

Prognostic implication of serum anion gap in sepsis: A prospective-observational study

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ABSTRACT

Background: To investigate the prognostic significance of serum anion gap (SAG) in patients with sepsis in terms of length of hospital stay, Intensive Care Unit (ICU) admission and in hospital mortality.

Material and Methods: This prospective observational cohort study was conducted in the emergency department of ISRA University Hospital Hyderabad from 1 May 2025 to 31 October 2025. Patients aged ≥ 18 years, with qSOFA score of 2 or more on admission were included in the study. Small amount of blood samples were drawn by using a 5cc syringe. SAG was calculated with the help of serum electrolytes. Data were analyzed using SPSS.

Results: A total of 360 patients with sepsis were analyzed; 219 (60.8%) were male and 141 (39.2%) females, with a mean age of 58.06 ± 13.81 years. The mean serum anion gap (AG) was 14.46 ± 3.77 mEq/L, and the average hospital stay was 5.67 ± 3.38 days. Overall mortality was 43.6%. High AG was significantly more common in non-survivors than survivors (71.6% vs 9.4%, $p < 0.001$). High AG was associated with increased odds of mortality in both univariate (OR = 4.265; 95% CI: 2.384–7.629) and multivariate analyses (OR = 4.197; 95% CI: 2.338–7.524), confirming it as an independent predictor of mortality.

Conclusion: Higher SAG is associated with increased mortality, ICU admission, ventilator and inotropic support.

Keywords: Sepsis, Intensive care unit, Mortality, Serum AG, Lactate levels

BACKGROUND

Sepsis and Septic shock are among the most prevalent causes of hospital and Intensive care unit (ICU) admissions¹ Sepsis is characterized as a life-threatening condition resulting from organ dysfunction due to an abnormal host response to infection.² Septic shock is a syndrome of pathologic, physiologic, and biochemical disturbances caused by infection.³ Every year, sepsis and septic shock result in the loss of millions of lives worldwide, posing a significant global health challenge.⁴ Despite advancements in healthcare and increased awareness, sepsis remains a leading cause of illness and mortality across the globe.⁵ The World Health Organization has recognized sepsis as a global health issue and has called for coordinated efforts to reduce its incidence. The occurrence of sepsis differs among various populations and regions, with higher incidences noted in low- and middle-income countries

compared to high-income nations.⁶ According to Zhu *et al.*, the mortality rate in hospitals for sepsis patients in the ICU reached 35.5%.¹

Timely identification and immediate treatment are crucial for improving sepsis outcomes. In sepsis patients, serum lactate levels have been linked to both morbidity and mortality.⁷ Lactate serves as a biomarker for shock, indicating the need for immediate fluid resuscitation. The Surviving Sepsis Campaigns of 2021 identified patients with serum lactate levels ≥ 4 mmol/L as requiring fluid resuscitation.⁸

The connection between lactate levels and prognosis in critically ill patients has been extensively studied. Lower sepsis severity has been associated with decreased lactate levels, including those within the normal range.⁹ In two cohorts, Wacharasint *et al.*¹⁰ found that patients with lactate levels within the normal range (between 1.4 and 2.3 mmol/L) faced a significantly higher risk of death and organ failure compared to those with lactate levels below 1.4 mmol/L. Moreover, Simpson recently expressed concerns that depending on qSOFA or SOFA criteria might result in a delay in diagnosing and treating severe infections.¹¹ Additionally, a systematic review and meta-analysis found that qSOFA had low sensitivity and moderate specificity for predicting mortality risk.¹² These gaps highlight the need for additional markers that are quick, inexpensive, and routinely available.

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Serum anion gap (SAG) calculated from the routinely available laboratory parameters of electrolytes, reflects difference between serum anions and cations.¹³ Research has indicated that a high AG is associated to the severity or unfavorable outcomes of numerous diseases¹⁴, and AG has been utilized to forecast mortality in conditions such as chronic kidney disease, coronary artery disease, aortic aneurysm, and acute kidney injury. There is limited information available regarding the connection between SAG and sepsis.

In addition to serum lactate, which is commonly used to assess tissue hypoperfusion in sepsis, serum anion gap (SAG) has emerged as a potentially valuable prognostic marker because it reflects the accumulation of unmeasured acids and overall metabolic derangement. Unlike lactate, SAG can capture a broader spectrum of metabolic disturbances including contributions from renal dysfunction, ketoacids, and other unmeasured anions. Moreover, SAG is inexpensive, rapidly available from routine electrolyte measurements, and particularly useful in resource-limited settings where advanced biomarkers may not be readily accessible. Previous studies have suggested that elevated SAG is associated with worse outcomes in critically ill patients, supporting its potential role as an additional prognostic indicator in sepsis.

MATERIAL AND METHODS

This prospective observational cohort study was conducted in emergency department of ISRA University Hospital, Hyderabad from 1 May 2025 to 31 October 2025. Written informed consent was taken from patients or their guardians. Participant confidentiality was ensured by assigning unique identification codes in place of personal information. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Sample size was calculated using WHO sample size calculator taking confidence level 95%, margin of error 5.16%, 52.7% of patients with sepsis and septic shock died within 30 days of diagnosis of sepsis and septic shock¹⁵. The estimated sample size came out to be 360 patients.

Patients aged ≥ 18 years, with qSOFA score of 1 or more on admission to emergency department were included in the study. Patients aged less than 18 or more than 70 years, patients with hypovolemic shock, cardiogenic shock, diabetic ketoacidosis, end stage renal disease and

suspected poisoning and those who had received care from any other healthcare facility prior to admission were excluded from the study. The sampling technique was purposive nonprobability sampling.

After the approval of Ethics Review Committee of Isra University Hospital, 360 patients having sepsis secondary to any cause were enrolled. Small amount of blood samples were drawn by using a 5cc syringe and serum electrolytes were measured by using Ion selective electrode (ISE) method. Samples were drawn within 15 minutes of arrival of patients. Patients were followed by the healthcare professional during the hospital stay to see the outcomes.

Statistical analysis:

The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 22.0. Categorical variables were presented as frequency and percentages. All the continuous variables were determined as means and standard deviations. The chi square was for qualitative variables and independent samples t test was used for quantitative variables. Logistic regression was performed to determine the predictors of mortality. Associations between serum anion gap and clinical outcomes, particularly in-hospital mortality, were evaluated using univariate and multivariate logistic regression analysis to determine independent predictors of mortality. Linear regression was performed using the AG to determine the length of stay. Pearson correlation was used for the relationship of AG with CRP, lactate and length of stay. Bonferroni correction for continuity was applied when necessary. The p value < 0.05 was considered statistically significant.

RESULTS

A total of 360 patients with sepsis were analyzed. Baseline characteristics of the study participants shown in Table-I. Among the participants, 219 (60.8%) were male and 141 (39.2%) were female. The mean age of the participants was 58.06 ± 13.81 years. The mean serum anion gap (AG) was 14.46 ± 3.77 mEq/L. The mean lactate level and C-reactive protein was 2.19 ± 0.97 mmol/L and 99.51 ± 45.36 mg/L respectively. However, regarding hemodynamic parameters, the mean systolic blood pressure (SBP) was 104.84 ± 15.54 mmHg, and the mean arterial pressure (MAP) was 76.06 ± 8.72 mmHg, consistent with septic physiology and relative hypotension. The mean white blood cell (WBC) count was $12.66 \pm 4.20 \times 10^9/L$, supporting the presence of

systemic inflammatory response. The mean QSOFA score was 1.48 ± 0.87 , and the mean SIRS score was 2.11 ± 1.20 , indicating that most patients met sepsis severity criteria.

Out of 360 patients, 67 (18.6%) patients had high level of serum anion gap while 293 (81.4%) had normal serum anion gap shown in Figure –I.

Table-II shows correlations between AG, CRP and length of stay. AG was significantly associated with CRP ($r = 0.45$; p value < 0.001), lactate ($r = 0.59$; p value < 0.001) and length of stay ($r = 0.37$; p value < 0.001). Patients with high serum anion gap (>18 mEq/L) had significantly higher CRP levels, higher lactate levels, and longer hospital stay compared with patients with normal anion gap (≤ 18 mEq/L) ($p < 0.001$ for all comparisons), indicating that elevated AG is associated with greater inflammatory burden and prolonged hospitalization.

Table-III shows association of high AG with clinical outcome. Mortality was markedly higher in the high AG group (71.6%) compared to the normal AG group (37.2%) ($p < 0.001$). Similarly, ICU admission, ventilator support, and inotropic support were significantly more frequent among patients with elevated AG ($p \leq 0.021$).

Table-IV shows correlation with AG and clinical parameters on multivariate analysis. A substantially

higher proportion of non-survivors had high AG compared to survivors (71.6% vs 9.4%, $p < 0.001$). In univariate analysis, high AG increased the odds of mortality by more than four times (OR = 4.265; 95% CI: 2.384–7.629; $p < 0.001$). This association remained statistically significant after adjustment in multivariate analysis (OR = 4.197; 95% CI: 2.338–7.524; $p < 0.001$), indicating that high AG is an independent predictor of mortality. The qSOFA score showed a significant association with mortality in univariate analysis (OR = 1.27; 95% CI: 1.007–1.601; $p = 0.003$). However, after adjustment, the association was no longer statistically significant (OR = 1.244; 95% CI: 0.978–1.583; $p = 0.075$). Lactate levels and age were not significantly associated with mortality.

In addition, serum AG showed a significant positive association with length of hospital stay ($\beta = 0.329$, $p < 0.001$). Each 1 mEq/L increase in AG resulted in an additional 0.33 days of hospitalization. The model explained 14% of the variability in hospital stay duration ($R^2 = 0.14$).

Arterial blood gas parameters were not consistently available for all patients at admission; therefore, analysis of the association between serum anion gap and ABG variables such as pH, bicarbonate, and lactate could not be performed.

Table-I: Baseline characteristics of the participants (n = 360).

Variable	Mean \pm SD
Age (years)	58.06 \pm 13.81
AG (mEq/L)	14.46 \pm 3.77
Lactate (mmol/L)	2.19 \pm 0.97
CRP (mg/L)	99.51 \pm 45.36
SBP (mmHg)	104.84 \pm 15.54
MAP (mmHg)	76.06 \pm 8.72
WBC ($\times 10^9$ /L)	12.66 \pm 4.20
QSOFA Score	1.48 \pm 0.87
SIRS Score	2.11 \pm 1.20
Length of Stay (days)	5.67 \pm 3.38
Gender	Frequency (%)
Male	219 (60.8%)
Female	141 (39.2%)
Mortality	157 (43.6%)
ICU admission	168 (46.7%)
Ventilator support	179 (49.7%)
Inotropic support	227 (63.1%)

Table-II: Relationship of AG with CRP, Lactate and Length of Stay (n=360)

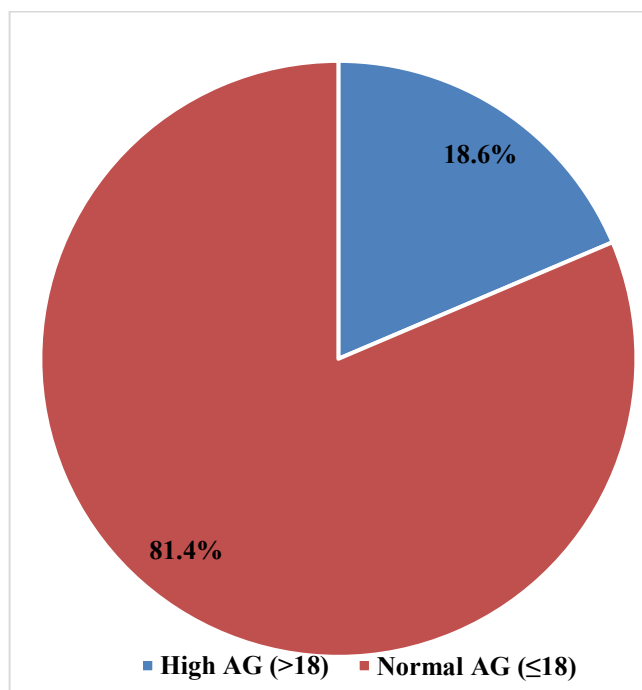
Variable	Normal AG (≤ 18) (n = 293)	High AG (>18) (n = 67)	p-value
CRP (mg/L), Mean \pm SD	92.6 \pm 41.3	126.8 \pm 46.5	<0.001
Lactate (mmol/L), Mean \pm SD	1.96 \pm 0.82	3.05 \pm 1.12	<0.001
Length of hospital stay (days), Mean \pm SD	5.14 \pm 2.96	7.88 \pm 3.74	<0.001

Table-III: Association between High AG and clinical outcomes (n=360).

Outcome	Normal AG (≤ 18) (n=293)	High AG (>18) (n=67)	p-value
Mortality	109 (37.2%)	48 (71.6%)	<0.001
ICU Admission	128 (43.7%)	40 (59.7%)	0.021
Ventilator Support	124 (42.3%)	55 (82.1%)	<0.001
Inotropic Support	170 (58.0%)	57 (85.1%)	<0.001

Table-4: Logistic Regression Analysis for Predictors of In-Hospital Mortality (n = 360)

Outcomes	Mortality			Univariate logistic regression				Multivariate logistic regression			
	Survival (n=203)	Non-Survival (n=157)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value				
AG (High)	19 (9.4%)	48 (71.6%)	<0.001	4.265 (2.384-7.629)	< 0.001	4.197 (2.338 – 7.524)	< 0.001				
QSOFA Score	1.61±0.95	1.41±0.87	0.043	1.27 (1.007 – 1.601)	0.003	1.244 (0.978 – 1.583)	0.075				
Lactate	2.22±0.98	2.15±0.96	0.509	-	-	-	-				
Age	58.17±13.67	57.90±14.03	0.855	-	-	-	-				

**Figure-I: Percentage of serum anion gap (n=60).**

DISCUSSION

The current study was undertaken to assess the prognostic value of SAG in adult patients who presented with suspected sepsis. Patients with higher AG levels had more severe biochemical profiles, a greater need for organ support, and a significantly higher mortality rate, according to the findings. These findings lend credence to the theory that the AG serves as a straightforward, early prognostic indicator and represents underlying metabolic stress in sepsis.

The significant correlation between an increased AG and lactate levels was a key finding in this investigation. Given that both represent the buildup of unmeasured acids during impaired tissue perfusion, this relationship

makes biological sense. Similar results have been shown in earlier research; for instance, Zhang *et al.*¹⁵ found that AG was linked to 28-day mortality and significantly correlated with lactate in septic shock patients. AG was found to be higher in patients with severe sepsis in another study by Dubey *et al.*¹⁶, and it was suggested that this could be used in conjunction with lactate to assess metabolic acidosis. Our findings support the idea that AG can capture the metabolic component of sepsis severity and are consistent with these observations.

In addition to lactate, this study discovered positive associations between AG and hospital stay duration and inflammatory markers like CRP. Previous studies have reported similar patterns. According to Liu *et al.*¹⁷, higher AG values were linked to increased inflammatory markers and longer hospital stays in critically ill patients. This supports the theory that the AG may indicate more widespread systemic inflammation and physiological disruption in addition to being a sign of metabolic acidosis.¹⁸

Through outcome analysis, the prognostic implications of an elevated AG were further illustrated. The rates of ICU admission, mechanical ventilation, inotropic use, and mortality were significantly higher in patients with AG values greater than 18 mEq/L. These results are consistent with those of Hoffmann *et al.*, who found that mortality in septic shock was predicted by a high admission AG regardless of other laboratory values¹⁹. In a similar vein, Huang *et al.*²⁰ reported that a higher AG was linked to a higher need for organ support. Our results offer more proof that AG may be helpful earlier in the clinical course in an emergency department population.

AG and qSOFA continued to be independent predictors of mortality in the multivariate model, but lactate did not. This pattern has been observed in other studies where adjustment did not affect the AG's predictive value. The cumulative metabolic burden, which includes contributions from renal impairment, ketoacids, and unmeasured anions that lactate alone cannot detect, may be reflected in the AG. Because of this, AG may be a more general indicator of physiologic instability, particularly in early sepsis before lactate levels rise noticeably.²¹ When considered collectively, these results lend credence to the notion that AG is more than simply a biochemical calculation; it could be a quick, inexpensive way to identify patients who are at risk of decline.²² A recent retrospective cohort study by Lou *et al.* (2024) evaluated the association between serum anion gap and mortality in critically ill patients with sepsis. The study analyzed ICU patients and found that individuals with higher anion gap levels at admission had significantly increased 28-day mortality rates compared with those with normal levels. Multivariate regression analysis confirmed that elevated anion gap remained an independent predictor of mortality even after adjusting for confounding variables. The authors concluded that serum anion gap can serve as a simple and readily available biomarker for early prognostic assessment in septic patients.²³ Local evidence from Pakistan also highlights the clinical relevance of anion gap in critically ill patients. A cross-sectional study conducted at Rehman Medical Institute, Peshawar, evaluated 200 critically ill patients and reported that high anion gap metabolic acidosis was present in 71.5% of cases, indicating that disturbances in anion gap are common among critically ill populations and may reflect severe metabolic derangements. These findings support the importance of evaluating serum anion gap as a useful indicator of acid-base imbalance and disease severity in hospitalized patients.²⁴ However, some limitations should be recognized. This was a single-center study, generalizability may be limited; as an observational design, no causality can be established. The threshold of AG may not be universally applicable and factors such as albumin level - influencing measured AG - were not included in analysis. Moreover, dynamic changes during the illness course were not considered and may provide additional value.

Further studies are required, including multicenter validation among various populations, assessment of albumin-corrected AG, and comparison with other prognostic scoring systems. Investigation of temporal trends in AG could also help to identify whether early changes correlate more closely with treatment response or clinical deterioration.

CONCLUSION

Elevated serum anion gap was significantly associated with increased mortality, higher requirement for ICU admission, ventilatory and inotropic support, and longer hospital stay among patients with sepsis. High AG also showed significant correlations with inflammatory markers and metabolic derangement, indicating greater disease severity. These findings suggest that serum anion gap is a simple, inexpensive, and readily available biomarker that can serve as an independent prognostic indicator for identifying high-risk septic patients early in the course of hospitalization.

CONFLICT OF INTEREST

None

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Declared none

AUTHOR CONTRIBUTION

Inshal Awan: Substantial contributions to study design, acquisition of data, manuscript drafting or reviewing it critical for important intellectual content, final approval, accountable for all aspects of the work.

Adnan Bawany: Substantial contributions to acquisition of data, manuscript drafting, final approval, accountable for all aspects of the work.

Ishrat Parveen, Hafsa Urooj: Substantial contributions to analysis and interpretation of data, critical review, has given final approval, accountable for all aspects of the work.

Aamna Memon, Akram Munir: Substantial contributions to concept, study design, critical review, final approval, accountable for all aspects of the work.

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