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Association between Acid-Base and Biochemical Parameters with Mortality in Neonates Admitted to NICU

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Abstract

Background: *Metabolic acidosis is a frequent and serious condition in critically ill neonates, often associated with high morbidity and mortality. Corrected anion gap (cAG) has emerged as a potential prognostic marker, but its clinical utility in neonatal populations remains underexplored.*

Methods: *This prospective observational study was carried out in the Neonatal Intensive Care Unit (NICU) of Bangladesh Shishu Hospital & Institute (BSH&I), Dhaka, over a two-year period from July 2021 to June 2023. Clinical data, arterial blood gas (ABG) parameters, and biochemical profiles were analyzed. Comparisons were made between survivors and non-survivors. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of cAG for mortality. Kaplan-Meier survival analysis assessed survival differences based on cAG levels.*

Results: *Out of 115 neonates, 64 (55.7%) survived and 51 (44.3%) died. Non-survivors had significantly shorter NICU stays (5 ± 3 vs. 18 ± 8 days; $p = 0.001$) and higher mechanical ventilation use (90.6% vs. 9.4%; $p = 0.001$). They also had significantly lower pH (7.24 ± 0.10 vs. 7.29 ± 0.06; $p = 0.011$), bicarbonate, and base excess levels, and significantly higher sodium, anion gap, and corrected anion gap ($p < 0.05$). ROC analysis showed cAG had strong predictive value for mortality (AUC: 0.861; 95% CI: 0.795–0.927; $p = 0.001$), with an optimal cut-off of 26.0 mEq/L (sensitivity: 74.5%, specificity: 81.2%). Kaplan-Meier analysis confirmed significantly lower survival in neonates with cAG ≥ 26.0 mEq/L ($p < 0.001$).*

Conclusion: *Corrected anion gap is a strong independent predictor of mortality in neonates with metabolic acidosis. A cAG threshold of ≥ 26.0 mEq/L may help in early identification of high-risk patients and guide clinical decision-making in the NICU.*

Keywords: *Neonates, Metabolic acidosis, Corrected anion gap, Mortality, Prognostic marker, NICU.*

1. INTRODUCTION

Neonatal intensive care units (NICUs) play a significant role in the management of critically ill, vulnerable neonates who are at risk of several metabolic derangements including acid-base imbalances [1]. Acid-base disturbances, particularly metabolic acidosis, are highly prevalent among NICU neonates and their intensity is generally correlated directly with ominous clinical outcomes like mortality [2].

Neonatal metabolic acidosis may be caused by a variety of underlying diseases such as sepsis,

renal dysfunction, respiratory distress, and gastrointestinal disease. These conditions tend to alter physiological parameters such as arterial blood gases (ABG), serum electrolytes, and albumin level, all of which are extremely crucial in assessing the metabolic status and outcome of the neonate [3, 4].

Corrected anion gap (cAG), which is an essential parameter obtained through ABG examination, is used to evaluate the existence and extent of metabolic acidosis and also as a predictive indicator in a variety of adult and pediatric ailments [5]. Recent evidence suggests that cAG, like other biochemical indices like serum electrolytes (sodium, potassium, chloride), albumin level, and complete blood count (CBC), could be used to predict mortality in critically ill patients [6]. However, the relationship of these parameters with neonatal mortality, particularly in infants with metabolic acidosis, continues to remain uncharted in neonatal intensive care units [7].

Knowledge of the relationship of acid-base imbalance and biochemical parameters with neonatal death is necessary for the early identification of high-risk newborns and appropriate intervention [8]. Previous research has identified that metabolic acidosis, particularly with increased anion gap, is associated with adverse outcomes in neonates, including increased NICU hospitalization duration and higher mechanical ventilation needs [9]. Studies have also suggested that correction of metabolic acidosis at an early stage may result in enhanced survival rates, but more specific studies need to be carried out to verify the predictive value of these biomarkers in neonates [10].

Several parameters have been identified as possible predictors of neonatal mortality, including clinical markers such as the need for mechanical ventilation, NICU length of stay, and laboratory values such as electrolyte imbalance and serum albumin [11]. While these are often used in clinical practice to assess illness severity, not much consensus exists on the optimal predictors of mortality in this high-risk population. This lack of knowledge underscores the importance of specific research to explore the clinical and biochemical factors most significant in establishing neonatal survival [12].

The present study aimed to establish the association of acid-base and biochemical parameters with neonatal mortality among NICU-admitted newborns with metabolic acidosis. Specifically, we aimed to evaluate whether markers like cAG, serum electrolytes, and albumin levels can serve as early predictors of neonatal mortality. Additionally, the study will explore the association of the parameters with other clinical outcomes such as mechanical ventilation, NICU length of stay, and survival.

2. Methodology & Materials

This prospective observational study was carried out in the Neonatal Intensive Care Unit (NICU) of Bangladesh Shishu Hospital & Institute (BSH&I), Dhaka, over a two-year period from July 2021 to June 2023. The study included critically ill neonates admitted with metabolic acidosis. A total of 115 neonates were enrolled using purposive sampling based on specific inclusion and exclusion criteria. Neonates with confirmed metabolic acidosis were included, while those without metabolic acidosis or already on mechanical ventilation at the time of evaluation were excluded.

Ethical approval was obtained from the Institutional Review Committee of BSH&I. Informed written consent or fingerprint authorization was secured from parents or legal guardians after explaining the purpose and procedures of the study. Upon admission to the NICU and before the initiation of definitive treatment, 2 ml of arterial blood was collected aseptically for laboratory evaluation. Investigations included arterial blood gas (ABG) analysis, serum electrolytes, serum albumin, and complete blood count. Corrected anion gap (cAG) was calculated for all participants.

Clinical data, relevant history, and physical examination findings were recorded using a structured questionnaire. Based on hospital outcomes, neonates were categorized into two groups: Group 1 (survivors) and Group 2 (non-survivors). Follow-up continued until discharge or in-hospital death, with documentation of key outcome variables such as mortality, NICU length of stay, and need for mechanical ventilation.

Data were analyzed using SPSS version 22.0. Descriptive statistics including frequency, percentage, mean, and standard deviation were used to summarize the data. Comparisons between survivor and non-survivor groups were made using the Student's t-test for continuous variables and the chi-square test for categorical variables. Pearson's correlation coefficient was applied to assess relationships between variables. Logistic regression was performed to identify independent predictors of mortality, with multivariate analysis to adjust for confounding

factors. The predictive performance of cAG was evaluated using receiver operating characteristic (ROC) curve analysis. Kaplan-Meier survival curves were constructed based on cAG cut-off values, and differences were analyzed using the log-rank test.

3. RESULTS

Table I. *Comparison of clinical characteristics between survivors and non- survivors (n = 115)*

Characteristics	Survivors (n =64)	Non-survivors (n=51)	p-value
Age, days	6±4	4±2	0.153^{NS}
Male %	52 (57.8)	38 (42.2)	0.496^{NS}
LOS, days	18±8	5±3	0.001*
Mechanical ventilator (%)	5 (9.4)	48 (90.6)	0.001*
LBW	26 (48.1)	28 (51.9)	0.091^{NS}
Reason for NICU admission Respiratory failure	17 (40.5)	25 (59.5)	0.019*
Neurological problem (%)	23 (42.6)	31 (57.4)	0.009*
Sepsis (%)	17 (40.5)	25 (59.5)	0.019*
Cardiovascular disorder (%)	10 (71.4)	4 (28.6)	0.164*
Post-resuscitation	23 (44.2)	29 (55.8)	0.038*
Renal failure	0 (0)	2 (100)	0.195^{NS}
Gastroenteritis	0 (0)	3 (100)	0.082^{NS}

Data express as number (percentage) or mean ± SD. For statistical analysis, Chi-square test or Fisher exact test or Independent t test was done which was appropriate. .p<0.05 considered as significant.

NS= Not significant, *=Significant.

Table I showed Comparison of clinical characteristics between survivors and non-survivors. Mean ± SD of LOS survivors and non-survivors were 18±8 and 5±3, respectively which was statistical significant (p<0.05). Mean ± SD age of Non-survivors and survivors were 4±2 days and 6±4 days which showed no statistical significant (p>0.05). Non-survivors tended to require mechanical ventilation (90.6%) which also statistical significant (p<0.05). Respiratory failure, neurologic problems, sepsis and post resuscitation was higher in non-survivors than in survivors which also statistical significant (p<0.05). No statistical significant was observed between survivors and non-survivors regarding male neonates, cardiovascular disorder, renal failure, gastroenteritis and LBW (p>0.05).

Table II. *Comparison of acid-base variables between survivors and non- survivors*

Characteristics	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^{NS}
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^{NS}
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^{NS}
PCO2	27.05±6.52	42.81±12.29	0.175^{NS}

Data expressed as mean ± SD. For statistical analysis, Independent t test was done. p<0.05 considered as significant. NS= Not significant, *=Significant

Table II showed 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 statistical significant (p<0.05). No statistical significant different was observed survivors and non-survivors regarding potassium, PO2, PCO2 and serum albumin (p>0.05). HCO3, Base excess was lower in non-survivor among survivors group which also statistical significant (p<0.05). High anion gap and elevated corrected anion gap along with hypernatremia was also observed in non-survivor group which was statistically significant (p<0.05).

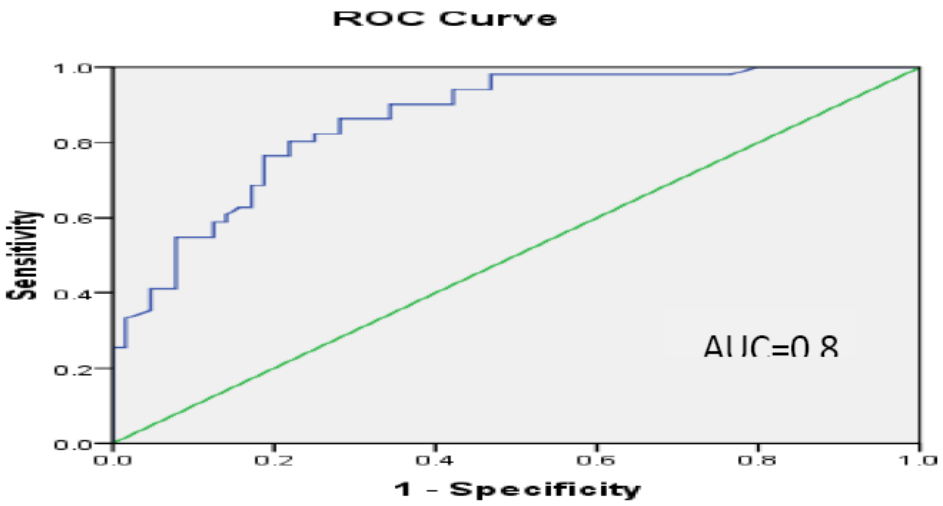

Figure 1. *Receiver operating characteristic (ROC) curves for corrected anion gap prediction mortality in NICU.*

Figure 1 showed Receiver operating characteristic (ROC) curves for corrected anion gap prediction mortality in NICU. ROC curve analysis for prediction of mortality showed that Area under the ROC curve, 0.861 [95% CI, 0.795–0.927], p=0.001) . In this study, the best cutoff value of cAG to predict mortality was 26.0 mEq/L (sensitivity 74.5%, specificity 81.2%) [p=0.001].

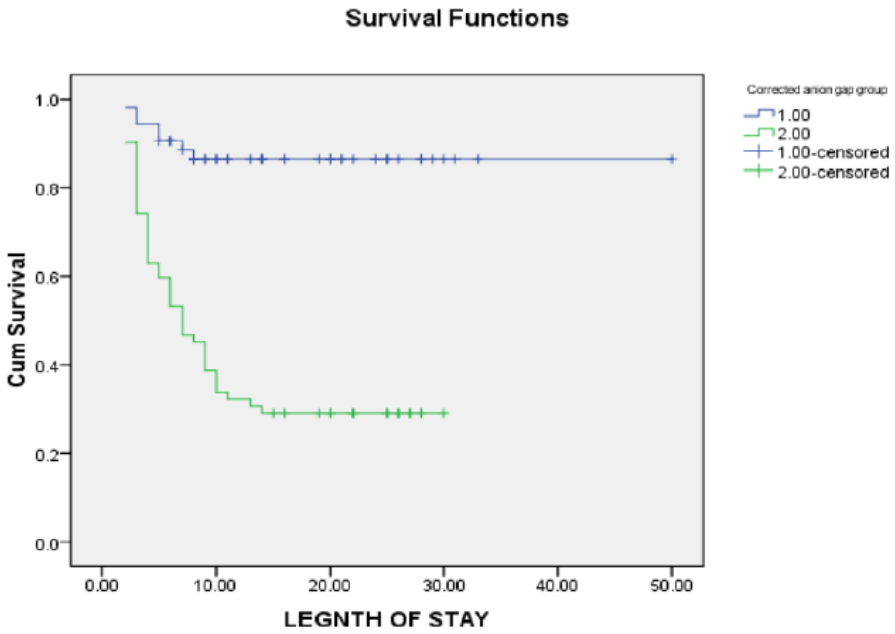

Figure 2. *Survival curves for the patients according to cutoff value of corrected anion gap.*

Figure 2 Showed Survival curves for the patients according to cutoff value of corrected anion gap. Survival curves using Kaplan Meier method based on data from all 115 neonates stratified by cutoff value of cAG (cAG < 26.0 vs. cAG ≥ 26.0 mEq/L, p < 0.001 by log-rank test). The cutoff value of initial corrected anion gap was defined by 26.0 mEq/L.

4. Discussion

The aim of this research was to assess clinical and biochemical profile of neonates with metabolic acidosis and ascertain the prognostic significance of corrected anion gap (cAG) to predict mortality. Of the 115 neonates who were recruited, the cumulative mortality rate was 44.3%, and marked differences existed between survivors and non-survivors in NICU stay length, need for mechanical ventilation, and underlying conditions such as sepsis, neurological compromise, and respiratory distress. The non-survivor group were significantly more acidic with reduced pH, bicarbonate, and base excess values, results previously documented to be

related to adverse neonatal outcomes [13-16]. For instance, Liu et al., highlighted the central role of bicarbonate levels in the severity and management direction of pediatric metabolic acidosis, and Trefz et al., demonstrated a strong association between deep acidemia and mortality in neonatal calves, confirming the broader relevance of acid-base status to critically ill neonates [15, 17].

Our findings of elevated sodium levels and significantly higher anion gap in conjunction with corrected anion gap in non-survivors correlate with that of other research. Bahatkar and Aundhakar similarly reported disturbances in electrolyte profile, particularly in sodium and acid-base balance, in neonates with birth asphyxia [14]. Increased anion gap is a sign of unmeasured anion accumulation such as lactate or ketones, which occurs in states of tissue hypoperfusion [18, 19].

Notably, our study sets the corrected anion gap (cAG) as an accurate mortality predictor in neonates with an ROC analysis AUC of 0.861. Such a high discriminative capability concurs with Trefz et al., who indicated that acid-base disturbances, including elevated anion gap, were highly predictive of outcome in neonates who were critically ill [16]. Further, Koti et al., showed similar predictive ability when they emphasized the use of lactate and ABG values in determining neonatal prognosis in NICU settings [20].

The optimal cut-off value for cAG in our study was 26.0 mEq/L, which provided a sensitivity of 74.5% and specificity of 81.2%. This cut-off value can be clinically useful to detect neonates at high risk of death and to initiate early aggressive treatment. Hadzic et al., and Wu et al., in their earlier studies also emphasized the prognostic significance of acid-base parameters like base excess and oxygenation indices in critically ill neonates [21, 22].

Increased neonatal mortality among patients on ventilators with conditions like sepsis, neurological, and post-resuscitative status is comparable to findings by Binh et al., where they stated the said clinical features exerted greater impact on the survival rate among neonates with birth asphyxia as well as metabolic complication [23]. Islam et al., also concluded significant correlations of acid-base disturbances with electrolyte abnormality along with Apgar score further establishing their prognostic value as biochemistry markers [24].

Interestingly, survivors and non-survivors were not different from each other in terms of potassium, PO_2, PCO_2, or serum albumin, and these parameters seem to be more reflective of acute physiological conditions but less predictive of outcome than cAG or bicarbonate levels a finding that is corroborated by Xu et al., in their assessment of neonatal asphyxia with blood gas and biochemical markers [25].

This study contributes to the evidence base for the prognostic utility of corrected anion gap in neonatal intensive care. In settings with limited resources, easily accessible biochemical markers like cAG can be valuable tools for early risk stratification and decision-making in the management of neonates with metabolic acidosis.

5. Limitations of the Study

This single-center study calculated corrected serum anion gap (cAG) using serum values rather than arterial blood gas data. Only the initial cAG at NICU admission was assessed to determine its association with neonatal mortality.

6. Conclusion

This study concluded that corrected anion gap (cAG) at NICU admission is a strong predictor of mortality in neonates, regardless of the underlying etiology. Elevated cAG values, particularly ≥26.0 mEq/L, are significantly associated with higher mortality rates, making it a more accurate marker than the standard anion gap. Additionally, respiratory failure and elevated serum creatinine levels were identified as key factors associated with poor outcomes, underlining the potential of cAG as an early marker for clinical decision-making and risk stratification in critically ill neonates.

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Conflicts of Interest

There are no conflicts of interest.

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