kidneys adaptively increase the breakdown of glutamine in the proximal tubule and the activity of endothelin-1 (ET-1). The resulting ammonium activates the alternative pathway of complement in the kidneys, promoting tubulointerstitial fibrosis. Meanwhile, ET-1 exacerbates renal failure progression by promoting the action of transforming growth factor-beta1 (TGF-β1) and connective tissue growth factor [28–35]. Additionally, metabolic acidosis can enhance protein catabolism through acidification-dependent activation of ubiquitin-protein ligases, leading to muscle mass loss and increased frailty [36].

Another possible explanation is that elevated serum AG levels activate the inflammatory system. The acute and chronic inflammation are the major underlying points of the complications of congestive heart failure [37–39]. High serum AG levels have been shown to be associated with elevated levels of inflammatory biomarkers [40]. In vitro studies suggest that elevated serum AG can activate the acid-sensing ion channels in immune cells, exacerbating the inflammatory response induced by myocardial infarction and thereby promoting cardiac remodeling. For example, lactic acid has been found to reduce neutrophil phagocytic capacity and inhibit T cell responses [41]. Meanwhile, the role of albumin is very important related to serum AG level since it has also direct links to inflammation [42]. Additionally, elevated serum AG triggers the production of inflammasomes, interleukin-1β (IL-1β), and the activation of the complement system [43].

Despite these findings, our study has several limitations. First, as the study was conducted with a retrospective design, there may be some selection bias. Second, due to the limitations of the MIMIC database, we did not collect certain potentially influential missing data, such as albumin, lactate, pH, and Hunt & Hess grade. It should be noted, however, that the potential impact of these variables would likely skew towards the null, possibly leading to an underestimation of the relationship between serum AG levels and all-cause mortality. Third, because we lacked albumin data, we did not perform albumin-corrected serum AG calculations, which some studies suggest might offer greater accuracy, potentially reducing the reliability of our findings. Fourth, we did not repeatedly measure serum AG to assess its dynamic changes over time. Fifth, although we progressively adjusted for many confounding factors, unmeasured potential confounders may still have influenced the study results. Nevertheless, the relationship between high serum AG levels and all-cause mortality was clearly demonstrated.

Conclusion

In conclusion, this retrospective observational study suggests that high serum AG levels are a significant risk factor for all-cause mortality in patients with acute myocardial infarction combined with heart failure. Further prospective studies with larger sample sizes are needed to assess the causal relationship between high serum AG levels and all-cause mortality.

Abbreviations

AG	Anion gap
MIMIC	Medical Information Mart for Intensive Care
MI	Myocardial infarction
HFpMI	Heart failure post-MI
SD	Standard deviation
IQR	Interquartile ranges
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
GFR	Glomerular filtration rate
ET-1	Endothelin-1
TGF-β1	Transforming growth factor-beta1
IL-1β	Interleukin-1β

Acknowledgements

Not Applicable.

Author contributions
QH Yuan designed the study and collected the data. MZ Li and CY Li wrote the first draft of the manuscript. JH wang contributed to the refinement of the manuscript. The final manuscript has been read and approved by all authors.

Funding
There were no external funding sources for this study.

Data availability
The corresponding author can be contacted to receive the datasets generated and utilized in this work upon reasonable request and with MIMIC's permission.

Declarations

Ethics approval and consent to participate
The studies involving human participants were examined and approved by Beth Israel Deaconess Medical Center. To protect patient privacy, all data were de-identified; therefore, the Ethical Committee of the Beth Israel Deaconess Medical Center waived the requirement for informed consent.

Consent for publication
All authors have participated in the work and have reviewed and agree with the content of the article.

Competing interests
The authors declare no competing interests.

Received: 30 November 2024 / Accepted: 4 February 2025
Published online: 24 February 2025

References

1. Choi Y, Lee KY, Kim SH, Kim KA, Hwang BH, Choo EH, Lim S, Kim CJ, Kim JJ, Byeon J, et al. Predictors for early cardiac death after discharge from successfully treated acute myocardial infarction. Front Med (Lausanne). 2023;10:1165400.
2. Dreyer RP, Arakaki A, Raparelli V, Murphy TE, Tsang SW, D'Onofrio G, Wood M, Wright CX, Pilote L. Young Women with Acute myocardial infarction: risk prediction model for 1-Year hospital readmission. CJC Open. 2023;5(5):335–44.
3. Ismail SR, Mohammad MSF, Butterworth AS, Chowdhury R, Danesh J, Di Angelantonio E, Griffin SJ, Pennells L, Wood AM, Md Noh MF et al. Risk factors of secondary Cardiovascular events in a multi-ethnic Asian Population with Acute myocardial infarction: a retrospective cohort study from Malaysia. J Cardiovasc Dev Dis 2023, 10(6).
4. WangZW, Zhu JH, Li CS. Risk factors for acute kidney injury in patients with acute myocardial infarction. Chin Med J (Engl). 2019;132(14):1660–5.
5. Çınar T, Şaylık F, Akbulut T, Korkmaz Y, Çiçek V, Asal S, Erdem A, Selçuk M, Hayıroğlu Mİ. Evaluation of Intermountain Risk score for short- and long-term mortality in ST Elevation myocardial infarction patients. Angiology. 2023;74(4):357–64. Epub 2022 May 29. PMID: 35635200.
6. Mert İlker H, Faysal S, Ahmet Çağdaş Y, Murat S, Tufan Ç. Prognostic value of Intermountain Risk Score for short- and long-term mortality in patients with cardiogenic shock. Coron Artery Dis. 2023;34(2):154–159. doi: 10.1097/MCA.0000000000001219. Epub 2023 Jan 4. PMID: 36720024.
7. Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. Nat Rev Nephrol. 2010;6(5):274–85.
8. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. First of two parts. N Engl J Med. 1998;338(1):26–34.
9. Tang Y, Lin W, Zha L, Zeng X, Zeng X, Li G, Liu Z, Yu Z. Serum Anion Gap Is Associated with All-Cause Mortality among Critically Ill Patients with Congestive Heart Failure. Dis Markers 2020, 2020:8833637.
10. Zhang T, Wang J, Li X. Association between Anion Gap and Mortality in critically ill patients with cardiogenic shock. Int J Gen Med. 2021;14:4765–73.
11. Jhou HJ, Chen PH, Yang LY, Chang SH, Lee CH. Plasma anion gap and risk of In-Hospital mortality in patients with Acute ischemic stroke: analysis from the MIMIC-IV Database. J Pers Med 2021, 11(10).
12. Liu X, Feng Y, Zhu X, Shi Y, Lin M, Song X, Tu J, Yuan E. Serum anion gap at admission predicts all-cause mortality in critically ill patients with cerebral infarction: evidence from the MIMIC-III database. Biomarkers. 2020;25(8):725–32.
13. Cheng B, Li D, Gong Y, Ying B, Wang B. Serum Anion Gap Predicts All-Cause Mortality in Critically Ill Patients with Acute Kidney Injury: Analysis of the MIMIC-III Database. Dis Markers 2020, 2020:6501272.
14. Gong F, Zhou Q, Gui C, Huang S, Qin Z. The Relationship between the serum anion gap and all-cause mortality in Acute Pancreatitis: an analysis of the MIMIC-III database. Int J Gen Med. 2021;14:531–8.
15. Xu C, Sun L, Dong M, Ullah H, Ullah H, Zhou J, Yuan Z. Serum anion gap is Associated with risk of all-cause mortality in critically ill patients with Acute myocardial infarction. Int J Gen Med. 2022;15:223–31.
16. Chen Q, Chen Q, Li L, Lin X, Chang SI, Li Y, Tian Z, Liu W, Huang K. Serum anion gap on admission predicts intensive care unit mortality in patients with aortic aneurysm. Exp Ther Med. 2018;16(3):1766–77.
17. Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF. Evaluation of acid-base balance in ST-elevation myocardial infarction in the early phase: a prognostic tool? Coron Artery Dis. 2010;21(5):266–72.
18. Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF. Acid-base imbalance in uncomplicated ST-elevation myocardial infarction: the clinical role of tissue acidosis. Intern Emerg Med. 2010;5(1):61–6.
19. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10(1):R22.
20. Rostami E, Engquist H, Howells T, Johnson U, Ronne-Engström E, Nilsson P, Hillered L, Lewén A, Enblad P. Early low cerebral blood flow and high cerebral lactate: prediction of delayed cerebral ischemia in subarachnoid hemorrhage. J Neurosurg. 2018;128(6):1762–70.
21. Martha SR, Collier LA, Davis SM, Seifert HA, Leonardo CC, Ajmo CT Jr., Foran EA, Fraser JF, Pennypacker KR. Translational evaluation of Acid/Base and electrolyte alterations in Rodent Model of Focal Ischemia. J Stroke Cerebrovasc Dis. 2018;27(10):2746–54.
22. Zhong C, Ye M, Hu L, Liu J. Association between High Serum Anion Gap and all-cause mortality in non-traumatic subarachnoid hemorrhage: a retrospective analysis of the MIMIC-IV Database. Front Neurol. 2022;13:922099. https://doi.org/10.3389/fneur.2022.922099. PMID: 35903118; PMCID: PMC9321397.
23. Zhao B, Li Y, Lang X, Fang S, Li Z, Li L, Xing L, Zhang Y. Increased serum albumin corrected anion gap levels are associated with increased incidence of new-onset HF and poor prognosis in patients with acute myocardial infarction. Clin Chim Acta. 2023;544:117354.
24. Wang R, Li J, Chen H, Xiao Z, Xu R, Hu Y, Chen S, Wang X, Zheng S. Preoperative albumin corrected anion gap is associated with in-hospital and long-term mortality in patients undergoing coronary artery bypass grafting in a retrospective cohort study. J Thorac Dis. 2022;14(12):4894–903.
25. Zhong L, Xie B, Ji XW, Yang XH. The association between albumin corrected anion gap and ICU mortality in acute kidney injury patients requiring continuous renal replacement therapy. Intern Emerg Med. 2022;17(8):2315–22.
26. Park M, Jung SJ, Yoon S, Yun JM, Yoon HJ. Association between the markers of metabolic acid load and higher all-cause and cardiovascular mortality in a general population with preserved renal function. Hypertens Res. 2015;38(6):433–8.
27. Guo W, Peng C, Liu Q, Zhao L, Guo W, Chen X, Li L. Association between base excess and mortality in patients with congestive heart failure. ESC Heart Fail. 2021;8(1):250–8.
28. Raphael KL. Metabolic acidosis in CKD: Pathogenesis, adverse effects, and Treatment effects. Int J Mol Sci 2024, 25(10).
29. Khanna A, Simoni J, Wesson DE. Endothelin-induced increased aldosterone activity mediates augmented distal nephron acidification as a result of dietary protein. J Am Soc Nephrol. 2005;16(7):1929–35.
30. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. Kidney Int. 2014;86(5):896–904.
31. Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. Kidney Int. 2010;78(11):1128–35.
32. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, Rajab MH, Wesson DE. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int. 2010;77(7):617–23.
33. Phisitkul S, Hacker C, Simoni J, Tran RM, Wesson DE. Dietary protein causes a decline in the glomerular filtration rate of the remnant kidney mediated by metabolic acidosis and endothelin receptors. Kidney Int. 2008;73(2):192–9.

34. Wesson DE, Nathan T, Rose T, Simoni J, Tran RM. Dietary protein induces endothelin-mediated kidney injury through enhanced intrinsic acid production. Kidney Int. 2007;71(3):210–7.
35. Wesson DE, Dolson GM. Endothelin-1 increases rat distal tubule acidification in vivo. Am J Physiol. 1997;273(4):F586–594.
36. Bailey JL, Wang X, England BK, Price SR, Ding X, Mitch WE. The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. J Clin Invest. 1996;97(6):1447–53.
37. Hayıroğlu Mİ, Çınar T, Çinier G, Pay L, Yumurtaş AÇ, Tezen O, Eren S, Kolak Z, Çetin T, Çiçek V, Tekkeşin Aİ. Evaluating systemic immune-inflammation index in patients with implantable cardioverter defibrillator for heart failure with reduced ejection fraction. Pacing Clin Electrophysiol. 2022;45(2):188–95. https://doi.org/10.1111/pace.14436. Epub 2022 Jan 13. PMID: 34978742.
38. Tezen O, Hayıroğlu Mİ, Pay L, Yumurtaş AÇ, Keskin K, Çetin T, Dereli Ş, Kadığoğlu H, Yücedağ FF, Arter E, Dayı ŞÜ. The role of systemic immune-inflammatory index in predicting contrast-induced nephropathy in non-ST-segment elevation myocardial infarction cases. Biomark Med. 2024;18(21–22):937–44. Epub 2024 Oct 29. PMID: 39469834; PMCID: PMC11633407.
39. Kalenderoglu K, Hayiroglu MI, Cinar T, Oz M, Bayraktar GA, Cam R, Gurkan K. Comparison of inflammatory markers for the prediction of atrial fibrillation recurrence following cryoablation. Biomark Med. 2024;18(17–18):717–25. Epub 2024 Sep 12. PMID: 39263796; PMCID: PMC11457599.
40. Farwell WR, Taylor EN. Serum anion gap, bicarbonate and biomarkers of inflammation in healthy individuals in a national survey. CMAJ. 2010;182(2):137–41.
41. Erra Díaz F, Dantas E, Geffner J. Unravelling the Interplay between Extracellular Acidosis and Immune Cells. Mediators Inflamm 2018, 2018:1218297.
42. Hayıroğlu Mİ, Altay S. Overlap between nutritional indices in patients with Acute Coronary Syndrome: a Focus on Albumin. Balkan Med J. 2024;41(5):324–5. https://doi.org/10.4274/balkanmedj.galenos.2024.190724. Epub 2024 Aug 1. PMID: 39086257; PMCID: PMC11588916.
43. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulointerstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. J Clin Invest. 1985;76(2):667–75.

Publisher's note