


# Serum Anion Gap is Associated with Risk of All-Cause Mortality in Critically Ill Patients with Acute Myocardial Infarction

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**Purpose:** Anion gap (AG) is a valuable and easily obtained clinical tool for differentially diagnosis of acid-base disorders. Current understanding of the prognostic impact of AG on mortality after acute myocardial infarction (AMI) is limited. We aimed to investigate whether AG is a predictor of short-term and long-term all-cause mortality after AMI.

**Patients and Methods:** We examined 1806 patients diagnosed with AMI in intensive care unit from the Medical Information Mart for Intensive Care III (MIMIC-III) database. We analyzed the association of AG with 30-day, 180-day and 1-year all-cause mortality on a continuous scale and in categories, using multivariable Cox regression. We utilized restricted cubic splines to evaluate the linearity between hazard ratio (HR) and AG concentrations.

**Results:** AG was associated with a higher risk of 30-day, 180-day and 1-year all-cause mortality, with adjusted HRs of 1.083 (95% CI 1.051 to 1.117), 1.077 (95% CI 1.049 to 1.105), and 1.074 (95% CI 1.047 to 1.101), respectively. The results were consistent in subgroup analyses. The association between AG and all-cause mortality was linear for 180-day and 1-year mortality, and near linear for 30-day mortality, as higher concentrations were associated with high all-cause mortality. When stratified according to quartiles, AG was associated with 30-day mortality (HR[95% CI]: second quartile, 2.243[1.273, 3.955]; third quartile, 3.026[1.763, 5.194]; top quartile, 4.402[2.573, 7.531]), 180-day mortality (HR[95% CI]: second quartile, 1.719[1.118, 2.645]; third quartile, 2.362[1.575, 3.542]; top quartile, 3.116[2.077, 4.676]), and 1-year mortality (HR[95% CI]: second quartile, 1.700[1.143, 2.528]; third quartile, 2.239[1.536, 3.264]; top quartile, 2.876[1.969, 4.201]) using bottom quartile as reference.

**Conclusion:** We firstly demonstrated that higher AG was significantly associated with increased 30-day, 180-day and 1-year all-cause mortality in AMI patients. AG as an easily obtained marker is of strong and reliable predictive value for AMI mortality during follow-up.

**Keywords:** acute myocardial infarction, anion gap, all-cause mortality

## Introduction

Acute coronary syndrome (ACS) is the leading cause of death worldwide. As an acute manifestation of ACS, acute myocardial infarction (AMI) incidence has been declined during the past few decades.<sup>1</sup> However, it still remains one of the top causes of disease burden especially in middle- and low-income countries.<sup>2,3</sup> Thus, increasing emphasis has been put on identifying the risk factors for mortality to guide risk stratification and treatment after AMI. In clinical practice, easily obtained predictors to determine prognosis are warranted.

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Anion gap (AG), most frequently calculated as the sum of serum chloride and bicarbonate concentrations subtracted from the sum of sodium and potassium concentrations, represents the differences between unmeasured anions and cations.<sup>4</sup> AG is a valuable and simple-to-use clinical tool for differential diagnosis of complex acid-base disorders,<sup>5</sup> which has been used for over half a century. Other than reflecting acid-base balance, more recent studies have shown the prognostic values of AG in general population and for various diseases.<sup>6,7</sup> AG is predictive of mortality in non-selected elderly population.<sup>8</sup> And a positive association between AG and inflammation markers, such as leukocyte count and C-reactive protein, has been demonstrated in general population.<sup>9</sup> In acute kidney injury<sup>10</sup> and advanced chronic kidney disease,<sup>11</sup> higher AG was associated with increased risk for death over a long-term follow-up. In cerebrovascular disease, AG also showed predictive values for short-term mortality in patients after cerebral infarction.<sup>12</sup> Furthermore, in coronary artery disease, higher AG was related to worse clinical type and mortality.<sup>13</sup> In AMI patients, AG was found to be associated with increased in-hospital mortality,<sup>14</sup> suggesting AG may be of importance for predicting cardiovascular mortality and risk stratification.

However, to our knowledge, there are no studies addressing the relationship between AG and AMI mortality during follow-up. Herein, the present study seeks to investigate the predictive value of AG for 30-day, 180-day and 1-year all-cause mortality in AMI patients.

## Methods

### Database

We conducted a retrospective analysis utilizing the Medical Information Mart for Intensive Care III (MIMIC-III) database.<sup>15</sup> The MIMIC database is comprised of deidentified and well-defined health-related data associated with patients admitted to intensive care units (ICU) of the Beth Israel Deaconess Medical Center (Boston, Massachusetts) between 2001 and 2012. It contains records of demographics, hourly vital signs, laboratory results, treatment, medications, mortality and other related clinical variables from 58,976 admissions of 46,520 patients. The access for author (CX) to the MIMIC database was approved (certification ID: 43375338). The use of database has been approved by Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA, USA). Since

patients were deidentified and MIMIC database does not contain protected information, a waiver of informed consent was granted by the ethical committee. Additional ethical approval from our institution was waived by our institutional ethics committee.

### Data Extraction and Outcomes

Data was extracted by structured query language (SQL).<sup>16</sup> After including only first admissions of patients to ICU, we identified a total of 1877 AMI patients who were older than 18 years old. AMI was diagnosed based on International Classification of Diseases, Ninth Revision (ICD-9) codes. Of these, 48 patients without lab results of sodium, 18 without results of potassium, and 5 without results of bicarbonates were excluded. Thus, we recruited 1806 AMI patients in our final study cohort. The following variables were extracted: age, sex, weight on admission, mean heart rate during the first 24h of ICU stay, serum creatinine, blood urea nitrogen (BUN), hemoglobin, platelet, white blood cells (WBC), sodium, potassium, chloride, bicarbonate, Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score II (SAPS II) on ICU admission. AG was calculated as:  $AG\text{ (mmol/L)} = [\text{sodium (mmol/L)} + \text{potassium (mmol/L)}] - [\text{chloride (mmol/L)} + \text{bicarbonate (mmol/L)}]$ .<sup>4</sup> The AG range in healthy individuals is 8–16 mmol/L with an average of 12 mmol/L. Lower AG level is most commonly due to laboratory error while elevated AG usually indicates metabolic acidosis.<sup>5</sup> The comorbidities of hypertension, atrial fibrillation (AF), congestive heart failure (CHF), diabetes, chronic renal disease and cardiogenic shock (CS) were identified based on ICD-9 codes. Sepsis was diagnosed according to the Angus criteria.<sup>17</sup> Acute kidney injury (AKI) was defined according to Kidney Disease Improving Global Outcomes (KDIGO) definition.<sup>18</sup> The outcomes in this study include 30-day all-cause mortality, 180-day all-cause mortality and 1-year all-cause mortality.

### Statistical Analysis

Patients were stratified based on quartiles of AG. Continuous variables were described as mean  $\pm$  standard deviation (SD) and categorical variables were expressed as numeral and percentage. The Kolmogorov–Smirnov tests were conducted to test the normal distribution of continuous variables. The comparisons among AG quartiles were performed using One-way ANOVA or Kruskal–Wallis test as appropriate. And chi-square tests were performed to evaluate the categorical variables.

Cox hazard regression models were conducted to examine the association between AG and 30-day, 180-day and 1-year outcomes. AG was modeled as continuous variable or categorical variable according to quartiles. Age, sex, SOFA score, creatinine, BUN, platelet, WBC, hemoglobin, mean heart rate, SAPS II score and comorbidities of hypertension, AF, CHF, diabetes and renal disease were entered into the final model. The results were presented as hazard ratios (HRs) with 95% confidence intervals (CI), and using AG <12mmol/L as reference for categorical AG. Risk-adjusted survival plot were performed to depict the survival rate across AG quartiles adjusted for the covariates above.

Restricted cubic spline (RCS) models with 3 knots were constructed to model AG as a continuous variable to assess for linearity visually. The RCS plots displaying the association between the hazards of mortality and AG was adjusted for the covariates in the Cox hazards regression model, using the 12mmol/L of AG as the reference.

Sensitivity analyses were performed for patients defined by age, sex, hypertension, AF, CHF and diabetes. Similarly, the adjusted HRs and 95% CIs of mortality were estimated. And the interactions between subgroups and AG were tested by including the interaction terms in the Cox model.

Missing data were <0.5% for all variables included in the Cox model, including mean heart rate (8 missing), hemoglobin (4 missing), platelet (1 missing), and WBC (1 missing). Missing data were imputed to the median of the non-missing values. All the statistical analyses were carried out using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P-value <0.05 was considered to be statistically significant.

## Results

### Baseline Characteristics

In this study, 1806 patients with AMI were enrolled, including 1184 (65.6%) male and 622 (34.4%) female. Baseline characteristics of patients stratified by quartiles of AG are shown in Table 1. Patients in the top quartile of AG were older with an average age of 69.9. As AG increased, patients were more likely to have higher heart rate, creatinine, BUN, platelet, WBC, SOFA score and SAPS II score, especially in the fourth quartile. Moreover, patients with higher AG had increased rates of AF, CHF, diabetes, chronic renal disease, and CS, but lower rates of hypertension. AMI patients with increased level of AG quartiles also suffered higher 30-day

( $p < 0.001$ ), 180-day ( $p < 0.001$ ) and 1-year ( $p < 0.001$ ) all-cause mortality.

### The Association of Anion Gap with AMI Mortality

In the unadjusted Cox hazard regression model (Table 2), AG (continuous) was significantly associated with the increased risk of 30-day (HR 1.198, 95% CI 1.173 to 1.225), 180-day (HR 1.192, 95% CI 1.169 to 1.216) and 1-year (HR 1.189, 95% CI 1.166 to 1.212) mortality. After further adjustment, the associations were slightly attenuated but remained significant, with a HR of 1.083 (95% CI 1.051 to 1.117) for 30-day mortality, a HR of 1.077 (95% CI 1.049 to 1.105) for 180-day mortality, and a HR of 1.074 (95% CI 1.047 to 1.101) for 1-year mortality in the final model (Table 2).

To further investigate the relationship between AG and mortality, the relative hazards depending on AG level are shown in Figure 1. In the adjusted restricted cubic spline model, the association between AG level and 30-day mortality was near linear (Figure 1A,  $p$  for nonlinear = 0.049). Similarly (Figure 1B and C), the restricted cubic splines for 180-day and 1-year all-cause mortality showed linearity ( $p$  for nonlinear = 0.078 and 0.092, respectively).

Given the above results showing linear association between HR and AG level, subsequently, associations of AG as a categorical variable and mortality were analyzed and presented in Table 3. In comparison with the reference level of less than 12mmol/L, the top quartile of AG was associated with increased risk for mortality in the unadjusted model ( $p$  for trend <0.001 for all), with a HR of 10.086 (95% CI 6.189 to 16.437) for 30-day mortality, a HR of 7.036 (95% CI 4.911 to 10.088) for 180-day mortality, and a HR of 6.622 (95% CI 4.740 to 9.251) for 1-year mortality. Further adjustments in the final model did not significantly change the results (Table 3 and Figure 2), showing HRs of 4.402 (95% CI 2.573 to 7.531), 3.116 (95% CI 2.077 to 4.676) and 2.876 (95% CI 1.969 to 4.201) for those three outcomes in the top quartile, respectively. Furthermore, the survival plot depicted increased risk for 30-day, 180-day and 1-year all-cause mortality in higher AG quartile after adjustment (Figure 2).

### Subgroup Analysis

In the subgroup analysis (Figure 3) conducted for age, sex, and comorbidities of hypertension, AF, CHF, diabetes, AKI and sepsis, the results remained generally similar

**Table 1** Baseline Characteristics of AMI Patients According to AG

| Characteristics               | AG (mmol/L)      |                        |                        |                  | p-value |
|-------------------------------|------------------|------------------------|------------------------|------------------|---------|
|                               | Quartile 1 <12.0 | Quartile 2 ≥12.0,<14.1 | Quartile 3 ≥14.1,<16.7 | Quartile 4 ≥16.7 |         |
| Number of patients            | 443              | 446                    | 463                    | 454              | -       |
| Age(years)                    | 67.1±13.0        | 66.5±14.5              | 67.66±14.7             | 69.9±14.5        | 0.001   |
| Male, n(%)                    | 297(67.0)        | 291(65.2)              | 313(67.6)              | 283(62.3)        | 0.334   |
| Weight(kg)                    | 80.28±17.00      | 82.32±18.93            | 81.84±20.45            | 80.32±22.16      | 0.102   |
| Mean heart rate(bpm)          | 79.81±14.23      | 79.22±13.69            | 80.82±14.13            | 86.28±16.91      | <0.001  |
| Creatinine(mg/dL)             | 0.89±0.41        | 0.98±0.46              | 1.15±0.70              | 1.96±1.82        | <0.001  |
| BUN(mg/dL)                    | 16.99±8.02       | 19.23±10.04            | 22.21±12.71            | 34.72±23.64      | <0.001  |
| Hemoglobin(g/dL)              | 11.28±2.13       | 12.15±1.96             | 12.09±2.04             | 11.88±2.29       | <0.001  |
| Platelet(×10 <sup>9</sup> /L) | 210.78±98.11     | 225.64±79.26           | 237.40±91.71           | 244.87±104.83    | <0.001  |
| WBC(×10 <sup>9</sup> /L)      | 11.52±5.08       | 11.50±4.05             | 12.45±4.82             | 15.21±6.81       | <0.001  |
| Sodium(mmol/L)                | 136.89±4.14      | 138.20±3.43            | 137.90±3.78            | 138.04±4.73      | <0.001  |
| Potassium(mmol/L)             | 4.15±0.69        | 4.12±0.64              | 4.22±0.65              | 4.37±0.87        | <0.001  |
| Chloride(mmol/L)              | 106.38±5.00      | 105.02±4.56            | 103.96±4.39            | 103.30±5.62      | <0.001  |
| Bicarbonate(mmol/L)           | 25.09±3.36       | 24.32±3.12             | 22.97±3.15             | 19.44±4.46       | <0.001  |
| SOFA score                    | 3.17±2.76        | 2.81±2.61              | 3.21±2.75              | 5.65±3.75        | <0.001  |
| SAPS II score                 | 32.08±12.13      | 30.46±12.26            | 32.50±13.50            | 43.95±16.90      | <0.001  |
| Hypertension, n(%)            | 244(55.1)        | 232(52.0)              | 229(49.5)              | 168(37.0)        | <0.001  |
| AF, n(%)                      | 102(23.0)        | 110(24.7)              | 103(22.2)              | 148(32.6)        | 0.001   |
| CHF, n(%)                     | 114(25.7)        | 161(36.1)              | 182(39.3)              | 247(54.4)        | <0.001  |
| Diabetes, n(%)                | 96(21.7)         | 100(22.4)              | 114(24.6)              | 155(34.1)        | <0.001  |
| Chronic renal disease, n(%)   | 20(4.5)          | 23(5.2)                | 36(7.8)                | 52(11.5)         | <0.001  |
| CS, n(%)                      | 29(6.5)          | 61(13.7)               | 71(15.3)               | 142(31.3)        | <0.001  |
| 30-day mortality, n(%)        | 18(4.1)          | 40(9.0)                | 58(12.5)               | 154(33.9)        | <0.001  |
| 180-day mortality, n(%)       | 35(7.9)          | 57(12.8)               | 84(18.1)               | 198(43.6)        | <0.001  |
| 1-year mortality, n(%)        | 41(9.3)          | 68(15.2)               | 95(20.5)               | 214(47.1)        | <0.001  |

**Abbreviations:** BUN, blood urea nitrogen; WBC, white blood cell; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; AF, atrial fibrillation; CHF, congestive heart failure; CS, cardiogenic shock.

**Table 2** Hazard Ratio of AG (Continuous) for Mortality

|            | 30-Day Mortality    |         | 180-Day Mortality   |         | 1-Year Mortality    |         |
|------------|---------------------|---------|---------------------|---------|---------------------|---------|
|            | HR (95% CI)         | P value | HR (95% CI)         | P value | HR (95% CI)         | P value |
| Unadjusted | 1.198 (1.173,1.225) | <0.001  | 1.192 (1.169,1.216) | <0.001  | 1.189 (1.166,1.212) | <0.001  |
| Model 1    | 1.190 (1.164,1.216) | <0.001  | 1.181 (1.158,1.205) | <0.001  | 1.178 (1.155,1.201) | <0.001  |
| Model 2    | 1.108 (1.076,1.141) | <0.001  | 1.098 (1.070,1.126) | <0.001  | 1.093 (1.066,1.120) | <0.001  |
| Model 3    | 1.083 (1.051,1.117) | <0.001  | 1.077 (1.049,1.105) | <0.001  | 1.074 (1.047,1.101) | <0.001  |

**Notes:** Model 1: adjusted for age and sex; Model 2: adjusted for model 1 plus SOFA score, creatinine, blood urea nitrogen, platelet, white blood cell, hemoglobin, and heart rate; Model 3: adjusted for model 2 plus hypertension, atrial fibrillation, congestive heart failure, diabetes, renal disease, cardiogenic shock and SAPS II score.

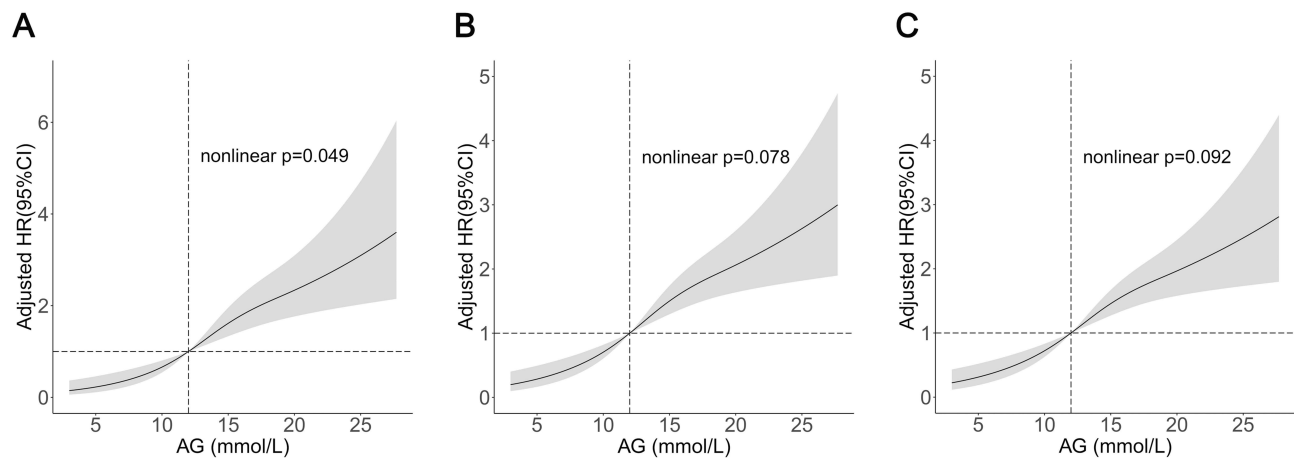
**Abbreviations:** HR, hazard ratio; CI, confidence interval; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II.

for the association between AG and mortality. And no significant interactions were observed.

## Discussion

In this retrospective study of 1806 patients with AMI in ICU, we found that AG was significantly associated with increased 30-day, 180-day and 1-year all-cause mortality. The associations were independent of other

cardiovascular risk factors, and were robust across subgroup analyses, indicating the predictive implications in clinical practice of AG. Moreover, a linear association between AG and 180-day and 1-year all-cause mortality were observed. To the best of our knowledge, this is the first study to investigate the association between AG and short-term and long-term AMI mortality during follow-up.



**Figure 1** Associations between AG on a continuous scale and adjusted-risk of mortality in AMI patients. Hazard ratio (line) and 95% confidence interval (grey area) from adjusted Cox regression for 30-day mortality (**A**), 180-day mortality (**B**) and 1-year mortality (**C**). 12mmol/L of AG concentration were used as reference. Cox regression was adjusted for Age, sex, SOFA score, creatinine, BUN, platelet, WBC, hemoglobin, mean heart rate, SAPS II score and comorbidities of hypertension, AF, CHF, diabetes and renal disease as Model 3 described in Tables 2 and 3.

**Abbreviations:** AG, anion gap; HR, hazard ratio.

Recently, a study of patients admitted to coronary care units with a broad array of cardiovascular diseases has discovered a predictive role of AG for in-hospital mortality.<sup>19</sup> Another previous study of 733 individuals with AMI reported a significant association between high AG and increased risk of in-hospital death, with an odds ratio of 4.2 (95% CI 2.3 to 7.5) in comparison with low AG after multivariable adjustments.<sup>14</sup> In the present study, we studied AG on a continuous scale and further categorized individuals in larger groups based on AG quartiles. The association between AG on a continuous scale and all-cause mortality was linear, as higher concentrations were associated with increased all-cause mortality. Moreover, the second to fourth quartile of AG were associated with increased risk of death in 30-day, 180-day and 1-year follow-up. The association attenuated but remain significant even after adjustment for potential cardiovascular risk factors and comorbidities. These findings suggest that AG is a novel risk factor for AMI mortality independent of conventional cardiovascular risk factors. Our finding expands on the association of AG to all-cause death in AMI, indicating the predictive value of AG during follow-up.

Several risk factors are related to AG concentration. Higher AG has been independently associated with insulin-resistance<sup>20</sup> and lower cardiorespiratory fitness in general population.<sup>21</sup> Besides, although AG was not associated with severity of coronary artery stenosis, it is reported that higher AG related to worse cardiac function in coronary artery disease.<sup>13</sup> Furthermore, AG has been

associated with outcomes of other critical illness like acute kidney injury,<sup>10</sup> advanced chronic kidney disease,<sup>11</sup> sepsis,<sup>6</sup> and cerebral infarction.<sup>12</sup> The evidence including the current study indicates that AG is a more general and reliable risk factor for cardiovascular and non-cardiovascular diseases, suggesting the clinical implications of this easily obtained predictor for prognosis.

The close association of AG to all-cause death in AMI might be explained by the relationship of AG to inflammation. A large study of 4525 healthy participants indicated increasing levels of leukocyte count and C-reactive protein with higher AG concentrations, even after various confounding factors were taken into account.<sup>9</sup> In our study, WBC increased with elevated AG. However, the association between AG and death remained significant after adjustment for WBC, and we were not able to adjust for other inflammation markers due to lack of information. Thus, inflammation may attribute to the hazard ratios, at least partly, in the current study. Furthermore, the major disorder that leads to the elevation of AG is metabolic acidosis, in which case increased AG is generally due to excessive production of organic acid such as lactate,  $\beta$ -hydroxybutyrate and acetoacetate.<sup>5</sup> It has been reported that two hours after symptom onset, most AMI patients had elevated lactate levels.<sup>22</sup> Many studies focusing on critically ill patients have reported that increased lactate level is a powerful predictor for short-term and long-term mortality in a spectrum of diseases,<sup>23,24</sup> including myocardial infarction.<sup>25</sup> On the other hand,  $\beta$ -hydroxybutyrate

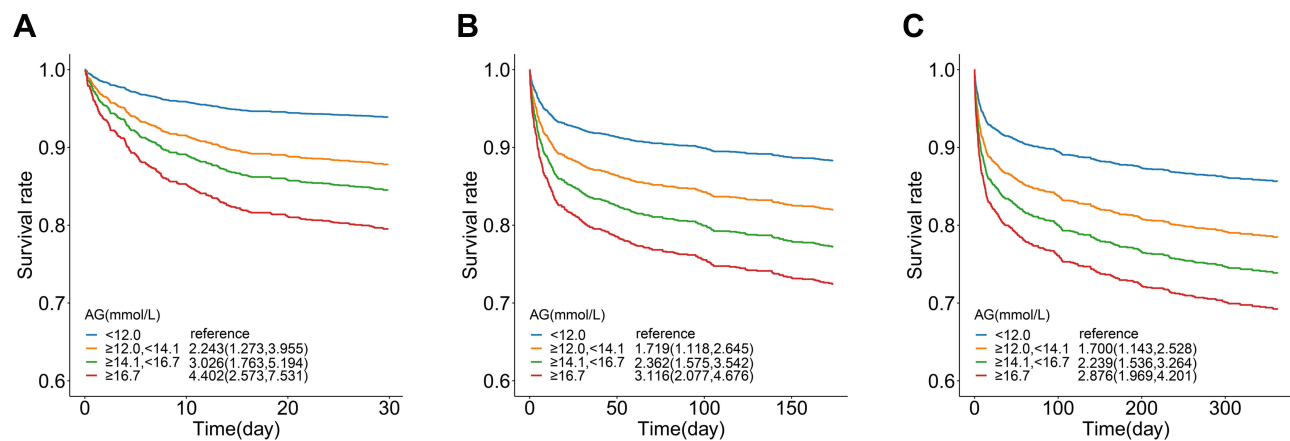


**Table 3** Hazard Ratio of AG (Quartile) for Mortality

| AG, mmol/L               | Unadjusted           |         | Model 1             |         | Model 2            |         | Model 3            |         |
|--------------------------|----------------------|---------|---------------------|---------|--------------------|---------|--------------------|---------|
|                          | HR (95% CI)          | P value | HR (95% CI)         | P value | HR (95% CI)        | P value | HR (95% CI)        | P value |
| <b>30-day mortality</b>  |                      |         |                     |         |                    |         |                    |         |
| <12.0                    | 1.0 (ref)            |         | 1.0 (ref)           |         | 1.0 (ref)          |         | 1.0 (ref)          |         |
| ≥12.0,<14.1              | 2.248(1.289, 3.920)  | 0.004   | 2.236(1.282,3.900)  | 0.005   | 2.424(1.380,4.256) | 0.002   | 2.243(1.273,3.955) | 0.005   |
| ≥14.1,<16.7              | 3.211(1.892,5.449)   | <0.001  | 3.162(1.863,5.366)  | <0.001  | 3.054(1.785,5.224) | <0.001  | 3.026(1.763,5.194) | <0.001  |
| ≥16.7                    | 10.086(6.189,16.437) | <0.001  | 9.287(5.694,15.146) | <0.001  | 5.090(3.017,8.586) | <0.001  | 4.402(2.573,7.531) | <0.001  |
| P for trend              | <0.001               |         | <0.001              |         | <0.001             |         | <0.001             |         |
| <b>180-day mortality</b> |                      |         |                     |         |                    |         |                    |         |
| <12.0                    | 1.0 (ref)            |         | 1.0 (ref)           |         | 1.0 (ref)          |         | 1.0 (ref)          |         |
| ≥12.0,<14.1              | 1.662(1.091,2.531)   | 0.018   | 1.647(1.081,2.510)  | <0.001  | 1.877(1.224,2.880) | 0.004   | 1.719(1.118,2.645) | 0.014   |
| ≥14.1,<16.7              | 2.418(1.630,3.587)   | <0.001  | 2.388(1.609,3.542)  | <0.001  | 2.376(1.588,3.553) | <0.001  | 2.362(1.575,3.542) | <0.001  |
| ≥16.7                    | 7.036(4.911,10.088)  | <0.001  | 6.468(4.511,9.273)  | <0.001  | 3.674(2.476,5.452) | <0.001  | 3.116(2.077,4.676) | <0.001  |
| P for trend              | <0.001               |         | <0.001              |         | <0.001             |         | <0.001             |         |
| <b>1-year mortality</b>  |                      |         |                     |         |                    |         |                    |         |
| <12.0                    | 1.0 (ref)            |         | 1.0 (ref)           |         | 1.0 (ref)          |         | 1.0 (ref)          |         |
| ≥12.0,<14.1              | 1.696(1.151,2.498)   | 0.008   | 1.647(1.136,2.467)  | <0.001  | 1.873(1.262,2.778) | 0.002   | 1.700(1.143,2.528) | 0.009   |
| ≥14.1,<16.7              | 2.342(1.623,3.377)   | <0.001  | 2.315(1.605,3.339)  | <0.001  | 2.265(1.558,3.294) | <0.001  | 2.239(1.536,3.264) | <0.001  |
| ≥16.7                    | 6.622(4.740,9.251)   | <0.001  | 6.098(4.362,8.525)  | <0.001  | 3.398(2.349,4.915) | <0.001  | 2.876(1.969,4.201) | <0.001  |
| P for trend              | <0.001               |         | <0.001              |         | <0.001             |         | <0.001             |         |

**Notes:** Model 1: adjusted for age and sex; Model 2: adjusted for model 1 plus SOFA score, creatinine, blood urea nitrogen, platelet, white blood cell, hemoglobin, and heart rate; Model 3: adjusted for model 2 plus hypertension, atrial fibrillation, congestive heart failure, diabetes, renal disease, cardiogenic shock and SAPS II score.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II.



**Figure 2** Adjusted survival rate by quartiles of AG. Risk-adjusted survival plots for 30-day mortality (A), 180-day mortality (B) and 1-year mortality (C). Cox regression was adjusted for age, sex, SOFA score, creatinine, BUN, platelet, WBC, hemoglobin, mean heart rate, SAPS II score and comorbidities of hypertension, AF, CHF, diabetes and renal disease as Model 3 described in Tables 2 and 3. The HRs and 95% CI were presented using the bottom quartile as reference.

**Abbreviation:** AG, anion gap.

| Subgroup      | p for interaction       |       | p for interaction        |       | p for interaction       |       |
|---------------|-------------------------|-------|--------------------------|-------|-------------------------|-------|
| Age           |                         |       |                          |       |                         |       |
| <65(n=783)    |                         | 0.727 |                          | 0.740 |                         | 0.700 |
| =65(n=1023)   |                         |       |                          |       |                         |       |
| Sex           |                         |       |                          |       |                         |       |
| Female(n=622) |                         | 0.769 |                          | 0.652 |                         | 0.588 |
| Male(n=1184)  |                         |       |                          |       |                         |       |
| Hypertension  |                         |       |                          |       |                         |       |
| Yes(n=873)    |                         | 0.071 |                          | 0.099 |                         | 0.148 |
| No(n=933)     |                         |       |                          |       |                         |       |
| AF            |                         |       |                          |       |                         |       |
| Yes(n=463)    |                         | 0.110 |                          | 0.148 |                         | 0.480 |
| No(n=1343)    |                         |       |                          |       |                         |       |
| CHF           |                         |       |                          |       |                         |       |
| Yes(n=704)    |                         | 0.268 |                          | 0.130 |                         | 0.128 |
| No(n=1102)    |                         |       |                          |       |                         |       |
| Diabetes      |                         |       |                          |       |                         |       |
| Yes(n=465)    |                         | 0.151 |                          | 0.328 |                         | 0.371 |
| No(n=1341)    |                         |       |                          |       |                         |       |
| AKI           |                         |       |                          |       |                         |       |
| Yes(n=1029)   |                         | 0.167 |                          | 0.324 |                         | 0.285 |
| No(n=773)     |                         |       |                          |       |                         |       |
| Sepsis        |                         |       |                          |       |                         |       |
| Yes(n=353)    |                         | 0.205 |                          | 0.834 |                         | 0.717 |
| No(n=1449)    |                         |       |                          |       |                         |       |
|               | 1 1.1 1.2               |       | 1 1.1 1.2                |       | 1 1.1 1.2               |       |
|               | HR for 30-day mortality |       | HR for 180-day mortality |       | HR for 1-year mortality |       |

**Figure 3** Associations between AG and risk of death in subgroups. Forest plot and adjusted hazard ratios with 95% CI for 30-day, 180-day and 1-year mortality.

**Abbreviations:** AF, atrial fibrillation; CHF, congestive heart failure; AKI, acute kidney injury.

and acetoacetate represent the two main ketone bodies.<sup>26</sup> A study showed that ketoacidosis associated to higher in-hospital mortality of ST-elevation myocardial infarction. Hence, organic acids that lead to elevated AG could also

relate to the mechanisms by which AG increased risk of mortality.

The current study has several strengths. First, this is the first study to demonstrate the predictive value of AG

on AMI mortality during follow-up. We have relatively large number of recruited individuals from a well-characterized database, and information on both short-term and long-term mortality. Second, to test the consistency of our results, we utilized both continuous scale and categories based on AG concentrations. And we also conducted subgroup analyses which obtained comparable results. Third, we performed restricted cubic splines to evaluate linearity, reflecting the efficient predictive role of increased AG levels. Our study adds to the understanding of AG-AMI outcome associations, which provides important information to determine AMI prognosis for clinicians. Further study to develop predictive scoring system for AMI mortality prediction using AG is warranted.

Our study also has some limitations. First, as this study was observational, we could not determine the causal effect of AG on AMI all-cause mortality. Second, although we included important risk factors in our multivariable models like lab tests, comorbidities and clinical assessment scores, residual confounding factors cannot be eliminated completely. Other relevant factors like lactate, cardiac function, and myocardial injury markers need to be taken into account in further studies. Moreover, we only have the information about AG during hospitalization, so we were not able to distinguish between acute and chronic AG elevation, which may have affected outcomes to a different extent.

## Conclusion

In summary, we firstly found higher AG was significantly associated with increased 30-day, 180-day and 1-year all-cause mortality in AMI patients. AG, as an easily obtained and inexpensive marker, is of reliable predictive value for AMI all-cause mortality during follow-up.

## Abbreviations

ACS, acute coronary syndrome; AMI, acute myocardial infarction; AG, anion gap; ICU, intensive care units; SQL, structured query language; BUN, blood urea nitrogen; WBC, white blood cells; SOFA, Sequential Organ Failure Assessment; SOFA II, Simplified Acute Physiology Score II; AF, atrial fibrillation; CHF, congestive heart failure; AKI, acute kidney injury; RCS, restricted cubic spline.

## Acknowledgments

Chenbo Xu wants to thank Fangzheng Lin for his valuable research assistance and support.

## Disclosure

All authors report no conflicts of interest for this work.

## References

1. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. *New Engl J Med*. 2010;362:2155–2165. doi:10.1056/NEJMoa0908610
2. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*. 2015;386:2145–2191. doi:10.1016/s0140-6736(15)61340-x
3. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222. doi:10.1016/s0140-6736(20)30925-9
4. Oh MS, Carroll HJ. The anion gap. *N Engl J Med*. 1977;297:814–817. doi:10.1056/nejm197710132971507
5. Kraut JA, Madias NE. Serum anion gap: its uses and limitations in clinical medicine. *Clin J Am Soc Nephrol*. 2007;2:162–174. doi:10.2215/CJN.03020906
6. Hu T, Zhang Z, Jiang Y. Albumin corrected anion gap for predicting in-hospital mortality among intensive care patients with sepsis: a retrospective propensity score matching analysis. *Clin Chim Acta*. 2021;521:272–277. doi:10.1016/j.cca.2021.07.021
7. Chen Q, Chen Q, Li L, et al. Serum anion gap on admission predicts intensive care unit mortality in patients with aortic aneurysm. *Exp Ther Med*. 2018;16:1766–1777. doi:10.3892/etm.2018.6391
8. Ahn SY, Ryu J, Baek SH, et al. Serum anion gap is predictive of mortality in an elderly population. *Exp Gerontol*. 2014;50:122–127. doi:10.1016/j.exger.2013.12.002
9. Farwell WR, Taylor EN. Serum anion gap, bicarbonate and biomarkers of inflammation in healthy individuals in a national survey. *CMAJ*. 2010;182:137–141. doi:10.1503/cmaj.090329
10. Cheng B, Li D, Gong Y, et al. 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. doi:10.1155/2020/6501272
11. Asahina Y, Sakaguchi Y, Kajimoto S, et al. Association of time-updated anion gap with risk of kidney failure in advanced CKD: a Cohort Study. *Am J Kidney Dis*. 2021. doi:10.1053/j.ajkd.2021.05.022
12. Liu X, Feng Y, Zhu X, et al. Serum anion gap at admission predicts all-cause mortality in critically ill patients with cerebral infarction: evidence from the MIMIC-III database. *Biomarkers*. 2020;25:725–732. doi:10.1080/1354750X.2020.1842497
13. Yang SW, Zhou YJ, Zhao YX, et al. The serum anion gap is associated with disease severity and all-cause mortality in coronary artery disease. *J Geriatr Cardiol*. 2017;14:392–400. doi:10.11909/j.issn.1671-5411.2017.06.008
14. Sahu A, Cooper HA, Panza JA. The initial anion gap is a predictor of mortality in acute myocardial infarction. *Coron Artery Dis*. 2006;17:409–412. doi:10.1097/00019501-200608000-00002
15. Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. *Sci Data*. 2016;3:160035. doi:10.1038/sdata.2016.35
16. Johnson AE, Stone DJ, Celi LA, et al. The MIMIC code repository: enabling reproducibility in critical care research. *J Am Med Inform Assoc*. 2018;25:32–39. doi:10.1093/jamia/ocx084
17. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303–1310. doi:10.1097/00003246-200107000-00002



18. Fliser D, Laville M, Covic A, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant*. 2012;27:4263–4272. doi:10.1093/ndt/gfs375
19. Sun T, Cai C, Shen H, et al. Anion gap was associated with in-hospital mortality and adverse clinical outcomes of coronary care unit patients. *Biomed Res Int*. 2020;2020:4598462. doi:10.1155/2020/4598462
20. Farwell WR, Taylor EN. Serum bicarbonate, anion gap and insulin resistance in the National Health and Nutrition Examination Survey. *Diabet Med*. 2008;25:798–804. doi:10.1111/j.1464-5491.2008.02471.x
21. Abramowitz MK, Hostetter TH, Melamed ML. Lower serum bicarbonate and a higher anion gap are associated with lower cardiorespiratory fitness in young adults. *Kidney Int*. 2012;81:1033–1042. doi:10.1038/ki.2011.479
22. Gatien M, Stiell I, Wielgosz A, et al. Diagnostic performance of venous lactate on arrival at the emergency department for myocardial infarction. *Acad Emerg Med*. 2005;12:106–113. doi:10.1197/j.aem.2004.10.012
23. Gutierrez G, Comignani P, Huespe L, et al. Central venous to mixed venous blood oxygen and lactate gradients are associated with outcome in critically ill patients. *Intensive Care Med*. 2008;34:1662–1668. doi:10.1007/s00134-008-1128-2
24. Watanabe I, Mayumi T, Arishima T, et al. Hyperlactemia can predict the prognosis of liver resection. *Shock*. 2007;28:35–38. doi:10.1097/shk.0b013e3180310ca9
25. Lazzeri C, Sori A, Chiostrì M, et al. Prognostic role of insulin resistance as assessed by homeostatic model assessment index in the acute phase of myocardial infarction in nondiabetic patients submitted to percutaneous coronary intervention. *Eur J Anaesthesiol*. 2009;26:856–862. doi:10.1097/EJA.0b013e32832a235c
26. Abdul Kadir A, Clarke K, Evans RD. Cardiac ketone body metabolism. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866:165739. doi:10.1016/j.bbadis.2020.165739

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