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THE PREDICTION OF IN-HOSPITAL MORTALITY BY INITIAL ALBUMIN CORRECTED ANION GAP IN CRITICALLY ILL PATIENTS WITH SEPSIS: AN OBSERVATIONAL PROSPECTIVE STUDY

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ABSTRACT

Background: Sepsis remains a leading cause of mortality despite therapeutic advances. Metabolic acidosis, particularly reflected through anion gap measurements, serves as an important prognostic marker in sepsis. However, conventional anion gap calculations may underestimate metabolic acidosis in hypoalbuminemic patients, who comprise the majority of critically ill sepsis populations. Albumin-corrected anion gap (ACAG) addresses this limitation by accounting for decreased albumin contribution to unmeasured anions, potentially providing superior prognostic accuracy. This study aimed to predict in-hospital mortality using initial albumin-corrected anion gap in critically ill patients with sepsis, and to correlate ACAG among study participants at a tertiary care hospital in Central India.

Materials and Methods: This prospective observational study was conducted at the Critical Care Unit, Ramkrishna Care Hospital, Raipur. Ninety consecutive adult patients with sepsis and metabolic acidosis were enrolled using purposive sampling. Upon admission, comprehensive evaluation included demographic assessment, APACHE II scoring, laboratory investigations, and calculation of conventional anion gap and ACAG using standard formulae. Patients were categorized into normal ACAG (12-20 mmol/L) and high ACAG (>20 mmol/L) groups.

Results: The initial ACAG cut-off of ≥17.9 mmol/L yielded was found to have the best sensitivity and specificity in predicting in-hospital mortality. The ACAG cut-off of ≥17.9 mmol/L yielded a sensitivity of 92.5%, specificity of 51.4%, PPV of 73.1%, NPV of 82.6%, and diagnostic accuracy of 75.6% in predicting in-hospital mortality in patients with sepsis.

Conclusion: Our study demonstrates that albumin-corrected anion gap serves as a valuable predictor of in-hospital mortality in critically ill patients with sepsis. With good discriminative ability (AUC 0.759), high sensitivity (92.5%), and reasonable diagnostic accuracy (75.6%).

Keywords: Sepsis, albumin corrected anion gap, in hospital mortality, metabolic acidosis, albumin.

INTRODUCTION

Sepsis is a life-threatening clinical syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection. It represents a major global healthcare challenge and remains one of the leading causes of morbidity and mortality among critically ill patients admitted to intensive care units (ICUs). The clinical manifestations of sepsis vary considerably, ranging from systemic inflammatory responses and metabolic disturbances to septic shock, multiple organ dysfunction, and death. Despite improvements in antimicrobial therapy, hemodynamic monitoring, and critical care

management, sepsis continues to impose a substantial burden on healthcare systems worldwide. Early identification of patients at increased risk of deterioration and mortality is therefore essential for improving clinical decision-making and optimizing treatment strategies.[1] The pathophysiology of sepsis involves complex interactions between infectious microorganisms, immune responses, endothelial dysfunction, inflammatory mediators, and disturbances in tissue perfusion. Excessive inflammatory activation may cause widespread cellular injury, impaired oxygen utilization, mitochondrial dysfunction, and progressive organ failure. These abnormalities frequently lead to metabolic acidosis, electrolyte disturbances, and alterations in circulating biochemical markers. Critically ill patients with sepsis often require intensive monitoring, intravenous fluids, antimicrobial therapy, vasopressor support, and mechanical ventilation. Early recognition of physiological deterioration and appropriate therapeutic intervention remain fundamental aspects of sepsis management. International clinical guidelines emphasize the importance of timely assessment, identification of organ dysfunction, and continuous evaluation of treatment response in patients with sepsis and septic shock.[2] Prediction of mortality in critically ill patients with sepsis remains challenging because of considerable variability in clinical presentation, underlying comorbidities, and disease progression. Several clinical scoring systems, including the Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score II (SAPS II), are commonly used to assess illness severity and estimate mortality risk. These scoring systems incorporate physiological, laboratory, and clinical parameters to provide an overall assessment of disease severity. However, their application may require multiple measurements and detailed calculations, which can limit immediate bedside evaluation. Consequently, considerable attention has been directed toward identifying readily available biochemical parameters that could supplement conventional scoring systems and improve early prognostic assessment.[3] Serum albumin is an important circulating plasma protein that contributes to the maintenance of colloid oncotic pressure, transportation of endogenous and exogenous substances, and regulation of inflammatory and antioxidant processes. In critically ill patients, serum albumin concentrations may decrease because of systemic inflammation, increased capillary permeability, redistribution into the interstitial compartment, and reduced hepatic synthesis. Hypoalbuminemia is particularly relevant in sepsis because of its association with physiological stress and organ dysfunction. Furthermore, albumin constitutes a major component of unmeasured plasma anions and therefore influences the interpretation of acid-base disturbances. Assessment of serum albumin levels may consequently provide valuable information regarding the metabolic condition and overall clinical status of critically ill patients.[4] The serum anion gap (AG) is a routinely used biochemical parameter for evaluating metabolic acidosis and identifying disturbances involving unmeasured circulating ions. It is calculated by subtracting the combined concentrations of serum chloride and bicarbonate from serum sodium. Elevated AG may occur because of the accumulation of organic acids, including lactate, ketone bodies, and other unmeasured anions. In patients with sepsis, impaired tissue perfusion, altered cellular metabolism, and organ dysfunction may contribute to these abnormalities. Anion gap assessment is relatively inexpensive, easily calculated, and based on laboratory investigations commonly performed during ICU admission. Its potential relationship with adverse clinical outcomes has encouraged further evaluation of its prognostic significance in patients with sepsis.[5] Despite its clinical usefulness, the conventional anion gap has certain limitations, particularly among patients with reduced serum albumin concentrations. Hypoalbuminemia decreases the contribution of negatively charged albumin to the measured AG, potentially masking the presence of increased unmeasured anions and clinically significant metabolic acidosis. To address this limitation, the albumin-corrected anion gap (ACAG) adjusts the conventional AG according to the patient's serum albumin concentration. A commonly used formula is ACAG = AG + 2.5 × [4.0 − serum albumin (g/dL)]. This correction allows a more appropriate interpretation of acid-base disturbances in patients with hypoalbuminemia. The corrected parameter may therefore provide additional information regarding metabolic abnormalities in critically ill septic patients, although its prognostic utility requires clinical validation.[6]

MATERIALS AND METHODS

The present study was designed as a hospital-based prospective observational study to predict in-hospital mortality using the initial albumin-corrected anion gap (ACAG) in critically ill patients with sepsis. The study was conducted in the Critical Care Unit of Ramkrishna Care Hospital, Raipur, from July 2023 to December 2024, of which 12 months were allotted for data collection. Approval was obtained from the Institutional Ethics Committee (IEC) of Ramkrishna Care Hospital, Raipur, before initiating the study. A final sample size of 90 patients was calculated for the present study.

Inclusion Criteria

All patients aged 18 years and above who were admitted to the ICU with a suspected diagnosis of sepsis and had metabolic acidosis (serum bicarbonate <22 mEq/L) were included in the study. Only patients who provided written informed consent for participation were enrolled.

Exclusion Criteria

Patients or their attendants who did not provide informed consent for participation, patients aged below 18 years, and patients with a definitive diagnosis other than sepsis were excluded from the study. Patients transferred to the ICU following surgery, those with associated cardiogenic or neurogenic shock, and patients presenting with pure respiratory acidosis or alkalosis were also excluded.

Sampling Method: Purposive selection of consecutive patients fulfilling the predefined eligibility criteria was carried out until the required sample size of 90 patients was achieved.

Method of Data Collection: All adult patients admitted to the ICU of Ramkrishna Care Hospital, Raipur, were screened for eligibility according to the predefined inclusion and exclusion criteria. Eligible participants were enrolled after explaining the study procedure and obtaining informed written consent from the patients or their legal representatives.

At the time of admission, baseline demographic characteristics and the presence of associated comorbidities were recorded for all study participants. The Glasgow Coma Scale (GCS) score was assessed. Vital parameters, including pulse rate, respiratory rate, body temperature, peripheral oxygen saturation (SpO_2), blood pressure, and the requirement for oxygen support, were also recorded.

Arterial blood gas (ABG) analysis was performed following aseptic measures. Blood samples were collected within 24 hours of ICU admission and sent for routine laboratory investigations, including complete blood count, serum albumin, serum creatinine, and serum electrolytes.

Serum albumin levels were classified into three categories: marked hypoalbuminemia (<2.5 g/dL), mild hypoalbuminemia (2.5–3.5 g/dL), and normal serum albumin (3.5–4.5 g/dL). The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated for all study participants.

The anion gap (AG) was calculated using the following formula:

AG (mmol/L) = Serum sodium − (Serum chloride + Serum bicarbonate)

The albumin-corrected anion gap (ACAG) was calculated using the following formula:

ACAG (mmol/L) = AG + [4.0 − Serum albumin (g/dL)] × 2.5

Based on the initial ACAG values, patients were categorized into two groups: the normal ACAG group (12–20 mmol/L) and the high ACAG group (>20 mmol/L), according to previous studies.

All enrolled patients received treatment according to the predefined ICU treatment protocol for sepsis, and any associated medical conditions were managed accordingly. Patient outcomes were assessed in terms of length of stay in the ICU and in-hospital 28-day mortality. All relevant clinical and laboratory details were documented in a predesigned study proforma.

Statistical Analysis: The collected data were organized and tabulated using Microsoft Excel 2016 (Microsoft Office 2016 package). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 16.0 (IBM Corp., Chicago, Illinois, USA). The data were analyzed using appropriate statistical methods and presented in the form of tables, graphs, and diagrams. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were expressed as frequencies and percentages. The independent samples Student's t-test was used to compare two independent groups of normally distributed continuous variables, while the Mann–Whitney U test was applied to compare two independent groups of non-normally distributed continuous variables. Bivariate and multivariable logistic regression analyses were performed to identify factors associated with mortality. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value of ACAG for predicting mortality, along with its sensitivity, specificity, and diagnostic accuracy. All statistical tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

RESULTS

[Table 1] Distribution of Study Participants According to Demographic Characteristics, Comorbidities, Mechanical Ventilation Requirement and APACHE II Scores (N=90)

[Table 1] shows the demographic and baseline clinical characteristics of the 90 study participants. The majority of patients belonged to the 41–60 years age group (36.67%), followed by ≤40 years (34.44%), 61–80 years (24.44%), and >80 years (4.44%). The mean age was 51.6 ± 17.7 years, with a median of 53 years. Male patients constituted 74.44%, while females accounted for 25.56%. Diabetes mellitus (48.89%) was the most common comorbidity, followed by hypertension (34.44%), coronary artery disease (10.00%), chronic liver disease and hypothyroidism (5.56% each), and chronic kidney disease (4.44%), whereas 32.22% had no comorbidities. Mechanical ventilation was required in 33.33% of patients at ICU admission. The majority had APACHE II scores of 21–30 (50.00%), followed by 11–20 (42.22%), with a mean APACHE II score of 20.2 ± 6.9.

[Table 2] Laboratory Parameters, Serum Albumin Categories and Albumin-Corrected Anion Gap at ICU Admission (N=90)

[Table 2] presents the laboratory parameters, serum albumin levels, and albumin-corrected anion gap (ACAG) at ICU admission. The mean serum sodium, potassium, chloride, and bicarbonate levels were 136.1 ± 8.3 mmol/L, 4.48 ± 1.13 mmol/L, 103.9 ± 12.6 mmol/L, and 12.7 ± 4.1 mmol/L, respectively. The mean serum albumin level was 2.63 ± 0.70 g/dL, while the mean creatinine level was 4.08 ± 2.88 in the reported units. The mean anion gap and ACAG values were 18.6 ± 4.85 mmol/L and 22.0 ± 5.17 mmol/L, respectively. Regarding serum albumin

categories, 47.78% of patients had mild hypoalbuminemia, 37.78% had marked hypoalbuminemia, and 14.44% had normal albumin levels. Based on ACAG classification, 58.89% of patients had high ACAG levels (>20 mmol/L), whereas 41.11% had normal ACAG levels (12–20 mmol/L).

[Table 3] Comparison of APACHE II Scores According to Mechanical Ventilation Requirement and ACAG Levels, Along With In-Hospital Outcomes (N=90)

[Table 3] demonstrates the comparison of APACHE II scores according to mechanical ventilation requirements and ACAG levels, along with hospitalization outcomes. Among the 90 patients, 30 (33.33%) required mechanical ventilation at ICU admission, whereas 60 (66.67%) did not require mechanical ventilation. Patients requiring mechanical ventilation had significantly higher mean APACHE II scores (23.9 ± 6.2) compared with those not requiring ventilation (18.3 ± 6.5), with a p-value of <0.001. Similarly, patients with high ACAG levels (>20 mmol/L) had significantly higher mean APACHE II scores (21.5 ± 7.2) than patients with normal ACAG levels (18.4 ± 6.0), with a p-value of 0.033. Regarding hospitalization outcomes, 53 patients (58.89%) died during hospitalization, whereas 37 patients (41.11%) were discharged.

[Table 4] Comparison of Demographic Characteristics, Clinical Parameters, Laboratory Findings and ACAG Levels Between Death and Survival Groups (N=90)

[Table 4] compares the demographic characteristics, clinical parameters, and laboratory findings between patients who died (n=53) and those who survived (n=37). The mean age was higher in the death group (53.6 ± 18.4 years) than in the survival group (48.8 ± 16.6 years), although the difference was statistically insignificant (p=0.214). Gender distribution (p=0.789) and the presence of comorbidities (p=0.972) were also not significantly associated with mortality. The mean APACHE II score was significantly higher in the death group (23.2 ± 6.1) compared with the survival group (16.0 ± 5.6; p<0.001), while mortality was significantly associated with mechanical ventilation requirement (73.33% vs. 51.67%; p=0.049). Serum sodium, potassium, chloride, bicarbonate, albumin, and creatinine levels showed no statistically significant differences between the groups (p>0.05). However, mean AG (20.1 ± 4.7 vs. 16.6 ± 4.3 mmol/L; p=0.001) and ACAG (23.8 ± 5.1 vs. 19.6 ± 4.2 mmol/L; p<0.001) were significantly higher in the death group. Mortality was observed in 73.58% of patients with high ACAG compared with 37.84% of those with normal ACAG (p=0.001).

[Table 5] Bivariate and Multivariable Logistic Regression Analysis of Factors Associated With In-Hospital Mortality and ROC Analysis of Initial ACAG (N=90)

[Table 5] presents the bivariate and multivariable logistic regression analyses of factors associated with in-hospital mortality, along with receiver operating characteristic (ROC) curve analysis of initial ACAG. In bivariate logistic regression analysis, AG was significantly associated with mortality, with an odds ratio (OR) of 1.90 (95% CI: 1.13–3.64; p=0.001). Similarly, ACAG showed a significant association with mortality, with an OR of 4.24 (95% CI: 1.99–8.17; p<0.001). In multivariable analysis, AG was not statistically significant (adjusted OR: 1.26; p=0.215), whereas ACAG remained significantly associated with mortality, with an adjusted OR of 3.88 (95% CI: 1.08–12.12; p<0.001). ROC curve analysis demonstrated an area under the curve (AUC) of 0.759, with a standard error of 0.052 and a 95% confidence interval of 0.657–0.861. The ROC analysis was statistically significant (p<0.001).

Table 1: Distribution of Study Participants According to Demographic Characteristics, Comorbidities, Mechanical Ventilation Requirement and APACHE II Scores (N=90)

Parameters	Frequency (n)	Percentage (%)
Age group (years)		
≤40	31	34.44
41–60	33	36.67
61–80	22	24.44
>80	4	4.44
Gender		
Male	67	74.44
Female	23	25.56
Comorbidities		
Diabetes mellitus	44	48.89
Hypertension	31	34.44
Coronary artery disease	9	10.00
Chronic liver disease	5	5.56
Chronic kidney disease	4	4.44
Hypothyroidism	5	5.56
Others (Alzheimer's disease, CA cervix, CVA, etc.)	4	4.44
No comorbidity	29	32.22
Mechanical ventilation at ICU admission		
Required	30	33.33
Not required	60	66.67
APACHE II score		
≤10	5	5.56

11–20	38	42.22
21–30	45	50.00
>30	2	2.22

Age: Mean ± SD: 51.6 ± 17.7 years; Median (IQR): 53 (37–63) years; Range: 18–88 years.
APACHE II score: Mean ± SD: 20.2 ± 6.9; Median (IQR): 21 (15–25); Range: 6–39.
Some patients had more than one comorbidity.

Table 2: Laboratory Parameters, Serum Albumin Categories and Albumin-Corrected Anion Gap at ICU Admission (N=90)

Parameters	Mean ± SD / Frequency (n)	Median (IQR) / Percentage (%)	Minimum–Maximum
Laboratory parameters			
Sodium (mmol/L)	136.1 ± 8.3	136 (132–140)	117–157
Potassium (mmol/L)	4.48 ± 1.13	4.5 (3.78–5.10)	1.90–6.97
Chloride (mmol/L)	103.9 ± 12.6	104.5 (100–110)	11.0–126
Bicarbonate (mmol/L)	12.7 ± 4.1	12.0 (10–15)	3.08–23.7
Albumin (g/dL)	2.63 ± 0.70	2.6 (2.2–3.1)	1.2–4.2
Creatinine (µmol/L)	4.08 ± 2.88	3.11 (2.2–5.23)	0.65–17.3
Anion gap (mmol/L)	18.6 ± 4.85	18 (15–22)	10–31
ACAG (mmol/L)	22.0 ± 5.17	21 (17.75–25.5)	13.15–35.5
Serum albumin categories	Frequency (n)	Percentage (%)	
Normal albumin (3.5–4.5 g/dL)	13	14.44	—
Mild hypoalbuminemia (2.5–3.5 g/dL)	43	47.78	—
Marked hypoalbuminemia (<2.5 g/dL)	34	37.78	—
Albumin-corrected anion gap categories	Frequency (n)	Percentage (%)	
Normal ACAG (12–20 mmol/L)	37	41.11	—
High ACAG (>20 mmol/L)	53	58.89	—

Table 3: Comparison of APACHE II Scores According to Mechanical Ventilation Requirement and ACAG Levels, Along With In-Hospital Outcomes (N=90)

Parameters	Frequency (n)	Percentage (%)	APACHE II score (Mean ± SD)	p-value
Mechanical ventilation at ICU admission				
Required	30	33.33	23.9 ± 6.2	<0.001*
Not required	60	66.67	18.3 ± 6.5	
ACAG at ICU admission				
Normal ACAG (12–20 mmol/L)	37	41.11	18.4 ± 6.0	0.033*
High ACAG (>20 mmol/L)	53	58.89	21.5 ± 7.2	
Outcome of hospitalization				
Discharged	37	41.11	—	—
Death	53	58.89	—	—
Total	90	100.00		

Reported p-values were retained from the original results. An asterisk () indicates statistical significance at p<0.05.*

Table 4: Comparison of Demographic Characteristics, Clinical Parameters, Laboratory Findings and ACAG Levels Between Death and Survival Groups (N=90)

Parameters	Death group (n=53)	Survival group (n=37)	p-value
Age (years)	53.6 ± 18.4	48.8 ± 16.6	0.214
Gender			0.789
Male	40 (59.70%)	27 (40.30%)	
Female	13 (56.52%)	10 (43.48%)	
Comorbidity			0.972
One or more comorbidities	36 (59.02%)	25 (40.98%)	
No comorbidity	17 (58.62%)	12 (41.38%)	
APACHE II score	23.2 ± 6.1	16.0 ± 5.6	<0.001*
Mechanical ventilation at ICU admission			0.049*
Required	22 (73.33%)	8 (26.67%)	
Not required	31 (51.67%)	29 (48.33%)	
Laboratory parameters			
Sodium (mmol/L)	136.7 ± 7.9	135.1 ± 8.9	0.360
Potassium (mmol/L)	4.4 ± 1.2	4.6 ± 1.0	0.537
Chloride (mmol/L)	102.4 ± 15.0	106.0 ± 7.6	0.187
Bicarbonate (mmol/L)	12.5 ± 4.1	13.0 ± 4.3	0.578
Albumin (g/dL)	2.5 ± 0.7	2.8 ± 0.6	0.061
Creatinine (µmol/L)	3.7 ± 3.0	4.5 ± 2.7	0.218
AG (mmol/L)	20.1 ± 4.7	16.6 ± 4.3	0.001*
ACAG (mmol/L)	23.8 ± 5.1	19.6 ± 4.2	<0.001*
ACAG status			0.001*
Normal ACAG (12–20 mmol/L)	14 (37.84%)	23 (62.16%)	
High ACAG (>20 mmol/L)	39 (73.58%)	14 (26.42%)	

*Values were presented as mean ± SD or n (%). Reported p-values were based on the Mann–Whitney U test for continuous variables and Chi-square test for categorical variables. p<0.05 was considered statistically significant.

Table 5: Bivariate and Multivariable Logistic Regression Analysis of Factors Associated With In-Hospital Mortality and ROC Analysis of Initial ACAG (N=90)

Parameters	Bivariate OR (95% CI)	p-value	Multivariable adjusted OR (95% CI)	p-value
Logistic regression analysis				
AG (mmol/L)	1.90 (1.13–3.64)	0.001*	1.26 (0.56–1.19)	0.215
ACAG (mmol/L)	4.24 (1.99–8.17)	<0.001*	3.88 (1.08–12.12)	<0.001*
ROC analysis of initial ACAG				
Area under the curve (AUC)	0.759	<0.001*	—	—
Standard error (SE)	0.052	—	—	—
95% CI of AUC	0.657–0.861	—	—	—

*OR: Odds ratio; CI: Confidence interval; AG: Anion gap; ACAG: Albumin-corrected anion gap; ROC: Receiver operating characteristic. p<0.05 was considered statistically significant.

Table 6: Association of Initial Albumin-Corrected Anion Gap (ACAG) Cut-off Value With In-Hospital Mortality (N=90)

ACAG level at cut-off	Total patients	In-hospital death (n=53)	Survival (n=37)	p-value
≥17.9 mmol/L	67 (74.44%)	49 (92.45%)	18 (48.65%)	<0.001*
<17.9 mmol/L	23 (25.56%)	4 (7.55%)	19 (51.35%)	
Total	90 (100.00%)	53 (100.00%)	37 (100.00%)	

*Values are presented as n (%). The p-value was calculated using the Chi-square test. p<0.05 was considered statistically significant.

Table 7: Diagnostic Performance of Initial Albumin-Corrected Anion Gap (ACAG) at a Cut-off Value of ≥17.9 mmol/L in Predicting In-Hospital Mortality (N=90)

Diagnostic parameters	Value (%)	95% Confidence Interval
Sensitivity	92.50	81.80–97.90
Specificity	51.40	34.40–68.10
Positive predictive value (PPV)	73.10	66.00–79.30
Negative predictive value (NPV)	82.60	63.80–92.80
Diagnostic accuracy	75.60	65.40–84.00

[Table 6] Association of Initial Albumin-Corrected Anion Gap (ACAG) Cut-off Value With In-Hospital Mortality (N=90)

[Table 6] illustrates the association between the initial ACAG cut-off value of 17.9 mmol/L and in-hospital mortality among the 90 study participants. A total of 67 patients (74.44%) had ACAG levels ≥17.9 mmol/L, whereas 23 patients (25.56%) had ACAG levels <17.9 mmol/L. Among the 53 patients who died, 49 (92.45%) had ACAG levels ≥17.9 mmol/L, while only 4 (7.55%) had ACAG levels below 17.9 mmol/L. Among the 37 surviving patients, 18 (48.65%) had ACAG levels ≥17.9 mmol/L, whereas 19 (51.35%) had levels below 17.9 mmol/L. The mortality proportion was 73.13% (49/67) among patients with ACAG ≥17.9 mmol/L compared with 17.39% (4/23) among those with lower ACAG levels. The association between ACAG cut-off levels and in-hospital mortality was statistically significant (p<0.001).

[Table 7] Diagnostic Performance of Initial Albumin-Corrected Anion Gap (ACAG) at a Cut-off Value of ≥17.9 mmol/L in Predicting In-Hospital Mortality (N=90)

[Table 7] presents the diagnostic performance of initial ACAG at a cut-off value of ≥17.9 mmol/L for predicting in-hospital mortality. At this cut-off, ACAG demonstrated a sensitivity of 92.50% (95% CI: 81.80–97.90%), indicating a high proportion of correctly identified patients who died during hospitalization. The specificity was 51.40% (95% CI: 34.40–68.10%), representing the proportion of surviving patients correctly identified by the cut-off. The positive predictive value (PPV) was 73.10% (95% CI: 66.00–79.30%), while the negative predictive value (NPV) was 82.60% (95% CI: 63.80–92.80%). The overall diagnostic accuracy of initial ACAG at the selected cut-off was 75.60%, with a 95% confidence interval of 65.40–84.00%. These findings demonstrated higher sensitivity than specificity for the prediction of in-hospital mortality using initial ACAG levels.

DISCUSSION

The present prospective observational study included 90 critically ill patients with sepsis, with a mean age of 51.6 ± 17.7 years. The majority belonged to the 41–60 years age group (36.67%), and males constituted 74.44% of the study population. Diabetes mellitus (48.89%) and hypertension (34.44%) were the most common comorbidities. Mechanical ventilation was required in 33.33% of patients at ICU admission, and the mean APACHE II score was 20.2 ± 6.9. Bloria et al. (2023) conducted a prospective observational study involving 128 patients with septic shock and reported a mean age of 41.49 ± 16.80 years, with 72.66% males and 27.34% females. Their study demonstrated a mean APACHE II score of 16.7 ± 5.53, while 87.50% of patients required

mechanical ventilation during their ICU stay. The present study showed a comparable male predominance but higher mean age and APACHE II scores. However, the mechanical ventilation rates were not directly comparable because the present study assessed ventilation at admission, whereas Bloria et al. reported ventilation throughout ICU hospitalization.[7] The present study demonstrated considerable abnormalities in laboratory parameters, particularly serum albumin and albumin-corrected anion gap levels. The mean serum bicarbonate concentration was 12.7 ± 4.1 mmol/L, while the mean serum albumin level was 2.63 ± 0.70 g/dL. Mild hypoalbuminemia was observed in 47.78% of patients, whereas 37.78% had marked hypoalbuminemia, indicating an overall hypoalbuminemia prevalence of 85.56%. The mean anion gap was 18.6 ± 4.85 mmol/L, and the mean ACAG was 22.0 ± 5.17 mmol/L, with 58.89% of patients having elevated ACAG levels. Kumar et al. (2024), in a longitudinal study involving 102 patients with sepsis, reported hypoalbuminemia in 56.90% of patients. They observed significantly higher mortality among patients with hypoalbuminemia compared with those without hypoalbuminemia (29.30% versus 11.40%; p=0.029). The prevalence of hypoalbuminemia was higher in the present study, although a direct association between albumin categories and mortality was not separately evaluated in the supplied results.[8]

The comparison of APACHE II scores according to mechanical ventilation requirements demonstrated significant differences in disease severity among the study participants. Patients requiring mechanical ventilation had a mean APACHE II score of 23.9 ± 6.2 compared with 18.3 ± 6.5 among those not requiring ventilation (p<0.001). Similarly, patients with elevated ACAG levels had higher APACHE II scores (21.5 ± 7.2) than those with normal ACAG levels (18.4 ± 6.0; p=0.033). Overall, in-hospital mortality was 58.89%, whereas 41.11% of patients survived. Daga et al. (2021), in a prospective observational study involving 150 patients with sepsis, evaluated clinical severity scores and biochemical indicators for mortality prediction. They reported significantly higher mean qSOFA scores among non-survivors compared with survivors (2.63 versus 1.81; p<0.0001). Admission lactate levels were also significantly higher among non-survivors (4.32 ± 2.35 mmol/L) than survivors (2.27 ± 0.91 mmol/L; p<0.001). Although different severity indicators were compared, both studies demonstrated significant associations between greater physiological derangement and adverse clinical outcomes.[9] The present study demonstrated significant differences in clinical severity and acid-base parameters between the death and survival groups. The mean APACHE II score was significantly higher among patients who died (23.2 ± 6.1) compared with survivors (16.0 ± 5.6; p<0.001). Similarly, the mean AG was 20.1 ± 4.7 mmol/L in non-survivors compared with 16.6 ± 4.3 mmol/L in survivors (p=0.001), while the corresponding ACAG values were 23.8 ± 5.1 mmol/L and 19.6 ± 4.2 mmol/L (p<0.001). Mortality was considerably higher among patients with elevated ACAG levels (73.58%) compared with those having normal ACAG levels (37.84%; p=0.001). Pan et al. (2024), in a retrospective study involving 1,340 patients with sepsis and liver cirrhosis, reported that elevated ACAG was significantly associated with 28-day mortality, with an adjusted hazard ratio of 1.604 (95% CI: 1.258–2.048; p<0.001). Their ROC analysis demonstrated an AUC of 0.703 for ACAG compared with 0.675 for uncorrected AG. These findings were consistent with the present study regarding the association of elevated ACAG with mortality, although the previous study involved a population restricted to patients with liver cirrhosis.[10] The bivariate and multivariable logistic regression analyses in the present study demonstrated that ACAG was significantly associated with in-hospital mortality. In bivariate analysis, the odds ratios for AG and ACAG were 1.90 (95% CI: 1.13–3.64; p=0.001) and 4.24 (95% CI: 1.99–8.17; p<0.001), respectively. Following multivariable adjustment, ACAG remained significantly associated with mortality, with an adjusted odds ratio of 3.88 (95% CI: 1.08–12.12), whereas AG was not statistically significant (p=0.215). The ROC analysis demonstrated an AUC of 0.759 (95% CI: 0.657–0.861; p<0.001), indicating moderate discriminatory ability. Guo et al. (2024), in a retrospective study of patients with sepsis-associated acute kidney injury, similarly reported that ACAG independently predicted in-hospital mortality, with an adjusted odds ratio of 1.129 (95% CI: 1.109–1.150; p<0.001). Their study demonstrated an AUC of 0.675 for ACAG, compared with 0.648 for AG and 0.598 for albumin. The present study demonstrated a higher AUC of 0.759, although differences in patient populations, outcome distributions, and statistical modelling may have contributed to the variation in predictive performance.[11] The present study identified an initial ACAG cut-off value of ≥17.9 mmol/L as significantly associated with in-hospital mortality. Among 67 patients with ACAG levels ≥17.9 mmol/L, 49 (73.13%) died, whereas only 4 of 23 patients (17.39%) with ACAG levels below 17.9 mmol/L experienced in-hospital mortality (p<0.001). Furthermore, 92.45% of all deaths occurred among patients with ACAG levels ≥17.9 mmol/L, indicating that the selected threshold identified most patients who subsequently died. Hu et al. (2021), in a retrospective propensity score-matched study involving critically ill patients with sepsis, similarly demonstrated a significant association between elevated ACAG and in-hospital mortality. Their ROC analysis reported AUC values of 0.689 before propensity score matching and 0.644 after matching. The optimal ACAG cut-off values were >20.25 mmol/L before matching and >21.25 mmol/L after matching. Compared with their findings, the present study identified a lower optimal threshold of 17.9

mmol/L and a higher AUC of 0.759. These findings support the association between elevated initial ACAG levels and mortality, although the optimal threshold may vary according to study population and methodology.[12] The diagnostic performance of initial ACAG in the present study demonstrated a sensitivity of 92.50% and specificity of 51.40% at a cut-off value of ≥17.9 mmol/L for predicting in-hospital mortality. The positive predictive value was 73.10%, the negative predictive value was 82.60%, and the overall diagnostic accuracy was 75.60%. The ROC curve demonstrated an AUC of 0.759, suggesting moderate predictive accuracy with relatively high sensitivity. Gao et al. (2023), in a retrospective study involving 9,625 critically ill patients with acute kidney injury, evaluated ACAG for mortality prediction and reported an optimal cut-off of 19.375 mmol/L for 360-day mortality, with a sensitivity of 55.90% and specificity of 60.30%. Their study demonstrated an AUC of 0.606 for ACAG, compared with 0.561 for uncorrected AG. The present study demonstrated higher sensitivity (92.50% versus 55.90%) but lower specificity (51.40% versus 60.30%). Differences in the underlying patient populations and mortality assessment periods limit direct comparison. Nevertheless, the present findings indicate that initial ACAG may be useful as an early screening indicator for identifying septic patients at increased risk of in-hospital mortality, particularly when interpreted alongside established clinical severity scores.[13]

CONCLUSION

In conclusion, our study demonstrates that albumin-corrected anion gap serves as a valuable predictor of in-hospital mortality in critically ill patients with sepsis. With good discriminative ability (AUC 0.759), high sensitivity (92.5%), and reasonable diagnostic accuracy (75.6%), ACAG provides clinically relevant prognostic information that complements existing severity assessment tools. The simplicity and immediate availability of ACAG calculations make this biomarker particularly attractive for clinical implementation, especially in resource-limited settings where complex scoring systems may not be feasible. These findings support the incorporation of ACAG into routine clinical assessment protocols for sepsis patients, potentially improving early identification of high-risk individuals, guiding clinical decision-making, and informing expectations about ICU resource requirements.

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