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Research article

Association between the anion gap and mortality in critically ill patients with influenza: A cohort study

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ABSTRACT

Introduction: Influenza is an important global health concern, particularly in critically ill patients. The anion gap, a marker of metabolic acidosis, is associated with mortality in various critical illnesses. However, its association with mortality in critically ill patients with influenza remains unclear. This study investigated the association between the anion gap on admission and 28-day mortality in critically ill patients with influenza.

Methods: A retrospective cohort study was conducted using data from MIMIC-IV database. Patients admitted to the intensive care unit (ICU) with influenza were included. The anion gap was measured within the first 24 h of ICU admission. The primary outcome was the 28-day mortality. The secondary outcomes were 60-day mortality and in-hospital mortality. Multivariable Cox regression was used to assess the association between the anion gap and mortality.

Results: A total of 276 critically ill patients with influenza were included in the study. The mean age was 65 years, and 60 % were male. The overall 28-day mortality was 15.5 %. A greater anion gap on admission was associated with significantly increased 28-day mortality in the unadjusted analysis (hazard ratio [HR], 1.11; 95 % confidence interval [CI], 1.03–1.2; $p < 0.001$). The association remained significant after adjusting for age, sex, race, and illness severity (adjusted HR, 1.09; 95 % CI, 1.02–1.17; $p = 0.017$). Subgroup analysis showed consistent results across the different groups.

Conclusion: A greater anion gap on admission was independently associated with increased 28-day mortality in critically ill patients with influenza. These findings suggest that the anion gap can be used as a prognostic marker in patients with influenza, aiding in risk stratification and guiding clinical management.

1. Introduction

The influenza virus is an important human pathogen that causes severe acute respiratory illness (SARI), which is associated with considerable morbidity and mortality globally [1]. Because the influenza virus spreads quickly from person to person owing to its high transmissibility, it can cause large epidemics and pandemics [2]. Antigenic changes in influenza viruses caused by genetic reassortment contribute to their transmissibility and wide range of clinical presentations, ranging from moderate flu to SARI. Influenza often causes moderate illness, but it can also cause severe illness, and is a major cause of death in susceptible groups, such as small children, pregnant women, older adults, and people with impaired immune systems [1,3]. Paget et al. [4] reported that seasonal influenza

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causes an average of 27,600 respiratory deaths in European countries each winter. Of these, 88 % were among people aged 65 years and older, with mortality rates in this age group being approximately 35 times higher than those in the younger age group. Hansen [5] also found that the mortality rate for influenza was highest among adults aged 65 years or older, with a mean of 20.5 (95 % CI, 19.4–21.5) deaths per 100,000 population per year. Ramos-Rincón et al. [6] reported that cancer is an independent risk factor for mortality in patients with influenza. Hence, influenza viruses make an important contribution to the disease burden, morbidity, and mortality in the general population, especially in critically ill individuals. Individuals with severe influenza can require admission to an intensive care unit (ICU) and have a greater risk of death. Critically ill patients with influenza are more susceptible to acidosis due to hypoxia and metabolic problems that cause excess acid production.

The advent of automated analyzers has made it possible to perform electrolyte testing on a mass scale, especially in critically ill patients. The serum anion gap (AG), which is an inexpensive and useful parameter, calculated from electrolyte measurements, has been widely used in clinical practice as an indicator of acid-base imbalance and metabolic acidosis. It reflects the balance between unmeasured anions and cations in the blood and is calculated using the formula [7]:

$$Anion\ gap = sodium\ -\ (chloride + bicarbonate).$$

The mean serum AG in healthy individuals is 12 ± 4 mEq/L. Previous studies have shown that an increase in the AG is associated with a worse prognosis in patients with critical illnesses [8,9], and that a greater AG is associated with higher mortality in several conditions, including sepsis [10], heart failure [11], acute renal injury [12], and asthma [9]. However, the relationship between the AG and mortality in critically ill patients with influenza has not been thoroughly investigated. The objective of this study was to investigate the relationship between the AG and mortality in critically ill patients with influenza. We hypothesized that a greater AG would be associated with increased risk of mortality in critically ill patients with influenza.

2. Methods

2.1. Database

The Medical Information Mart for Intensive Care IV (MIMIC-IV) database v2.2 (https://mimic.mit.edu/) was used in this study. It includes details of 73,181 hospitalizations of critically ill patients admitted to Boston's Beth Israel Deaconess Medical Center between 2008 and 2019 [13]. The database contained multiple variables, including survival status, vital signs, laboratory indicators, diagnoses, and treatment plans. Because of the abundance of high-quality data in the MIMIC-IV database and its other benefits, an increasing number of academics are using it to conduct research [14–16]. Two of the authors, Yingxiu Huang and Ting Ao, were given access to the database following successful completion of an online course and test (Certificate ID: 56513391, Yingxiu Huang, Certificate ID: 58844105 Ting Ao). As the database is anonymized, informed consent was not required. This cohort study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [17].

We conducted a retrospective cohort study using data from the MIMIC-IV 2.2. We included all patients with influenza admitted to the ICU for the first time. The primary outcome was 28-day mortality. The secondary outcomes were 60-day and in-hospital mortality.

2.2. Study population

We included patients who had been admitted to an ICU with influenza between 2008 and 2019. The diagnosis was based on the International Classification of Diseases, Ninth and Tenth Revisions (codes 487×, 488×, J09, J09×, J10×, J100×, and J11×). In patients with more than one ICU admission with influenza, only the first ICU admission record was selected. The analysis was restricted to individuals whose serum electrolytes were measured within 24 h of ICU admission, enabling their AG to be calculated.

2.3. Covariates

Relevant patient information was extracted from the MIMIC-IV database using a structured query language and stored in PostgreSQL. The extracted data included patient demographics such as age, sex, race, comorbidity (sepsis, diabetes, renal disease, congestive heart failure, malignant cancer, hypertension, shock, acute kidney injury), treatment (vasoactive agent use, ventilation, antibiotics, antivirus agent use, continuous renal replacement therapy (CRRT)), Sequential Organ Failure Assessment (SOFA) score, simplified acute physiology score II (SAPSII), and laboratory indicators such as the AG, white blood cell count, platelet count, and levels of hemoglobin, blood urea nitrogen, creatinine, and glucose on the first day of ICU admission. Illness severity was assessed using the SOFA score and SAPSII.

2.4. Statistical analysis

Patient characteristics were summarized using descriptive statistics. Continuous variables were reported as means and standard deviations. Categorical variables were reported as counts and percentages. For the analysis of baseline characteristics, data the Mann–Whitney *U* test was used to compare continuous variables and the chi-square test was used to compare categorical variables between groups.

Multivariable Cox regression models were used to evaluate the independent relationship between serum AG and 28-day mortality.

An extended Cox model was used to adjust for time-dependent covariates. Stratified subgroup analyses were performed for potential effect modifiers (age, sex, race, and SOFA score). We constructed receiver operating characteristic (ROC) curves and calculated AUCs to compare the predictive abilities of AG, SOFA, and SAPS II for 28-day ICU mortality. Furthermore, Kaplan-Meier curves were generated to illustrate the variations in survival among different patient groups based on AG levels. The analysis was performed using the statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation for Statistical Computing, Vienna, Austria) and Free Statistics version 1.9 [18]. Two-tailed p values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 276 critically ill patients with influenza were included in this study. The mean age was 65 years, and 60 % were male. Of the 276 patients included in the analysis, 239 survived (survival group), and 37 died (non-survival group) (Fig. 1). The overall 28-day mortality rate was 15.5 %. The AG was greater in the patients in the non-survival group (Table 1).

3.2. Association between anion gap and 28-day mortality

The univariate analyses of risk factors associated with 28-day mortality are summarized in Table 2. The blood glucose level, SOFA score, sepsis, hypertension, CRRT, and serum AG were significantly associated with the 28-day mortality. Conversely, potential confounders such as hemoglobin level, platelet count, and other laboratory results were not significantly associated with the 28-day

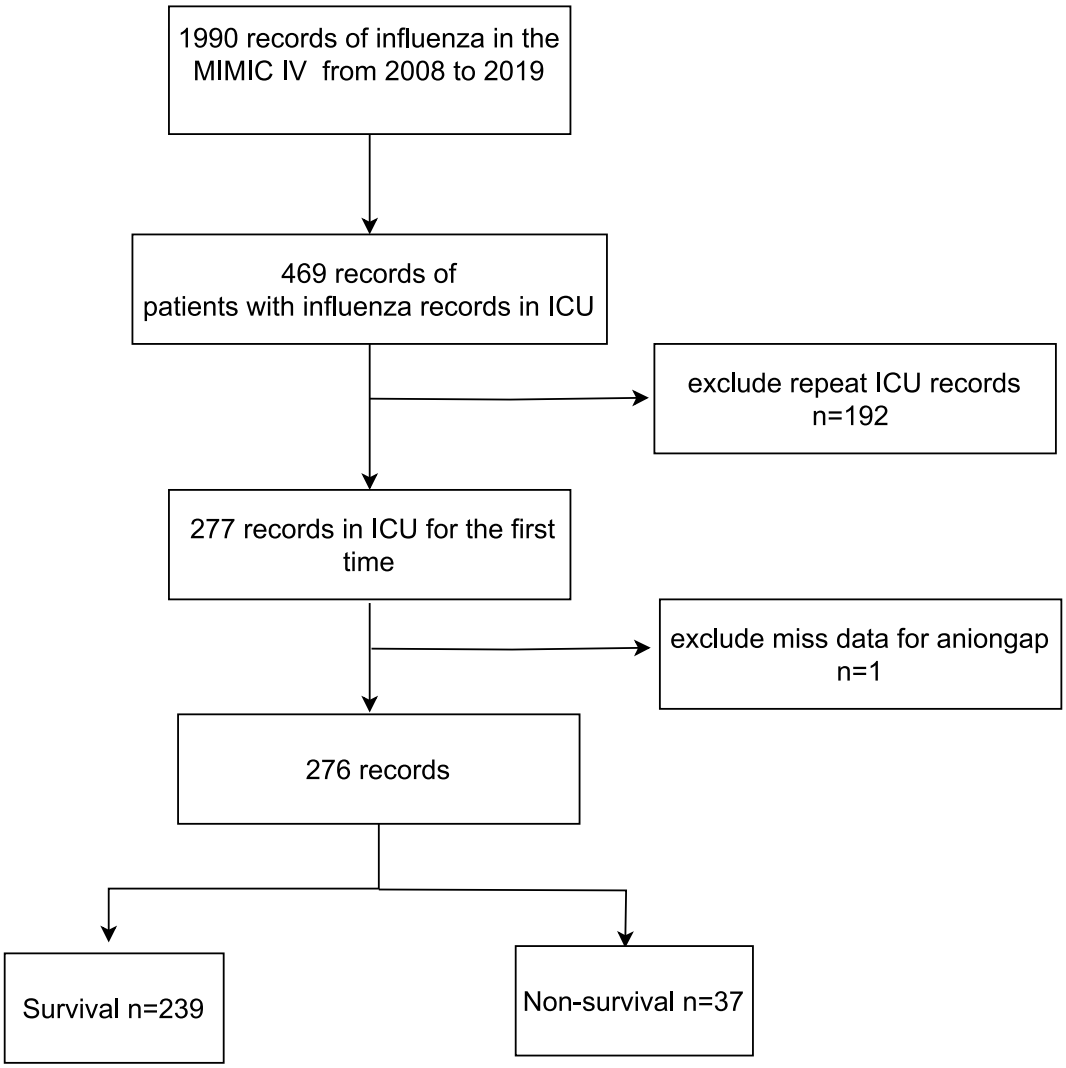

Fig. 1. Flowchart of the study.

Table 1
Baseline characteristics of participants.

Variables	Total (n = 276)	Survival (n = 239)	Non-survival (n = 37)	P
Sex, n (%)				0.75
Female	141 (51.1)	123 (51.5)	18 (48.6)	
Male	135 (48.9)	116 (48.5)	19 (51.4)	
Age , years, Mean ± SD	65.2 ± 19.4	64.7 ± 19.6	68.4 ± 17.6	0.283
Race/white, n (%)			0.199	
No	115 (41.7)	96 (40.2)	19 (51.4)	
Yes	161 (58.3)	143 (59.8)	18 (48.6)	
Laboratory parameters				
Platelets, k/uL, Mean ± SD	172.9 ± 85.6	174.4 ± 82.7	163.2 ± 103.0	0.462
Hemoglobin, g/dL Mean ± SD	10.4 ± 2.3	10.6 ± 2.3	9.5 ± 1.8	0.005
WBC, k/uL, Mean ± SD	13.4 ± 18.2	13.4 ± 19.0	13.8 ± 11.7	0.901
BUN, mg/dL, Mean ± SD	29.7 ± 23.0	28.2 ± 22.5	39.1 ± 24.2	0.007
Creatinine, mg/dL, Mean ± SD	1.7 ± 1.8	1.7 ± 1.8	2.0 ± 1.7	0.266
Glucose, mg/dL, Mean ± SD	189.7 ± 124.5	184.6 ± 117.8	222.5 ± 159.7	0.085
Aniongap, mEq/L, Mean ± SD	17.2 ± 4.9	16.9 ± 4.4	19.5 ± 7.1	0.003
Scoring system				
Sofa score, Mean ± SD	4.9 ± 3.6	4.6 ± 3.2	7.3 ± 4.8	<0.001
sapsii, Mean ± SD	37.3 ± 15.2	35.3 ± 14.2	50.4 ± 15.0	<0.001
Comorbidity				
Sepsis, n (%)	180 (65.2)	150 (62.8)	30 (81.1)	0.029
Diabetes, n (%)	75 (27.2)	64 (26.8)	11 (29.7)	0.707
Renal disease, n (%)	50 (18.1)	47 (19.7)	3 (8.1)	0.089
Congestive heart failure, n (%)	94 (34.1)	83 (34.7)	11 (29.7)	0.551
Malignant cancer, n (%)	40 (14.5)	32 (13.4)	8 (21.6)	0.186
Chronic pulmonary disease, n (%)	115 (41.7)	102 (42.7)	13 (35.1)	0.386
Hypertension, n (%)	48 (17.4)	37 (15.5)	11 (29.7)	0.033
Acute kidney injury, n (%)	173 (62.7)	145 (60.7)	28 (75.7)	0.079
Shock	81 (29.3)	67 (28)	14 (37.8)	0.223
Treatment				
Antibiotic Day1, n (%)	213 (77.2)	184 (77)	29 (78.4)	0.851
Antivirus, n (%)	156 (56.5)	135 (56.5)	21 (56.8)	0.975
Vasoactive agent Day1, n (%)	81 (29.3)	67 (28)	14 (37.8)	0.223
Ventilation Day1, n (%)	89 (32.2)	76 (31.8)	13 (35.1)	0.686

Table 2
Association of covariates and 28-day morality in patients with critical influenzae

Item	HR (95%CI)	*P*
Sex	1.25 (0.65,2.38)	0.504
age	1.0066 (0.9861,1.0275)	0.532
Race	0.53 (0.27,1.02)	0.056
Platelets	0.9995 (0.9961,1.0029)	0.752
Hemoglobin	0.96 (0.82,1.12)	0.597
WBC	0.9953 (0.9775,1.0134)	0.607
BUN	1.01 (1,1.02)	0.062
Creatinine	1.08 (0.92,1.27)	0.352
Glucose	1.003 (1.0007,1.0052)	0.009
Sofa score	1.11 (1.02,1.21)	0.021
Aniongap	1.11 (1.05,1.17)	<0.001
Diabetes	1.14 (0.56,2.31)	0.71
Sepsis	2.46 (1.08,5.61)	0.032
Renal disease	0.38 (0.12,1.22)	0.104
Malignant cancer	1.7 (0.78,3.73)	0.183
Chronic pulmonary disease	0.73 (0.37,1.44)	0.369
Congestive heart failure	0.82 (0.4,1.66)	0.58
Hypertension	2.09 (1.03,4.22)	0.041
Acute kidney injury	1.96 (0.92,4.15)	0.08
Shock	1.56 (0.8,3.02)	0.192
CRRT	3.47 (1.35,8.91)	0.01
Vasoactive agent Day1	1.56 (0.8,3.02)	0.192
Antibiotics	1.08 (0.49,2.36)	0.85
Antivirus	1.03 (0.54,1.98)	0.926

mortality (Table 2). In the multivariable Cox regression analysis (Table 3), a greater AG on admission was associated with significantly increased 28-day mortality in unadjusted analysis (HR, 1.11; 95 % confidence interval [CI], 1.02–1.2; $p < 0.007$). After adjusting for sex, age, race, SOFA score, urea nitrogen, creatinine, platelet, hemoglobin, WBC, glucose, sepsis, renal disease, hypertension, acute

Table 3
Relationship between serum AG and 28-day morality in different models.

	Model 1		Model 2		Model 3	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Aniongap	1.11 (1.03–1.2)	0.007	1.11 (1.04–1.17)	0.001	1.08 (1.02–1.15)	0.013

Model 1 : unadjusted.
Model 2 : adjust for sex, age, race.
Model 3: adjust for sex, age, race, SOFA score, urea nitrogen, hemoglobin, glucose, sepsis, renal disease, hypertension, acute kidney injury, CRRT.

kidney injury, CRRT, the association remained significant (model 3 adjusted HR, 1.08; 95 % CI, 1.02–1.15; p = 0.013).

3.3. Subgroup analyses

Subgroup analyses showed consistent results across different groups based on age, sex, race, and SOFA score, indicating that the association between serum AG and mortality was robust. The subgroup analysis showed that the association between AG and mortality was more marked in the age <60 years, SOFA score ≥6, and "white race" subgroups. The interaction analysis showed an interaction between the SOFA score and age (Fig. 2).

3.4. Kaplan-Meier survival curve analysis

Based on the cut-off values from the ROC curve, we categorized AG into two groups, AG<19 and AG≥19, and conducted survival curve analysis. The Kaplan-Meier curve showed that the 28-day cumulative survival rates were lower in the AG≥19 group than that in the AG<19 group (log-rank test, p = 0.015) (Fig. 3).

3.5. ROC curve analysis

The area under the curve (AUC) of the ROC curve was 0.598 (95 % CI: 0.491–0.706) of AG for predicting 28-day mortality in patients with influenza in ICU, which is slightly inferior to SOFA score (AUC 0.673, 95 % CI: 0.576–0.770) and SAPSII (AUC 0.766, 95 % CI: 0.685–0.847) (Fig. 4). The result suggests that AG moderately predicts 28-day mortality in patients with influenza. While SAPS II and SOFA demonstrate stronger predictive discrimination for 28-day mortality in patients with influenza compared to AG.

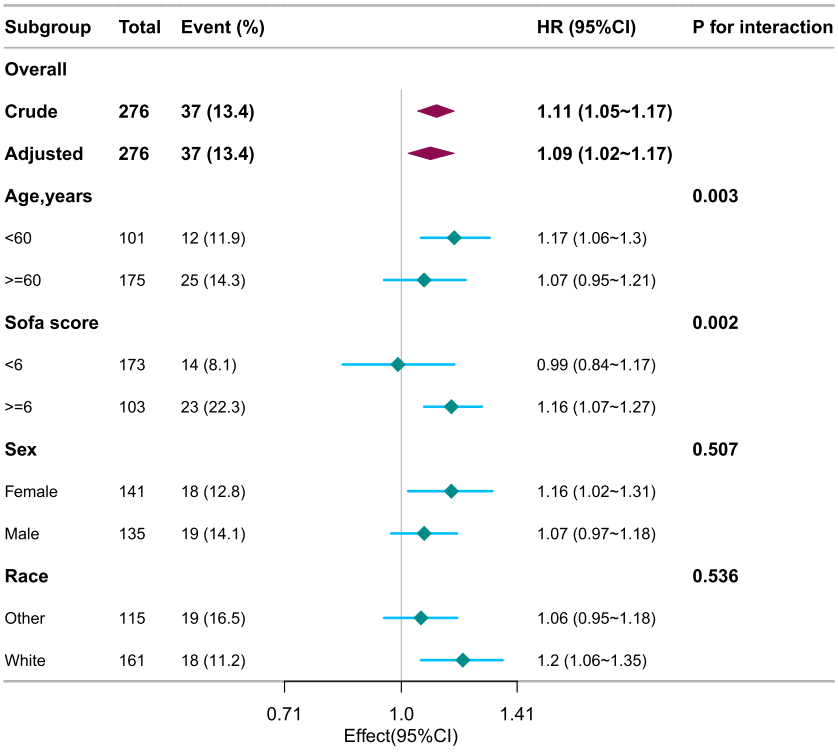

Fig. 2. Subgroup analyses for the association of serum AG with 28-day mortality in the patients with critically influenza.

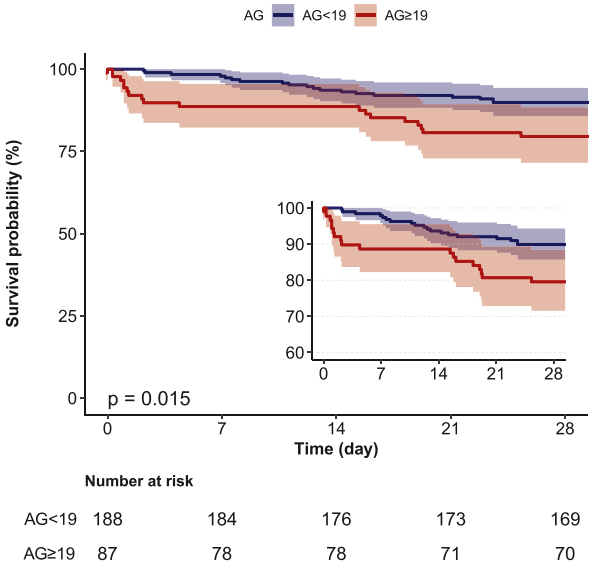

Fig. 3. Kaplan–Meier survival curves for critically ill patients with influenza based on serum Anion Gap.

3.6. Secondary outcomes

A greater serum AG was also associated with increased in-hospital mortality (adjusted HR, 1.09; 95 % CI, 1.02–1.16; p = 0.017) and 60-day mortality (adjusted HR 1.08; 95 % CI, 1.01–1.16; p = 0.026) (Table 4).

4. Discussion

This study highlights the association between serum AG and 28-day mortality in critically ill patients with influenza admitted to the ICU. A greater serum AG was associated with a significantly increase the risk of mortality. To our knowledge, this is the first study to examine the relationship between the serum AG and severe influenza.

Serum AG is an inexpensive and useful method for differentiating between distinct acid-base imbalances and metabolic acidosis. Either serum and plasma electrolyte levels can be used to compute the AG. Serum values are more commonly used and show the variations in the amounts of unmeasured anions and cations. In healthy individuals, the mean serum AG is 12 ± 4 mEq/L. The development of automated analyzers that make mass electrolyte testing possible has made it easier to measure the serum AG, particularly in critically ill patients. An increased AG may have prognostic value for several diseases in critically ill patients. Previous studies have shown that the AG is associated with the outcomes of other critical illnesses such as chronic obstructive pulmonary disease [19], COVID-19 [20], asthma [21], acute kidney injury [22], sepsis [10], and cerebral infarction [23], and acute pancreatitis [24]. The evidence, including the results of this study, indicates that serum AG is a reliable general risk factor in critically ill patients [25], suggesting that it has potential clinical utility as a predictor of prognosis. A prospective cohort study of 500 critically ill patients admitted to an ICU showed a significant association between AG, higher mortality rates, and longer hospital stays [26]. Another large multicenter cohort study by Li et al. [8] found that an initial serum AG ≥16 mmol/L after ICU admission was associated with increased mortality in critically ill patients. This study found that a greater AG within 24 h of ICU admission is associated with an increased risk of 28-day mortality in critically ill patients with influenza, which is consistent with the findings of previous studies, demonstrating the importance of paying attention to AG results and intervention to reduce mortality in patients with an increased AG.

Patients with severe influenza frequently have an increased AG, which can occur for several reasons. First, hypoxemia might result in insufficient tissue perfusion and increased lactate generation [27]. Second, the accumulation of other acids, such as beta-hydroxybutyric acid and acetoacetic acid, in the extracellular fluid can also contribute to an increased AG. Third, patients with severe influenza are susceptible to acute kidney injury, and impaired renal function can lead to decreased urinary excretion of unmeasured anions, which can also increase the AG [28]. Therefore, impaired kidney function might also contribute to the association between AG and mortality [22].

Our ROC result suggests that AG moderately predicts 28-day mortality in patients with influenza. However, it is evident that SAPS II and SOFA demonstrate stronger predictive discrimination for 28-day mortality in patients with influenza compared to AG. These findings indicate that the concurrent utilization of AG, SOFA, and SAPS II may enhance the prediction of the prognosis for influenza patients. Those with elevated AG, SOFA, and SAPS II require increased attention. This study has several strengths. First, it has a relatively large sample size and the data were obtained from the MIMIC-IV database, which is a large, real-world database with high-quality data. Second, subgroup analyses, provide evidence of the robustness of the results. However, this study also has certain limitations. First, it is a retrospective study, so was susceptible to selection bias. Second, we only extracted AG data on patients admitted to

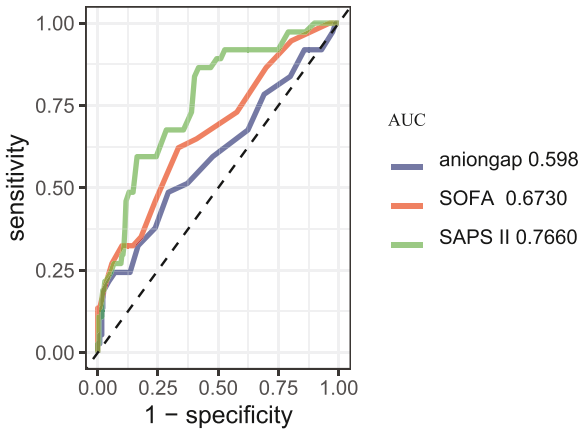

Fig. 4. ROC curves of SAPSII, SOFA score and anion gap.

Table 4
Secondary outcomes adjusted for sex, age, race, bun, creatinine, sofa sore.

Variable	No. of patients	No. of events (%)	Crude coefficient (95%CI)	Crude P_value	Adjusted coefficient (95 % CI)	Adjusted p-value
Secondary outcomes						
In-hospital mortality	276	33 (12)	1.1 (1.04–1.17)	0.002	1.09 (1.02–1.16)	0.017
60-day mortality	276	44 (15.9)	1.09 (1.03–1.15)	0.003	1.08 (1.01–1.16)	0.026

the ICU. Therefore, we were unable to assess the effect of changes in the AG after ICU admission on mortality, which might have affected the accuracy of the results. Third, we were unable to adjust for all relevant confounders because data on prognostic factors such as lactate, β-hydroxybutyrate, and acetoacetate, were missing for some patients in the database. Lastly, because this was an observational study, we were unable to verify the hypothesized mechanism of action linking a greater AG to the severity and prognosis of influenza.

5. Conclusion

This study found that a greater AG on admission to the ICU was independently associated with increased 28-day mortality in critically ill patients with influenza. These findings highlight the potential utility of the AG as a prognostic marker in patients with severe influenza. The AG could assist with risk stratification and guiding clinical management in critically ill patients admitted to the ICU with influenza. Further research is warranted to validate these findings and explore the underlying mechanisms.

Ethical approval

Two of the authors, Yingxiu Huang and Ting Ao, were given access to the database following successful completion of an online course and test (Certificate ID: 56513391, Yingxiu Huang, Certificate ID: 58844105 Ting Ao). MIMIC-IV database used in the present study was approved by the Institutional Review Boards (IRB) of Institutional Review Boards of Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206) both approved the use of the database for research. We have also complied with all relevant ethical regulations regarding the use of the data for our study.

Consent for publication

Not applicable.

Funding statement

None.

Data availability statement

Data in the article can be obtained from mimic-IV database (https://mimic.physionet.org/). The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Yingxiu Huang: Writing – original draft. **Ting Ao:** Data curation. **Peng Zhen:** Formal analysis. **Ming Hu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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