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The serum anion gap is associated with disease severity and all-cause mortality in coronary artery disease

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Abstract

Objective To evaluate the associations between the serum anion gap (AG) with the severity and prognosis of coronary artery disease (CAD). **Methods** We measured serum electrolytes in 18,115 CAD patients indicated by coronary angiography. The serum AG was calculated according to the equation: AG = Na^+[(mmol/L) + K^+ (mmol/L)] − [Cl^- (mmol/L) + $HCO3^-$ (mmol/L)]. **Results** A total of 4510 (24.9%) participants had their AG levels greater than 16 mmol/L. The serum AG was independently associated with measures of CAD severity, including more severe clinical types of CAD ($P < 0.001$) and worse cardiac function ($P = 0.004$). Patients in the 4th quartile of serum AG (≥ 15.92 mmol/L) had a 5.171-fold increased risk of 30 days all-cause death ($P < 0.001$). This association was robust, even after adjustment for age, sex, evaluated glomerular filtration rate [hazard ratio (HR): 4.861, 95% confidence interval (CI): 2.150–10.993, $P < 0.001$], clinical diagnosis, severity of coronary artery stenosis, cardiac function grades, and other confounders (HR: 3.318, 95% CI: 1.76–2.27, $P = 0.009$). **Conclusion** In this large population-based study, our findings reveal a high percentage of increased serum AG in CAD. Higher AG is associated with more severe clinical types of CAD and worse cardiac function. Furthermore, the increased serum AG is an independent, significant, and strong predictor of all-cause mortality. These findings support a role for the serum AG in the risk-stratification of CAD.

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Keywords: All-cause death; Anion gap; Coronary artery disease

1 Introduction

Although considerable progress has been made in basic and clinical research in atherosclerosis over the past decades, coronary artery disease (CAD) remains one of the leading causes of deaths worldwide.[1] New prognostic features in CAD patients are always welcomed by clinicians, especially when so easy to obtain and understand! The serum anion gap (AG) is such a mathematically derivated parameter that has been used for more than 50 years.[2] Although it has its widest application in the diagnosis of various forms of metabolic acidosis, it may sometimes provide an important clue to the diagnosis or prognosis of disorders such as advanced kidney disease (AKD).[2] Furthermore, in the general population largely free of AKD the increase in AG may be of prognostic significance as higher levels of AG have been associated with hypertension,[3] insulin resistance,[4] low cardiorespiratory fitness,[5] all-cause[6] and cardiac deaths.[7] Novel risk factors can improve the Framingham risk score. However, it is largely unknown whether such changes of AG occur in the course of CAD might exist a risk difference for either CAD severity or mortality. To date, there have been no population-based studies of acid-base status and CAD. The current study aimed to evaluate the associations between the serum AG with the severity and prognosis of CAD.

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2 Methods

2.1 Study population

The study protocol was approved by the Institutional Review Boards of all participating hospitals and informed consent have been obtained. All methods were performed in accordance with the relevant guidelines and regulations by including a statement in the methods section to this effect. From April 2004 to October 2010, a total of 21,620 consecutive patients with complete measurements of serum electrolytes and creatinine were recruited from five centers. All participants aged ≥ 18 years and underwent clinically indicated coronary angiography and percutaneous coronary intervention (PCI). We excluded participants who were missing covariate or mortality data (n = 3465), or had a diagnosed terminal illness (n = 40). Thus there were 18,115 participants remaining in the study cohort.

2.2 Calculation of the serum AG and evaluated glomerular filtration rate (eGFR)

Although methods used to calculate AG may be susceptible to some parameters (including haemoconcentration, albumin concentration, Ca^{2+} concentration, some medications, and renal function, etc.) and some authors advise to correct AG value by such parameters, the equation used in the present study, [AG = Na^+ (mmol/L) + K^+(mmol/L)] − [Cl^- (mmol/L) + $HCO3^-$ (mmol/L)], was generally acknowledged.[8] Furthermore, eGFR was calculated according to the simplified Modification of Diet in Renal Disease Study prediction equation.[9]

2.3 Assessment of severity of CAD

The severity of CAD was comprehensively evaluated through three ordinal variables: clinical diagnosis, severity of coronary artery stenosis, and cardiac function grades based on left ventricular ejection fraction (LVEF). Although not exactly, all of the variables reflected the severity of CAD to some extent. The levels of clinical diagnosis included stable coronary atherosclerotic disease (SCAD), unstable angina pectoris (UAP), or acute myocardial infarction (AMI).[10–12] Significant coronary artery stenosis was defined as ≥ 75% narrowing of the diameter of at least one major epicardial vessel.[13,14] Severity of coronary artery stenosis was defined according to the number of significantly diseased vessels, namely 1-vessel, 2-vessel, and 3-vesse and/or left main (LM). Simultaneously, the SYNTAX score was calculated retrospectively by reviewing the original diagnostic angiograms.[15] Grades of cardiac function comprised normal (defined as ≥ 50%), preserved (40%–49%), and reduced (< 40%) LVEF.[16]

2.4 Assessment of patient characteristics

Demographic characteristics, medical history, risk factors and medication usage were obtained from the electronic medical records. Baseline fasting venous blood samples were drawn and tested for hemoglobin, leukocytes, platelet counts, serum lipids, alanine aminotransferase, electrolytes, albumin, and glucose, etc.

2.5 Outcome

Thirty days all-cause mortality was collected for 12,946 (71.5%) patients from the electronic medical record system, 4237 (23.4%) from telephone contact, and 932 (5.1%) from household registration system.

2.6 Statistical analysis

Non-normally distributed data were presented as median [interquartile (25th–75th percentiles) range], and normally distributed variables as mean ± SD. Where indicated, one-way analysis of variance and Kruskal–Wallis test or chi-square test were applied to evaluate statistical differences among AG quartile groups. The serum AG was modeled as continuous variable and according to quartiles in multivariate analyses (P for trend was calculated). Ordinal logistic regressions were used to evaluate associations between AG with the severity of CAD. The Kaplan–Meier estimates were used to describe the event-free survival on follow-up. To further evaluate the prognostic value of AG, a Cox proportional hazard analysis was performed. Adjusted models included covariates on the basis of statistical evidence for confounding and clinical judgment. To determine whether our results were driven by participants with AKD, we re-evaluated associations of the serum AG with the severity and prognosis of CAD after excluding those with eGFR < 60 mL/min per 1.73m^2.[17] All statistical tests were two-sided and P-values of < 0.05 was considered to be statistically significant. SPSS 22.0 (IBM Corporation) was used to conduct statistical analysis.

3 Results

3.1 Patient characteristics

Across the cohort, the serum AG followed an approximately normal distribution. It ranged from 0.20 to 53.30 mmol/L, with a mean ± SD of 13.73 ± 3.59 mmol/L. The median level was 13.52 (interquartile range: 11.40–15.92) mmol/L. A total of 4510 (24.9%) participants had their AG levels greater than 16 mmol/L, which was usually suggested the upper limit of a normal AG. AG exceeding 24 mmol/L was rare (0.6%). The serum AG was significantly higher in

patients with AKD, AMI, and reduced LVEF (< 40%) (Figure 1). Overall, patients with higher levels of AG were younger and taking more medications, more likely to have lower levels of eGFR, higher levels of clinical diagnosis and cardiac function grades (Table 1). It should be noted that patients with higher AG levels had lower low-density lipoprotein cholesterol (LDL-C) and higher high-density lipoprotein cholesterol (HDL-C) concentrations probably secondary to better control of risk factors and higher intake of statins in these groups.

3.2 Independent determinants of baseline serum AG levels

As shown in Supplemental Table 1, clinical diagnosis of AMI, angiotensin receptor blockers (ARBs) use, higher hemoglobin, leukocyte, platelet, ALT, fasting plasma plasma glucose, HDL-C, and albumin were each independently associated with higher levels of serum AG. In contrast, male sex, a history of prior MI, higher eGFR, LDL-C, and LVEF were each independently associated with lower levels of serum AG.

3.3 Association of AG with clinical diagnosis of CAD

The risk of having higher levels of clinical diagnosis increased by 5.7%, 5.5%, and 1.8% for each millimole-per-liter increment in the serum AG in unadjusted, age/sex adjusted, and fully adjusted models, respectively (Table 2). In unadjusted ordinal Logistic models comparing the 4th versus 1st quartile, those patients with AG ≥ 15.92 mmol/L had a 1.595-fold increased risk of higher levels of clinical diagnosis ($P < 0.001$). After adjustment for all confounders, this association was attenuated in magnitude but remained statistically significant (OR: 1.170, 95% CI: 1.066 to 1.283, $P = 0.001$).

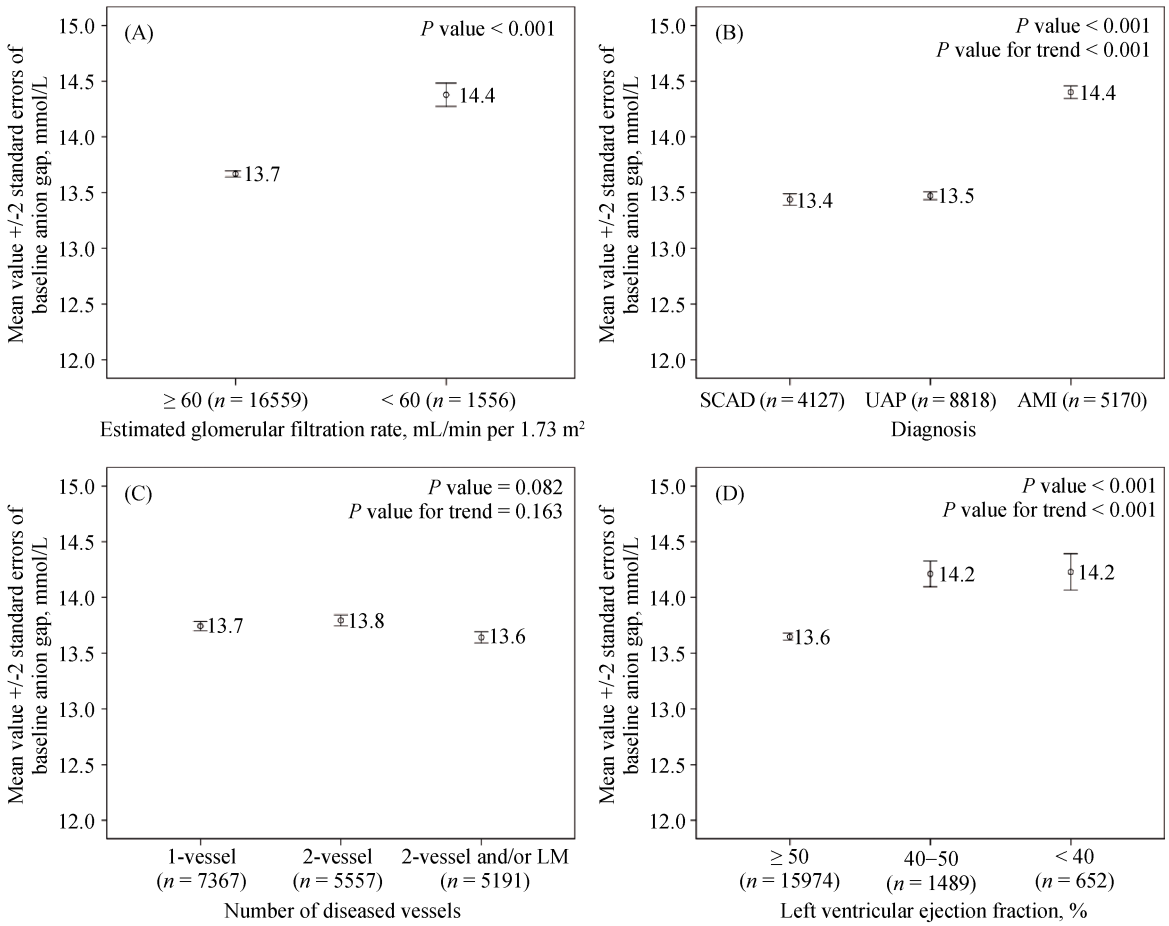

Figure 1. Comparisons of the serum anion gap among different groups. (A): Comparison of the serum AG between patients with eGFR ≥ and < 60 mL/min per 1.73m^2; (B): comparison of the serum AG among patients with SCAD, UAP, and AMI; (C): comparison of the serum AG among patients with 1-vessel, 2-vessel, and 3-vesse and/or LM disease; (D): comparison of the serum AG among patients with LVEF ≥ 50%, 40%–50%, and < 40%. AG: anion gap; AMI: acute myocardial infarction; eGFR: evaluated glomerular filtration rate; LM: left main; LVEF: left ventricular ejection fraction; SCAD: stable coronary atherosclerotic disease; UAP: unstable angina pectoris.

Table 1. Baseline clinical and biochemical characteristics by AG quartiles.

Characteristics	Cohort (n = 18115)	Quartiles of AG (mmol/L)				*P* value	*P* value for trend
		Q1 (n = 4537) < 11.40	Q2 (n = 4558) 11.40–13.52	Q3 (n = 4508) 13.52–15.92	Q4 (n = 4512) ≥ 15.92		
Demographic characteristics							
Age, yrs	60 ± 11	61 ± 11	60 ± 11	59 ± 11	59 ± 11	< 0.001	< 0.001
Male	13,455 (74.3%)	3440 (75.8%)	3367 (73.9%)	3283 (72.8%)	3365 (74.6%)	0.011	0.100
Medical history and coronary risk factors							
Hypertension	11,040 (60.9%)	2734 (60.3%)	2779 (61.0%)	2725 (60.4%)	2802 (62.1%)	0.273	0.123
Diabetes	5220 (28.8%)	1242 (27.4%)	1260 (27.6%)	1336 (29.6%)	1382 (30.6%)	0.001	< 0.001
Hypercholesterolemia	2741 (15.1%)	619 (13.6%)	678 (14.9%)	719 (15.9%)	725 (16.1%)	0.004	< 0.001
Smoking	5733 (31.6%)	1433 (31.6%)	1453 (31.9%)	1418 (31.5%)	1429 (31.7%)	0.602	0.787
Body mass index, kg/m^2	28 ± 6	28 ± 6	28 ± 6	28 ± 7	28 ± 9	0.116	0.098
Prior MI	2825 (15.6%)	724 (16.0%)	746 (16.4%)	709 (15.7%)	646 (14.3%)	0.043	0.021
Prior stroke	770 (4.3%)	186 (4.1%)	197 (4.3%)	199 (4.4%)	188 (4.2%)	0.876	0.826
Diagnosis							
SCAD	4127 (22.8%)	1110 (24.5%)	1060 (23.3%)	1056 (23.4%)	901 (20.0%)		
UAP	8818 (48.7%)	2316 (51.0%)	2324 (51.0%)	2240 (49.7%)	1938 (43.0%)	< 0.001	< 0.001
AMI	5170 (28.5%)	1111 (24.5%)	1174 (25.8%)	1212 (26.9%)	1673 (37.1%)		
Medication use							
Aspirin	17,206 (95.0%)	4291 (94.6%)	4316 (94.7%)	4264 (94.6%)	4335 (96.1%)	0.002	0.002
Thienopyridines	17,934 (99.0%)	4485 (98.9%)	4517 (99.1%)	4455 (98.8%)	4477 (99.2%)	0.161	0.207
Beta-blockers	12,608 (69.6%)	3099 (68.3%)	3153 (69.2%)	3148 (69.8%)	3208 (71.1%)	0.031	0.003
ACEIs	9226 (50.9%)	2329 (51.3%)	2295 (50.4%)	2219 (49.2%)	2383 (52.8%)	0.006	0.320
ARBs	3192 (17.6%)	723 (15.9%)	807 (17.7%)	810 (18.0%)	852 (18.9%)	0.003	< 0.001
Statins	16,588 (91.6%)	4115 (90.7%)	4158 (91.2%)	4134 (91.7%)	4181 (92.7%)	0.007	0.001
Laboratory variables							
Hemoglobin, g/L	109 ± 56	104 ± 57	108 ± 56	111 ± 55	115 ± 54	< 0.001	< 0.001
Leukocyte, ×10^9/L	7.53 ± 2.62	7.10 ± 2.29	7.23 ± 2.24	7.52 ± 2.53	8.28 ± 3.17	< 0.001	< 0.001
Neutrophil, ×10^9/L	4.70 ± 2.29	4.33 ± 1.93	4.42 ± 1.90	4.64 ± 2.14	5.39 ± 2.89	< 0.001	< 0.001
Lymphocyte, ×10^9/L	2.01 ± 0.70	1.96 ± 0.66	2.00 ± 0.68	2.05 ± 0.71	2.02 ± 0.75	< 0.001	< 0.001
Platelet, ×10^9/L	206 ± 60	197 ± 56	206 ± 60	209 ± 61	213 ± 61	< 0.001	< 0.001
eGFR, mL/min per 1.73m^2	89 (74–105)	89 (75–106)	89 (75–106)	89 (74–105)	87 (73–103)	< 0.001	< 0.001
Alanine aminotransferase, U/L	30 (19–47)	26 (17–41)	28 (18–44)	31 (19–47)	35 (22–55)	< 0.001	< 0.001
Glucose, mmol/L	6.75 ± 2.57	6.64 ± 2.55	6.54 ± 2.38	6.73 ± 2.54	7.09 ± 2.78	< 0.001	< 0.001
LDL-C, mmol/L	2.91 ± 0.94	2.86 ± 0.93	2.19 ± 0.94	2.93 ± 0.95	2.93 ± 0.93	0.001	< 0.001
HDL-C, mmol/L	0.97 ± 0.23	0.95 ± 0.22	0.97 ± 0.23	0.98 ± 0.24	0.99 ± 0.24	< 0.001	< 0.001
Albumin, g/L	42.86 ± 4.87	42.31 ± 4.56	42.86 ± 4.69	43.12 ± 4.81	43.15 ± 5.36	< 0.001	< 0.001
Potassium, mmol/L	4.12 ± 0.45	4.13 ± 0.41	4.12 ± 0.43	4.12 ± 0.43	4.10 ± 0.51	0.016	0.002
Anion gap, mmol/L	13.73 ± 3.59	9.41 ± 1.65	12.48 ± 0.62	14.70 ± 0.69	18.37 ± 2.35		
Cardiac functional grades							
LVEF, %	61.02 ± 10.23	61.70 ± 10.12	61.59 ± 10.11	60.97 ± 10.20	59.80 ± 10.39	< 0.001	< 0.001
< 40%	652 (3.6%)	136(3.0%)	164 (3.6%)	167 (3.7%)	185 (4.1%)		
40%–50%	1489 (8.2%)	349 (7.7%)	319 (7.0%)	374 (8.3%)	447 (9.9%)	< 0.001	< 0.001
≧ 50%	15,974 (88.2%)	4052 (89.3%)	4075 (89.4%)	3967 (88.0%)	3880 (86.0%)		
Number of significantly diseased vessels							
1-vessel	7367 (40.7%)	1832 (40.4%)	1858 (40.8%)	1837 (40.7%)	1840 (40.8%)		
2-vessel	5557 (30.7%)	1402 (30.9%)	1327 (29.1%)	1388 (30.8%)	1440 (31.9%)	0.052	0.195
3-vessel and/or LM	5191 (28.7%)	1303 (28.7%)	1373 (30.1%)	1283 (28.5%)	1232 (27.3%)		
Syntax score	19.56 ± 3.44	19.17 ± 3.49	20.50 ± 3.58	19.38 ± 3.32	20.21 ± 3.55	0.372	0.525

Data were presented as n (%), mean ± SD or mean (interquartile range). ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ARBs: angiotensin receptor blockers; eGFR: evaluated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction; SCAD: stable coronary atherosclerotic disease; UAP: unstable angina pectoris.

Table 2. Association of AG with an increase in the levels of clinical diagnosis.

	AG		
	OR (95% CI)	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		< 0.001
Quartile 2	1.067 (0.987–1.153)	0.101	
Quartile 3	1.094 (1.013–1.183)	0.022	
Quartile 4	1.595 (1.476–1.723)	< 0.001	
Continuous	1.057 (1.048–1.065)	< 0.001	
Model 2			
Quartile 1	Referent		< 0.001
Quartile 2	1.064 (0.985–1.149)	0.117	
Quartile 3	1.089 (1.007–1.177)	0.032	
Quartile 4	1.570 (1.452–1.697)	< 0.001	
Continuous	1.055 (1.047–1.063)	< 0.001	
Model 3			
Quartile 1	Referent		< 0.001
Quartile 2	1.064 (0.984–1.149)	0.118	
Quartile 3	1.084 (1.003–1.172)	0.041	
Quartile 4	1.553 (1.436–1.680)	< 0.001	
Continuous	1.053 (1.046–1.062)	< 0.001	
Model 4			
Quartile 1	Referent		< 0.001
Quartile 2	1.035 (0.945–1.132)	0.464	
Quartile 3	1.050 (0.960–1.148)	0.286	
Quartile 4	1.170 (1.066–1.283)	0.001	
Continuous	1.018 (1.009–1.027)	< 0.001	

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, prior MI, prior stroke, aspirin use, thienopyridines use, beta-blockers use, ACEIs use, ARBs use, statins use, hemoglobin, leukocyte, platelet, eGFR, ALT, glucose, LDL-C, HDL-C, anion gap, phosphorus, potassium, calcium, LVEF, and number of significantly diseased vessels. ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ALT: alanine aminotransferase; ARBs: angiotensin receptor blockers; BMI: body mass index; CI: confidence interval; eGFR: evaluated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Table 3. Association of AG with an increase in the number of significantly diseased vessels

	AG		
	OR (95% CI)	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		0.229
Quartile 2	1.019 (0.946–1.100)	0.617	
Quartile 3	0.986 (0.914–1.064)	0.714	
Quartile 4	0.963 (0.892–1.039)	0.327	
Continuous	0.995 (0.988–1.003)	0.194	
Model 2			
Quartile 1	Referent		0.948
Quartile 2	1.042 (0.966–1.125)	0.286	
Quartile 3	1.022 (0.946–1.103)	0.581	
Quartile 4	1.009 (0.935–1.090)	0.811	
Continuous	1.000 (0.992–1.007)	0.939	
Model 3			
Quartile 1	Referent		0.938
Quartile 2	1.042 (0.966–1.125)	0.287	
Quartile 3	1.019 (0.945–1.101)	0.622	
Quartile 4	1.004 (0.930–1.084)	0.916	
Continuous	0.999 (0.991–1.007)	0.802	
Model 4			
Quartile 1	Referent		0.548
Quartile 2	1.042 (0.965–1.124)	0.297	
Quartile 3	1.010 (0.936–1.091)	0.790	
Quartile 4	0.985 (0.912–1.064)	0.705	
Continuous	0.997 (0.990–1.005)	0.494	

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, and eGFR. AG: anion gap; BMI: body mass index; CI: confidence interval; eGFR: evaluated glomerular filtration rate.

3.4 Association of AG with severity of coronary artery stenosis

Either in unadjusted or fully adjusted models, the findings did not support a role for the serum AG levels as an independent biomarker for severity of coronary artery stenosis (Table 3).

3.5 Association of AG with cardiac function grades

The risk of having higher grades of cardiac function increased by 4.3%, 4.6%, and 2.1% for each millimole-per-liter increment in the serum AG in unadjusted, age/sex adjusted, and fully adjusted models, respectively (Table 4). In unadjusted ordinal Logistic models comparing the 4th versus 1st quartile, those patients with AG ≥ 15.92 mmol/L had a 1.355-fold increased risk of higher grades of cardiac function ($P < 0.001$). After adjustment for all confounders, this association remained statistically significant (OR: 1.158, 95% CI: 1.001 to 1.340, $P = 0.049$).

3.6 Association of AG with all-cause mortality

During the 30 days follow-up time, 73 (0.40%) patients died. Kaplan-Meier survival curve demonstrated significantly lower cumulative survivals for patients with higher AG quartiles: 7 deaths (0.15%) in the 1st quartile, 11 deaths (0.24%) in the 2nd quartile, 19 deaths (0.42%) in the 3rd

Table 4. Association of AG with cardiac function grades.

	AG		
	OR (95% CI)	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		< 0.001
Quartile 2	0.991 (0.855–1.149)	0.902	
Quartile 3	1.150 (0.996–1.328)	0.057	
Quartile 4	1.355 (1.179–1.559)	< 0.001	
Continuous	1.043 (1.029–1.058)	< 0.001	
Model 2			
Quartile 1	Referent		< 0.001
Quartile 2	1.010 (0.871–1.171)	0.897	
Quartile 3	1.183 (1.024–1.368)	0.022	
Quartile 4	1.394 (1.212–1.605)	< 0.001	
Continuous	1.046 (1.031–1.061)	< 0.001	
Model 3			
Quartile 1	Referent		< 0.001
Quartile 2	1.008 (0.869–1.169)	0.917	
Quartile 3	1.172 (1.014–1.355)	0.031	
Quartile 4	1.365 (1.186–1.571)	< 0.001	
Continuous	1.043 (1.029–1.058)	< 0.001	
Model 4			
Quartile 1	Referent		0.015
Quartile 2	0.983 (0.844–1.146)	0.828	
Quartile 3	1.125 (0.969–1.306)	0.123	
Quartile 4	1.158 (1.001–1.340)	0.049	
Continuous	1.021 (1.007–1.035)	0.004	

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, prior MI, prior stroke, diagnosis, aspirin use, thienopyridines use, beta-blockers use, ACEIs use, ARBs use, statins use, eGFR, anion gap, phosphorus, potassium, calcium, and numbers of diseased vessels. ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ARBs: angiotensin receptor blockers; BMI: body mass index; CI: confidence interval; eGFR: evaluated glomerular filtration rate.

quartile and 36 deaths (0.80%) in the 4th quartile (Log rank $P < 0.001$, Figure 2). In unadjusted Cox models comparing the 4th *vs*. 1st quartile, those patients with AG ≥ 15.92 mmol/L had a 5.171-fold increased risk of all-cause death ($P < 0.001$, Table 5). After adjustment for age, sex, eGFR, risk factors and comorbidities, clinical diagnosis, LVEF, Syntax score, and all other confounders, there remained a significant association of higher AG with all-cause mortality [hazard ratio (HR) for the 4th *vs*. 1st quartile: 3.318, 95% CI: 1.342 to 8.205]. When examined as continuous variables, each millimole-per-liter higher AG was associated with increased risk of all-cause mortality in unadjusted (HR: 1.244, 95% CI: 1.203 to 1.286, $P < 0.001$), age/sex adjusted (HR: 1.135, 95% CI: 1.098 to 1.174, $P < 0.001$), and fully adjusted models (HR: 1.069, 95% CI: 1.020 to 1.121, $P = 0.005$).

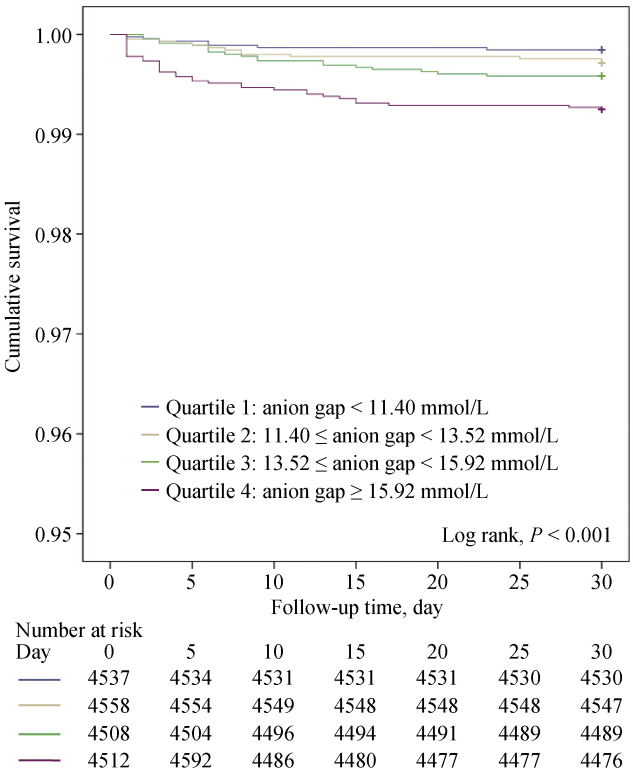

Figure 2. Kaplan–Meier survival curve among quartile groups of the serum AG. AG: anion gap.

3.7 Sensitivity analyses

After excluding participants with eGFR < 60 mL/min per 1.73m^2, increased AG was still associated with higher levels of clinical diagnosis (Supplemental Table 2), cardiac function grades (Supplemental Table 3), and all-cause mortality (Supplemental Table 4). Furthermore, a similar, non-significant association with severity of coronary artery stenosis remained (Supplemental Table 5).

4 Discussion

Gamble is one of the first individuals to emphasize the importance of charge balance in the ionic environment of the blood and other body fluids, which means the sum of serum cations must equal that of serum anions.[2] Because normally the total unmeasured anions exceed the total unmeasured cations, there is an AG. By contrast to a low serum AG, an elevated serum AG is a common occurrence. Examination of 6868 sets of serum electrolyte among miscellaneous hospitalized patients revealed an elevated serum AG in 37.6%.[18] There have been no population-based studies of the incidence of elevated serum AG in CAD. Our

Table 5. Association of AG with all-cause deaths

	AG		
	HR (95% CI)	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		< 0.001
Quartile 2	1.564 (0.746–4.687)	0.182	
Quartile 3	2.732 (1.137–6.432)	0.024	
Quartile 4	5.171 (2.172–11.053)	< 0.001	
Continuous	1.244 (1.203–1.286)	< 0.001	
Model 2			
Quartile 1	Referent		< 0.001
Quartile 2	1.996 (0.796–5.006)	0.141	
Quartile 3	2.794 (1.174–6.647)	0.020	
Quartile 4	5.407 (2.395–12.208)	< 0.001	
Continuous	1.135 (1.098–1.174)	< 0.001	
Model 3			
Quartile 1	Referent		< 0.001
Quartile 2	1.897 (0.756–4.759)	0.172	
Quartile 3	2.776 (1.167–6.603)	0.021	
Quartile 4	4.861 (2.150–10.993)	< 0.001	
Continuous	1.128 (1.089–1.168)	< 0.001	
Model 4			
Quartile 1	Referent		< 0.001
Quartile 2	1.660 (0.602–4.579)	0.328	
Quartile 3	2.932 (1.163–7.392)	0.023	
Quartile 4	3.318 (1.342–8.205)	0.009	
Continuous	1.069 (1.020–1.121)	0.005	

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, prior MI, prior stroke, diagnosis, aspirin use, thienopyridines use, beta-blockers use, ACEIs use, ARBs use, statins use, hemoglobin, leukocyte, platelet, eGFR, ALT, glucose, LDL-C, HDL-C, ALB, anion gap, phosphorus, potassium, calcium, LVEF, and Syntax score. ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ARBs: angiotensin receptor blockers; ALB: albumin; ALT: alanine aminotransferase; BMI: body mass index; CI: confidence interval; eGFR: evaluated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

findings reveal a relatively high percentage (24.9%) of increased serum AG (greater than 16 mmol/L) in CAD.

Elevation in the serum AG generally is caused by overproduction of organic acid anions and/or the concomitant and proportionate reduction in the excretion of anions, while changes in the equivalents of total proteins, phosphorus, potassium, and calcium are unusual causes.[2] It has been reported that lactate and ketoanions accounted for 62% of the increments in AG.[19] In animals and patients with heart failure (HF) or acute coronary syndrome (ACS), marked increments in metabolic rate, sympathetic nervous system activation, accelerated glycolysis and a modified bioenergetic supply associated with increased lactate levels were described.[20] Lommi, *et al*.[21] found that patients with HF had elevated blood ketone bodies compared with control subjects. Furthermore, blood ketone bodies were related to LVEF and LVEF was an independent predictor of ketonemia. Most recently, Bedi, *et al*.[22] observed an increased abundance of ketogenic β-hydroxybutyryl-CoA in HF. Similar results were also found in patients with ACS.[23–25] All these data strongly suggest that organic acid anions accumulation might be one of the potential mechanisms, by which higher AG is associated with more severe clinical types of CAD and worse cardiac function. Another potential mechanism lies in the impairment of glomerular filtration accounting for the retention of non-chloride anions, as acid retention has been demonstrated in subjects with only mild reductions in eGFR.[17]

In many cases, the identity of anions that contribute to the elevated AG can be determined, especially when the serum AG > 30 mmol/L.[26] A lesser increase in the serum AG (≤ 24 mmol/L) can be present without an identifiable, accumulating acid in > 30% of cases.[26] In the current study, AG exceeding 24 mmol/L was rare (0.6%). Therefore, it is unclear to what degree these prior results can be extrapolated to our findings.

It has been shown that increased serum AG may be of prognostic significance as higher levels of AG were associated with hypertension,[3] insulin resistance,[4] and low cardiorespiratory fitness.[5] In a large study that included 31590 subjects who underwent a health screening, a trend for increased mortality risk with higher levels of serum AG was present.[6] In another community-based cohort study, higher levels of serum AG was associated with an increased risk of all-cause and cardiac deaths.[7] Our results indicate that the serum AG is strongly associated with all-cause mortality in CAD. Although several observational studies suggested that elevated levels of lactate and ketone bodies were associated with worse outcomes, none of the previous studies provided direct evidence.[27–29]

4.1 Limitations

First of all, in light of its observational nature, we cannot conclude the increase in the serum AG is a cause or consequence of more severe clinical types of CAD and worse cardiac function. Secondly, SCAD and UAP diagnoses might be broadened excessively because of some patients with vague symptoms, atypical electrocardiograms, or incomplete myocardial injury markers tests. Thirdly, although we adjusted for eGFR in the multivariate analyses and per-

formed sensitivity analyses excluding participants with AKD, we could not completely rule out the impact of mild renal dysfunction. Additionally, we did not have measurements of lactate, β-hydroxybutyrate and acetoacetate. Thus, we speculate without direct evidence the potential mechanisms by which higher AG is associated with the severity and outcome of CAD.

4.2 Conclusions

In this large population-based study, our findings reveal a high percentage of increased serum AG in CAD. And higher AG is associated with more severe clinical types of CAD and worse cardiac function. Furthermore, the increased serum AG is an independent, significant, and strong predictor of all-cause mortality.

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Supplemental Table 1. Independent determinants of baseline AG levels.

	Difference in AG	95% CI	*P* value
Demographic characteristics			
Male (*vs.* female)	–0.325	(–0.465 to –0.185)	< 0.001
Medical history and coronary risk factors			
Prior MI (*vs.* none)	–0.180	(–0.342 to –0.018)	0.029
Diagnosis			
UAP (*vs.* SCAD)	0.047	(–0.099 to 0.192)	0.529
AMI (*vs.* SCAD)	0.431	(0.259 to 0.603)	< 0.001
Medication use			
ARBs (*vs.* none)	0.323	(0.172 to 0.474)	< 0.001
Laboratory variables			
Hemoglobin (1 g/L difference)	0.005	(0.004 to 0.006)	< 0.001
Leukocyte (1×10^9/L difference)	0.188	(0.164 to 0.213)	< 0.001
Platelet (1×10^9/L difference)	0.004	(0.003 to 0.004)	< 0.001
eGFR (10 ml/min per 1.73 m^2 difference)	–0.015	(–0.027 to –0.004)	0.010
ALT (10 U/L difference)	0.066	(0.054 to 0.078)	< 0.001
Glucose (1 mmol/L difference)	0.055	(0.032 to 0.078)	< 0.001
LDL-C (1 mmol/L difference)	–0.063	(–0.125 to 0.000)	0.048
HDL-C (1 mmol/L difference)	1.114	(0.851–1.377)	< 0.001
ALB (1 g/L difference)	0.056	(0.044–0.069)	< 0.001
Cardiac functional characteristics			
LVEF (10% difference)	–0.071	(–0.101 to –0.042)	< 0.001

AG: anion gap; ALB: albumin; ALT, alanine aminotransferase; ARBs: angiotensin receptor blockers; CI: confidence interval; eGFR: evaluated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction; SCAD: stable coronary atherosclerotic disease; UAP: unstable angina pectoris.

Supplemental Table 2. Sensitivity analysis of association of AG with an increase in the clinical diagnosis.

	AG		
	OR (95% CI)	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		< 0.001
Quartile 2	1.053 (0.972–1.141)	0.206	
Quartile 3	1.081 (0.997–1.172)	0.058	
Quartile 4	1.531 (1.411–1.660)	< 0.001	
Continuous	1.051 (1.043–1.060)	< 0.001	
Model 2			
Quartile 1	Referent		< 0.001
Quartile 2	1.048 (0.967–1.135)	0.256	
Quartile 3	1.070 (0.986–1.161)	0.103	
Quartile 4	1.492 (1.374–1.619)	< 0.001	
Continuous	1.049 (1.040–1.058)	< 0.001	
Model 3			
Quartile 1	Referent		< 0.001
Quartile 2	1.047 (0.967–1.135)	0.259	
Quartile 3	1.069 (0.986–1.160)	0.107	
Quartile 4	1.489 (1.372–1.616)	< 0.001	
Continuous	1.048 (1.040–1.057)	< 0.001	
Model 4			
Quartile 1	Referent		0.003
Quartile 2	1.019 (0.928–1.121)	0.689	
Quartile 3	1.029 (0.937–1.130)	0.547	
Quartile 4	1.126 (1.021–1.241)	0.017	
Continuous	1.014 (1.004–1.024)	0.005	

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, prior MI, prior stroke, aspirin use, thienopyridines use, beta-blockers use, ACEIs use, ARBs use, statins use, hemoglobin, leukocyte, platelet, eGFR, ALT, glucose, LDL-C, HDL-C, anion gap, phosphorus, potassium, calcium, LVEF, and number of significantly diseased vessels. ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ALT: alanine aminotransferase; ARBs: angiotensin receptor blockers; BMI: body mass index; eGFR: evaluated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Supplemental Table 3. Sensitivity analysis of association of AG with cardiac function grades.

	Anion gap		
	OR (95% CI)*	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		< 0.001
Quartile 2	0.972 (0.831–1.138)	0.724	
Quartile 3	1.137 (0.975–1.324)	0.102	
Quartile 4	1.340 (1.155–1.557)	< 0.001	
Continuous	1.042 (1.026–1.058)	< 0.001	
Model 2			
Quartile 1	Referent		< 0.001
Quartile 2	0.992 (0.847–1.161)	0.916	
Quartile 3	1.169 (1.003–1.363)	0.046	
Quartile 4	1.376 (1.184–1.598)	< 0.001	
Continuous	1.045 (1.029–1.060)	< 0.001	
Model 3			
Quartile 1	Referent		< 0.001
Quartile 2	0.991 (0.846–1.160)	0.910	
Quartile 3	1.168 (1.001–1.361)	0.048	
Quartile 4	1.372 (1.181–1.594)	< 0.001	
Continuous	1.044 (1.028–1.060)	< 0.001	
Model 4			
Quartile 1	Referent		0.008
Quartile 2	0.978 (0.832–1.151)	0.793	
Quartile 3	1.125 (0.960–1.319)	0.146	
Quartile 4	1.191 (1.019–1.392)	0.027	
Continuous	1.025 (1.010–1.041)	0.001	

*OR in patients with eGFR ≥ 60 mL/min per 1.73m^2 (n = 16,559, 550 patients with LVEF < 40%, 1315 patients with 40% ≤ LVEF < 50%, and 14,694 patients with LVEF ≥ 50%). Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, prior MI, prior stroke, diagnosis, aspirin use, thienopyridines use, beta-blockers use, ACEIs use, ARBs use, statins use, eGFR, anion gap, phosphorus, potassium, calcium, and numbers of diseased vessels. ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ARBs: angiotensin receptor blockers; BMI: body mass index; eGFR: evaluated glomerular filtration rate; MI: myocardial infarction.

Supplemental Table 4. Sensitivity analysis of association of AG with risk of all-cause death.

	AG		
	HR* (95% CI)	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		< 0.001
Quartile 2	1.687 (0.613–4.640)	0.311	
Quartile 3	2.312 (0.888–6.016)	0.086	
Quartile 4	3.465 (1.392–8.629)	0.008	
Continuous	1.121 (1.056–1.1.191)	< 0.001	
Model 2			
Quartile 1	Referent		< 0.001
Quartile 2	1.724 (0.626–4.749)	0.292	
Quartile 3	2.331 (0.896–6.068)	0.083	
Quartile 4	3.685 (1.477–9.195)	0.005	
Continuous	1.120 (1.059–1.185)	< 0.001	
Model 3			
Quartile 1	Referent		< 0.001
Quartile 2	1.699 (0.617–4.682)	0.305	
Quartile 3	2.318 (0.891–6.034)	0.085	
Quartile 4	3.589 (1.438–8.960)	0.006	
Continuous	1.121 (1.058–1.189)	< 0.001	
Model 4			
Quartile 1	Referent		0.003
Quartile 2	1.591 (0.519–4.873)	0.416	
Quartile 3	2.728 (0.982–7.584)	0.054	
Quartile 4	2.967 (1.080–8.149)	0.035	
Continuous	1.084 (1.012–1.162)	0.022	

*HR in patients with eGFR ≥ 60 mL/min per 1.73m^2 (n = 16559, 50 deaths). Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, prior MI, prior stroke, diagnosis, aspirin use, thienopyridines use, beta-blockers use, ACEIs use, ARBs use, statins use, hemoglobin, leukocyte, platelet, eGFR, ALT, fasting plasma glucose, LDL-C, HDL-C, ALB, potassium ion, anion gap, phosphorus, potassium, calcium, LVEF, and Syntax score. ACEIs: angiotensin-converting enzyme inhibitors; AG: anion gap; ALT: alanine aminotransferase; ALB: albumin; ARBs: angiotensin receptor blockers; BMI: body mass index; eGFR: evaluated glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction.

Supplemental Table 5. Sensitivity analysis of association of AG with an increase in the number of significantly diseased vessels

	AG		
	OR (95% CI)*	***P* value**	***P* value for trend**
Model 1			
Quartile 1	Referent		0.091
Quartile 2	0.988 (0.913–1.069)	0.766	
Quartile 3	0.967 (0.892–1.046)	0.399	
Quartile 4	0.937 (0.865–1.015)	0.109	
Continuous	0.992 (0.985–1.000)	0.065	
Model 2			
Quartile 1	Referent		0.728
Quartile 2	1.009 (0.932–1.092)	0.822	
Quartile 3	1.004 (0.927–1.088)	0.927	
Quartile 4	0.987 (0.910–1.069)	0.743	
Continuous	0.998 (0.990–1.006)	0.667	
Model 3			
Quartile 1	Referent		0.713
Quartile 2	1.009 (0.931–1.092)	0.829	
Quartile 3	1.003 (0.927–1.087)	0.933	
Quartile 4	0.986 (0.909–1.068)	0.727	
Continuous	0.998 (0.990–1.006)	0.649	
Model 4			
Quartile 1	Referent		0.371
Quartile 2	1.005 (0.928–1.089)	0.900	
Quartile 3	0.993 (0.917–1.076)	0.865	
Quartile 4	0.966 (0.890–1.047)	0.395	
Continuous	0.996 (0.988–1.004)	0.361	

*OR in patients with eGFR ≥ 60 mL/min per 1.73m^2 (n = 16559, 6878 patients with 1-vessel CAD, 5069 patients with 2-vessel CAD, and 4612 patients with 3-vessel and/or LM CAD). Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, and eGFR; Model 4: adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, BMI, and eGFR. AG: anion gap; BMI: body mass index; CAD: coronary artery disease; eGFR: evaluated glomerular filtration rate; LM: left main; OR: odds ratio.