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Role of Albumin-corrected Anion Gap and Lactate Clearance in Predicting Mortality in Pediatric Intensive Care Patients

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Background: Identifying mortality risk in critically ill children is central to diagnostic and treatment practices. For this purpose, scoring systems, such as the Pediatric Index of Mortality 3 (PIM 3), have been proposed; however, the role of biochemical markers, such as albumin-corrected anion gap (cAG) and lactate clearance (LC), in predicting mortality in pediatric intensive care unit (PICU) patients is yet to be explored.

Aims: To evaluate the predictive value of the cAG and LC for mortality in pediatric patients admitted to a PICU.

Study Design: Retrospective single-center cohort study.

Methods: Clinical and laboratory data from the time of PICU admission were collected, and patients were classified into based on their 0- and 6-hour of admission lactate levels into an LC(+) group (patients with normal or decreasing lactate levels) or an LC(−) group (increasing lactate levels). LC and cAG levels were compared using the Mann-Whitney U test and Student's t-test, respectively. Additionally, multiple logistic regression analysis was performed to evaluate the effect of LC and cAG on mortality.

Results: We included 825 patients in the study; the mortality rate was 8.6%. The absence of LC [adjusted odds ratio (AOR) =4.735; 95% confidence interval (CI): 2.163-10.367; $p < 0.001$], cAG (AOR =1.064; 95% CI: 1.010-1.122; $p = 0.019$) and PIM 3 (AOR = 1.871; 95% CI: 1.553-2.254; $p < 0.001$) were independent risk factors for mortality. Using the receiver operating characteristic curve analysis of PIM 3 as a predictor of mortality, area under the curve values of 0.832 (95% CI: 0.805-0.857; $p < 0.001$) for the original score and 0.858 for a revised PIM 3 score (based on the β coefficients obtained for cAG and LC; 95% CI 0.832-0.881; $p < 0.001$) were obtained, which was significantly different ($p = 0.027$).

Conclusion: A cAG value > 18 at the time of PICU admission high lactate levels which do not decrease within 6 hours of hospitalization are associated with an increased risk of mortality. The revised PIM 3 score, which includes cAG and LC, is a better predictor of mortality than the classical PIM 3 score.

INTRODUCTION

Identifying patients with a high mortality risk when dealing with critically ill children is essential to guide diagnostic and treatment practices. For this purpose, certain biomarkers and scoring systems, such as the pediatric index of mortality 3 (PIM 3), have been proposed to evaluate the risk of mortality in children[1]. The utility of a scoring system depends on its discrimination ability and calibration. The former is determined via receiver operating characteristic (ROC) analysis; an adequate discrimination ability is reflected by > 0.80 value for the area under the curve (AUC). Calibration, on the other hand, is computed by comparing the expected mortality predicted by the scoring system with the actual mortality of the target group.

Biochemically, lactate concentration levels is a valuable non-specific and indirect marker of the adequacy of oxygen delivery to tissues. Tissue hypoxia causes anaerobic metabolism and an increase in the serum lactate level.[2] In adults, a blood lactate level of > 2 mmol/l is incorporated into the definition of septic shock, as it serves as an indicator of metabolic dysfunction at the cellular level; however, the sepsis guidelines recommend repeated lactate measurement. In children, although an ideal cutoff value is yet to

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be established, lactate levels of > 4 mmol/l are strongly associated with mortality during the acute period.[3-5] A return of the lactate level to normal within the first 4 h is associated with a decreased risk of persistent organ failure.[6]

Another biochemical marker, anion gap (AG), which is defined as the difference between measurable serum cation and anion concentrations, is useful for determining the diagnosis and prognosis of many diseases.[7]. In an intensive care unit, AG is used to screen out patients with metabolic acidosis by using the mathematically calculated AG value (based on serum albumin levels) into Figge's equation.[8]. A 1 g/dl decrease in albumin causes a 2.5 mEq/l decrease in the AG. A recent study reported that combining albumin-corrected AG (cAG) values with mortality scores, such as those from the PIM 3 and PRISM III, yielded more accurate predictions of mortality than those obtained using either of these models alone.[9] Therefore, this study aimed to evaluate the role of cAG and lactate clearance (LC) for predicting mortality in pediatric intensive care unit (PICU) patients.

MATERIALS AND METHODS

This retrospective study was approved by the Clinical Research Ethics Review Board of the Akdeniz University. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and the Helsinki Declaration of 1975. We reviewed clinical records of pediatric patients admitted to a tertiary-care surgical-medical PICU over a 3-year period. Patients with an ICU stay of < 24 h, those who could not be stabilized within the first 2 h after ICU admission due to cardiopulmonary arrest, who underwent bone marrow transplantation, had a defined chromosomal anomaly, or those with missing records were excluded from the analysis.

The following data were collected for all patients: age, sex, diagnosis at hospitalization, presence of chronic disease, history of cardiopulmonary resuscitation before hospitalization, lactate level in the first 6 h of admission, cAG values, PIM 3 scores, and prognosis. The included patients were divided into two groups based on their 0- and 6-h lactate levels: LC (+) group - patients whose serum lactate level was within the normal limits at hospitalization or whose serum lactate level decreased during the first 6 h of hospitalization, and LC (-) group - patients with increased serum lactate level in the first 6 h of hospitalization. The AG was calculated as (Na + K) - (Cl + bicarbonate), and the cAG value as AG + [2.5 × (4 - albumin in g/dl)]. Electrolyte values were calculated for all patients based on standard biochemistry laboratory test results analyzed using the indirect ion-selective electrode method. Lactate and bicarbonate levels were measured using a Siemens RapidLab 1,265© blood gas analyzer, installed in our hospital's PICU; the equipment was calibrated daily.

Statistical Analysis

Statistical analysis was performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA). The two study groups were compared using the Mann-Whitney U test for LC and Student's t-test for cAG levels. A p-value of < 0.05 was considered for statistical significance. In addition to the variables included in the calculation of the PIM 3 score, the effects of LC and cAG on mortality were evaluated by logistic regression analysis. Also, Kaplan-Meier survival analysis was performed to examine the effects of LC and cAG on survival. The variance inflation factor values all variables evaluated in the logistic regression were < 5; a revised PIM 3 score was created using the obtained β coefficients. The ROC analysis was then repeated according to the revised PIM score, and the AUC for mortality was compared with the PIM 3 score. Scores were calibrated according to the Hosmer-Lemeshow goodness of fit test.

RESULTS

We screened 1,149 patients admitted to the PICU in the study period, of which 324 were excluded. A total of 825 patients were included in the study having a mean age of 46.7 months (range: 1-222 months); 45.8% of the patients were female. There were no statistically significant age- or sex-related differences between the patients who survived and those who died in the hospital ($p > 0.05$). The diagnoses at ICU admission and details of the chronic diseases in the study patients are reported in Table 1.

A comparison of the diagnoses at hospitalization between patients who did and did not survive showed that the survival rate was higher in the postoperative follow-up group while the rate of hemodynamic instability was higher in the mortality group. The majority of the patients (n = 493; 59.8%) had at least one chronic disease, with oncological and liver diseases being more common in the mortality group ($p < 0.001$). Seven patients (9.9%) who died and 17 (2.3%) who survived were hospitalized in the ICU after cardiopulmonary resuscitation ($p < 0.001$). The mean mechanical ventilation time was significantly longer in the mortality group ($p < 0.001$). However, there was no statistically significant difference between the two groups in terms of the length of ICU stay (Table 1).

The mortality rate was 8.6% in the study group. The cAG values of patients who died were significantly higher than those of patients who survived (21.84 and 18.27, respectively, $p < 0.001$). When categorized according to LC values, 685 (90.8%) of the survivors were LC (+) and 69 (9.2%) were LC (-); among the deceased patients, 48 (67.6%) were LC (+) and 23 (32.4%) were LC (-) ($p < 0.01$). There was a statistically significant difference between LC (+) and LC (-) patients as determined by Kaplan-Meier survival analysis ($p < 0.001$). The Kaplan-Meier survival analysis also showed that at a cAG value of 18.93 (sensitivity =67.6%; specificity =60.9%) was the optimal cutoff for predicting survival, i.e., the likelihood of survival decreased significantly ($p < 0.001$) for patients with cAG values exceeding 18.93 (Figure 1).

The mean (standard deviation [SD]) PIM 3 score of the mortality group was 37.87 (36.18), while that of the surviving patients was 6.04 (11.38); the difference was statistically significant ($p < 0.001$; Table 1). According to multivariate logistic regression analysis, the absence of LC [adjusted odds ratio, (AOR) =4.735; 95% confidence intervals, (CI): 2.163-10.367; $p < 0.001$], cAG (AOR =1.064; 95% CI: 1.010-1.122; $p = 0.019$), and PIM 3 (AOR = 1.871; 95% CI:

TABLE 1. Demographic characteristics.

	Survival (n = 754)	Mortality (n = 71)	p
Age (month)	73.14 (67.70)	87.04 (73.68)	0.203
Gender (female), n (%)	341 (45.20)	37 (52.10)	0.265
Reason for admission to PICU, n (%)			<0.001
Trauma	140 (18.60)	12 (16.90)	
Respiratory distress	146 (19.4)	18 (25.40)	
Congenital heart surgery	131 (17.40)	2 (2.80)	
Postoperative follow-up*	127 (16.80)	5 (7.00)	
Cognitive disorder	93 (12.30)	6 (8.50)	
Hemodynamic instability*	54 (7.20)	21 (29.60)	
Intoxication	46 (6.10)		
After CPR*	17 (2.20)	7 (9.8)	
Comorbid chronic disease, n (%)	439 (58.2%)	54 (76.1%)	<0.003
Oncological disease*	56 (12.80)	18 (33.20)	<0.001
Neuro-metabolic disease	135 (30.80)	9 (16.60)	
Renal disease	34 (7.70)	5 (9.30)	
Lower airway disease	24 (5.50)		
Immunodeficiency	18 (4.10)	3 (5.60)	
Liver diseases*	11 (2.50)	7 (13.00)	
Acyanotic CHD	137 (31.10)	6 (11.10)	
Cyanotic CHD	14 (3.20)	3 (5.60)	
Hematological diseases	10 (2.30)	3 (5.60)	
The duration of mechanical ventilation (day)	3.08 (5.52)	9.11 (7.92)	< 0.001
Length of stay in PICU (day)	6.86 (12.50)	9.8 (8.26)	0.052
Lactate clearance, n (%)			
LC (+)	685 (90.80)	48 (67.60)	< 0.001
LC (-)	69 (9.20)	23 (32.40)	
cAG	18.27 (5.72)	21.84 (7.06)	< 0.001
PIM3	6.04 (11.38)	37.87 (36.18)	< 0.001
Revised PIM3	21.21 (23.18)	58.28 (34.45)	< 0.001

*Variables with statistical significance
CHD:, Congenital heart disease,; CPR:, cardiopulmonary resuscitation,; PICU: pediatric intensive care unit; LC:, lactate clearance, cAG:, albumin-corrected anion gap

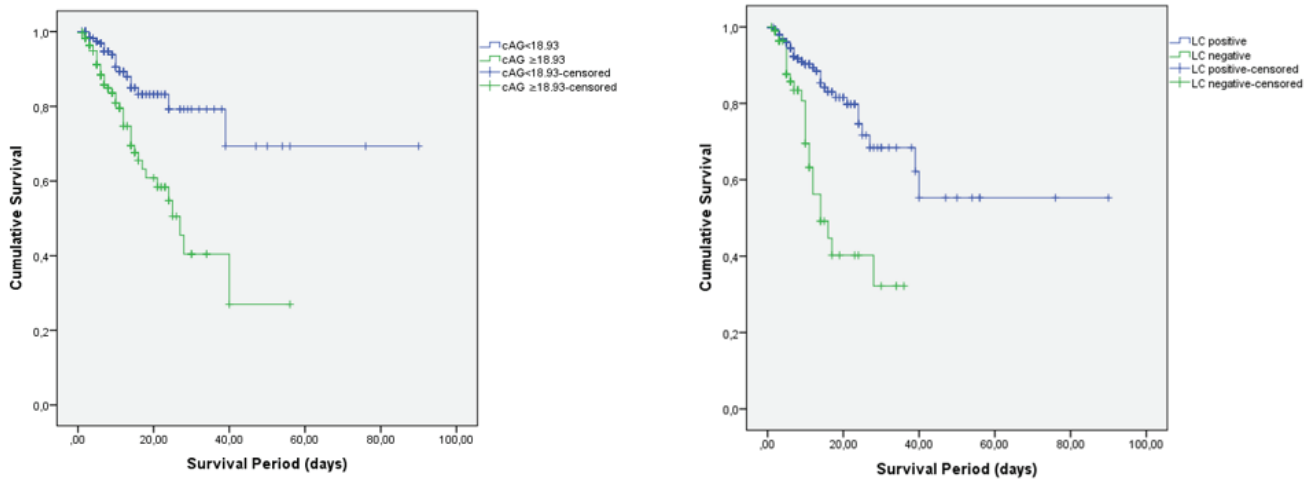

FIG. 1. Survival curves for the patients according to cut-off value of cAG (the cut-off value of initial cAG was defined by 18.93 mEq/L) and LC (p<0.001)

1.553-2.254; $p < 0.001$) were independent risk factors for mortality (Table 2).

The ROC analysis of the PIM 3 score as a predictor of mortality revealed an AUC value of 0.832 (95% CI: 0.805-0.857; $p < 0.001$). Furthermore, in the multivariate logistic regression analysis, the AUC for the revised PIM 3 score, based on the β coefficients obtained for cAG and LC, was 0.858 (95% CI: 0.832-0.881; $p < 0.001$). There was a statistically significant difference between the AUC values of the PIM 3 and revised PIM 3 scores ($p = 0.027$; Table 3, Figure 2).

Since the AUC value of both the PIM 3 and revised PIM 3 scores was > 0.8, discrimination was considered good. The Hosmer-Lemeshow goodness of fit test showed that there was no significant difference between the predicted and actual mortality obtained using the PIM 3 or revised PIM 3 score ($p = 0.087$ and $p = 0.641$, respectively). The score calibration was also good (Table 4).

DISCUSSION

Lactate is a valuable marker of tissue perfusion. Although the current sepsis guidelines do not recommend the use of blood lactate levels to classify pediatric patients with suspected septic shock or organ dysfunction as being at low or high risk of sepsis, this marker is frequently used in clinical practice for this purpose.[5] In a study that included 77 children with infection and acute organ dysfunction admitted to a pediatric emergency department, a decrease in lactate levels to < 2 mmol/l within 4 h was associated with reduced risk of permanent organ dysfunction;[6]; however, the authors also reported that LC alone did not reduce the risk. In another study with 140 PICU patients that reported a mortality rate of 16.42%, lactate normalization at 6 h was reported as a good predictor of survival (AUC =0.823, $p < 0.001$); however, the authors did not include a multiple logistic regression analysis to confirm these results.[10]. Likewise, LC was described as associated with mortality in pediatric patients with septic shock, but the study only reported the percent change in lactate level and the severity of hyperlactatemia was not considered.[11]. Nevertheless, the lactate area calculated according to periodic measurements was significantly associated with survival.[11]. Apart from this, a study followed up patients after undergoing a modified Norwood procedure and noted that the lactate level at the time of ICU admission after open heart surgery and minimum lactate level in the first 24 h postoperatively were associated with survival.[2,12] In our study with a relatively large sample size, mortality rates were significantly lower in the LC (+) group as compared to the LC (-) group patients who required hospitalization in the PICU. The mortality rate was 4.735-fold higher in LC (-) patients compared to the LC (+) patients (95% CI: 2.163-10.367; $p < 0.001$) (Table 2).

Patients with low albumin levels have a low cAG; accordingly, cAG should be calculated in critically ill children whose serum albumin levels fall below threshold values.[8] In a prospective observational study involving patients presenting with shock (defined as hypotension or prolonged capillary filling requiring fluid resuscitation or inotropic support), a relationship between the AG and mortality could not be demonstrated; notably, the study has excluded children with inherited metabolic disease and those with congenital heart disease admitted after trauma or cardiac surgery.[13]. In adult patients with sepsis, cAG was associated with 1-year mortality.[14] In another study including 461 patients hospitalized in the PICU, the cAG was significantly lower in survivors ($p < 0.001$), and a low cAG was determined as an independent risk factor for mortality as per multiple regression

TABLE 2. Results of Multiple Logistic Regression Analysis to Predict Mortality.

				95% CI AOR	
	β	p	AOR	Lower	Upper
LC (-)	1.555	**0.001**	4.735	2.163	10.367
cAG value	0.063	**0.019**	1.064	1.010	1.122
PIM3 score	0.627	**0.001**	1.871	1.553	2.254
Constant	-2.477	0.001	0.084		

LC, Lactate clearance; cAG, albumin-corrected anion gap; AOR, adjusted odds ratio; CI, confidence interval

TABLE 3. Results of the Receiver Operating Characteristic Curve Analysis for the PIM3 and Revised PIM3.

	AUC (%95 CI)	p
Revised PIM3 score	0.858 (0.832 - 0.881)	0.027
PIM3 score	0.832 (0.805 - 0.857)	

PIM 3,: Pediatric index of mortality 3 score; CI, confidence interval

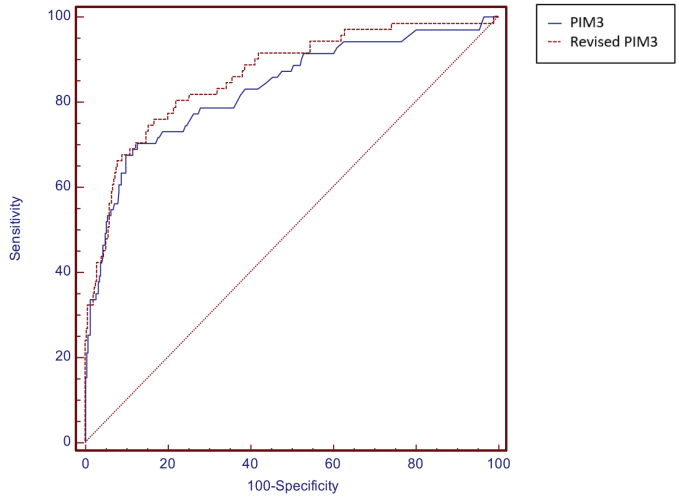

FIG. 2. ROC curves for the PIM3 and revised PIM3

TABLE 4. Calibration of the Revised PIM3 Score (Hosmer-Lemeshow Goodness of Fit Test).

	HL χ 2 (df)	HL p-value	AUC (95% CI)
PIM3 score	13.816 (8)	0.087	0.832 (0.775 - 0.889)
Revised PIM3 score	6.055 (8)	0.641	0.816 (0.763 - 0.869)

PIM 3: Pediatric index of mortality 3 score; CI, confidence interval; AUC,

analysis (odds ratio, (OR) = 1.110; 95% CI 1.06-1.17; $p < 0.001$). Therefore, regardless of the underlying disease, the cAG calculated at the time of admission to the PICU can be used to predict mortality in children, and inclusion of the pre-existing cAG data in death prediction models increases their predictive power.[9] In our study, the cAG value calculated according to biochemical values obtained during hospitalization was significantly higher in patients who died ($p < 0.001$), and an independent risk factor for mortality (AOR = 1.064; 95% CI: 1.010-1.122; $p = 0.019$). For patients with a cAG below the cut-off value of 18.93, the survival decreased significantly as per the Kaplan-Meier survival analysis ($p < 0.001$).

We also computed a revised PIM 3 score by adding the LC and cAG. The revised score had a significantly higher AUC than the original score for predicting mortality (Table 3). Since both scores had AUC > 0.8, their discrimination was considered good, as was their calibration evaluated using the Hosmer-Lemeshow goodness of fit test (Table 4). Increasing the predictiveness of mortality scores is important for a superior comparison of the disease severity between treatment groups.

There were certain limitations to this study. First, it was a single-center retrospective study. Second, the cAG value was calculated based on laboratory results obtained at the time of ICU admission, and the LC was calculated according to blood gas analysis results from the first 6 h after admission. Other factors potentially affecting mortality that may have been present during the ICU follow-up of critically ill children were not included in this analysis. However, the study population was relatively large and recruited over a period of 3 years. Also, we obtained favorable results for the revised PIM 3 score for predicting mortality than that for the original PIM 3 score.

In conclusion, we observed that the revised PIM 3 score, which includes both cAG and LC values, is better at predicting mortality than the original PIM 3 score. However, multicenter prospective studies are required to confirm these results.

Ethics

Ethics Committee Approval: Data collection and retrospective analysis were conducted under the approval of Akdeniz Universty Clinical Research Ethics Review Board (title: Value of the Albumin-corrected Anion Gap and Lactate Clearance for Predicting Mortality in Pediatric Intensive Care Patients; date: 01.12.2021, no: KAEK-979).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- B.G.U., A.K.; Design- F.G., C.R.; Data Collection or Processing- A.K.; Analysis or Interpretation- N.Ü.T., O.D.; Literature Search- L.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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