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Original Article

Admission serum lactate is associated with all-cause mortality in the pediatric intensive care unit

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Abstract: Objective: Our aim was to assess the relationship between serum lactate levels at intensive care unit (ICU) admission and all-cause mortality in the pediatric ICU. Methods: We used the pediatric intensive care (PIC) database (a large pediatric intensive care database in China from 2010 to 2018) to conduct a retrospective analysis to evaluate the serum lactate levels at ICU admission of 12,213 critically ill children admitted to the ICU. We analyzed the association between serum lactate and all-cause mortality. Adjusted smoothing spline plots, subgroup analysis, and segmented multivariate logistic regression analysis were conducted to estimate the relative risk between proportional risk between serum lactate and all-cause mortality. Results: Of the 12,213 children, 755 (6.18%) died. After fully adjusting for confounding factors, serum lactate was an independent risk factor for all-cause mortality in pediatric ICU (adjusted OR=1.14, 95% CI: 1.12, 1.17). The results of sensitivity analysis showed that in different stratified analyses, the effect of serum lactate on all-cause mortality remained stable. Conclusions: Admission serum lactate is a risk factor, which is independent of the presence of acid-base disorders, inflammation, malnutrition, and renal or hepatic dysfunction, for all-cause mortality in the pediatric intensive care unit.

Keywords: Lactate, pediatric ICU, mortality

Introduction

Lactate is converted from pyruvate during anaerobic respiration (glycolysis) by cells involved in the process [1]. Under physiological conditions, this pathway accounts for only one-tenth of the total pyruvate metabolism [2], with various organs including muscle, intestine, red blood cells, brain and skin producing approximately 1500 mmol of lactate per day, which is rapidly metabolized by the liver (~60%), kidneys (~30%) and other organs [3]. Under physiologic conditions lactate production and metabolism is in dynamic equilibrium [1]; however, in a state of hypoperfusion, hypoxia, or shock, adenosine triphosphate production is accomplished by anaerobic metabolism of glucose [4] and pyruvate will no longer enter the mitochondria for aerobic metabolism but will be preferentially reduced to lactate, which grows exponentially intracellularly and causes lactate to accumulate in the blood. This process is an adaptive mechanism for energy production in the presence of inadequate oxygen supply, but at the cost of worsening acidosis [5]. A normal blood lactate concentration of <1.5 mmol/L increases the risk of a poorer outcome, even if it is slightly elevated [3].

Lactate accumulation is a marker of altered tissue perfusion in critically ill patients and is associated with poor prognosis in different patient groups, and the degree of lactate elevation is associated with increased mortality, including trauma, cardiac arrest, sepsis, multiorgan failure, and elderly age [4-6]. Single lactate levels, particularly those measured at intensive care unit (ICU) entry or arrival in the emergency department, are considered strong predictors of subsequent organ dysfunction and mortality [2]. In the above report, the study population was limited to adults. Reports on the relationship between lactate and prognosis of critical illness in children are far less abundant than in adults [2, 4-6]. In pediatric patients, the association between elevated lactate and mortality is currently controversial. A subset of findings support lactate as a predictor of poor

prognosis [7-13], but others suggest no relationship between lactate and mortality [14-17]. Even in studies that support lactate as a risk factor of poor prognosis, there is no consensus on the choice of timing of lactate measurement; whether lactate at admission, mean lactate within 6 hours, lactate after 12 or 24 hours, or lactate clearance; and which time point of a lactate result can be used as the best risk factor of poor prognosis needs to be further investigated.

In the present study, we investigated arterial lactate levels at admission in a large cohort of unselected ICU children and assess the relationship with all-cause mortality in pediatric ICU patients. This is the first study to date to link all-cause mortality in unselected ICU children with admission lactate.

Methods

Subjects

We performed a retrospective analysis using the Pediatric Intensive Care (PIC) database, selecting 12,213 critically ill children with comprehensive laboratory test results. PIC is a large pediatric-specific, single-center, bilingual database containing information related to children in the intensive care unit at the Children's Hospital of Zhejiang University School of Medicine, China, from 2010 to 2018. The PIC database includes vital sign measurements, medications, laboratory measurements, fluid balance, diagnosis codes, length of stay, survival data, and more [18]. The laboratory indicators such as potential of hydrogen (PH), alanine aminotransferase (ALT), albumin (Alb), activated partial thromboplastin time (APTT), total cholesterol (Tcho), creatinine (Cr), hemoglobin, white blood cell (WBC) count, which we included, were the results of the first inspection after admission to the hospital. Inclusion criteria: the information of lactate is not missing. ICU categories include neonatal intensive care unit (NICU), surgery intensive care unit (SICU), pediatric Intensive Care Unit (PICU), and cardiac intensive care unit (CICU). Vasoactive drugs including dopamine hydrochloride Injection, dobutamine hydrochloride injection, adrenaline hydrochloride injection, isoprenaline hydrochloride injection, phenylephrine hydrochloride injection and norepinephrine bitartrate injection.

These data are publicly available after registration, including completing research training courses with human subjects and signing data usage agreements. We handled data responsibly and adhered to the principle of cooperative research.

Statistical analysis

Data are expressed as mean (SD) or median (Q1-Q3) for continuous variables and percentage (%) for dichotomous variables. We used generalized additive model to fit a smooth curve to examine the relationship of the relationship between serum lactate and all-cause mortality. Subgroup analyses examined the relationship between serum lactate and the risk of all-cause mortality according to age and ICU category. Interaction tests in the logistic regression model were used to compare odds ratios between the subgroups analyzed. Interaction test compared two regression models by log likelihood ratio test. Logistic regression models were used to examine the effect of serum lactate and other variables on the occurrence of all-cause mortality. Multivariate regression models included other variables, including gender, vasoactive drugs, age, ICU category, PH, ALT, Alb, APTT, Tcho, Cr, hemoglobin, and WBC Count. The risk associated with all-cause mortality was reported as continuous serum lactate or group by clinical cutoffs. Data were analyzed with the use of the statistical package R (The R Foundation; http://www.r-project.org; version 3.4.3). All *P* values for statistics were 2-tailed, and $P<0.05$ was regarded as significant.

Results

Our study included 12213 children, including 6974 boys and 5239 girls. Median age at ICU admission was 7.69 months (Q1-Q3: 0.99-38.82), median length of stay in ICU was 2.82 days (Q1-Q3: 0.92-9.93), and 6.18% percent (755 patients) died. The median serum lactate concentration was 1.90 mmol/L (Min-Max: 0.10-30.00).

Tables 1, **2** describe the baseline characteristics of the subjects, including demographic characteristics and some laboratory test results that may be related to mortality.

Sensitivity analyses are shown in **Table 3**. We found that according to age and ICU type, the

Table 1. Baseline characteristics of the study participants

Clinical cutoff	Lactate (mmol/L)			*P*-value
	<2 n=6271	2≤ lactate <3 n=2563	≥3 n=3379	
Age (months), mean (SD)	14.30 (3.32-49.33)	6.71 (0.49-43.13)	1.35 (0.07-10.80)	<0.001
Gender, N (%)				0.002
male	3492 (55.68%)	1476 (57.59%)	2006 (59.37%)	
female	2779 (44.32%)	1087 (42.41%)	1373 (40.63%)	
Vasoactive drugs				<0.001
0	4593 (73.24%)	1986 (77.49%)	2686 (79.49%)	
1	1678 (26.76%)	577 (22.51%)	693 (20.51%)	
ICU category, N (%)				<0.001
NICU	989 (15.77%)	778 (30.36%)	1587 (46.97%)	
SICU	1302 (20.76%)	607 (23.68%)	586 (17.34%)	
CICU	1963 (31.30%)	284 (11.08%)	224 (6.63%)	
PICU	925 (14.75%)	456 (17.79%)	535 (15.83%)	
General ICU	1092 (17.41%)	438 (17.09%)	447 (13.23%)	
mortality, N (%)				<0.001
0	6056 (96.57%)	2414 (94.19%)	2988 (88.43%)	
1	215 (3.43%)	149 (5.81%)	391 (11.57%)	
LOS	2.12 (0.90-7.72)	2.92 (0.93-12.12)	3.83 (0.98-12.84)	<0.001

Abbreviations: ICU: intensive care unit; NICU: neonatal intensive care unit; SICU: surgery intensive care unit; PICU: pediatric Intensive Care Unit; CICU: cardiac intensive care unit; LOS: length of stay.

Table 2. Characteristics of clinical laboratory results of study participants

Clinical cutoff	Lactate (mmol/L)			*P*-value
	<2 n=6271	2≤ lactate <3 n=2563	≥3 n=3379	
Lactate (mmol/L)	1.22±0.39	2.39±0.28	5.51±3.62	<0.001
pH	7.40 (7.36-7.44)	7.39 (7.34-7.43)	7.36 (7.29-7.42)	<0.001
ALT (U/L)	17 (11-28)	16 (10-29)	19 (11-39)	<0.001
Alb (g/L)	39.81±6.91	38.04±7.24	36.41±7.38	<0.001
Cr (μmol/L)	44 (37-54)	49 (39-70)	62 (44-88)	<0.001
APTT (s)	35.49±14.49	39.09±19.45	48.57±25.60	<0.001
Tcho (mmol/L)	3.53±1.17	3.29±1.41	2.78±1.43	<0.001
Hemoglobin (g/L)	117.31±23.92	127.35±30.70	133.33±39.64	<0.001
WBC Count (×10^9/L)	8.84 (6.79-11.58)	9.68 (7.07-13.43)	12.40 (8.48-18.12)	<0.001

Abbreviations: pH: potential of hydrogen; ALT: alanine aminotransferase; Alb: albumin; Cr: creatinine; APTT: activated partial thromboplastin time; Tcho: total cholesterol; WBC: white blood cells.

effect of serum lactate on all-cause mortality remained consistent between the subgroups analyzed. Subgroup analysis showed a stronger association between lactate on admission and all-cause mortality in pediatric Intensive Care Unit and in children >12 months of age. Thus, lactate level on admission is an independently useful risk factor for all-cause mortality in the pediatric ICU.

Table 4 shows multiple regression analysis of serum lactate on the risk of death. Without adjustment for confounders, the odds Ratio (OR) value of regression analysis was 1.22, 95% CI: 1.2-1.25; after full adjustment for confounders, the OR value of regression analysis was 1.14, 95% CI: 1.12-1.17. Serum lactate was grouped according to cutoff values of 2 mmol/L and 3 mmol/L, and after full adjust-

Table 3. Sensitivity analysis between lactate and mortality according to baseline

Sub-group	n	OR (95% CI)	*P*-value	*P*-value for interaction
Age (months)				<0.0001
≤1	3086	1.06 (1.01, 1.12)	0.0144	
(1, 12]	3816	1.08 (1.03, 1.13)	0.0033	
>12	5311	1.27 (1.22, 1.33)	<0.0001	
ICU category				0.0133
NICU	3354	1.07 (1.01, 1.12)	0.0158	
SICU	2495	1.18 (1.01, 1.37)	0.0374	
CICU	2471	1.14 (1.00, 1.31)	0.0479	
PICU	1916	1.18 (1.13, 1.23)	<0.0001	
General ICU	1977	1.05 (0.98, 1.12)	0.1368	

Abbreviations: ICU: intensive care unit; NICU: neonatal intensive care unit; SICU: surgery intensive care unit; PICU: pediatric Intensive Care Unit; CICU: cardiac intensive care unit; LOS: length of stay.

ment for confounding, compared to patients with serum lactate <2 mmol/L, the risk of death increased statistically significantly by 1.55-fold at 2 mmol/L-3 mmol/L and 2.39-fold at serum lactate ≥3 mmol/L.

Figure 1 shows the curve fits for serum lactate and risk of all-cause mortality in the PICU after full adjustment for confounders.

Discussion

Early indicators of poor ICU outcome can help identify high-risk patients who may benefit from early intervention. We investigated the clinical use of lactate as an early predictive marker of all-cause mortality in the pediatric ICU in a large unselected group of critically ill patients. Our study is the largest analysis of the prognostic value of lactate levels on admission to a pediatric ICU population, including 1105 children in unselected multiple ICU types. Our study is the first to identify lactate on admission as an independent risk factor for mortality in unselected pediatric ICU patients and an important prognostic biomarker for care and management. In a heterogeneous ICU population, the risk of all-cause mortality was 14% higher for every 1 mmol/L increase in arterial lactate on admission, after full adjustment for confounders.

However, the literature shows conflicting results; one study evaluated lactate levels at PICU admission in 65 children with infectious shock and found that non-survivors had significantly higher lactate levels at PICU admission than survivors [12]. Serum lactate at admission can be used as a prognostic biomarker for mortality in children with moderate to severe traumatic brain injury [7]. In children with systemic inflammatory response syndrome, early hyperlactatemia is significantly associated with increased risk of organ dysfunction, resuscitation therapy, and critical illness. The addition of serum lactate testing to the currently recommended clinical assessment may improve early identification of pediatric sepsis requiring resuscitation, and testing for lactate in a mixed population with an average lactate of 2 mmol/L was found to remain useful in identifying severe disease [9]. In the studies that failed to identify an association between lactate and outcome, some studies included relatively few research subjects, 74 and 113, respectively [14, 17]. One review pointed out that it is too much to ask a single isolated biochemical measurement to predict the course of a complex critically ill patient [15]. Another study suggested that hyperlactemia during cardiopulmonary bypass in patients with congenital heart disease may be an early indicator of postoperative morbidity and mortality, but its positive predictive value is low [16]. Even among the reports that suggested an association between lactate and prognosis, there was no consensus on which time period of lactate levels had the most prognostic value, and results were conflicting .Some studies considered serum lactate level at admission as a biomarker of prognosis [7, 19-23]. Yet, one study noted that mortality was positively correlated only with elevated lactate levels 12 and 24 hours after PICU admission and not with lactate levels collected at PICU admission [24]. Another study noted that mean lactate values at 6 hours prior to pediatric intensive care unit admission were a better prognostic indicator than contemporaneous lactate clearance and could be used as a component of a scoring system to predict mortality, and that lactate clearance had little correlation with PRISM or mortality [25].

With the exception of studies on lactate and prognosis in childhood trauma or sepsis, which have focused on cardiac disease, some single-center retrospective studies support a positive predictive value of elevated initial intraopera-

Table 4. Individual effect of lactate (mmol/L) on all-cause mortality

Exposure	Incidence, n (%)	Non-adjusted		Adjust model I		Adjust model II	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Continuous lactate	755 (6.18%)	1.22 (1.20, 1.25)	<0.0001	1.21 (1.19, 1.23)	<0.0001	1.14 (1.12, 1.17)	<0.0001
Clinical cutoff							
<2	215 (3.43%)	Reference		Reference		Reference	
2≤ lactate <3	149 (5.81%)	1.74 (1.40, 2.15)	<0.0001	1.58 (1.27, 1.97)	<0.0001	1.55 (1.22, 1.98)	0.0004
≥3	391 (11.57%)	3.69 (3.10, 4.38)	<0.0001	3.37 (2.81, 4.05)	<0.0001	2.39 (1.93, 2.96)	<0.0001

Adjust model I: Adjusted for gender, age, ICU category. Adjust model II: Adjusted for gender, vasoactive drugs, age, intensive care unit category, potential of hydrogen, alanine aminotransferase, albumin, creatinine, activated partial thromboplastin time, total cholesterol, hemoglobin, white blood cell count.

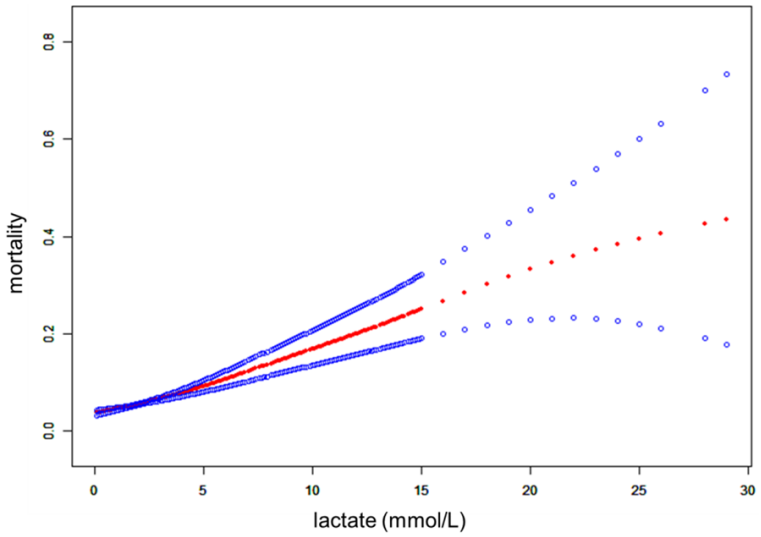

Figure 1. Association between serum lactate and all-cause mortality. Note: Smooth fitting curve adjusted for gender, vasoactive drugs, age, intensive care unit category, pH, alanine aminotransferase, albumin, creatinine, activated partial thromboplastin time, total cholesterol, hemoglobin, white blood cell count. Red lines represent the spline plots of lactate concentration and blue lines represent the 95% confidence intervals of the spline plots.

tive or postoperative lactate level on mortality after cardiac surgery [8, 10-11]. Other studies did not observe this role [16, 17, 26]. Although the presence of hyperlactatemia on admission appears to be associated with mortality and morbidity in the intensive care unit, the significant overlap between survivors and non-survivors means that it is not possible to predict non-survivors from admission lactate measurements [15]. One study noted that low lactate levels were highly predictive of survival (97%), but high lactate levels had only moderate and variable predictive value for non-survival (43%) [26]. Thus, persistently elevated postoperative lactate is associated with increased morbidity and mortality in pediatric cardiac patients, but to date there have been no randomized controlled trials of lactate normalization as goal-directed therapy in adult or pediatric cardiac care.

We believe that serum lactate level measurement at admission helps predict mortality and helps clinicians assess the severity of the child and optimize decision-making. A single initial lactate measurement may be a more convenient and clinically useful tool for predicting mortality than calculating lactate clearance. Since there is no need to wait for a second lactate result to calculate clearance, admission lactate can provide clinicians with decision support in the first instance, buying valuable time to get timely and effective intervention for critically ill children.

Some previous studies support our conclusion that admission lactate levels are convenient and valid prognostic risk factors, and one study noted that initial lactate was strongly associated with Pediatric Risk of Mortality III (PRISM-III). However, calculating the PRISM-III score is expensive, time-consuming, and it is not calculated until 12 to 24 hours after admission. This makes it ineffective for immediate clinical use and more of a research tool. In addition, the prognostic ability of PRISM-III in disease-specific states, such as sepsis or septic shock, has not been evaluated. Instead, lactate levels are checked once a systemic inflammatory response syndrome or sepsis is present, which is quick, inexpensive, and requires little skill. The significant correlation between initial lactate level and PRISM-III score sug-

gests the use of lactate as a prognostic variable, if measured in the first few hours of critical illness [14]. Similarly, another study also noted that a dynamic lactate index was not superior to "static" lactate variables, i.e., admission lactate and maximum lactate [27].

Although inadequate tissue perfusion and/or oxygen supply is an important cause of elevated arterial lactate, since lactate is primarily metabolized in the liver, it is removed in the kidneys by the secretory elimination pathway. In a subset of patients with hepatic and renal dysfunction, glycolysis in the liver is accele rated and the ability of the kidneys to secrete lactate for elimination is subsequently reduced, with a subsequent increase in lactate concentration in the body [28]. Increased catecholamines (endogenous and exogenous) may also increase glycolysis, leading to hyperlactatemia in critically ill patients [8, 10, 15]. Elevated lactate in patients with hepatic and renal dysfunction is challenging for physicians who are faced with the task of finding out whether elevated lactate is caused by acute disease or due to hepatic and renal injury, and somestudies have questioned whether blood lactate concentrations can be used to indicate inadequate tissue perfusion in critically ill patients with hepatic and renal dysfunction [4]. Elevated lactate levels coupled with severe inflammation and coagulation disorders may reflect the early stages of organ dysfunction, as microcirculatory dysfunction due to persistent microthrombosis can lead to a reduction in tissue blood flow and cause organ dysfunction in later stages [29]. In our findings, elevated lactate was associated with higher mortality regardless of impaired liver and kidney function. Adjusting for inflammatory and coagulation-related indicators, as well as epinephrine use, elevated lactate was associated with higher mortality, suggesting that lactate levels at admission are an independent risk factor for all-cause mortality, independent of liver and kidney function, inflammation, coagulation, or epinephrine.

The etiology of severe hyperlactatemia must be considered multifactorial. Elevated lactate can be considered a nonspecific marker of tissue hypoxemia, and hyperlactatemia itself is not a direct cause of high mortality, but a pathophysiological indicator of underlying disease, with various forms of shock being the main cause of elevated lactate in the ICU population, such as cardiogenic shock, hypovolemic shock, or obstructive shock. Organ microcirculation and oxygen utilization dysfunction, such as distributive shock, can also lead to hyperlactatemia [30]. Lactate offers several advantages in the resuscitation of infectious shock in terms of pathophysiology and practicality. Lactate reflects the pathophysiological process requiring immediate resuscitation rather than the source of infection. As such, it may be particularly useful in children, where hypotension is usually a late finding in shock, and by reflecting tissue oxygen delivery and organ function, lactate is independent of hemodynamic status, allowing independent risk stratification of patients [4, 9]. Regardless of the cause of hyper lactic acidemia, most studies believe that elevated lactic acid levels are a sign of clinical criticality and a sign of poor prognosis [30]. In our study, we also adjusted for the type of ICU admission as a confounder and showed that arterial lactate on admission was a risk factor for all-cause mortality in different ICU types.

This study also has some limitations. First, it was a single-center retrospective observational study. The effect of residual confounding factors cannot be completely excluded. Second, although we demonstrated that arterial lactate was a risk factor for death in PICU patients, the study did not elucidate the clinical utility of lactate as a therapeutic target, and prospective clinical trials are needed to elucidate whether all-cause mortality in PICU can be reduced by lowering arterial lactate. Third, high levels of lactate could downregulate the rate-limiting glycolytic enzymes hexokinase and phosphofructokinase in a variety of tissues and immune cells. Downregulation of these rate-limiting glycolytic enzymes may have important implications for immune cell function [31, 32]. Lactate has also been reported to influence the functioning and differentiation of macrophages. In the late stage of sepsis, macrophages are often observed as having a predominantly immunosuppressive M2 phenotype configuration that may have a critical role in the pathogenesis of immune system dysfunction [33]. Observation of macrophage function and differentiation changes in children admitted to ICU with high lactate warrants further exploration. Finally, this study included only Chinese children, so careful interpretation is needed before our data can be applied globally.

Conclusion

Lactate level on admission is an predictor of all-cause mortality in the pediatric ICU, independent of the presence of acid-base disorders, inflammation, malnutrition, and renal or hepatic dysfunction. Lactate level on admission as a risk factor of poor prognosis in the pediatric ICU can be a value that helps stratify critically ill patients. It is recommended to test for lactic acid when critically ill patients are admitted to the hospital. Focusing on the relationship between admission lactate and all-cause mortality in the pediatric ICU will enhance our ability to identify, treat, and improve the prognosis of critically ill children.

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Disclosure of conflict of interest

None.

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