Serum anion gap versus lactate clearance as mortality predictors in critically ill children

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Abstract

Introduction: Mortality prediction is important for optimal resource allocation in the paediatric intensive care unit (PICU).

Objectives: To estimate the predictive value of serum corrected anion gap (cAG) and lactate clearance for predicting mortality in the PICU.

Method: We conducted a prospective study of children admitted to the PICU of a tertiary hospital. PRISM III and IV score, cAG and lactate clearance were done in all patients, and the predictive value was calculated for mortality.

Results: The mortality in the study group was 12%. The cAG was significantly lower in survivors than in non-survivors ($p < 0.001$). The lactate levels at 6 hours (AUC 0.898) had the best mortality prediction, followed by admission lactate (AUC 0.804) and cAG (AUC 0.742). However, the lactate clearance did not show good predictive value.

Conclusions: The cAG is an excellent mortality predictor in a low-resource setting.

(Key words: Sepsis, Predictive value, Prognosis, Morbidity, Hyperlactataemia)

Introduction

Mortality indicators help achieve different goals like assessing patient prognosis, evaluating therapies and right resource allocation for the treatment. The clinical assessment by the physician at admission to the paediatric intensive care unit (PICU) is insufficient to predict the outcome since the clinical condition is dynamic and may deteriorate eventually in an initially stable child. Over time, different scoring systems based on physiologic and biochemical variables have been developed to help detect the severity of illness[1]. The recent scoring system is the updated Paediatric Risk of Mortality Score (PRISM IV) in which data collection improvements have been made to minimize bias and reduce potential sources of error[2]. These scoring systems have limitations related to the high proportion of missing data, because the variables required are too many, and may not be available at admission, especially in a resource poor setting. All the parameters may not be collected for all patients at admission or not required for direct patient management. Therefore, it is necessary to identify easy tools for mortality prediction in the PICU.

Corrected anion gap (cAG), the anion gap compensated for abnormal albumin levels, has been suggested as a sensitive and specific tool to predict prognosis or mortality[4]. In addition, adult patients with an initial high serum cAG have increased severity of illness, independent of concomitant electrolyte abnormalities. However, there is a lack of data related to paediatric patients. Another parameter which reflects severity of illness with significant prognostic implications is hyperlactataemia, which is an indicator of inadequate tissue perfusion, particularly in sepsis[4]. Lactate clearance, the rate of fall in lactate after resuscitation, has shown more promise in predicting mortality[5]. There are very few paediatric studies looking at lactate clearance and mortality. In pursuit of better mortality prediction with fewer parameters, research on cAG and lactate clearance as a mortality predictor is meaningful. In this study, we investigated whether serum cAG and lactate clearance measured at the admission to PICU could be a strong predictor of mortality, and their predictive value is compared with other mortality prediction models.

Objectives

To estimate the predictive value of serum corrected anion gap (cAG) and lactate clearance for predicting mortality in PICU.

Method

Inclusion and exclusion criteria: The children admitted to the PICU (aged >1 month and <13 years) between May 2020 and June 2021 were included in the study after obtaining informed written consent from parents. The sample size of 150 was derived considering the predicted death rate of 24.4% in children with PRISM III score of 10-19, with 95% CI and 5% precision Children with lactate levels >2 mmol/L were eligible for enrolment. Post-operative patients and those with inherited metabolic disease were excluded.

Baseline investigations were done and the updated PRISM IV score was calculated[2]. A heparinized syringe was used to collect venous blood for lactate estimation by Radiometer Copenhagen ABL 555 blood gas analyser. Lactate levels were estimated at admission and after six hours and the clearance was calculated as follows: Lactate clearance = [(Initial lactate – current lactate) × 100 / Initial

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lactate]. A positive value denotes clearance of lactate, whereas a negative value denotes an increase in lactate after intervention. Anion gap was calculated for every patient at admission and corrected for serum albumin to determine the cAG. AG is calculated as AG = [Na+] − ([Cl−] + [HCO3]). Corrected anion gap (cAG) = AG + 2.5 x (4 − albumin(g/dL)). All the admitted patients were followed up during the stay until discharge or death. The primary outcome was in-hospital mortality and secondary outcomes were length of PICU stay and hospital stay.

Ethical issues: The study was approved by the Institutional Ethics Committee of K S Hedge Medical Academy, Mangalore, India (No. Inst.EC/EC/123/2019-20) on 9.10.2019. Written informed consent was obtained from the parents/guardians of the study participants.

Statistical analysis: Survivors and non-survivors were compared by Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables. For nonparametric data, pairwise comparisons were made using Wilcoxon's signed-rank test. For continuous variables, we used t-test. A *p*-value <0.05 was taken as statistically significant. SPSS version 22.0 was used.

Results

A total of 150 children admitted to PICU was enrolled in the study. The mortality was 12% (18/150). Median (IQR) age among survivors and non-survivors were 5 (1, 10.2) years vs 1 (0.25, 5) years respectively. Baseline characteristics of the study population are described in Table 1. Respiratory illness was the cause of admission in 34%, followed by sepsis/ multiorgan dysfunction syndrome (MODS) (22%). Central nervous system (CNS) aetiology comprised 16% cases, which included meningitis, encephalitis, seizure disorders and intracranial space-occupying lesions. In addition, 3% were newly diagnosed cases of inborn errors of metabolism, 10% were trauma, 7% renal and 8% cases of cardiac aetiology.

It was observed that sepsis with multiorgan dysfunction was the most common cause of in-hospital mortality followed by cardiac illness.

Table 1: ***Baseline characteristics of the study group***

Characteristic	Median (IQR)
Age (years)	4 (0.62, 10)
Length of stay (days)	3 (2, 4.75)
PRISM III score	5 (1, 13.75)
PRISM IV (%)	1 (1, 5)
cAG (mEq/L)	13 (7.2, 18)
Lactate at admission (mmol/L)	2.1 (0.8, 2.8)
Lactate at 6 hours (mmol/L)	0.9 (0.3, 1.6)
Lactate clearance (%)	33 (44, 100)

The median cAG [21.5meq/L vs 13meq/L (p<0.001)] and lactate levels [8.5mmol/L vs 1mmol/L (p<0.001)] at admission was significantly higher among the non-survivor group when compared to the survivors respectively. Lactate clearance was significantly lower in those who died (-9.6%) than those who survived (41.4%) (p<0.001). The comparison of various parameters among the two groups is shown in Table 2.

Table 2: ***Comparison of variables between survivor and non-survivor group***

Variable	Survivors	Non-survivors	p-value
Lactate at admission (mmol/L)	3.4 (1)	8.5 (10)	<0.001
Lactate at 6 hours (mmol/L)	1 (1)	10 (11)	<0.001
cAG (meq/L)	13 (9)	21.5 (20)	<0.001
Lactate Clearance (%)	41.4 (72)	-9.6 (72)	<0.001
PRISM III score	3 (8)	22 (6)	<0.001
Prism IV (%)	1 (1)	34.5 (45)	<0.001
Age (years)	5 (1, 10.2)	1 (0.25, 5)	0.118
PICU stay(days)	3 (2.5, 4.5)	1 (1, 7)	0.048

With PRISM IV as the gold standard, a cAG >10.5meq/L predicted the mortality with 89% sensitivity and 76% specificity; lactate at admission of 2.5mmol/L predicted the mortality with 77% sensitivity and 80% specificity and lactate at 6 hours of 2.05 mmol/L predicted the mortality with 83% sensitivity and 93% specificity. We compared the predictive value of PRISM IV, PRISM III, cAG and serum lactate levels at 0 hours, 6 hours and the lactate clearance by ROC analysis. The ROC curves are shown in Figure 1. The lactate at admission and 6 hours showed good predictive ability with area under the curve (AUC) of 0.804 and 0.898, respectively. However, the lactate clearance did not show good predictive power with the AUC of only 0.165.

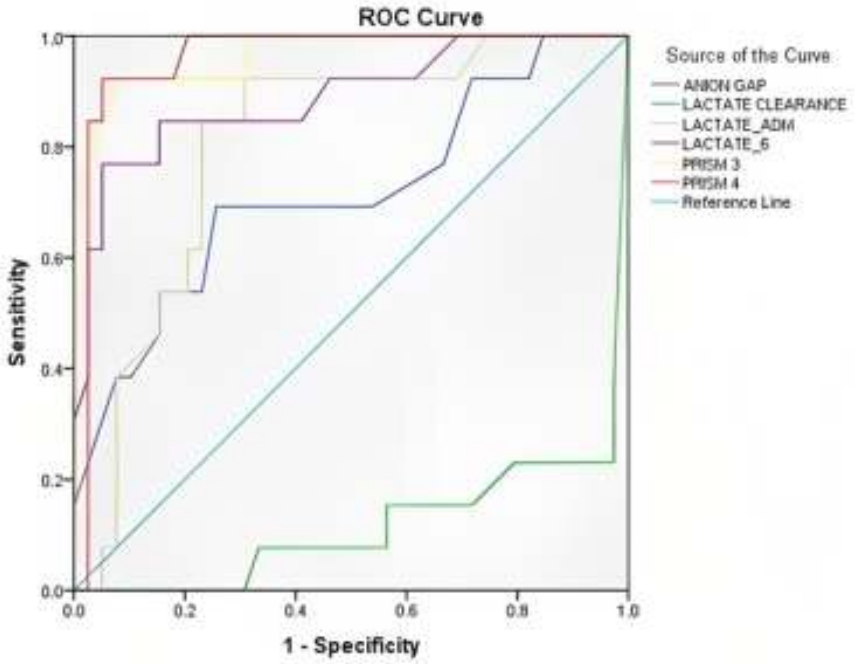

Figure 1: ***Predictive value of PRISM scores, lactate and cAG by ROC analysis***
AUC: lactate at 6 hours (LACTATE_6) - 0.898; lactate at admission (LACTATE_ADM) - 0.804; cAG – 0.742; lactate clearance- 0.165

Discussion

Our study had 150 patients admitted to PICU for a duration of one year with respiratory illness being the most common aetiology. The in-hospital mortality was 12%. We observed that the children who died had high cAG and lactate levels when compared to those who survived. The cAG and lactate levels were good mortality predictors while lactate clearance was not. The lactate at six hours post admission had the best sensitivity and specificity in predicting mortality.

Acid-base derangements are common in critically ill patients and a strong association between acidosis and increased organ dysfunction and mortality have been described in previous studies. Quantitative approaches to acid-base disturbances have been increasingly applied in the ICU to give information about unmeasured anions or strong ion differences[6]. Previous studies compared traditional biomarkers, such as pH, base excess, or lactate, as means of assessing acid-base disorders and predicting prognosis in critically ill patients[7,8]. An elevated cAG usually reflects the presence of metabolic acidosis caused by the overproduction or decreased excretion of organic acids. In addition, elevated cAG has been reported as a predictor of mortality in critically ill patients but the reliability in children has not been established yet[9,10]. Our study reassessed the clinical application of cAG, the easiest and most readily available way to calculate acid-base disequilibrium and which has been shown to be useful for mortality prediction. The cAG of greater than 10.5meq/L predicted the mortality with 89% sensitivity and 76% specificity with an AUC of 0.78. The cAG also correlated with pre-existing mortality prediction models for children like PRISM III and PRISM IV. Similar results were described by Kim MJ, *et al*[3]. in their study. We also observed that cAG could be a mortality predictor in critically ill children, regardless of the presence of metabolic acidosis or their underlying aetiology.

The utility of lactate levels for mortality prediction in the paediatric population is lacking. In a study done in adults, patients with a lactate clearance >10%, relative to patients with a lactate clearance <10%, had a lower 60-day mortality[11]. In our study, lactate level at 6 hours had the best sensitivity and specificity to predict mortality whereas the lactate clearance was a poor predictor. This finding is in concordance with a study by Ryoo SM, *et al*[8] in adults where the lactate had a significantly higher prognostic value than lactate clearance (AUC- 0.70 vs 0.65; p <0.01). Hatherill M, *et al*[13] was one of the few authors who conducted a study in the paediatric age group; he calculated clearance at 24 hours and showed that hyper-lactataemia >2 mmol/L after 24 hours was associated with 93% mortality compared to 30% with normal levels. A study by Munde A, *et al*[14] found that a lactate clearance ≤30% at six hours and PRISM score more than 30 have high prediction for mortality.

The limitation of our study was the small sample size and would require a larger cohort to validate these results. Few children with good lactate clearance after 6 hours had died after prolonged stay in the hospital due to secondary infections. This factor might have altered the statistical analysis for mortality prediction using lactate clearance. In a limited resource setting like a peripheral health centre, using PRISM scoring system or lactate may not be feasible. However, a test like the corrected anion gap, which can be estimated for any patient irrespective of underlying aetiology, can be used for prognostication and early referral.

Conclusions

The corrected anion gap is a reliable parameter for prognostication and mortality prediction. However, lactate clearance did not prove to be a valuable measure for the same.

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