นิพนธ์ต้นฉบับ

ความสัมพันธ์ของค่าการพยากรณ์ของคอร์เรคเตดแอนไอออนแกปและการเสียชีวิตในผู้ป่วยเด็กวิกฤต

กัญฑิมาศ สิทธิกูล

กลุ่มงานกุมารเวชศาสตร์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี วิทยาลัยแพทยศาสตร์ มหาวิทยาลัยรังสิ

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บทคัดย่อ

ความเป็นมา: ตัวพยากรณ์การเสียชีวิตในหอผู้ป่วยวิกฤตเด็กมีความสำคัญอย่างยิ่งต่อการปรับปรุงผลการรักษาของผู้ป่วย คอร์เรคเตดแอนไอออนแกปถือเป็นตัวชี้วัดทางชีวภาพแบบดั้งเดิม สามารถทำได้ง่ายและถูกใช้เป็นตัวทำนายในผู้ป่วยวิกฤตผู้ใหญ่ อย่างไรก็ตามการศึกษาในผู้ป่วยเด็กยังมีค่อนข้างน้อย

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ระหว่างคอร์เรคเตดแอนไอออนแกปกับการเสียชีวิต

วิธีการศึกษา: observative study ศึกษาในเด็กอายุระหว่าง 1 เดือนถึง 15 ปี ที่เข้ารับการรักษาในหอผู้ป่วยเด็กวิกฤตสถาบันสุขภาพเด็กแห่งชาติมหาราชินีเป็น โดยเก็บข้อมูลพื้นฐาน โรคประจำตัว ผลตรวจทางห้องปฏิบัติการ (ค่าความเป็นกรดด่าง ระดับเกลือแร่ในเลือด อัลบูมิน คอร์เรคเตดแอนไอออนแกป และแลคเตท) ตั้งแต่แรกรับ

ผลการศึกษา: ผู้ป่วยทั้งหมด 235 ราย มีค่าอายุมัธยฐานที่ 25 เดือน อัตราการเสียชีวิตอยู่ที่ร้อยละ 3.8 แบ่งผู้ป่วยออกเป็นกลุ่มผู้รอดชีวิตและผู้ไม่รอดชีวิต พบว่า อายุ เพศ เหตุผลในการเข้ารับการรักษา และโรคประจำตัวไม่มีความแตกต่างกันระหว่างทั้งสองกลุ่ม กลุ่มที่ไม่รอดชีวิตมีคะแนน PRISM III (p value 0.023) คอร์เรคเตดแอนไอออนแกป (p value 0.009) และระดับแลคเตต (p value 0.001) สูงกว่าอย่างมีนัยสำคัญ ในการวิเคราะห์พหุตัวแปร ไม่พบความสัมพันธ์ระหว่างคอร์เรคเตดแอนไอออนแกปกับอัตราการเสียชีวิต

สรุป: คอร์เรคเตดแอนไอออนแกปมีค่าสูงในกลุ่มผู้ไม่รอดชีวิต แต่ไม่มีความสัมพันธ์กับการเสียชีวิตอย่างมีนัยสำคัญ

คำสำคัญ: คอร์เรคเตดแอนไอออนแกป แอนไอออนแกป การเสียชีวิต ค่าการพยากรณ์ หอผู้ป่วยเด็กวิกฤต

Association between corrected anion gap and mortality in pediatric critical illness

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Abstract

Background: The predictor for mortality in pediatric intensive care units (PICU) is crucial for improving the outcomes of patients. Corrected anion gap is traditionally a biomarker and simple to perform. It has been used as a predictive factor in critically ill adult patients. However, there is a lack of data related to pediatric patients.

Objectives: To investigate the association between corrected anion gap and mortality.

Methods: This observational study was conducted among children aged between 1 month and 15 years admitted to the PICU at Queen Sirikit National Institute of Child Health. Baseline characteristics and medical comorbidities were reviewed. Laboratory variables (pH, base excess, electrolyte, albumin, anion gap, corrected anion gap, and lactate) were measured at the time of admission.

Results: A total of 235 patients with a median age of 25 months were enrolled. The mortality rate was 3.8%. Patients were divided into the survivor and non-survivor groups. Age, gender, reason for admission, and comorbidities were not different between the two groups. The non-survivor group had a significantly higher PRISM III score (p value 0.023), corrected anion gap (p value 0.009), and lactate levels (p value 0.001).

In multivariate analysis, there was no association between the corrected anion gap and mortality.

Conclusions: The corrected anion gap was higher in the non-survivor group but had no significant correlation with mortality.

Keywords: corrected anion gap, anion gap, mortality, predictive value, pediatric intensive care unit

Introduction

The Pediatric Intensive Care Unit (PICU) is a place for critically ill patients. The mortality rate worldwide is between 2.6% and 37%.[1-3] Therefore, mortality prediction is important to improve the quality of care in the intensive care unit.

The anion gap can be calculated from the assessment of serum electrolytes. It is an inexpensive, easy-to-perform, and effective biochemical marker, commonly used to detect acid-base disorders. In a state of severe illness, metabolism and changes in the circulatory system become abnormal, leading to increased production of acid or reduced acid excretion from the body, which affects the body's acid-base balance and anion gap. However, interpreting the anion gap must be done with caution because the anion gap may appear lower in patients with low albumin levels. A decrease in albumin by 1 gram/liter will cause the anion gap to decrease by 0.25 millimoles/liter. Therefore, the anion gap will be more accurate if the albumin value is included in the calculation, referred to as the corrected anion gap.[4-6] A previous study has shown that patients with a high anion gap are associated with an increased severity of disease. Additionally, the anion gap could be used as a predictor of mortality.[7-9] However, there is a lack of studies investigating the predictive value of the corrected anion gap in critically ill pediatric patients.

Objectives

This study aimed to investigate the association between corrected anion gap and mortality.

Methods

This observational study was conducted in the Pediatric Intensive Care Unit (PICU) at Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok from November 2023 to October 2024. The study aimed to analyze patients aged 1 month to 15 years admitted to the PICU. Patients who were discharged or died within 24 hours of PICU admission, palliative care patients and insufficient medical records were excluded from the study. The study was approved by the Institute's ethics committees.

On admission to PICU, baseline characteristics, PRISM III score and medical comorbidities were assessed, including laboratory variables (pH, base excess, electrolyte, albumin, anion gap, corrected anion gap, and lactate). The anion gap was calculated as $Na - (Cl + HCO_3)$, and the corrected anion gap value as anion gap + [2.5 x (4 - albumin in g/dL)].

Statistical analysis

Mean and median were analyzed for continuous variables, and percentage was used for categorical variables. Chi-square tests were utilized for comparison between groups of categorical variables. Kruskal-Wallis tests were used for non-normally distributed continuous data, and ANOVA was used for normally distributed continuous data. Group differences associated with a p value of $\leq$ 0.05 were considered statistically significant. Univariate logistic regression was used to test for unadjusted association between factors and mortality. Multivariate logistic regression was used to test for associations between factors and mortality after adjusting for potentially confounding covariates. Independent variables with p value 0.1 in univariate models were incorporated as covariates into the multivariate regression model.

Statistical analysis was performed using SPSS Version 26 (SPSS Inc., Chicago, IL).

Results

The study was composed of 235 patients. The median age of the patients was 25 months (6-73), and 57% were male. The mortality was 3.8%. The reasons for PICU admission were respiratory failure (57%), followed by septic shock (10.6%). Patients were divided into the survivor and non-survivor groups. Baseline characteristics were shown in Table 1. Patients in the non-survivor group were older and had a higher prevalence of comorbidities, including genetic, cardiovascular, and hematological diseases. Respiratory problems were the most common diagnosis in both groups. However, sex, age, comorbidities, diagnosis, and length of PICU stay were not statistically different between the two groups. PRISM III score was significantly higher in the non-survivor group.

Table 1 Baseline characteristics

Variables	**Survivor group (n=226)**	**Non-survivor group (n=9)**	**p value**
Age (months), median (IQR)	25 (6-73)	45 (15.5-147.5)	0.154
Male, n (%)	127 (56.4)	6 (66.6)	0.544
Comorbidities, n (%)			
• Respiratory	16 (7.1)	0 (0)	0.505
• Cardiovascular	22 (9.7)	2 (22.2)	0.084

Variables	Survivor group (n=226)	Non-survivor group (n=9)	p value
• Neurological	30 (13.3)	1 (11.1)	1.000
• Hematological	10 (4.4)	2 (22.2)	1.000
• Genetics	38 (16.8)	3 (33.3)	1.000
• Renal	5 (2.2)	0 (0)	1.000
• Others (diabetes mellitus, obesity, hypothyroidism)	5 (2.2)	0 (0)	1.000
Reason for PICU admission, n (%)			
• Respiratory	130 (57.5)	4 (44.5)	0.550
• Cardiovascular	12 (5.4)	2 (22.2)	0.074
• Septic Shock	22 (9.7)	3 (33.3)	0.055
• Neurological	17 (7.5)	0 (0)	0.094
• Renal	7 (3.1)	0 (0)	1.000
• Eye Nose Throat	17 (7.5)	0 (0)	0.094
• Others (post-arrest, snake bite, anaphylaxis, severe diabetic ketoacidosis)	21 (9.3)	0 (0)	0.087
PRISM III admission, median (IQR)	4 (2-7)	7 (4-16.5)	0.023
PICU length of stay (days), median (IQR)	5 (3-9)	6 (1-17.5)	0.984

Laboratory variables (pH, base excess, electrolyte, albumin, anion gap, corrected anion gap) were measured in all recruited patients but lactate levels were assessed in 91 recruited patients. Base excess, HCO_3 levels, and albumin levels were lower in the non-survivor group but no significant difference. The non-survivor group had significantly higher anion gap, corrected anion gap, and lactate levels, as shown in Table 2.

Table 2 Laboratory profile in survivor and non-survivor groups

Variables	Survivor group (n=226)	Non-survivor group (n=9)	p value
pH	7.4 (7.30-7.42)	7.4 (7.11-7.50)	0.669
Base Excess (mEq/L), mean (SD)	-2.1 (7.41)	-6.8 (10.35)	0.068
HCO_3 (mEq/L), mean (SD)	23.3 (7.7)	18.6 (8.54)	0.077
Albumin (g/dL), median (IQR)	3.7 (3.24-4.05)	3.2 (2.47-4.01)	0.179
Anion Gap (mEq/L), median (IQR)	7.5 (4-10.6)	10.5 (7.85-15.95)	0.016
Corrected anion Gap (mEq/L), median (IQR)	8.4 (5.1-11.67)	12.5 (9.75-18.46)	0.009
Lactate (mmol/L), median (IQR)	1.8 (1.17-3.09) (n=84)	6.0 (3.59-9.91) (n=7)	0.001

Table 3 Univariate and multivariate logistic regression model to test the association of mortality and anion gap, corrected anion gap, PRISM III, and lactate.

	Univariate Analysis		Multivariate Analysis	
	odds ratio (95%CI)	p value	odds ratio (95%CI)	p value
Corrected Anion Gap	0.89 (0.82-0.97)	0.015	0.94 (0.72-1.24)	0.698
PRISM III	0.82 (0.72-0.93)	0.002	0.87 (0.76-1.00)	0.060
Lactate	0.71 (0.57-0.)	<0.001	0.81 (0.64-1.01)	0.070

Univariate and multivariate analysis

Univariate analysis showed that corrected anion gap, PRISM III, and lactate levels were associated with mortality with odds ratios of 0.89, 0.82, and 0.71, respectively. The multivariate logistic regression model was adjusted by baseline differences and incorporating all potentially confounding factors (with $p < 0.1$ in univariate logistic), including age, gender, underlying disease, base excess, and albumin. There was no association between corrected anion gap, PRISM III, lactate levels, and mortality (Table 3).

Discussion

This observational study aimed to investigate the association between corrected anion gap and mortality. All subjects were critically ill patients who were admitted to the PICU at QSNICH. The study showed higher corrected anion gap levels in the non-survivor group during admission. However, there was no association between the corrected anion gap and mortality.

Electrolyte imbalance and metabolic acidosis were common in critically ill patients. Thus, serum anion gap was used to detect those conditions. Several adult studies indicated that anion gap was associated with the outcome and had prognostic value for mortality in critical illness such as pneumococcal bacteremia,[7] acute myocardial infarction chronic,[8] major vascular injury,[10] sepsis,[11-12] chronic obstructive pulmonary disease,[13] COVID-19,[14] asthma,[15] acute kidney injury,[16] cerebral infarction,[17] and acute pancreatitis.[18] In contrast, few pediatric studies were focusing on corrected anion gap and mortality.

We found that the non-survivor group was older and admitted with respiratory failure. A similar previous study reported that patients died in an age range of 2 to 9.8 years and were commonly admitted with respiratory failure.[9] Genetic diseases had the highest prevalence of underlying diseases in the study. In contrast, the study by Uzunay BG reported a higher proportion of oncological diseases.[19] The mortality rate in this study was 3.8%, which differs from the previous studies reporting an in-hospital mortality rate of 8.6-75.8%.[9,19-21] The reason might be attributed to lower initial PRISM III scores, causing less severe, resulting in a low mortality rate in this study.

Regarding acid-base disturbance, the non-survivor group had lower levels of base excess, and HCO_3 but no statistical significance. Kim MJ indicated that base excess and HCO_3 were significantly lower in the non-survivor group.[9] However, a small number of non-survivors in this study might affect the validity of statistics. Patients in the non-survivor group had a significantly higher corrected anion gap. This finding aligned with previous studies.[19-21]

The multivariate logistic regression analysis was used to find the association between the corrected anion gap and mortality, adjusted by baseline differences and incorporating all potentially confounding factors. The result showed that the corrected anion gap was not associated with mortality, which contrasts with the previous studies. A case in point was Kim et al.'s work, in which the corrected anion gap was associated with mortality, and the cutoff value of more than 18 mEq/L could be a predictive factor for mortality (AUC = 0.72).[9] However, there were a variety of cutoff points of corrected anion gap to predict mortality. Abootty S demonstrated that the corrected anion gap > 10.5 mEq/L had

89% sensitivity and 76% specificity in predicting mortality.[20] In another study, a corrected anion gap > 18.93 mEq/L was found to increase mortality.[19] Meanwhile, research by Afify MF discovered the cutoff point of corrected anion gap > 42.1 (57.37% sensitivity and 70.25% specificity).[21] These findings suggest that cutoff, sensitivity, and specificity values were varied across studies depending on the population, the reason for admission, and the patient's severity scores. Our findings differred from previous studies, which could be attributed to a low mortality rate, fewer patients with metabolic acidosis, less severe diseases, and a small sample size.

Limitations to this study were (1) The low mortality rate might affect the validity and statistical power, thus, a larger sample size would improve the result (2) The study was conducted at a single center which limited the generalizability of the findings to other settings. To overcome these limitations, future studies should be conducted in multi-centers, enabling more comprehensive understanding of the predictive value of the corrected anion gap in a broader population.

Conclusion

The non-survivor group had significantly higher PRISM III scores and lactate levels. While the corrected anion gap was higher in the non-survivor group, it showed no significant correlation with mortality. However, we may suggest to use acid base disorder to tricker of effective management in critically ill children.

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References

1. Solomon LJ, Naidoo KD, Appel I, Doedens LG, Green RJ, Long MA, et al. Pediatric index of mortality 3 an evaluation of function among ICUs in South Africa. Pediatr Crit Care Med. 2021;22:813–21.
2. Rashma R, Remya S, Jayakumar C, Shanavas M, Manu R, Remya R. Mortality profile of children admitted to intensive care unit of a tertiary care hospital in Kerala, South India. Int J Med Clin Sci. 2018;1:13–6.

3. Humoodi MO, Aldabbagh MA, Salem MM, Al Talhi YM, Osman SM, Bakhsh M, et al. Epidemiology of pediatric sepsis in the pediatric intensive care unit of King Abdulaziz Medical City, Jeddah, Saudi Arabia. BMC Pediatr. 2021;21:1–6.
4. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med. 1998;26:1807-10.
5. Hatherill M, Sajjanhar T, Tibby SM, Durward A, Murdoch IA. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. Arch Dis Child. 2002;87:526–9.
6. Chawla LS, Shih S, Davison D, Junker C, Seneff MG. Anion gap, anion gap corrected for albumin, base deficit and unmeasured anions in critically ill patients: implications on the assessment of metabolic acidosis and the diagnosis of hyperlactatemia. BMC Emerg Med. 2008;16:8:18.
7. Balakrishnan I, Crook P, Morris R, Gillespie SH. Early predictors of mortality in pneumococcal bacteraemia. J Infect. 2000;40:256-61.
8. Sahu A, Cooper HA, Panza JA. The initial anion gap is a predictor of mortality in acute myocardial infarction. Coron Artery Dis. 2006;17:409-12.
9. Kim MJ, Kim YH, Sol IS, Kim SY, Kim JD, Kim HY, et al. Serum anion gap at admission as a predictor of mortality in the pediatric intensive care unit. Sci Rep. 2017;7:1456.
10. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. Crit Care Med. 2004;32:1120-4.
11. Dubey A, Acharya S, Kumar S, Shukla S, Mahajan S, Bawankule S, et al. Anion gap (AG) or serum lactate-in search of a better prognostic marker in sepsis a cross-sectional study in a rural tertiary care hospital. F1000Research. 2023;12:536.
12. Zhu Y, He Z, Jin Y, Zhu S, Xu W, Li B, et al. Serum anion gap level predicts all-cause mortality in septic patients: a retrospective study based on the MIMIC III database. J Int Care Med. 2023; 38:349-57.
13. Chen X, Yang Q, Gao L, Chen W, Gao X, Li Y, et al. Association between serum anion gap and mortality in critically ill patients with COPD in ICU: Data from the MIMIC IV database. Int J Chron Obstruct Pulmon Dis. 2024;19:579-87.
14. Zemlin AE, Sigwadhi LN, Wiese OJ, Jalavu TP, Chapanduka ZC, Allwood BW, et al. COVID-19 Research Response Collaboration, the association between acid-base status and clinical outcome

in critically ill COVID-19 patients admitted to intensive care unit with an emphasis on high anion gap metabolic acidosis. Ann Clin Biochem. 2023;6:86-91.

15. Wang S, Teng H, Han H, Xu Y. The relationship between albumin corrected anion gap levels and mortality in patients with asthma in the ICU. Sci Rep. 2023;13:16903.
16. Zhong L, Xie B, Ji XW, Yang XH. The association between albumin corrected anion gap and ICU mortality in acute kidney injury patients requiring continuous renal replacement therapy. Intern Emerg Med. 2022;17:2315-22.
17. Liu X, Feng Y, Zhu X, Shi Y, Lin M, Song X, et al. Serum anion gap at admission predicts all-cause mortality in critically ill patients with cerebral infarction: Evidence from the MIMIC-III database. Biomarkers. 2020;25:725-32.
18. Gong F, Zhou Q, Gui C, Huang S, Qin Z. The relationship between the serum anion gap and all-cause mortality in acute pancreatitis: an analysis of the MIMIC-III database. Int J Gen Med. 2021;14:531-8.
19. Uzunay BG, Köker A, Tekerek NU, Dönmez L, Dursun O. Role of albumin-corrected anion gap and lactate clearance in predicting mortality in pediatric intensive care patients. Balkan Med J. 2023;40:430-4.
20. Abootty S, Rao S, Shenoy VD, Ameer A. Serum anion gap versus lactate clearance as mortality predictors in critically ill children. Sri Lanka Journal of Child Health. 2024;53:26-9.
21. Afify MF, Hamdy YE, Aziz RAA. Corrected anion gap and hypernatremia as predictors of mortality in pediatric intensive care unit, Minia University Hospital: A retrospective study. Int J Pediatr. 2020; 8:12369-79.