

Corrected Anion Gap and Hypernatremia as Predictors of Mortality in Pediatric Intensive Care Unit, Minia University Hospital: A Retrospective Study

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Abstract

Background

Hypernatremia commonly occurs in ICUs, mostly developing soon after admission. It has been associated with prolonged ICU stay and has a mortality rate of 40–60%. The aim of our study is to estimate the values of serum anion gap (AG), corrected anion gap (CAG), and hypernatremia for an early prediction of mortality in pediatric intensive care units (PICUs).

Materials and Methods

This retrospective comparative study used data collected from the records of children admitted to the PICU at Minia University Hospital between June, 2017 and June, 2019.

Results

Patients were from 1 month to 18 years old. ROC curve analysis for the prediction of mortality showed the cutoff point of Na >154 (64.04% sensitivity and 79.75% specificity) and of cAG > 42.1 (57.37% sensitivity and 70.25% specificity).

Conclusion

Ventilation, respiratory failure, severe and moderate GCS, PH, CO₂, anion gap, high cAG, hypernatremia, K, CL, CRP, PLT, and creatinine were significant predictors of mortality among children admitted to the PICU.

Key Words: Anion gap, Corrected anion gap, Hypernatremia, Pediatric Intensive Care Unit.

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1- INTRODUCTION

A pediatric intensive care unit (PICU) is a physical unit exclusively designed for the treatment of pediatric patients with severe illnesses or life-threatening conditions. An early and comprehensive intervention for the patients in the intensive care units would reduce mortality, morbidity, and their length of stay (1). Caring for critically ill children is one of the most challenging aspects in pediatrics. Here, the aim is promoting the early intervention, quality care, and achieving good results and a better prognosis with the help of well-equipped and well-staffed intensive care units (2). The anion gap is the difference between serum levels of primary measured cations (sodium Na^+ and potassium K^+) and primary measured anions (chloride Cl^- and bicarbonate HCO_3^-) (3). The anion gap (AG) is used to assess the severity of acid-base disorders. It is generally calculated by subtracting the sum of HCO_3^- and chloride from sodium:

Anion gap = sodium (Na^+) - [chloride (Cl^-) + bicarbonate (HCO_3^-)] (4).

AG must be corrected for the serum albumin level because hypoalbuminemia could affect its interpretation:

Corrected anion gap (cAG) = AG + 2.5 x (4 - albumin (g/dL)) (5).

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 (6). The most common cause of hypernatremia is the net water loss, which can be further subcategorized into renal and non-renal losses.

Renal water loss: neurogenic or central diabetes insipidus, nephrogenic diabetes insipidus, loop diuretics, or osmotic diuresis. Non-renal water loss: unreplaced insensible losses from the respiratory system, dermal loss

(sweating, burns). Gastrointestinal losses: vomiting, nasogastric drainage, diarrhea (especially osmotic diarrhea), and viral gastroenteritis are the most common gastrointestinal causes of hypernatremia (7). Hypernatremia has a prevalence of almost 30% in intensive care units and is a risk factor for poor prognosis (8). We aimed to estimate the value of serum anion gap (AG), corrected anion gap (CAG), and hypernatremia for the early prediction of mortality in the Pediatric Intensive Care Unit (PICU), Minia University Hospital, Egypt.

2- MATERIALS AND METHODS

2-1. Subjects and methods

This is a retrospective study using data collected from the records of children admitted to PICU at Minia University Hospital, Minia, Egypt, from June, 2017 to June, 2019. The study was approved by the ethical committee of the Faculty of Medicine, Minia University, with the approval received from the director of the University. Confidentiality of patients was observed by keeping their records anonymous. Before extension, this PICU had 4 beds and 4 mechanical ventilators, admitting about 300 children per year.

2-2. Subjects

This study included 653 children admitted to the PICU from June, 2017 to June, 2019. From the included children 350 were male (53.5%), and 303 female (46.4%). Patients were divided into survivors (158 children) and non-survivors (495 children) on the basis of in-hospital mortality.

2-3. Data collection

All data were collected and analyzed retrospectively including demographic and medical data; age, sex, recorded Glasgow Coma Scale on admission to PICU, length of stay in PICU, underlying etiology, cause of admission, pre- and post-surgical

condition, and necessity of mechanical ventilation.

2-4. Laboratory investigations

Routine blood samples recorded on patients' admission to PICU were immediately sent to the central laboratory of the hospital. We obtained the sample results, including: arterial blood gases, complete blood counts, serum chloride levels, serum electrolytes, renal functions, and serum albumin levels.

Both AG and cAG were calculated for every patient included in our study, as follows:

$$AG = [Na + K] - [Cl + HCO_3] \quad (4)$$

$$cAG = AG + 2.5 \times [4 - \text{albumin (g/dL)}] \quad (5).$$

The reference range for the serum anion gap is:

16 ± 4 mEq/L (if the calculation employs potassium)

12 ± 4 mEq/L (if the calculation does not employ potassium) (9).

Normal cAG values were calculated as 3–12 mEq/L using the ion-specific electrodes method (Hitachi 747 Manual; Roche Diagnostics, Sydney, NSW, Australia) (3, 10). All patients' records were included in our study with no exclusion.

2-5. 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 non-parametric 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 <5) or Fisher's exact test (if more than 20% of cells had expected count <5). Correlations between different variables were measured using Pearson's correlation coefficient. A simple logistic regression analysis of variables was conducted to predict mortality. ROC curve analysis for calculation of AUC, optimal cutoff point, sensitivity, specificity, PPV, NPV, and accuracy of Na and CAG were used for predicting the mortality. The level of significance was at (P- value <0.05).

3- RESULTS

This retrospective study used data from the records of children admitted to the PICU at Minia University Hospital, Egypt, between June, 2017 and June, 2019. This study included 653 children (survivors and non-survivors) with the age range of 1 to 156 months. The analysis of the baseline characteristics of patients admitted to PICU and their outcomes showed that out of 653 patients, 158 cases (24.2%) were improved and discharged while 495 (75.8%) died. The length of stay in the PICU varied from one to 22 days with a mean of 6.6 ± 4.4 days.

The mean length of hospital stay was significantly lower among non- survivors compared to survivors (6.5 ± 4.5 and 7.1 ± 3.9 , respectively). In 488 cases (74.7%), mechanical ventilation was required and the mortality rate among these patients was higher (86.3%). Glasgow Coma Scale showed that 402 of patients were in severe coma, 146 in moderate coma and 105 in minor coma and death rates in each scale were 78.6%, 16.6%, and 4.8%, respectively (**Table. 1**).

Table-1: Demographic and clinical data of patients admitted to the PICU and their outcome.

Variables	Sub-group	All Cases n= 653(%)	Outcome		P- value
			Survivals n=158	Non survivals n=495	
			Age group	<1 year 1-5 years > 5years	
Gender	Male Female	325(49.8%) 328(50.2%)	58(17.85%) 100(30.49%)	267(82.15%) 228(69.51%)	<0.001*
LOS (days)	Range Mean ± SD Median/IQR	(1-22) 6.6±4.4 6/(4-8)	(1-22) 7.1±3.9 6/(5-7)	(1-22) 6.5±4.5 5/(3-9)	0.007*
MV	On MV Without MV	488(74.7%) 165(25.3%)	61(12.5%) 97(58.79%)	427(87.5%) 68(41.21%)	<0.001*
Respiratory failure	Yes No	283(43.3%) 370(56.7%)	11(3.89%) 147(39.72%)	272(96.11%) 223(60.2%)	<0.001*
GCS	Median/IQR	8/(7-10)	13/(10-15)	8/(7-8)	<0.001*
GCS2	Severe <9 Moderate 9-13 Minor 13-15	402(61.6%) 146(22.4%) 105(16.1%)	13(3.2%) 64(43.83%) 81(77.14%)	389(96.76%) 82(56.1%) 24(22.8%)	<0.001*

LOS: Length of stay, MV: Mechanical ventilation, GCS: Glasgow Coma Scale.

Septicemia was the most common cause of admission in PICU (51.1%), followed by gastroenteritis, respiratory disorders, and neurological disorders (22.5%, 14.5%, and 8.6%, respectively). These had death rates of 87.43%, 80.27%, 67.37%, and 26.79%, respectively (**Table. 2**). Death as a result of sepsis accounted for 59% of all deaths, while gastroenteritis for 23.8%, respiratory disorders for 12.9%, and neurological disorders

accounted for 3% of all deaths. Hypernatremia and cAG at the time of PICU admission were higher in non-survivors than in survivors (**Table. 3**). Hypernatremia and increased cAG were associated with in-hospital mortality. Also, higher mortality rates were associated with increased C - reactive protein, increased serum creatinine level, increased CO₂, and lower PH and platelets levels (**Table. 3**).

Table-2: Causes of admission to PICU and their outcome.

Variable	Disease on admission	All Cases n= 653	Mortality	
			Survivals n=158	Non survivals n=495
			Etiology	Sepsis Gastroenteritis Respiratory CNS disorders Cardiovascular Others

CNS: Central Nervous System.

Table-3: Laboratory investigations of all patients admitted to PICU.

Parameters	Status	All Cases	Survivals	Non survivals	P-value
		n= 653	n=158	n=495	
PH	Median/IQR	7.1/(7-7.2)	7.2/(7.1-7.4)	7.1/(6.9-7.2)	<0.001*
Co2 (mm Hg)	Median/IQR	25/(18-47)	21/(18-33.3)	26/(19-52)	0.006*
HCO ₃ (mmol/L)	Median/IQR	11/(6-20)	11/(6.5-20)	11/(5.5-21)	0.375
Anion gap (mEq/L)	Median/IQR	39/(28.1-54)	31.3/(24.6-43.6)	40.2/(29.5-58.1)	<0.001*
CAG (mEq/L)	Median/IQR	42.3/(30.5-56.8)	34.4/(25.6-47.3)	43.3/(33.3-58.6)	<0.001*
CAG	Low CAG	11(1.7%)	6(54.54%)	5(45.45%)	0.017*
	Normal CAG	26(4%)	11(42.3%)	16(61.53%)	
	High CAG	616(94.3%)	142(23%)	474(76.94%)	
Na (mEq/L)	Median/IQR	155/(148-163)	149/(143-153.3)	158/(150-165)	<0.001*
Na	Hypernatremia	425(65.1%)	56(13.17%)	369(86.82%)	<0.001*
	Normonatremia	226(34.6%)	100(44.24%)	126(55.75%)	
	Hyponatremia	2(0.3%)	2(100%)	0(0%)	
K (mEq/L)	Median/IQR	3.5/(3-4.4)	4/(3.3-4.7)	3.4/(3-4.1)	<0.001*
Ca (mg/dl)	Median/IQR	1/(0.8-1.1)	1.1/(.8-1.2)	1/(0.8-1.1)	0.001*
CL (mEq/L)	Median/IQR	108/(93-111)	109/(96.8-112)	107/(93-110)	0.001*
Albumin (g/dL)	Median/IQR	3/(2.1-3)	3/(2.5-3.5)	3/(2-3)	0.104
CRP (mg/dl)	Median/IQR	48/(48-96)	12/(6-48)	48/(48-96)	<0.001*
Hb (g/dL)	Median/IQR	9.9/(9-11)	10/(9.5-11)	9.8/(9-11)	0.311
TLC	Median/IQR	12/(8.3-16.8)	12/(8-17.1)	12/(8.5-16)	0.592
PLT count $\times 10^3$	Median/IQR	234/(145-372)	330/(221.5-438.3)	190/(118-345)	<0.001*
Urea (mg/dl)	Median/IQR	33/(28-73)	30.5/(28-53)	35/(28-83)	0.092
Creatinine (mg/dl)	Median/IQR	0.7/(0.6-1.2)	0.7/(0.6-1)	0.8/(0.6-1.2)	<0.001*

Co₂: Carbon dioxide, HCO₃: Bicarbonate, IQR: Interquartile range, CAG: Corrected anion gap, Na: Sodium, K: Potassium, Ca: Calcium, CL: Chloride, CRP: C reactive protein, Hb: Hemoglobin, TLC: Total Leucocytic Count, PLT: Platelet.

There was a negative correlation between the corrected anion gap (cAG) and the length of stay in PICU ($r = -0.291$, $P < 0.001$) (**Table. 4**). Logistic regression analysis showed that male gender, ventilation, respiratory failure, severe and moderate GCS, PH, CO₂, anion gap, high cAG, hypernatremia, K, CL, CRP, and Creatinine levels were significant

predictors of mortality among children admitted to the PICU (**Table. 5**). ROC curve analysis for prediction of mortality showed that the cutoff point of Na was >154 (64.04% sensitivity and 79.75% specificity) and that of cAG was >42.1 (57.37% sensitivity and 70.25% specificity) (**Table. 6**).

Table-4: Correlation between the length of stay and corrected anion gap.

Variables	Length of stay vs. CAG (corrected anion gap)	
	Pearson's Correlation coefficient	P- value
Survivals	-0.223	0.005*
Non survivals	-0.303	< 0.001*

*: Significant difference at P value < 0.05.

Table-5: Simple logistic regression analysis for prediction of mortality.

Variables	Sub-group	OR	95% CI	P- value
Gender	Male	2.02	1.4-2.9	<0.001*
	Female	Ref.		
LOS		0.97	0.94-1.01	0.172
MV	On MV	9.99	6.63-15.05	<0.001*
	Without MV	Ref.		
Respiratory failure	Respiratory failure	16.3	8.61-30.84	<0.001*
	No respiratory failure	Ref.		
GCS		0.53	0.48-0.59	<0.001*
GCS2	Sever	100.99	49.35-206.68	<0.001*
	Moderate	4.32	2.47-7.58	<0.001*
	Minor	Ref.		
PH		0.03	0.011-0.083	<0.001*
CO2		1.014	1.006-1.023	0.001*
Anion gap		1.029	1.019-1.04	<0.001*
CAG		1.099	1.08-1.12	<0.001*
CAG	Normal CAG	Ref.	0.16-0.296	0.614
	Low CAG	0.688		
	High CAG	2.295		
Na		1.099	1.08-1.12	<0.001*
Na	Hypnatremia	5.23	3.56-7.68	<0.001*
	Normonatremia	Ref.		
K		0.86	0.74-0.99	0.038*
Ca		0.72	0.5-1.02	0.063
CL		0.978	0.96-0.995	0.013*
CRP		1.032	1.025-1.039	<0.001*
PLT		0.996	0.995-0.997	<0.001*
Creatinine		1.52	1.13-2.02	0.005*
		OR	95% CI	P value
Gender	Male	2.02	1.4-2.9	<0.001*
	Female	Ref.		
LOS		0.97	0.94-1.01	0.172
MV	On MV	9.99	6.63-15.05	<0.001*
	Without MV	Ref.		
Respiratory failure	Respiratory failure	16.3	8.61-30.84	<0.001*
	No respiratory failure	Ref.		
GCS		0.53	0.48-0.59	<0.001*

GCS2	Sever Moderate Minor	100.99 4.32 Ref.	49.35-206.68 2.47-7.58	<0.001* <0.001*
PH		0.03	0.011-0.083	<0.001*
CO2		1.014	1.006-1.023	0.001*
Anion gap		1.029	1.019-1.04	<0.001*
CAG		1.099	1.08-1.12	<0.001*
CAG	Normal CAG Low CAG High CAG	Ref. 0.688 2.295	0.16-0.296 1.041-5.058	0.614 0.039*
Na		1.099	1.08-1.12	<0.001*
Na	Hypnatremia Normonatremia	5.23 Ref.	3.56-7.68	<0.001*
K		0.86	0.74-0.99	0.038*
Ca		0.72	0.5-1.02	0.063
CL		0.978	0.96-0.995	0.013*
CRP		1.032	1.025-1.039	<0.001*
PLT		0.996	0.995-0.997	<0.001*
Creatinine		1.52	1.13-2.02	0.005*

OR: Odds Ratio, CI: Confidence Interval, Ref.: Reference, *: Significant level at P value < 0.05, LOS: Late Onset Sepsis, GCS: Glasgow Coma Scale, MV: mechanical ventilator, Na: Sodium.

Table-6: ROC curve analysis for prediction of mortality.

Variables	Na	CAG (Corrected anion gap)
Optimal cutoff point	> 154	> 42.1
AUC	0.743	0.654
95% CI	0.708-0.776	0.616-0.690
P value	<0.001*	<0.001*
Sensitivity	64.04%	57.37%
Specificity	79.75%	70.25%
PPV	90.8%	85.8%
NPV	41.4%	34.5%
Accuracy	67.8%	60.5%

CI: Confidence Interval, PPV: positive predictive value, NPV: negative predictive value, ROC: receiver operating curve, Na: sodium, AUC: area under the curve.

4- DISCUSSION

Hypernatremia is defined as a serum sodium level above 145 mmol/L. It is a frequently encountered electrolyte disturbance in the hospital settings and has an unappreciated high mortality (6, 11). The mortality rate of hypernatremia can be as high as 40–60%. It commonly occurs in

ICUs, mostly developing after admission, and has been associated with increased mortality and prolonged ICU stay (12). This retrospective comparative study used data collected from the records of children admitted to the PICU at Minia University Hospital, Egypt, during the period between June, 2017 and June, 2019. Patients' ages ranged from 1 month to 18 years. The

study aimed to estimate the value of serum anion gap (AG), cAG, and hypernatremia for the early prediction of mortality in the pediatric intensive care unit (PICU). Data were gathered from the medical files and statistically analyzed after the permission of the ethical committee. The mortality rate in this study was 75.8% (495/653), comparable to the 72% reported by El Hamshary et al. (2017) (13). However, a study in Cairo University Hospital reported a mortality rate of 33.1% (Rady, 2014) (14) and an Indian study reported a mortality of 4.1% (Sahoo et al., 2017) (2).

Different mortality rates in these studies (2, 13, 14) can be due to the different criteria of admission, infection control measures, nursing staff experiences, and equipment facilities. Generally, the PICUs in developed countries have lower mortality rates than developing countries (15). Regarding the age distribution, the majority of admitted patients in our PICU were younger than one year (74.7%), while 20.1% of children were 1 to 5 years old and 5.2% were older than 5 (Table. 1). These results are consistent with Sahoo et al. (2017) in Eastern India, who reported that children admitted to their PICU were only those with a weight less than 10 kg because of the presence condition of ventilation facilities (2).

Of the total of 653 pediatric patients included in our study, 50.2% were females and 49.8% males. This female predominance was contradictory to Sahoo et al. (2017) whose patients were predominantly male 61.3% (2). In our study, however, the mortality rates were higher among males than females (82.15% vs. 69.51%, respectively) (Table. 1). That is comparable to the studies by Nyirasafari et al. (2017) in Kigali, Rwanda, who reported increased mortality rates in male patients (13), and Rashma et al. (2018) in Kerala, South India, who reported that 52 male patients died of the total 100 dead patients (16).

The mean length of stay in our PICU was 6.6 ± 4.4 days, which was significantly lower among non-survivors compared to survivors (6.5 ± 4.5 vs. 7.1 ± 3.9 , respectively) (Table 1). Sahoo et al. (2017) reported a shorter stay (3.7 ± 2.5 days) in their PICU in Eastern India (2). Many factors may influence the length of stay; including disease severity, medical treatment effect, admission and discharge criteria, and hospital resources (17). The mortality rate of our ventilated children was 87.5%, which is a very high (Table 1).

This rate is worse than the 62.5% survival rate reported by of Sahoo et al. in Eastern India (2). In contrast to our results, Rashma et al. (2018) in Kerala, South India, reported that among 100 deaths, only 26% of the children needed mechanical ventilation (14). In developed countries, the overall mortality rate in mechanically ventilated patients in PICUs is <2% (18). The most common cause of admission in our PICU was septicemia (334 patients, 51.1%), followed by gastroenteritis (147 patients, 22.5%), respiratory disorders (95 patients, 14.5%), and neurological disorders (56 patients, 8.6%) (Table 2).

Similarly, Sahoo et al. (2017) reported infectious diseases (20.7%) followed by respiratory (19.1%) and central nervous system diseases (14.3%) as the three most common causes of admission to their PICU (2). Improper cleaning, ignorance, poverty, crowding, and poor sanitation are the most common causes of our high sepsis rates. In contrast to our study, Rady (2014) reported pneumonia and other respiratory disorders followed by encephalopathy as the major causes of admission to PICU in Cairo University Hospital (14). Also, Nyirasafari et al. (2017) in Kigali, Rwanda, reported that admission data included diagnoses of respiratory failure (54%), gastrointestinal (GI) syndromes (11%), and septic shock (9.4%) (15).

The differences in disease patterns may be due to the prevalence of different diseases in different areas in Egypt. Other studies from Bangladesh and Pakistan reported different patterns of diagnosis. They reported that bronchopneumonia (21%), acute bacterial meningitis (16%), septicemia (10.1%), and encephalitis (4.2%), Guillain-Barre syndrome (11.8%), and surgical complications (15.1%) accounted for the largest number of cases (20, 21). Sepsis and respiratory system infection were associated with the highest mortality. The mortality and morbidity of sepsis remain high despite widespread advances in treatment (2). Rashma et al. (2018) in Kerala, South India, reported cardio-pulmonary arrest (29%), sepsis (19%), pneumonia (16%), multiple organ dysfunction syndrome (MODs) (14%), liver disease (7%), inborn error of metabolism (6%), adult respiratory distress syndrome (ARDS) (6%), and acute renal failure (ARF) (3%) had the highest mortality rates (16).

The mortality rate in our study was 75.8% (495/653) (Table 1), comparable to the 72% reported by El Hamshary et al. (2017) from Cairo University Hospital (13). However, another Egyptian study done by Rady (2014) from Cairo University Hospital reported a mortality rate of 33.1% (17). Nyirasafari et al. (2017) in Kigali, Rwanda, reported an overall mortality of 50% (15). The study by Sahoo et al. (2017) in Eastern India reported a mortality of 4.1% (2). We conducted this study to determine whether cAG and hypernatremia on admission could predict the patient mortality in the PICU. Comparing survivals and non-survivals, our study determined that, regardless of the underlying etiology, an increased cAG and hypernatremia on admission to the PICU were strongly associated with in-hospital mortality (76.94% and 86.82%, respectively) with P-values = 0.017 and P-value <0.001, respectively, (Table 6-7).

Our results are consistent with Kim et al. (2017) in Yonsei University, in Seoul, Korea, who reported that cAG and hypernatremia on admission were significantly higher in non-survivals than in survivals (5). We also studied other less critical yet significant predictors of high mortality rates, including increased C-reactive protein, increased serum creatinine level, increased CO₂, lower PH levels and patients with thrombocytopenia. There were significant differences in their median values (P-value <0.001). Other studies compared traditional biomarkers, such as pH, base excess, or lactate to assess acid-base disorders and prognosis in critically ill patients. Measuring pH can determine acidosis, which in turn might be an independent predictor of mortality because of its deleterious effects on homeostasis. However, their reliability has not been established so far (21). Therefore, reassessing the clinical application of AG and hypernatremia is the easiest and most readily available way to calculate acid-base disequilibrium (5).

Quantitative approaches to acid-base disturbances have been increasingly applied to the clinical practice. Their aim is to provide information about unmeasured anions or strong ion differences for quantitative evaluations of acid-base derangements in ICU (22). AG is a traditional tool to assess acid-base status and aid the differential diagnosis of metabolic acidosis. An elevated cAG usually reflects the presence of metabolic acidosis caused by overproduction or decreased excretion of organic acids (5). However, several biomarkers, such as delta neutrophils index (DNI) (23), CRP (24), procalcitonin (25), thrombocytopenia (26), and eosinopenia (27) have been suggested for use in PICU. In terms of the multivariable logistic regression analysis for mortality prediction, our study showed that ventilation, respiratory failure, severe and moderate GCS, pH, Co₂, high AG,

high cAG, hypernatremia, K, Cl, CRP, PLT, and creatinine levels were the most significant predictors of mortality among children admitted to our PICU (P-value <0.001) (Table 5). A similar logistic regression analysis by Kim et al. (2017) in Yonsei University, Korea, showed that cAG and hypernatremia on admission were the strongest predictors of in-hospital mortality (5).

5- CONCLUSION

Corrected anion gap is more accurate than anion gap in prediction of mortality. Elevated CAG and hypernatremia on admission were associated with higher mortality rate in PICU. Also, sepsis and central nervous system affection were associated with higher mortality.

6- AUTHORS' CONTRIBUTIONS

Reem A. Abdel Aziz, Yomna E. Hamdy and Mohamed F. Afify conceived the study, carried out its design, coordinated the implementation, helped to perform the statistical analysis and drafted the manuscript. RA designed the study, participated in the analysis and interpretation of data and revised the statistics and final draft of the manuscript. All authors read and approved the final manuscript.

7- CONFLICT OF INTEREST: None.

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