


# Albumin Corrected Anion Gap and the Risk of in-Hospital Mortality in Patients with Acute Pancreatitis: A Retrospective Cohort Study

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**Purpose:** To explore the prognostic value of albumin corrected anion gap (ACAG) within 24 hours of admission to the intensive care unit (ICU) for acute pancreatitis (AP).

**Patients and Methods:** This was a retrospective cohort study. Adult AP patients admitted to ICU from June 2016 to December 2019 were included in the study, who were divided into three groups according to initial serum ACAG within 24 hours upon ICU admission:  $ACAG \leq 14.87$  mmol/L,  $14.87 < ACAG \leq 19.03$  mmol/L, and  $ACAG > 19.03$  mmol/L. The primary study outcome indicator was in-hospital mortality. Age, sex, Glasgow Coma Scale score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were matched through propensity score matching (PSM) method to balance the baseline between the survivors and non-survivors. Multivariate Cox regression was used to determine the relationship between ACAG and in-hospital mortality.

**Results:** A total of 344 patients (of them 81 non-survivors) were analyzed in this study. Patients with higher ACAG intended to present significantly higher in-hospital mortality, APACHE II score, creatine, lower albumin, and bicarbonate. Multivariate Cox regression analysis after matching demonstrated that white blood cell count, platelet count, and higher ACAG were independently associated with higher in-hospital mortality ( $ACAG \leq 14.87$  as a reference,  $14.87 < ACAG \leq 19.03$  mmol/L with HR of 2.34 and 95% CI of 1.15–4.76,  $ACAG > 19.03$  with HR of 3.46 and 95% CI of 1.75–6.84).

**Conclusion:** Higher ACAG was independently associated with higher in-hospital mortality in patients with AP after matching the baseline between the survivors and non-survivors.

**Keywords:** anion gap, albumin corrected anion gap, acute pancreatitis, mortality

## Introduction

Acute pancreatitis (AP), the most common gastrointestinal disease with an annual incidence of 13–45 cases per 100,000 people worldwide,<sup>1,2</sup> has been the fifth disease of in-hospital death in America with an annual cost exceeding 2.6 billion dollars.<sup>3</sup> Exploring new predictors of AP prognosis may help in the early identification of high-risk patients with poor outcome and help physicians to select those patients who would benefit the most from close surveillance or aggressive intervention.

Anion gap (AG), reflecting the difference in serum unmeasured cation and anion concentrations, is one of the most commonly used biomarkers for diagnosing acid-base imbalance as well as identifying the reason for metabolic acidosis. AG consists of serum albumin, lactate, acetoacetate, sulfate, phosphate, and other anions. For patients with hypoproteinemia, the low level of albumin leads to the reduction of protein anions, which makes the false-negative result of AG and affects the judgment of results. Albumin corrected anion gap (ACAG) was proposed to avoid false-negative results. One study based on Medical Information Mart for Intensive Care database version III (MIMIC III) database presented that AG value was associated with all-cause mortality in patients with acute pancreatitis.<sup>4</sup>

Nevertheless, the association between the simple and inexpensive index, ACAG, and the prognosis of AP is not clarified. The objective of this study was to explore the prognostic value of ACAG for AP.

## Materials and Methods

### Diagnosis of Acute Pancreatitis

AP is diagnosed based on two of three criteria: (1) upper abdominal pain, (2) serum amylase or lipase (or both) of at least three times the upper limit of normal, or (3) findings on imaging consistent with AP.<sup>1</sup>

### Patients and Data Collection

We retrospectively collected the patients who were diagnosed with AP at the West China Hospital of Sichuan University from June 2016 to December 2019. The inclusion criteria were as follows: (1) diagnosis of AP; (2) with age  $\geq 18$  years; (3) having been hospitalized in Intensive Care Unit (ICU). The pregnant patients were excluded.

This study complies with the Declaration of Helsinki and was approved by the biomedical ethics committee of West China Hospital of Sichuan University, and the approval ID was 2021 (1694). Considering its retrospective characteristic and no intervention implemented to the included patients, the study applied for the exemption from informed consent from these patients and the biomedical ethics committee of West China Hospital of Sichuan University passed the application. This work has been reported in compliance with the STROBE criteria.<sup>5</sup>

Patient demographics, serum data, Glasgow Coma Scale (GCS) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and in-hospital outcomes of the included patients were collected. Demographic information included sex and age. Serum data including White Blood Cell (WBC) count, Neutrophil count, Lymphocyte count, Hemoglobin (Hb), Platelet count (PLT), Total Bilirubin (TB), Direct Bilirubin (DB), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Creatine (Cr), Albumin (Alb), sodium, potassium, chlorine, bicarbonate were measured within 24 hours on admission to ICU. AG was calculated according to the formulae:  $AG\text{ (mmol/l)} = (\text{sodium} + \text{potassium}) - (\text{chloride} + \text{bicarbonate})$ . ACAG was calculated according to the following equation:  $ACAG\text{ (mmol/l)} = [4.4 - \text{albumin (g/dl)}] \times 2.5 + AG$ . GCS score was determined within 1 hour of being admitted to ICU. APACHE II score was calculated according to Knaus WA<sup>6</sup> within 24 hours of being admitted to ICU. The primary outcome indicator was in-hospital mortality.

### Statistical Analysis

Statistical analysis was performed by IBM SPSS software, version 23.0 (SPSS, Chicago, USA). Variables with normal distributions were presented as the means  $\pm$  SD and compared with one way analysis of variance (ANOVA). Nonnormally distributed variables were expressed as medians and interquartile ranges (IQRs) and compared with the Kruskal–Wallis *H*-test. Categorical variables were described as count and percentages and compared by Chi-square test. Continuous variables were transformed into categorical variables based on their median value.

A propensity score matching (PSM) analysis model with a caliper of 0.2 was used to balance differences between the survivors and non-survivors, eliminate possible selection bias and increase the evidence level of the retrospective study. A 1:2 nearest neighbor matching was applied to select statistically matched pairs of AP patients according to age, sex, GCS, and APACHE II score. The standardized mean differences (SMDs) and *p* values were calculated to evaluate the effectiveness of the PSM. An SMD  $> 0.1$  is considered to be a significant difference between the two groups.

Multivariate Cox regression was applied to determine the relationship between ACAG and in-hospital mortality. Sensitivity analysis was performed to evaluate the stability of the results. The results were expressed as hazard ratio (HR) with 95% confidence interval (CI). A *p*-value  $< 0.05$  was considered to indicate statistical significance.

## Results

### Population and Baseline Characteristics

A total of 350 patients were included according to the inclusion criteria. We excluded six pregnancy patients. In total, 344 patients were analyzed in this study, of them 81 were non-survivors and 263 survivors. Patient baseline characteristics are listed in Table 1. The tri-tile of ACAG was 14.87 and 19.03, according to which the included patients were divided into

**Table 1** Baseline Characteristics Comparison Among the Albumin Corrected Anion Gap Groups Before Propensity Score Matching

	ACAG≤14.87	14.87<ACAG≤19.03	ACAG>19.03	P*
Number	114	116	114	–
In-hospital mortality	13 (11.40%)	27 (23.28%)	41 (35.96%)	<0.001
Female	46 (40.35%)	42 (36.21%)	32 (28.07%)	0.41
Age (years)	44.31±13.50	49.34±13.73	47.26±14.73	0.03
APACHE II	18.11±7.46	18.71±8.25	22.25±7.36	<0.001
Glasgow Coma Scale	6 (5,8)	6 (5,9)	7 (5,10)	0.27
Survival time (days)	28 (18,42)	20 (13,25,32)	22 (14,33,25)	0.01
Hemoglobin (g/L)	114 (85.75,150.75)	103.5 (89.25,129.5)	107 (82.5,152.25)	0.38
WBC (10 <sup>9</sup> /L)	12.38 (8.57,16.53)	11.72 (8.38,16.20)	13.26 (9.78,18.37)	0.10
Neutrophil (10 <sup>9</sup> /L0029)	10.13 (6.63,14.35)	10.45 (6.61,14.09)	11.2 (7.60,15.28)	0.23
Lymphocyte (10 <sup>9</sup> /L)	1.01 (0.67,1.45)	0.96 (0.61,1.16)	1 (0.71,1.41)	0.11
Platelet (10 <sup>9</sup> /L)	172 (112,235.25)	166.5 (103.25,251.25)	161 (107,221)	0.76
Total Bilirubin (umol/L)	16.8 (12.1,29.58)	19.05 (11.85,28.20)	21.85 (12.85,27.08)	0.22
Direct Bilirubin (umol/L)	8.75 (6.05,17.50)	11.15 (6.63,19.68)	12.65 (7.63,27.08)	0.06
ALT (IU/L)	24 (15.75,46.75)	26.5 (15,49.75)	33 (16.75,77.25)	0.09
AST (IU/L)	43.5 (26.75,73.75)	41 (22,70.75)	61 (29,122)	0.01
Creatin (umol/L)	90 (63.25,183.25)	66.5 (49.25,121.50)	186 (89,381)	<0.001
Albumin (g/L)	33.87±7.34	33.48±6.19	30.70±6.31	0.001
Sodium (mmol/L)	137.83±6.66	138.55±6.44	140.26±7.72	0.03
Potassium (mmol/L)	4.17±0.73	4.08±0.76	4.32±0.86	0.06
Chloride (mmol/L)	107.45±7.05	105.16±6.81	104.34±7.81	0.002
Bicarbonate (mmol/L)	20.16 (17.76,23.30)	19.57 (15.38,22.92)	15.04 (12.83,10.05)	<0.001
Anion Gap (mmol/L)	9.67±2.46	14.2±11.94	19.94±3.67	<0.001
ACAG (mmol/L)	12.20±2.10	17.04±1.23	23.26±3.56	<0.001

**Notes:** \*Variables with normal distributions were compared with one way analysis of variance (ANOVA). Nonnormally distributed variables were compared with the Kruskal–Wallis *H*-test. Categorical variables were compared by Chi-square test.

**Abbreviations:** APACHE II, Acute Physiology and Chronic Health Evaluation II; WBC, White Blood Cell; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ACAG, Albumin Corrected Anion Gap.

three groups: ACAG ≤ 14.87 mmol/L, 14.87 < ACAG ≤ 19.03 mmol/L, and ACAG > 19.03 mmol/L. Patients with higher ACAG intended to present significantly higher in-hospital mortality, APACHE II score, creatine, sodium, and lower albumin, chloride, and bicarbonate. Patients with lower ACAG showed to be younger. There were no differences in gender composition. The levels of GCS score, WBC count, neutrophil count, lymphocyte count, HB, PLT, TB, DB, and ALT were similar in the three groups.

## Association Between ACAG and Mortality Before PSM

Univariate Cox regression before PSM was performed to explore the relationship between the mortality in AP and the included variables (Table 2). And the variates with *p* < 0.05 in the Univariate Cox regression were included in the Multivariate Cox regression, and the results are shown in Table 2. Multivariate Cox regression found that WBC count, PLT count, and higher ACAG were independently associated with higher in-hospital mortality. Figure 1 presents the Kaplan–Meier survival curves before PSM.

## Association Between ACAG and Mortality After PSM

To balance the baseline between the survivors and non-survivors, the included patients were matched by age, gender, GCS, and APACHE II score. After matching, there were 75 non-survivors and 130 survivors. The PSM results are displayed in Supplementary Table 1. All SMDs of the matched variables were <0.1 after PSM.

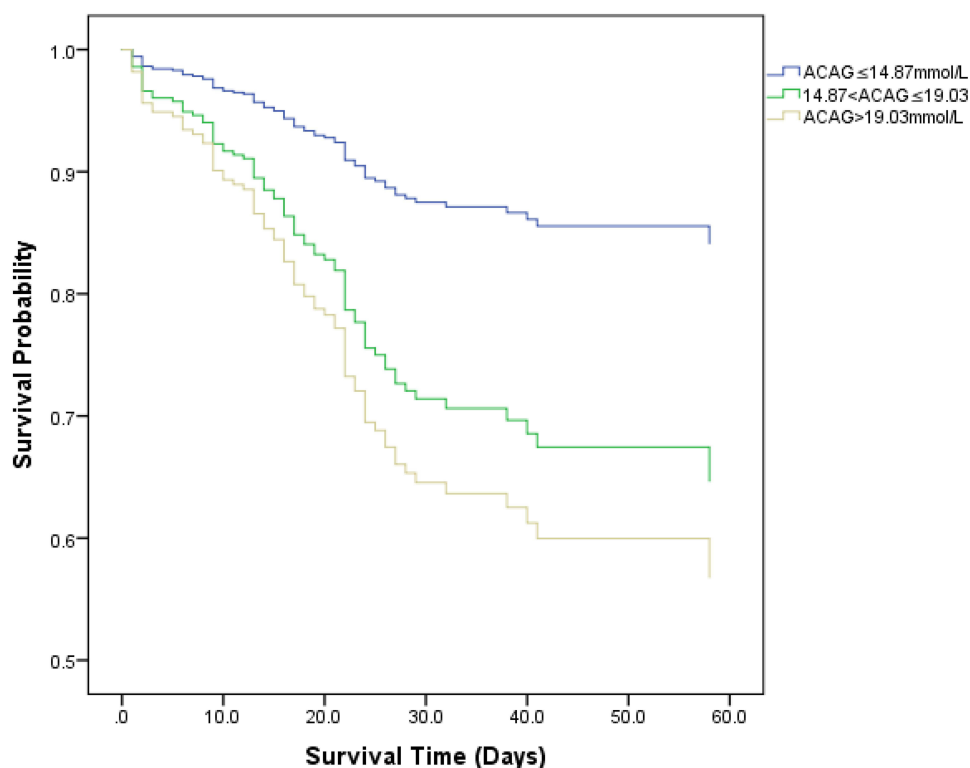
**Table 2** Cox Regression of the Patients with Acute Pancreatitis Before Propensity Score Matching

	Univariate Cox Regression			Multivariate Cox Regression		
	B	p	HR (95% CI)	B	p	HR (95% CI)
Hemoglobin (g/L)	0.001	0.67	1.003 (0.996,1.007)	-0.004	0.001	0.996 (0.994,0.998)
WBC ( $10^9/L$ )	0.03	0.02	1.03 (1.01,1.06)			
Neutrophil ( $10^9/L$ )	0.04	0.02	1.04 (1.01,1.07)			
Lymphocyte ( $10^9/L$ )	0.03	0.87	1.03 (0.761,1.38)			
Platelet ( $10^9/L$ )	-0.004	0.003	0.996 (0.994,0.999)			
TB ( $\mu\text{mol/L}$ )	0.002	0.18	1.002 (0.999,1.006)			
DB ( $\mu\text{mol/L}$ )	0.003	0.23	1.003 (0.998,1.008)			
ALT (IU/L)	0.00	0.27	1 (1,1.001)			
AST (IU/L)	0.00	0.24	1 (1,1)			
Creatin ( $\mu\text{mol/L}$ )	0.001	0.06	1.001 (1,1.002)			
Albumin (g/L)	-0.03	0.11	0.97 (0.94,1.01)			
AG>14.5 mmol/L <sup>a</sup>	0.62	0.01	1.86 (1.18, 2.91)			
ACAG $\leq$ 14.87	Reference			Reference		
14.87<ACAG $\leq$ 19.03	0.87	0.010	2.40 (1.24,4.65)	0.926	<0.001	2.52 (1.30,4.90)
ACAG >19.03	1.29	<0.001	3.62 (1.94,6.76)	1.187	<0.001	3.28 (1.75,6.14)

**Note:** <sup>a</sup>Anion Gap was divided into two groups based on its median value of 14.5.

**Abbreviations:** WBC, White Blood Cell; TB, Total Bilirubin; DB, Direct Bilirubin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AG, Anion Gap; ACAG, Albumin Corrected Anion Gap; HR, Hazard Ratio; CI, Confidential Ratio; ACAG, Albumin Corrected Anion Gap.

Univariate Cox regression analysis showed that high WBC, PLT count, high Neutrophil count, AG >14.50 mmol/L, and ACAG group were all associated with poor outcome of AP with p value <0.05 (Table 3). Multivariate Cox regression analysis demonstrated that WBC count, PLT count, and higher ACAG were independently associated with worse in-hospital outcomes (Table 3, Figure 2).

**Figure 1** Kaplan-Meier survival curves of in-hospital survival in acute pancreatitis patients with three ACAG groups before propensity score matching.

**Abbreviation:** ACAG, Albumin Corrected Anion Gap.

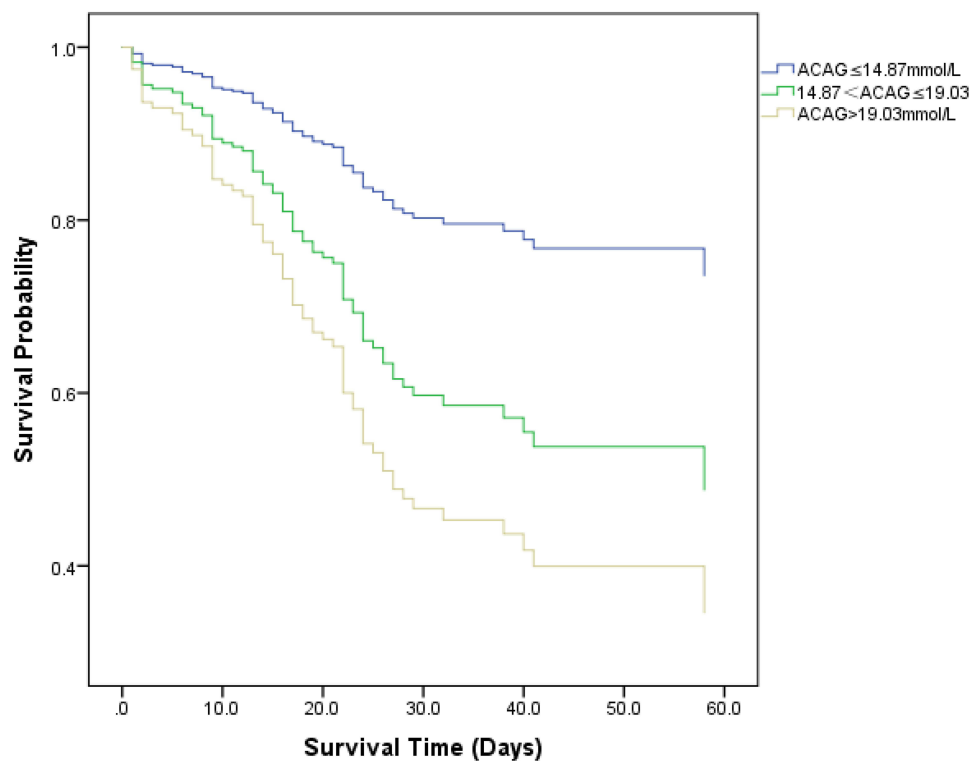
**Table 3** Cox Regression of the Patients with Acute Pancreatitis After Propensity Score Matching

	Univariate Cox Regression			Multivariate Cox Regression		
	B	p	HR (95% CI)	B	p	HR (95% CI)
Hemoglobin (g/L)	0.001	0.75	1.001 (0.995,1.01)	-0.003	0.01	0.997 (0.99, 0.999)
WBC ( $10^9/L$ )	0.03	0.02	1.03 (1.01,1.06)			
Neutrophil ( $10^9/L$ )	0.03	0.03	1.03 (1.003,1.07)			
Lymphocyte ( $10^9/L$ )	0.16	0.31	1.17 (0.86,1.59)			
Platelet ( $10^9/L$ )	-0.003	0.01	0.997 (0.99,0.999)			
TB (umol/L)	0.002	0.30	1.002 (0.998,1.01)			
DB (umol/L)	0.002	0.46	1.002 (0.997,1.01)			
ALT (IU/L)	0.000	0.76	1 (1,1)			
AST (IU/L)	0.000	0.61	1 (1,1)			
Creatin (umol/L)	0.001	0.28	1.001 (0.999,1.002)			
Albumin (g/L)	-0.03	0.11	0.97 (0.94,1.006)	Reference	0.01	2.34 (1.15, 4.76)
AG > 14.5mmol/L <sup>a</sup>	0.66	0.01	1.93 (1.20, 3.10)			
ACAG ≤14.87	Reference					
14.87<ACAG≤19.03	0.86	0.02	1.37 (1.17,4.83)			
ACAG >19.03	1.42	<0.001	4.12 (2.10,8.08)	1.24	<0.001	3.46 (1.75,6.84)

**Note:** <sup>a</sup>Anion Gap was divided into two groups based on its median value of 14.5.

**Abbreviations:** WBC, White Blood Cell; TB, Total Bilirubin; DB, Direct Bilirubin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AG, Anion Gap; ACAG, Albumin Corrected Anion Gap; HR, Hazard Ratio; CI, Confidential Ratio; ACAG, Albumin Corrected Anion Gap.

Sensitivity analysis was performed by dividing ACAG into two groups based on its median value: ACAG ≤ 17.14 mmol/L, ACAG > 17.14 mmol/L. Multivariate Cox regression after PSM showed similar results presented in [Supplementary Table 2](#) and [Supplementary Figure](#).

**Figure 2** Kaplan-Meier survival curves of in-hospital survival in acute pancreatitis patients with three ACAG groups after propensity score matching.

**Abbreviation:** ACAG, Albumin Corrected Anion Gap.

## Discussion

After balancing the basal information of the non-survivors and the survivors, this study found that higher initial serum ACAG within the first 24 hours after ICU admission was independently associated with higher in-hospital mortality in AP patients. The study presented that we could predict the in-hospital mortality for the patients with AP with the help of ACAG, which can be calculated easily from the inexpensive and convenient examine.

AG, as a biomarker for assessing the acid–base of the biotic internal environment, is associated with higher in-hospital mortality in patients presenting with cardiac arrest and sepsis;<sup>7,8</sup> with higher ICU and in-hospital mortality in critically ill patients.<sup>9</sup> An elevated level of AG increases all-cause mortality in unselected adults.<sup>10</sup> Moreover, AG can predict short-time prognosis for cerebral infarction patients.<sup>11</sup> Although the specific mechanisms were not well understood and explained. Additionally, the change in AG also indicates bromide intoxication, lithium intoxication, iodide intoxication,<sup>12</sup> and pesticide poisoning.<sup>13</sup>

Fang Gong et al<sup>4</sup> have studied the relationship between AG and mortality in AP based on 279 cases extracted from the MIMIC III. The results showed that serum AG was related to 90-day all-cause mortality in patients with AP after adjusting potential confounders. However, hypoalbuminemia occurred in 19–39% of patients with AP and was one of the risk factors for mortality.<sup>14,15</sup> In the present study, the level of albumin was  $32.69 \pm 6.76$ . Kraut JA indicated that every 1 g/dl change in serum albumin resulted in 2.3 to 2.5 mmol/L change in the serum anion gap.<sup>12</sup> Hypoalbuminemia may contribute to the false-negative value of AG and influence the interpretation of the results. Therefore, we focused to explore the relationship between ACAG and in-hospital mortality of AP.

According to the Atlanta classification system revised in 2012,<sup>16</sup> AP was classified into three types: mild, moderate, and severe. Severe acute pancreatitis (SAP) is characterized as persistent (>48 hours) either single or multiple organ failure. The majority of AP patients present with a mild form,<sup>17</sup> however approximately 20% progressed to SAP with higher in-hospital mortality ranging from 36% to 50%.<sup>16,18–20</sup> The APACHE-II system has been verified to discriminate mild pancreatitis and SAP,<sup>21,22</sup> and to predict the prognosis of AP.<sup>22</sup> In this study, APACHE II score was matched between the non-survivors and the survivors through PSM method, which could exclude the effect of disease severity on the mortality of AP and contribute to the more credible conclusion. The present study found that higher ACAG showed higher in-hospital mortality. Furthermore, the sensitivity analysis presented similar results.

The main causes of elevated level of serum AG include excessive synthesis of organic acids, such as lactate, and/or decreased excretion of anions. SAP is usually accompanied by hypovolemic shock and infectious shock, presenting with microcirculatory dysfunction and the increase of lactate. Elevated arterial lactate was independently related to poor outcomes for AP<sup>23</sup> and could predict SAP.<sup>24</sup> There is controversy on the relevance between AG and lactate. Some research found AG was related to lactate,<sup>7,9</sup> while some insisted that AG cannot predict hyperlactatemia<sup>25</sup> and the use of AG as an alternative to lactate cannot be recommended.<sup>26</sup> The possible reason results from the various baseline AG levels, albumin levels, clinical setting among individuals, and differences between arterial, venous, and capillary lactate.<sup>12,25,26</sup> Studies have demonstrated that ACAG increased the sensitivity of identifying hyperlactatemia by 36–37%.<sup>25,27,28</sup> Additionally, SAP is characterized as multiple organ dysfunction syndrome (MODS) including acute liver insufficiency, disseminated intravascular coagulation (DIC), acute kidney injury (AKI), and so on. Patients with renal dysfunction presented with decreased excretion of anions, which contributed to an increase in AG. Meanwhile, AKI, particularly if kidney replacement therapy was required, increased the mortality rates to 75%.<sup>29</sup>

Our study has some limitations. Firstly, the included serum AG was measured within 24 hours upon ICU admission without follow-up data, because the objective of this study was to investigate the prognostic value of early serum AG on the outcome of AP. Further studies on the relationship between the dynamic variation of serum AG and the prognosis of AP are expected to provide a novel idea. Secondly, the change in serum AG indicated not only acidosis, but also intoxication, laboratory error, and other disorders.<sup>11</sup> Potential covariates may exist even after comprehensive adjustment for measurable variables. Finally, the conclusions found in this study were constricted by the single-center retrospective study.

## Conclusion

Higher ACAG was independently associated with higher in-hospital mortality in patients with AP after matching the baseline between the survivors and non-survivors.



## Ethics Approval and Informed Consent

This study was approved by the biomedical ethics committee of West China Hospital of Sichuan University, and the approval ID was 2021 (1694).

## Consent for Publication

We have confirmed that the details included in this study can be published.

## Acknowledgments

We would like to thank all the volunteers who took part in this study and all the participants for their contribution to data collection and analysis.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests, and confirm that there are no financial or personal relationships with other people or organizations.

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