SERUM ANION GAP AND HYPERNATREMIA AT ADMISSION AS A PREDICTOR OF MORTALITY IN THE PEDIATRIC INTENSIVE CARE UNIT

By

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ABSTRACT

Background: *Anion gap (AG) is a commonly used indicator in patients with metabolic acidosis. Anion gap, along with clinical symptoms, helps to orient the cause. In addition, it contributes to the prognosis of severity and mortality in metabolic acidosis. Hypernatremia represents a state of total body water deficiency in absolute or relative to total body Na and potassium.*

Aim and objectives: *to investigate if both serum sodium and anion gap are linked to mortality in hospitalized kids admitted to PICUs. We specifically looked into whether serum anion gap level and hypernatremia at the time of PICU admission are a reliable predictor for mortality and how well it performed in comparison to other mortality prediction models.*

Subjects and methods: *This prospective study was conducted at pediatric intensive care units at Bab El-Sheria university hospital. The study included 100 cases that divided into 4 groups: A) Children with Normal anion gap and normal sodium. B) Children with High anion gap and normal sodium. C) Children with High anion gap and hypernatremia. D) Children with Normal anion gap and hypernatremia.*

Results: *There was a statistically significant difference between the studied groups as regard Serum electrolyte test results, Outcome and Pediatric disease severity indices.*

Conclusion: *We concluded that patients with corrected high anion gap as well as with hypernatremia have poor prognosis and outcome. They also have high mortality rate than those with normal anion gap and normal serum sodium.*

Keywords: *Serum Anion Gap; Hypernatremia; Pediatric Intensive Care Unit.*

INTRODUCTION

To improve the quality of pediatric intensive care unit (PICU) care, mortality prediction is important. However, estimation of mortality is difficult in critically ill patients whose condition may deteriorate **Sridharan, Aadhavi,**

et al. (2022). There are some invasive methods to assess the status of patients, such as pulmonary artery wedge pressure measurement, but these take time to institute and have side effects, such as infection **Saxena, Abhinav, et al. (2020)**.

Recently developed assessments based on physiologic variables have limitations related to the high proportion of missing data, because the variables required are not collected for all patients admitted to ICU or not required for direct patient management. Therefore, it is necessary to identify noninvasive, easy tools for mortality prediction in ICUs, especially for pediatric ICU (PICU) patients **Morrow, Brenda et al. (2021)**.

Hypernatremia indicates a serum sodium level above 145 mmol/L. It represents a state of total body water deficiency in absolute or relative to total body Na and potassium. **Moradi, Asaad et al. (2020)**, The most common cause of hypernatremia is the net water loss, which can be further subcategorized into renal and non-renal losses **Tinawi, Mohammad et al. (2020)**.

Anion gap (AG) is traditionally one of the most commonly used biomarkers. It is the simplest mean for evaluating the acid-base status of patients, and is calculated from the difference between the measured concentration of serum cations and anions. It helps to identify the presence and causes of metabolic acidosis **Cheng, Bihuan, et al. (2020)**.

In addition, calculation of an initial serum AG in adult patients admitted to ICU has been suggested as a sensitive and specific tool to predict prognosis or mortality **Perman, Sarah et al. (2020)**.

An elevated AG is also associated with increased in-hospital mortality compared with patients having a normal AG. However, there is lack of data related to pediatric patients. In pursuit of better mortality prediction and proper management of patients in PICU, research on AG as a mortality predictor is meaningful **Khawaja, Shabnum, et al. (2019)**.

The aim of this study was to investigate a number of variables linked to mortality in hospitalized kids admitted to PICUs. We specifically looked into whether serum anion gap level and hypernatremia at the time of PICU admission are a reliable predictor for mortality and how well it performed in comparison to other mortality prediction models.

Ethical considerations:

1. An informed consent was taken from all parents before getting involved in study.
2. Confidentiality of all data was ensured.
3. The study was done after approval of ethical committees of Pediatrics department & faculty of medicine for Al-Azhar University.
4. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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6. The patient has the right to withdraw from the study at any time.

Sample size:

This study base on study carried out by Farias et al. used to calculate the sample size by considering the following assumptions:- 95% two-sided confidence level, with a power of 80%. & α error of 5%. The final maximum sample size taken from output was 94. Thus, the sample size was increased to 100 subjects to assume any drop out cases during follow up.

PATIENTS AND METHODS

This prospective study was conducted at pediatric intensive care units at Bab El-Sheria university hospital. The study included 100 of critically ill patients including comatose, pneumonic with respiratory distress, post traumatic, acute and chronic kidney failure, uncontrolled epileptic patients.

Inclusion Criteria: critically ill patients admitted to pediatric intensive care unit at Bab El-Sheria university hospital aged over 1 month and under 18 years of age.

Exclusion Criteria: Patients who were discharged or died within 24 hours of PICU admission were excluded and Neonates, patients with cardiac diseases, and patients requiring post-operative care were admitted to and treated in separate specialized units, and were thus excluded from this study.

Study procedures: For all patients who fulfilled the inclusion criteria in the absence of the exclusion criteria, the following data will be collected as follows:

1. **History taking:** Detailed history of age, sex, complaint, history of present illness onset, course, duration, relevant past

and family history and history of, underlying etiology, reasons for admission, and requirement for mechanical ventilation within 24 hours of PICU admission.

2. **Physical examination:** general examination including vital data of patients (heart rate, blood pressure, temperature, respiratory rate) and systematic examination including chest stressing on air entry bilateral, central nervous system stressing on conscious level and abnormal movements, cardiovascular system and abdominal examination.
3. **Laboratory evaluation including:**
   - Arterial blood gases.
   - complete blood counts using sysmex kx 21N.
   - C-reactive protein.
   - serum electrolytes as serum sodium (Na), potassium (k) and chloride (Cl).
   - liver and kidney function tests.
4. **Pediatric Index of Mortality:**

(PIM) 2 and PIM 3 were recorded at admission, and the Pediatric Risk of Mortality III (PRISM III) was recorded at 24 hours after admission to PICU. PIM and PRISM III scores were calculated on the basis of required variables of each. And then PIM2 and PIM3 were expressed as 'logit-probability' based on the logistic regression equation for the derived scores. But PRISM III was expressed as calculated scores.

Statistical analysis: The collected data were coded, tabulated, and statistically analyzed using SPSS (Statistical Package for Social Sciences) software version 25.0. Descriptive statistics were conducted by median and interquartile range (IQR) for nonparametric quantitative data and by number and percentage for categorical data. Kolmogorov Smirnov test was used for data distribution. For non-parametric quantitative data, the analyses were done between the two groups using Mann Whitney test. For qualitative data, the analyses were done using Chi square test (if less than 20% of cells had expected count <0.05).

The study cases were divided into 4 groups:

A. Children with Normal anion gap and normal sodium.

B. Children with High anion gap and normal sodium.

C. Children with High anion gap and hypernatremia.

D. Children with Normal anion gap and hypernatremia.

RESULTS

Our results will be demonstrated in the following tables:

Table (1): Demographic and clinical data of cases

	Group A (n= 20)	Group B (n= 56)	Group C (n= 20)	Group D (n= 4)	Test of sig.	P
Gender Male/ female	12/8	26/30	12/8	3/1	X2= 0.524	0.469
Age (months)	45.64 ± 36.97	37.29 ± 16.66	54.95 ± 41.04	45 ± 59.57	F=1.083	0.375

This table showed that Regarding Gender, Age (Months), There was no statistically significant difference between the studied groups (p= 0.375, 0.469 respectively).

Table (2): vital data of studied cases

	Group A	Group B	Group C	Group D	Test of sig	p
Respiratory rate	45.85 ± 12.37	47.91 ± 10.55	44.8 ± 12.54	55.5 ± 13.96	F= 0.679	0.640
Temperature	37.67 ± 0.78	38.2 ± 0.94	37.78 ± 0.86	38.58 ± 0.83	F= 1.631	0.159
Heart rate	121.75 ± 22.1	133.79 ± 22.77	134.3 ± 20.63	146.25 ± 23.80	F= 1.264	0.286
Systolic blood pressure	95.55 ± 7.87	99.82 ± 8.13	99.65 ± 8.27	104.5 ± 9.61	F= 1.188	0.321
Diastolic blood pressure	57.05 ± 3.62	60.16 ± 3.68	59.80 ± 3.79	62.75 ± 4.19	F= 2.682	0.026

There were no statistically significant differences among the studied groups regarding respiratory rate, temperature, heart rate and systolic blood pressure (p= 0.64, 0.159, 0.286 and 0.321 respectively) but there was statistically significant difference of diastolic blood pressure among the studied groups (p= 0.026).

Table (3): Final diagnosis among studied cases

	Group A	Group B	Group C	Group D	Test of sig	p
Pneumonia	10 (50%)	35 (62.50%)	13 (65%)	3 (75%)		
Diabetic ketoacidosis	1 (5%)	14 (25%)	3 (15%)	0 (0%)	X2= 3.342	0.647
Epilepsy	2 (10%)	2 (3.57%)	3 (15%)	1 (25%)		
Acute kidney injury	1 (5%)	2 (3.57%)	1 (5%)	0 (0%)		
Chronic kidney injury	0 (0%)	1 (0%)	0 (0%)	0 (0%)		
Trauma	2 (10%)	2 (3.57%)	0 (0%)	0 (0%)		
Post-operative	4 (20%)	0 (0%)	0 (0%)	0 (0%)		

There was no statistically significant difference between the studied groups Regarding Final diagnosis, (p= 0.647).

Table (4): Laboratory data of studied cases

	Group A	Group B	Group C	Group D	Test of sig	p
Haemoglobin	10.62 ± 1.79	10.42 ± 1.31	11.07 ± 1.61	11.65 ± 0.88	F = 0.95	0.453
Total leukocyte count	16.42 ± 5.84	16.02 ± 4.28	17.07 ± 6.49	21.93 ± 8.05	F = 0.974	0.438
Platelets	399.95 ± 99.97	447.82 ± 105.38	427.85 ± 87.95	392 ± 47.19	F = 0.814	0.543
C-Reactive Protein (CRP)	120.53 ± 118	133.62 ± 115.16	140.6 ± 113.75	191.2 ± 125.31	F = 0.256	0.936
Sodium (Na)	138.6 ± 4.56	138.79 ± 3.87	152.75 ± 5.39	148 ± 1.41	F = 34.515	<0.001
Potassium (K)	3.58 ± 0.64	3.66 ± 0.58	3.3 ± 0.52	2.78 ± 0.3	F = 2.587	0.031
Chloride (CL)	107 ± 2.51	105.46 ± 2.04	106.55 ± 1.7	108.75 ± 0.5	F = 3.288	0.009
Anion gap	10.54 ± 1.44	20.51 ± 5.87	28.88 ± 8.1	9.08 ± 3.04	F = 22.422	<0.001
Arterial blood gases:						
pH	7.3 ± 0.12	7.16 ± 0.16	7.12 ± 0.18	7.22 ± 0.14	F = 3.258	0.009
CO2	42.5 ± 12.06	41.75 ± 12.74	44.65 ± 18.84	56.25 ± 12.89	F = 0.843	0.523
HCO3	24.77 ± 5.3	16.42 ± 7.44	17.14 ± 9.37	28.15 ± 2.32	F = 5.114	<0.001

There was no significant difference regarding hemoglobin level, total leukocytic count, platelets, CRP.

Regarding potassium, chloride levels there was significant difference and highly significant difference regarding sodium and anion gap (p= <0.001).

Regarding pH there was a significant difference, and Hco3, there was a highly significant difference between the studied groups (p=<0.001).

Table (5): Pediatric disease severity indices of study cases

	Group A	Group B	Group C	Group D	Test of sig	p
PIM-2	6.43 ± 1.78	6.74 ± 1.37	7.24 ± 2.05	8.62 ± 1.07	F = 1.510	0.194
PIM-3	1.66 ± 0.29	1.69 ± 0.26	1.83 ± 0.4	1.92 ± 0.22	F = 1.215	0.308
PRISM IV	2.75 ± 0.97	2.89 ± 0.78	3.6 ± 0.68	4 ± 0.82	F = 3.9	0.003

Regarding PIM-2, PIM-3 there was no statistically significant difference while Regarding PRISM IV; there was a significant difference between the studied groups.

Table (6): Outcome among study cases

	Group A (n= 20)	Group B (n= 56)	Group C (n= 20)	Group D (n= 4)	Test of sig	p
Survived	**18 (90%)**	**40 (71.43%)**	**7 (35%)**	**3 (75%)**		
Died	**2 (10%)**	**16 (28.57%)**	**13 (65%)**	**1 (25%)**	X2 = 9.597	0.002

This table showed that Regarding Outcome, there was a significant difference between the studied groups.

Table (7): Outcome in relation to serum sodium and corrected anion gap

	Hypernatremia (n= 24)	Normal serum Na (n= 76)	Test of sig.	P
Survived	10 (41.67%)	58 (76.32%)		
Died	14 (58.33%)	18 (23.68%)	X2 = 10.064	0.002
	Corrected high anion gap (n= 76)	**Normal anion gap (n= 24)**	**Test of sig.**	**P**
Survived	47 (61.84%)	21 (87.50%)		
Died	29 (38.16%)	3 (12.50%)	X2 = 5.518	0.019

Regarding outcome, there was a significant difference in between the normal and high serum Na concentrations groups (p= 0.002) and in between normal and high corrected anion gap groups (p= 0.019).

DISCUSSION

The current study did not find any statistically significant difference between the studied groups regarding the gender and age (p= 0.469 and 0.375) respectively. The mean age (month) was 42.8±39.8 and male were 53%. Compared with **Ishaque et al. (2021)** who aimed to determine the frequency and predictors of poor outcome of metabolic acidosis in children on admission in the first 24 hour of PICU. Their study included 200 children. The mean age was higher than our study 63.20±61.31 versus to 42.8±39.8 months while with **Mirza et al. (2020)** with total of consecutive 572 patients were approached for their study; The mean age of the participants was lower than our study 27±33 versus to 42.8±39.8 months.

Also, **Labib Youssef et al.** who reported that there was no significance between the studied groups regarding age, weight and sex and final diagnosis.

Also showed that there were no statistically significant differences among the studied groups regarding respiratory rate, temperature, heart rate and systolic blood pressure (p= 0.64, 0.159, 0.286 and 0.321 respectively) but there was statistically significant difference of diastolic blood pressure among the studied groups (p= 0.026).

Our study showed that blood picture test results among the study population. Regarding Hb, WBCs, platelets There was no statistically significant difference between the studied groups (p= 0.453), (p= 0.438), (p= 0.543) respectively. Arterial blood gases test results among the study population. Regarding pH, there was a significant difference between the studied groups (p= 0.009). Regarding Co2, there was no statistically significant difference between the studied groups (p= 0.523). Regarding Hco3, there was a highly significant difference between the studied groups (p= <.001).

Our results supported with **Zingg et al.** who reported that Acid–base disorders are frequently identified in critically ill patients and may be associated with increased mortality.

Also, **Denver D. Brown et al.** who studied relationship between Low Serum Bicarbonate and CKD Progression in Children reported that in children with glomerular diseases low bicarbonate was linked to a higher risk of CKD progression.

Our study showed that serum electrolyte test results among the study population. Regarding Na, there was a highly significant difference between the studied groups (p= <.001). Regarding K, there was a significant difference between the studied groups (p= 0.031). Regarding Cl, there was a significant difference between the studied groups (p= 0.009). Regarding anion gap, there was a highly significant difference between the studied groups (p= <.001).

Our current study found that the serum cAG calculated at the time of PICU admission was higher in non-survivors 29 out of 32 (90.06%) than in survivors 3 out of 32 (9.84%) and was an independent predictor of mortality in PICU patients so, Increased cAG was associated with in-hospital mortality This in agreement with previous study **Cheng et al. (2020)** who reported that higher AG was a significant predictor of 30-day, 90-day, and 365-day all-cause mortality and they concluded that a positive correlation between AG and all-cause mortality in these patients after adjusting for potential confounders such as lactate, pH, and bicarbonate. Moreover, our results supported with **Feldman, M., Soni, N. J., & Dickson, B. (2006)** who aimed to. examine the relationship between chloride and bicarbonate before and after adjusting for anion gap and serum sodium concentration. Their results showed that there was a significance between the studied groups regarding anion gap, Cl, K, and Na.

The ROC curve indicated that cAG has acceptable discrimination for predicting in-hospital mortality. The AUC value was found to be 0.608 (95% CI 0.646–0.698) with high sensitivity (90.6%) but low specificity (30.9%) and these results approximate the results of Jun **Chen and Chuxing Dai study, 2022**.

In our current study hypernatremia was found in critically ill children with severe dehydration, acute kidney injury, and septic shock. Those patients have poor prognosis with high mortality rate.

Our results supported with **Michael L. Moritz et al. (2005)** about changing pattern of hypernatremia in hospitalized children who reported that the mortality among critically ill patients with hypernatremia was 10 times higher than the mortality among patients without hypernatremia admitted to intensive care unit during 1-year period.

In our study, Pediatric disease severity indices among the study population. Regarding PIM-2, There was no statistically significant difference between the studied groups (p= 0.194). Regarding PIM-3, There was no statistically significant difference between the studied groups (p= 0.308). Regarding PRISM IV, there was a significant difference between the studied groups (p= 0.003).

Siddique et al. who demonstrated PRISM IV to have a good discriminative and predictive ability with an area under the ROC curve of 0.885 and 0.780, respectively.

Moreover, **Murray M. Pollack et al.** who studied The Pediatric Risk of Mortality Score Concluded that the new Pediatric Risk of Mortality IV algorithm for survival and death has excellent prediction performance.

CONCLUSIONS

We concluded that patients with:

1- Corrected high anion gap as well as with hypernatremia have poor prognosis and outcome. They also have high mortality rate than those with normal anion gap and normal serum sodium.

2- Serum anion gap level and hypernatremia at the time of PICU admission are a reliable predictor for mortality.

RECOMMENDATION

- Mandatory evaluation for serum electrolytes and anion gap for critically ill patients in PICU.
- Further studies are needed with large scale to confirm these results.

LIMITATIONS

- Refusal of some parents.
- Withdrawal of some cases.

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