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Association Between Corrected Anion Gap Metabolic Acidosis and Mechanical Ventilation Requirement in Critically Ill Neonates

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Abstract

Background: Metabolic acidosis is a frequent biochemical abnormality in critically ill neonates, often contributing to poor clinical outcomes. The corrected anion gap (cAG) serves as a valuable marker for unmeasured anions and acid-base disturbances, yet its role in predicting mortality and mechanical ventilation requirement in neonates remains underexplored. This study aimed to assess the prognostic significance of cAG in critically ill neonates with metabolic acidosis.

Methods: This prospective observational study was conducted at Bangladesh Shishu Hospital & Institute (BSH&I) from July 2021 to June 2023, including 115 critically ill neonates with metabolic acidosis admitted to the NICU. Clinical and biochemical data were collected, including pH, bicarbonate, sodium, anion gap (AG), corrected anion gap (cAG), and base excess. Neonates were categorized into survivors (n=64) and non-survivors (n=51). Statistical analyses, including Pearson's correlation, Student's t-test, chi-square test, and logistic regression, were performed using SPSS version 22.0, with $p < 0.05$ considered statistically significant.

Results: The mean cAG was significantly higher in non-survivors (31.53 mEq/L) compared to survivors (18.60 mEq/L) ($p = 0.001$). Severe metabolic acidosis (lower pH and bicarbonate, higher AG and cAG) was strongly associated with increased mortality. Mechanical ventilation was required in 90.6% of non-survivors, reinforcing its role as a predictor of poor outcomes. A strong negative correlation was observed between cAG and mechanical ventilation requirement ($r = -0.607$, $p = 0.001$). Additionally, a weak but statistically significant negative correlation between cAG and NICU length of stay ($r = -0.213$, $p = 0.023$) suggested that higher cAG values were associated with shorter LOS due to increased mortality.

Conclusion: cAG is a strong predictor of mortality and mechanical ventilation requirement in critically ill neonates with metabolic acidosis. The severity of metabolic acidosis, as indicated by lower pH, bicarbonate levels, and elevated AG and cAG, was significantly associated with poor outcomes. Routine monitoring of cAG in NICU settings could serve as a valuable tool for early risk stratification and clinical decision-making.

Keywords: Corrected Anion Gap, Metabolic Acidosis, Neonatal Intensive Care, Mechanical Ventilation, Neonatal Mortality, Acid-Base Imbalance, NICU, Prognosis, Critical Care, Anion Gap Correction.

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Introduction

Neonatal metabolic acidosis is a significant biochemical abnormality observed in critically ill neonates, particularly those requiring intensive care. It is frequently associated with various pathological conditions, including sepsis, birth asphyxia, respiratory distress syndrome (RDS), renal dysfunction, and multi-organ failure, all of which can contribute to increased morbidity and mortality in neonatal intensive care units (NICUs).[1,2] The traditional approach to diagnosing metabolic acidosis relies on measuring pH, base deficit, serum bicarbonate, and lactate levels, which provide insights into the severity of acid-base disturbances. However, these parameters often fail to account for unmeasured anions, leading to a potential underestimation of the metabolic burden in critically ill neonates.[3] The corrected anion gap (cAG), which adjusts the traditional anion gap (AG) for albumin levels, has emerged as a more accurate predictor of unmeasured anions and acid-base disturbances in critical care settings.[4,5] Despite its clinical relevance, the role of cAG in predicting mechanical ventilation requirements in neonates remains largely unexplored, creating a crucial gap in neonatal critical care research. Acid-base imbalances have been extensively linked to hemodynamic instability, multi-organ dysfunction, and increased mortality rates in neonates.[6] Severe metabolic acidosis, particularly high anion gap metabolic acidosis (HAGMA), correlates with progressive respiratory distress, necessitating mechanical ventilation (MV) to maintain adequate oxygenation and CO_2 clearance. Previous studies have demonstrated that metabolic acidosis is a major contributor to prolonged MV duration and poor neonatal outcomes, with higher lactate levels and severe bicarbonate deficits significantly correlating with increased ventilation time and higher mortality rates.[6,7] While pH, base deficit, and lactate have been widely studied as prognostic markers in neonatal intensive care, they do not fully capture the extent of metabolic derangement caused by unmeasured anions. The corrected anion gap (cAG) is proposed to offer superior predictive value, as it accounts for albumin's buffering effect and provides a more precise assessment of metabolic acidosis severity. Given that hypoalbuminemia is common among critically ill neonates, failing to correct AG for albumin may result in a systematic underestimation of acidosis severity, potentially delaying critical interventions such as mechanical ventilation. Mechanical ventilation, while life-saving, presents several complications, including barotrauma, ventilator-associated pneumonia (VAP), bronchopulmonary dysplasia (BPD), prolonged NICU stay, and increased healthcare costs.[8] The ability to predict the need for MV early in the disease course using biochemical markers such as cAG can enable clinicians to initiate timely and targeted interventions, potentially reducing ventilation-associated morbidity and optimizing NICU resource allocation.[9] However, existing studies lack sufficient data on the relationship between cAG and the likelihood of requiring MV in neonates. Most available research has focused on the traditional acid-base parameters, while corrected anion gap remains an underutilized and under-researched prognostic tool in neonatology. Moreover, region-specific studies on neonatal metabolic acidosis and mechanical ventilation requirements, particularly in low-resource settings such as Bangladesh, are scarce. Neonatal critical care in Bangladesh is often challenged by resource limitations, including inconsistent access to advanced ventilatory support, delayed diagnosis of metabolic abnormalities, and restricted availability of point-of-care biochemical markers.[10] The lack of standardized approaches for managing acid-base disorders in neonates may further exacerbate neonatal morbidity and mortality in resource-constrained NICU settings. Conducting a region-specific study evaluating the predictive role of cAG in determining ventilation requirements can provide valuable insights into neonatal critical care management in Bangladesh and similar low-resource settings. This study aims to address these gaps by investigating the association between corrected anion gap (cAG) metabolic acidosis and the need for mechanical ventilation in critically ill neonates. By assessing whether elevated cAG values serve as an early predictor of respiratory deterioration, this research can facilitate better risk stratification and timely intervention, ultimately improving neonatal outcomes in NICU settings. Additionally, this study seeks to explore the potential prognostic utility of cAG in comparison to traditional acid-base markers, providing evidence-based recommendations for its clinical implementation in neonatal intensive care.

Methods

This prospective observational study was conducted at Bangladesh Shishu Hospital & Institute (BSH&I) over a two-year period from July 2021 to June 2023. The study population included critically ill neonates admitted to the Neonatal Intensive Care Unit (NICU), with a total sample size of 115 neonates selected using purposive sampling. Inclusion criteria consisted of neonates admitted to the NICU with metabolic acidosis, while exclusion criteria included neonates without metabolic acidosis and those already on mechanical ventilation before evaluation. Based on hospital mortality, the study participants were categorized into two groups:

- Group 1 (Survival Group): Neonates who survived until discharge.
- Group 2 (Non-Survival Group): Neonates who succumbed during the hospital stay.

All clinical and biochemical data were systematically recorded, including arterial blood gas (ABG) parameters, corrected anion gap (cAG), lactate levels, and other relevant laboratory findings. Mechanical ventilation requirements and associated clinical outcomes were also documented. For statistical analysis, all collected data were entered into SPSS version 22.0 after thorough validation. Data were presented as frequency, percentage, mean, and standard deviation (SD) as applicable. Student's t-test was used to compare continuous variables, while categorical variables were analyzed using the chi-square test. A *p*-value of <0.05 was considered statistically significant. Correlations between variables were evaluated using Pearson's correlation coefficient, and findings were visually represented using scatter plots. To assess the predictive value of the corrected anion gap (cAG) on mortality, a simple logistic regression analysis was initially performed, followed by multivariate logistic regression analysis to adjust for potential confounding factors. A Receiver Operating Characteristic (ROC) curve was generated to determine the area under the curve (AUC), optimal cut-off point, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of cAG in predicting neonatal mortality.

Results

Table I : Baseline characteristics distribution among the participants (N=115)

Variables	(n=115)
Age, Median Days (Min-Max)	5.12±1.07 (4-6)
Male, n (%)	90 (78.3%)
LOS in NICU, mean days (Min-Max)	12.34±1.72 (11-14)
In-hospital mortality, n (%),	51 (44.3%)
Requirement for mechanical ventilation, n (%)	53 (46.1%)

The study included 115 critically ill neonates admitted to the NICU with metabolic acidosis. The median age of the neonates was 5.12±1.07 days, ranging from 4 to 6 days. The majority of the participants were male (78.3%). The length of stay (LOS) in the NICU had a mean duration of 12.34±1.72 days, ranging from 11 to 14 days. Among the participants, the in-hospital mortality rate was 44.3% (51 out of 115 neonates), highlighting a substantial burden of critical illness. Additionally, mechanical ventilation was required in 46.1% (53 neonates), indicating a high prevalence of respiratory compromise among the study population.

Table II : Distribution of reasons for PICU admission among the participants (N=115)

Reasons for PICU admission	n (%)
Respiratory failure	40 (34.8%)
Neurologic problem	48(41.7%)
Sepsis	37(32.2%)
Cardiovascular disorder	14(12.2%)
Renal failure	2(1.7%)
Gastroenteritis	3(2.6%)
Post-resuscitation	49(42.6%)
LBW	54 (47%)

The primary reasons for NICU admission among the 115 critically ill neonates varied, reflecting a diverse range of life-threatening conditions. The most frequent cause of admission was low birth weight (LBW), observed in 47% (54 neonates), followed closely by post-resuscitation cases, which accounted for 42.6% (49 neonates). Neurologic problems were another significant contributor to NICU admissions, affecting 41.7% (48 neonates), while respiratory failure was noted in 34.8% (40 neonates), underscoring the high prevalence of severe respiratory compromise in this population. Sepsis was also a common admission cause, affecting 32.2% (37 neonates), further highlighting the systemic inflammatory burden in critically ill neonates. Among the other contributing conditions, cardiovascular disorders accounted for 12.2% (14 neonates), while gastroenteritis and renal failure were less common, affecting 2.6% (3 neonates) and 1.7% (2 neonates), respectively.

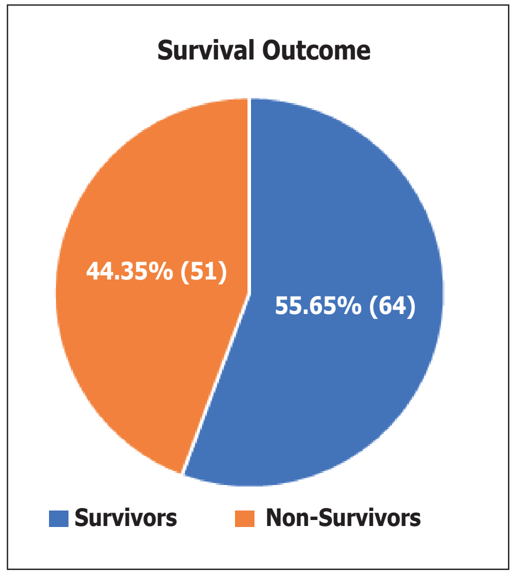

Figure 1: Distribution of patient survival among the participants (N=115)

The survival outcome of the study participants revealed that 55.65% (64 neonates) survived, while 44.35% (51 neonates) did not survive, as illustrated in Figure 1.

Table III : Comparison of clinical characteristics between survivors and non-survivor

Variables	Survivors (n =64)	Non-survivors (n=51)	p-value
Age, mean days (Min-Max)	6.14±2.07 (4-8)	4.35±2.52 (3.0-8)	.153^{NS*}
Male,%	52 (57.8)	38 (42.2)	0.496^{NS**}
LOS, mean days (Min-Max)	18.75±3.17 (12-21)	5.82±1.65 (3-9)	0.001^{S*}
Mechanical ventilator (%)	5 (9.4)	48 (90.6)	0.001^{S**}

While the mean age at admission was slightly higher in survivors (6.14±2.07 days) compared to non-survivors (4.35±2.52 days), this difference was not statistically significant (p = 0.153). Similarly, the proportion of male neonates was comparable between groups (57.8% in survivors vs. 42.2% in non-survivors), showing no significant association with survival outcome (p = 0.496). However, a significant difference in length of NICU stay (LOS) was observed (p = 0.001). Survivors had a longer mean LOS (18.75±3.17 days) compared to non-survivors, who had a significantly shorter LOS (5.82±1.65 days), suggesting that neonates who succumbed had a more severe and rapidly progressing illness. A highly significant association was found between mechanical ventilation (MV) requirement and survival (p = 0.001). Among non-survivors, 90.6% required MV, whereas only 9.4% of survivors required ventilatory support, indicating that mechanical ventilation was strongly linked to higher mortality rates in neonates with metabolic acidosis.

Table IV : Distribution of NICU Admission reasons among the participants (N=115)

Reason for NICU admission	Survivors (n =64)	Non-survivors (n=51)	*p*-value
Respiratory failure	17 (40.5)	25 (59.5)	0.019S**
Neurological problem (%)	23 (42.6)	31 (57.4)	0.009S**
Sepsis (%)	17 (40.5)	25 (59.5)	0.019S**
Cardiovascular disorder (%)	10 (71.4)	4 (28.6)	0.164NS**
Post-resuscitation	23 (44.2)	29 (55.8)	0.038NS**
Renal failure	0 (0)	2 (100)	0.195NS**
Gastroenteritis	0 (0)	3 (100)	0.082NS**
LBW	26 (48.1%)	28 (51.9%)	0.091NS**

Among neonates admitted with respiratory failure, 59.5% (25 out of 42) did not survive, whereas 40.5% (17 out of 42) survived, showing a statistically significant association with mortality (p = 0.019). Similarly, neurologic problems were significantly more common in non-survivors (57.4%) than in survivors (42.6%) (p = 0.009). Additionally, sepsis was associated with higher mortality, with 59.5% of affected neonates not surviving, compared to 40.5% who survived (p = 0.019). In contrast, low birth weight (LBW), cardiovascular disorders, post-resuscitation cases, renal failure, and gastroenteritis did not show statistically significant differences between survivors and non-survivors. Although LBW was slightly more common among non-survivors (51.9%) than survivors (48.1%), the difference was not statistically significant (p = 0.091). Similarly, cardiovascular disorders (p = 0.164) and post-resuscitation cases (p = 0.038) showed no significant survival differences. Notably, 100% of neonates admitted with renal failure (n = 2) and gastroenteritis (n = 3) succumbed to their illness, but the small sample size resulted in non-significant p-values (p = 0.195 and p = 0.082, respectively).

The median pH was significantly lower in non-survivors (7.24, min-max: 7.22-7.26) compared to survivors (7.29, min-max: 7.23-7.34), with p = 0.011, indicating that more profound acidosis was associated with increased mortality. Similarly, serum bicarbonate (HCO_3) levels were markedly lower in non-survivors (12.82 mEq/L) than in survivors (16.07 mEq/L) (p = 0.002), further supporting the association of severe metabolic acidosis with poor outcomes. Sodium levels were significantly higher in non-survivors (144 mEq/L) than in survivors (138 mEq/L) (p = 0.001), suggesting a possible relationship between electrolyte disturbances and disease severity. However, potassium levels showed no significant difference between groups (p = 0.695), indicating that hyperkalemia or hypokalemia did not play a major role in survival outcomes.

Table V : Comparison of acid-base variables between survivors and non-survivor (N=115)

Acid-base variables	Survivors (n =64) median (min-max)	Non-survivors (n=51) median (min-max)	*p*-value
PH	7.29 (7.23-7.34)	7.24 (7.22-7.26)	0.011S*
HCO3, mEq/L	16.07 (14.23-17.34)	12.82 (10.23-14.34)	0.002S*
Sodium, mEq/L	138 (142-135)	144 (147-138)	0.001S*
Potasium, mEq/L	4.72 (4.23-4.94)	4.64 (3.93-4.84)	0.695NS*
AG, mEq/L	15.07 (11.23-20.94)	27.45 (23.33-31.44)	0.001S*
Albumin, g/dl	2.54 (2.52-2.56)	2.77 (2.63-2.94)	0.095NS*
cAG, mEq/L	18.60 (14.23-22.94)	31.53 (24.23-34.94)	0.001S*
Base Excess mEq/L	-8.56 (-10.94-6.23)	-12.54 (-14.23-7.94)	0.001S*
PO2	128.33 (100.23-140.94)	115.21 (90.23-140.94)	0.241NS*
PCO2	27.05 (20.23-30.94)	42.81 (20.23-64.94)	0.175NS*

A notable difference was observed in the anion gap (AG), which was significantly elevated in non-survivors (27.45 mEq/L) compared to survivors (15.07 mEq/L) (p = 0.001), suggesting a strong association between high AG metabolic acidosis and mortality. Likewise, the corrected anion gap (cAG) was significantly higher in non-survivors (31.53 mEq/L) than in survivors (18.60 mEq/L) (p = 0.001), reinforcing its role as a potential predictor of neonatal mortality. The base excess was significantly lower in non-survivors (-12.54 mEq/L) compared to survivors (-8.56 mEq/L) (p = 0.001), indicating greater metabolic derangement in neonates who did not survive. Conversely, albumin levels did not show a statistically significant difference between groups (p = 0.095), suggesting that hypoalbuminemia alone was not a major determinant of survival. Regarding respiratory parameters, partial oxygen pressure (PO_2) and partial carbon dioxide pressure (PCO_2) did not show significant differences between survivors and non-survivors (p = 0.241 and p = 0.175, respectively), indicating that ventilation-perfusion abnormalities may not have played a primary role in the observed mortality differences.

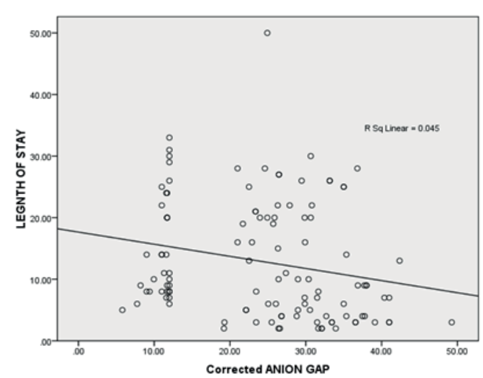

Figure 2: Correlation between the length of stay and corrected anion gap

Figure 2 illustrates the correlation between the corrected anion gap (cAG) and the length of stay (LOS) in the NICU. A negative correlation was observed between cAG and LOS, with a Pearson's correlation coefficient (r) of -0.213 and a *p*-value of 0.023, indicating a statistically significant but weak inverse relationship.

Table VI : Correlation between the Need of mechanical ventilation and corrected anion gap

Variables	Pearson's Correlation coefficient	*p*-value
Need of mechanical ventilation vs. Corrected anion gap	-0.607	0.001

A significant negative correlation was observed between the need for mechanical ventilation (MV) and the corrected anion gap (cAG), as shown in Table VI . The Pearson's correlation coefficient (r) was -0.607, with a *p*-value of 0.001, indicating a strong and statistically significant inverse relationship.

Discussion

Metabolic acidosis is a critical determinant of neonatal outcomes, with corrected anion gap (cAG) serving as a valuable biochemical marker for assessing disease severity. In this study, cAG was significantly higher in non-survivors compared to survivors (31.53 vs. 18.60 mEq/L, $p = 0.001$), emphasizing its role as a predictor of mortality. This finding aligns with previous research indicating that unmeasured anions, including cAG, strongly correlate with mortality in mechanically ventilated critically ill patients.[11] Similarly, a study by Zampieri et al. demonstrated that cAG is a reliable predictor of strong ion gap, further supporting its prognostic value in neonates with metabolic acidosis.[5] The severity of metabolic acidosis in this cohort was reflected in significantly lower pH levels (7.24 in non-survivors vs. 7.29 in survivors, $p = 0.011$) and bicarbonate levels (12.82 vs. 16.07 mEq/L, $p = 0.002$). These findings are consistent with prior studies, where lower pH and bicarbonate nadir were strongly associated with increased mortality in critically ill childre[6] The strong correlation between metabolic acidosis severity and mortality risk reinforces the necessity of timely acid-base management in neonates.[12-14] Mechanical ventilation was required in 90.6% of non-survivors, highlighting its role as a predictor of poor outcomes. This finding is consistent with previous studies showing that neonates with higher cAG values are more likely to require mechanical ventilation and exhibit increased mortality rates.[15] Furthermore, elevated cAG has been linked to greater ventilator dependence and prolonged respiratory support in critically ill pediatric patients.[16,17] The necessity of mechanical ventilation in most non-survivors in the present study suggests that metabolic acidosis, indicated by high cAG, contributes significantly to the progression of respiratory failure. Among NICU admission reasons, respiratory failure, neurologic issues, and sepsis emerged as the strongest predictors of mortality in the present study. A study by Yu & Chen also found that anion gap values were reliable predictors of mortality in ventilated patients with respiratory complications.[18] Additionally, a study by Datta et al. found that metabolic acidosis was frequently associated with multi-organ dysfunction and sepsis, further reinforcing the critical role of acid-base disturbances in neonatal survival outcomes.[6] Interestingly, the current study found a statistically significant negative correlation between cAG and length of NICU stay ($r = -0.213$, $p = 0.023$), suggesting that higher cAG values were associated with shorter LOS due to increased mortality rather than prolonged recovery. This contrasts with studies in adult ICU populations, where higher AG values were associated with longer ICU stays.[19] The shorter LOS in non-survivors observed in this study likely reflects the rapid deterioration of critically ill neonates rather than prolonged treatment durations. Overall, these findings emphasize the prognostic significance of cAG in critically ill neonates, supporting its use as an early predictor of mechanical ventilation requirement and mortality. The strong correlation between cAG, metabolic acidosis severity, and clinical outcomes highlights the need for routine acid-base monitoring and timely intervention in neonates with high cAG values. Future research should explore whether early metabolic correction strategies can improve outcomes in neonates at high risk of mortality due to metabolic acidosis.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

Conclusion

This study highlights the significant role of corrected anion gap (cAG) as a predictor of disease severity, mechanical ventilation requirement, and mortality in critically ill neonates with metabolic acidosis. The findings demonstrate that non-survivors had significantly higher cAG values (31.53 vs. 18.60 mEq/L, $p = 0.001$), lower pH, and bicarbonate levels, reinforcing the strong association between severe metabolic acidosis and poor outcomes. Respiratory failure, neurologic issues, and sepsis emerged as the strongest predictors of mortality, reinforcing the importance of prompt recognition and intervention in neonates presenting with these conditions. Given these findings, cAG can serve as a valuable early prognostic biomarker in neonatal intensive care settings, aiding clinicians in making timely decisions regarding ventilation support and metabolic correction strategies. Future research should explore intervention-based strategies aimed at reducing acidosis severity and its impact on neonatal survival.

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