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Role of Corrected Anion Gap in Predicting Mortality and Mechanical Ventilation Requirement in Neonatal Intensive Care Unit

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Abstract **Original Research Article**

Background: Metabolic acidosis is a frequent condition among neonates in the Neonatal Intensive Care Unit (NICU), often reflecting disorders such as sepsis, perinatal asphyxia, or respiratory failure. The corrected anion gap (cAG), which adjusts for serum albumin, may offer better prognostic value than traditional acid-base parameters. Limited data exist on its predictive role in neonatal outcomes. This study aims to evaluate the corrected anion gap (cAG) role in predicting in-hospital mortality and mechanical ventilation requirements among NICU neonates with metabolic acidosis. ***Methods:*** This prospective observational study was conducted at the NICU of Bangladesh Shishu Hospital & Institute, Dhaka, from July 2021 to June 2023. A total of 115 neonates with metabolic acidosis were included. Participants were divided into survival (n=64) and non-survival (n=51) groups based on in-hospital outcomes. Data on acid-base variables, clinical conditions, and outcomes were collected. Statistical analyses included t-tests, logistic regression, and Pearson's correlation, using SPSS version 25.0. ***Results:*** Mean cAG was significantly higher in non-survivors (31.53±7.01) than survivors (18.60±8.74) ($p<0.001$). cAG positively correlated with mechanical ventilation need ($r=0.607$, $p=0.001$) and negatively with NICU length of stay ($r=-0.213$, $p=0.023$). Multivariate logistic regression identified cAG as an independent predictor of mortality (OR: 1.321; 95% CI: 1.140–1.532; $p<0.001$), along with respiratory failure and elevated serum creatinine. ***Conclusion:*** Corrected anion gap is a reliable and independent marker for predicting mortality and mechanical ventilation in critically ill neonates and should be integrated into early NICU assessment protocols.

Keywords: Corrected anion gap, metabolic acidosis, neonatal mortality, mechanical ventilation, NICU.

INTRODUCTION

Metabolic acidosis is a frequent and life-threatening complication of neonates admitted to intensive care units, which typically indicates some form of physiological abnormality, including sepsis, respiratory failure, or renal dysfunction. The traditional approach of how to assess the acid-base status using such parameters as pH, bicarbonate, with base excess is informative to clinicians. However, the impact of unmeasured anions that could affect morbidity and mortality endpoints is not considered. The anion gap (AG), and especially the corrected anion gap (cAG), which accounts for hypoalbuminemia, has become a useful measure in assessing metabolic acidosis and in making prognostic estimates in critically ill patients [1,2].

The corrected anion gap is especially valuable in neonates, who commonly present with complex multifactorial situations associated with relatively immature organ systems and extreme vulnerability to perinatal stressors, including asphyxia, infection, or birth trauma. Several studies have supported the value of AG and cAG for outcome prediction in pediatric and adult ICU settings [3,4]. Kim *et al.*, demonstrated that AG at admission is significantly indicative of mortality in pediatric intensive care units [5]. In a similar light, Afify *et al.*, point out cAG and hypernatremia as independent

predictors of mortality in children hospitalized in the PICU [6]. However, there is very little literature on the specific evaluation of these parameters in neonates, especially in NICU settings in low-resource countries.

Neonatal mortality continues to pose a vital problem in Bangladesh and other underdeveloped countries, and their mortality rates reported in NICUs are from 20% to 40%. Most of them are preventable, such as perinatal asphyxia, neonatal sepsis, and respiratory distress syndrome [7,8]. These conditions are therefore also major causes of neonatal metabolic acidosis, highlighting the need for early and precise prognostic markers to enhance optimal allocation of resources and facilitate clinical decision-making. In the absence of advanced diagnostic modalities, the use of reliable bedside markers such as cAG may help aid early interventions, especially in poorly resourced NICUs.

Corrected anion gap allows for the correction of hypoalbuminemia (a common problem in the critically ill neonates), and it better reflects the corrected severity of unmeasured anions in metabolic acidosis. Feldman et al. demonstrated the relation between albumin levels to the anion gap range, although the rationale behind the correction to increase the sensitivity of diagnosis has been put forward [2]. Further, cAG has been proven to be a strong predictor of poor outcomes such as an MVR and in-hospital mortality in adults and pediatric cohort studies [9, 10]. However, the prognostic relevance of cAG in neonatal care has not been exploited.

This study aims to evaluate the use of corrected anion gap as a predictor of mortality and the need for mechanical ventilation in neonates admitted to the NICU of Bangladesh Shishu Hospital & Institute. Based on robust statistical analysis of acid–base variables, the present study attempts to determine whether cAG might be a valid biomarker for the risk stratification in critically ill neonates. The results are anticipated to benefit better neonatal outcomes and evidence-based care protocols adapted to low- and middle-income countries (LMIC) settings.

Objective

The objective of this study was to evaluate the role of corrected anion gap in predicting in-hospital mortality and the need for mechanical ventilation among neonates admitted to the NICU with metabolic acidosis.

METHODOLOGY & MATERIALS

This prospective observational study was conducted in the Department of Pediatrics, Bangladesh Shishu Hospital & Institute (BSH&I), Dhaka, from July 2021 to June 2023. The study population consisted of critically ill neonates with metabolic acidosis admitted to the Neonatal Intensive Care Unit (NICU). A total of 115 neonates meeting the eligibility criteria were enrolled and categorized into two groups based on in-hospital mortality: the survival group (n=64) and the non-survival group (n=51).

Sample Selection

Inclusion Criteria

- Neonates admitted to the NICU with metabolic acidosis.
- Admission during the study period (July 2021 to June 2023).
- Availability of necessary biochemical parameters to calculate corrected anion gap (cAG).

Exclusion Criteria

- Neonates without metabolic acidosis at admission.
- Neonates who were on mechanical ventilation before initial evaluation.
- Incomplete medical records are preventing the cAG calculation.

Data Collection Procedure: Data were collected during NICU admission using a structured questionnaire designed to record demographic, clinical, and biochemical parameters. Prior to definitive treatment, 2 mL of blood was drawn under aseptic conditions and sent to the hospital laboratory for analysis of arterial blood gases, serum electrolytes, albumin, and complete blood counts. The corrected anion gap (cAG) was calculated for each neonate. Additional data on clinical outcomes, including mortality, length of NICU stay, and requirement for mechanical ventilation, were recorded during hospitalization and monitored until discharge or death.

Ethical Consideration: Ethical approval was obtained from the Institutional Review Board of BSH&I. Written informed consent or a thumbprint was secured from the parents or legal guardians of all enrolled neonates after providing a full explanation of the study's objectives, procedures, and significance. Confidentiality of participant information was strictly maintained, and participation did not result in any additional risk or financial burden to the patients or families.

Statistical Analysis: All data were analyzed using SPSS version 25.0. Descriptive statistics (means, standard deviations, frequencies, percentages) were computed for baseline characteristics. Inferential analyses included independent samples t-tests, chi-square tests, Pearson's correlation, and univariate and multivariate logistic regression to identify predictors of mortality and mechanical ventilation. A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves and Kaplan-Meier survival analyses were used to assess diagnostic performance and survival outcomes related to corrected anion gap.

RESULTS

This Prospective Observational study was conducted in the Department of Pediatrics of Bangladesh Shishu Hospital & Institute (BSH&I), Dhaka, from July, 2021 to June, 2023. Total 115 neonates were included in the study. They were divided into two groups into survival & non survival groups on the basis of hospital mortality. Group I: survival group, n = 64. Group II: Non survival group, n= 51. Observations and results of the study was as follows:

Table 1: Clinical characteristics of patients in NICU

Characteristics	Frequency (n=115)
Age, Days	5 (4-6)
Male, n (%)	90 (78.3%)
LOS in NICU, days	12 (11-14)
In-hospital mortality, n (%),	51 (44.3%)
Requirement for mechanical ventilation, n (%)	53 (46.1%)
Respiratory failure	42 (36%)
Neurologic problem	54 (47%)
Sepsis	42 (36%)
Cardiovascular disorder	14(12.2%)
Renal failure	2(1.7%)
Gastroenteritis	3(2.6%)
Post-resuscitation	52(45.2%)
LBW	54 (47%)

Table 1 shows the Clinical characteristics of patients in the NICU. The median age of the patients was 5 days. Male patients were 78.3% (90/115). Overall, in-hospital mortality was 44.3% (51/115) with a median length of stay (LOS) in the NICU of 12 days. A total of 53 (46.1%) required mechanical ventilation within 24 hours of NICU admission. Medical diseases were neurologic problems (54 patients, 47.5%), such as perinatal asphyxia; respiratory problems (42 patients, 36%), such as respiratory distress syndrome; and neonatal sepsis (42 patients, 36%). The most common reason for NICU admission was neurological problems (47.5%).

Table 2: Comparison of acid-base variables between survivors and non- survivors

Parameter	Survivors (n =64)	Non-survivors (n=51)	p-value
P^H	7.29±0.06	7.24±0.10	0.011
HCO3, mEq/L	16.07±3.42	12.82±4.68	0.002
Sodium, mEq/L	138±7.04	144±9.31	0.001
Potasium, mEq/L	4.72±0.834	4.64±1.35	0.695
AG, mEq/L	15.07±8.18	27.45±6.89	0.001
Albumin, g/dl	2.54±0.40	2.77±0.94	0.095
cAG, mEq/L	18.60±8.74	31.53±7.01	0.001
Base Excess mEq/L	-8.56±4.07	-12.54±7.94	0.001
PO2	128.33 ±54.81	115.21±64.47	0.241
PCO2	27.05±6.52	42.81±12.29	0.175

Table 2 shows a Comparison of acid-base variables between survivors and non-survivors. Mean ±SD PH survivors and non-survivors were 7.29±0.06 and 7.24±0.10, respectively, which was statistically significant ($p<0.05$). No statistically significant different was observed between survivors and non-survivors regarding potassium, PO2, PCO2, and serum albumin ($p>0.05$). HCO3, Base excess was lower in non-survivors among the survivor group, which was also statistically significant ($p<0.05$). High anion gap and elevated corrected anion gap, along with hypernatremia, were also observed in the non-survivor group, which was statistically significant ($p<0.05$).

Table 3: Logistic regression for independent factor in mortality prediction.

OR (95% CI)	P value	OR (95% CI)	P value
Age 0.950 (0.885-1.020)	0.156		
Sex 1.482 (0.609-3.607)	0.385		
Respiratory Failure 2.658(1.218-5.802)	0.014	10.617(2.190-51.479)	0.003
Neurological Problem 2.763 (1.293-5.905)	0.009	8.024 (0.841-76.589)	0.7

OR (95% CI)	P value	OR (95% CI)	P value
Sepsis 2.658 (1.218-5.802)	0.014	3.076 (0.672-14.087)	0.148
Post Resuscitation 2.350 (1.106-4.992)	0.026	0.403 (0.044-3.668)	0.42
Renal Failure 2.110 (0.001-3.110)	0.999		
Cardiovascular Disorder 0.460 (0.135-1.562)	0.213		
Gastroenteritis 2.200 (0.001-3.210)	0.999		
LBW 0.562 (0.267-1.182)	0.129		
Hemoglobin 0.825 (0.730 -1.124)	0.631		
TLC 1.000 (0.990 -1.001)	0.925		
PLT 1.000 (0.980-1.002)	0.009	1.00 (0.099-1.002)	0.106
RBS 0.997 (0.885-1.125)	0.966		
S. Creatinine 1.050 (1.023-1.078)	0.001	1.091 (1.033-1.151)	0.002
CRP 1.003 (0.989-1.018)	0.643		
S. Albumin 1.053 (0.874-1.269)	0.588		
S. Calcium 0.576 (0.165-2.012)	0.387		
PH 0.001 (0.001-0.135)	0.008	0.149 (0.001-0.865)	0.734
Sodium 1.101 (1.044-1.160)	0.001	0.906 (0.814-1.009)	0.071
Potassium 0.934 (0.665-1.311)	0.692		
Base Excess 0.890 (0.828-0.957)	0.002	0.970 (0.794-1.185)	0.765
P02 0.996 (0.990-1.003)	0.239		
PC02 1.012 (0.987-1.037)	0.351		
HCO3 0.820 (0.738-0.911)	0.001	1.131 (0.877-1.458)	0.344
cAG 1.204 (1.125-1.289)	0.001	1.321 (1.140-1.532)	0.001

Table 3 shows Logistic regression for the independent factors in mortality prediction. Univariate Logistic regression was performed to identify predictors of mortality. Respiratory failure (OR 2.65), neurological involvement (OR 2.76), neonatal sepsis (OR 2.65), post-resuscitation (OR 2.35), PH (OR 0.OO1), HCO3 (OR 0.820), base excess (OR 0.89), high cAG (OR 1.204), low platelet count (OR 1.00), hypernatremia (OR 1.101) and Creatinine levels (OR 1.05) were statistically significant independent predictors of mortality among neonates admitted to the NICU ($p<0.05$). Sex, renal failure, gastroenteritis, TLC, CRP, S. Albumin, PCo2 were also risk factors (OR>1) but statistically not significant ($p>0.05$). 11 variables were introduced into the multivariable logistic regression analysis. cAG was identified as an independent predictor of mortality [odds ratio (OR) 1.321, 95% confidence interval (CI) 1.140–1.532, $p < 0.001$] along with respiratory failure (OR 10.61) and elevated serum creatinine (OR 1.091) ($p<0.05$).

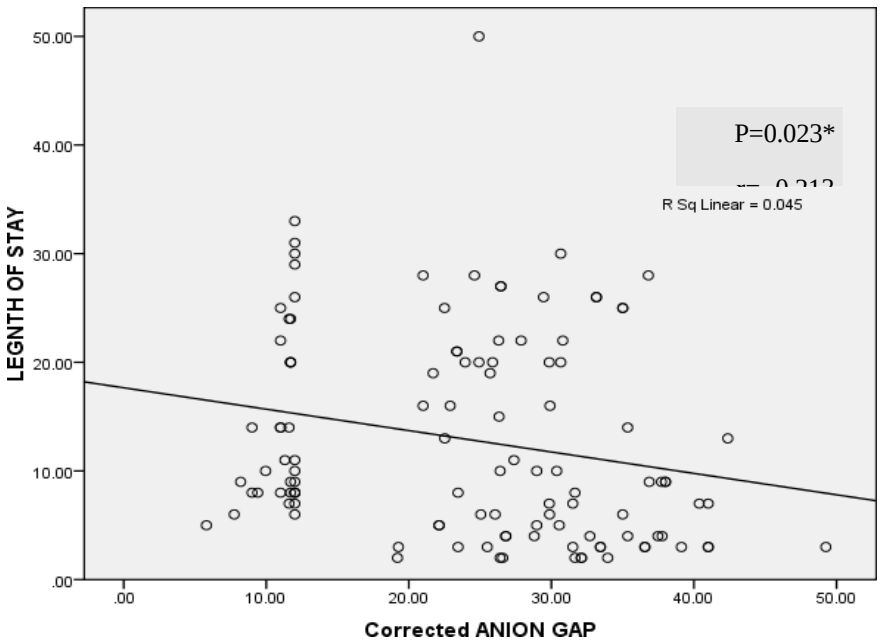

Figure 1: Correlation between the length of stay and corrected anion gap

Figure 1 shows the Correlation between the length of stay and corrected anion gap. There was a significant weak negative correlation (r = -0.213, 0.023) between the corrected anion gap (cAG) and the length of stay in NICU.

Table 4: Correlation between the Need for mechanical ventilation and corrected anion gap

Variables	Pearson's Correlation coefficient (r)	P value
Need of mechanical ventilation vs. cAG (corrected anion gap)	0.607	0.001

Table 4 shows the Correlation between the need for mechanical ventilation and corrected anion gap. There was a significant positive correlation (r = 0.607, p=0.001) between the cAG and the need for mechanical ventilation in the NICU.

DISCUSSION

This prospective observational study was conducted to determine the predictive value of the corrected anion gap (cAG) in forecasting mechanical ventilation and in-hospital mortality among neonates who were admitted to the NICU with metabolic acidosis. The study showed that cAG was much more significant in non-survivors than survivors, and it correlates positively with the need for mechanical ventilation to prove its value as an independent predictor of poor neonatal outcomes.

Our results support other researchers who reported the prognostic value of increased AG and cAG in critically ill people. Mehta *et al.,* demonstrated that high AG on admission was significantly related to poor outcomes for the patients admitted to ICUs, which further supported its role as a prognostic marker [11]. Similarly, Tuhay *et al.*, demonstrated that such severely deranged acid-base profiles, in conjunction with an elevated AG, were strongly correlated with a poor prognosis, even in cases where traditional markers like base excess are within normal range [12]. In the present study, the mean cAG was significantly greater in non-survivors than in survivors (31.53±7.01 vs. 18.60±8.74, p<0.001), properly indicating the degree of metabolic severity among fatal cases.

In a multivariate analysis, cAG was a strong independent predictor of mortality (OR: 1.321; 95% CI: 1.140–1.532; p<0.001), even after adjusting for other major factors such as respiratory failure and raised serum creatinine. Noritomi *et al.*, presented evidence that accumulation of unmeasured anions, which is expressed by increased AG, is highly correlated with mortality in septic patients with severe sepsis and septic shock [13]. Similarly, Mamo *et al.*, associated higher AG levels and acidosis with increased risk of perinatal asphyxia and neonatal death, confirming the usefulness of cAG as a predictor of poor outcomes in the NICU environment [14].

The underlying mechanisms correlating raised cAG to poor outcome may involve the accumulation of unmeasured anions (e.g., lactate, phosphates, sulfates) due to impaired perfusion, a renal or septic defect. Kraut and Madias underscored that aggravated cellular metabolism and organ dysfunction caused high AG metabolic acidosis, which frequently occurred due to lactic acidosis or renal failure, resulting in higher mortality [3]. Using our study population, we show that sepsis and respiratory failure are both strongly associated with mortality, and cAG allows a representation of the burden of underlying metabolic disturbances in these conditions.

Notably, our study identified a strong positive correlation (r = 0.607, p=0.001) between cAG and the need for mechanical ventilation. Thus, neonates with high cAG tended to require more need of respiratory support. These findings are backed up (Jung *et al.,* who reported a strong association between acidemia with the need for ventilatory support within the ICU [15]. Furthermore, Srikrishna *et al.,* noted that the severity of metabolic acidosis in neonates is directly connected with more respiratory complications as well as mechanical intervention [16].

It is also worth mentioning that cAG also showed reverse correlation with NICU LOS (LOS) (r = -0.213 p=0.023), implying that the neonate with high cAG either expired earlier or had a short stay because of poor prognosis. Despite the difference in studied regions, Paul *et al.,* and Seaton *et al.,* observed comparable associations of acid-base disturbances with reduced LOS in NICUs, which usually was an indication of early mortality [17,18].

It is also worth mentioning that even though hypoalbuminemia is more prevalent in the non-survivor population, it did not reach any statistical significance in this study. Nevertheless, the necessity of albumin correction is clear; a reduction in the AG due to hypoalbuminemia and the inability to cover the severity of the acidosis if not corrected is obvious too. Feldman *et al.,* vigorously argued in support of AG correction during hypoalbuminemic states to prevent underestimation of metabolic derangements [9].

Our findings have practical implications, particularly in resource-poor settings. In the lack of sophisticated diagnostics, a straightforward calculation of cAG via routinely available laboratory parameters provides a useful instrument for early stratification of

risk. This is particularly relevant for LMICs such as Bangladesh, where neonatal mortality continues to be a major public health problem. According to Hoque *et al.*, sepsis, perinatal asphyxia, and respiratory distress are the main causes of neonatal deaths in NICUs throughout the country [7]. Effective early detection of high-risk neonates by means such as cAG may help in instituting timely interventions and rationalizing resources.

Some limitations need consideration while interpreting our results. cAG is significantly associated with mortality and ventilator support, but does not prove causality alone. Other parameters, like lactic acid levels and coexisting electrolyte abnormalities, not discussed separately, may affect results. The use of single-point cAG at admission versus serial monitoring limits our knowledge of dynamic changes. Although limited, our findings highlight cAG's clinical importance in neonatal critical care. This paper adds to the literature supporting corrected anion gap as a prognostic marker in critically ill neonates. It confirms cAG's strong association with mortality and mechanical ventilation needs in neonates with metabolic acidosis. Integrating cAG into NICU assessment protocols can facilitate early recognition of high-risk neonates and enhance outcome-oriented interventions.

Limitations of the study

The study was limited by its single-center design, relatively small sample size, and reliance on single-time-point laboratory values without serial cAG monitoring. Additional unmeasured variables, such as lactate and other organic acids, may have influenced outcomes. Future multicenter studies with larger cohorts and longitudinal monitoring of acid-base status are recommended to validate these findings. Incorporating cAG into NICU protocols could enhance clinical decision-making. However, further research is needed to establish standardized thresholds and integrate them with other severity scoring systems for comprehensive neonatal risk assessment.

CONCLUSION

This study demonstrates that corrected anion gap (cAG) is a significant independent predictor of in-hospital mortality and the need for mechanical ventilation in neonates with metabolic acidosis admitted to the NICU. Elevated cAG was strongly associated with poor outcomes, including early mortality and greater need for ventilatory support. The findings suggest that routine calculation of cAG at admission could serve as a valuable, cost-effective tool for early risk stratification, especially in resource-limited neonatal care settings.

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