UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Valor prognóstico da cinética do lactato na criança gravemente doente

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE PEDIATRIA

Trabalho realizado sob a orientação de:

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MAIO 2020

UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

VALOR PROGNÓSTICO DA CINÉTICA DO LACTATO NA CRIANÇA GRAVEMENTE DOENTE

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The prognostic value of lactate kinetics in critically ill children

ORIGINAL RESEARCH

ACRONYMS

PICU – pediatric intensive care unit

D1 – day 1

D2 – day 2

ΔL – delta-lactate

$ScvO_2$ - central venous oxygen saturation

PIM3 – pediatric index of mortality-3

HMR – high mortality risk

LMR – low mortality risk

Max – maximum

PCT – procalcitonin

IMV – invasive mechanical ventilation

AKI – acute kidney injury

ROC – receiver operating characteristic

SPSS – statistical package for the social sciences

IQR – inter-quartile range

GI – gastro-intestinal

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ABSTRACT

Purpose: Serum lactate levels and their trend over the first hours after admission have been reported as good outcome predictors of critically ill patients. We aimed to test the applicability of lactate kinetics as a short-term risk stratification method in critically ill children.

Methods: Exploratory study with retrospective data collection of patients admitted to PICU (pediatric intensive care unit) from 2016 to 2019. Exclusion criteria included neonatal period, post-operative admissions or length of stay shorter than 48 hours. The difference between the maximum lactate concentration in Day1 (D1) and in Day2 (D2) was used to calculate delta-lactate (ΔL). According to ΔL's cut-off, two groups were considered: low mortality risk (LMR) - decrease in lactate levels of ≥0.05 mmol/L - and high mortality risk (HMR) - increase in lactate levels or a decrease of <0.05 mmol/L. Demographic and clinical data were analyzed using SPSS®. The Youden Index was used to calculate the optimal cut-off.

Results: From the 1564 patients admitted to PICU in the mentioned time frame, 249 were selected. The median age was 5.6 years old [IQR 0.9-13.7], 60.6% were males and the median length of stay was 7.0 days [IQR 3.0-10.0]. The most frequent diagnosis on admission was respiratory disorder (33.7%), followed by trauma (15.7%) and shock (15.3%). The median PIM3 (pediatric index of mortality-3) was 3.10 [IQR 1.14-6.86]; 7.2% (n=18) of the patients died during PICU stay and two more children died in the following 28 days. Mortality, both during PICU stay and at 28 days, was statistically associated with elevated serum lactate in D1 and in D2. Considering the 93 cases with a maximum lactate in D1 above normal (≥2.0 mmol/L), the area under the ROC curve was 0.698 [CI95% 0.47;0.93], for a ΔL's cut-off of 0.05 mmol/L. The demographic data were similar between both groups (LMR and HMR). Trauma and shock were important admission diagnoses for the age range with the highest mortality in both groups. HMR had a statistically significant association with the maximum lactate levels in D2, scored higher PIM3 and were never discharged home; they counted fewer ventilation-free-days and needed renal replacement therapy more often.

Discussion: Higher lactate levels, both in D1 and in D2 proved to be good predictors for short-term mortality. When maximum lactate level in D1 was higher than normal, death was likelier to occur. With the optimal cut-off for ΔL taken into consideration, it was possible to predict higher mortality risk during PICU stay and at 28 days: if, from D1 to D2, an increase or slight decrease in lactate maximum levels occurred (versus a decrease greater than or equal to 0.05 mmol/L), death was almost eight times more probable. The worse the disease, the less likely was the patient discharged home.

Conclusion: In critically ill children, as for adults, lactate's kinetics in the first hours after admission, rather than its absolute values, may predict a short-term outcome.

Keywords: critically ill, critically ill children, Delta-Lactate, lactate clearance, risk stratification

INTRODUCTION

In anaerobic conditions, cells under stress increase glycolysis and the excess pyruvate produced is converted to lactate as an end product. It then serves gluconeogenesis as a substrate (1). The anaerobic pathway is initiated due to hypoperfusion (2). Several studies proved that in context of macro and microcirculatory failure, like sepsis and shock (3,4), hyperlactatemia occurs as a result of this pathway.

Hyperlactatemia is probably a multifactorial result, depending on each patient's disease pathophysiology (1). The clearance of the lactate produced in the human body tissues relies mainly on the liver (up to 70%) (5) and kidney function. In case of hepatic or kidney failure, high lactate levels may arise, independently from the presence of shock. Therefore, increased production, decreased clearance or the combination of both can lead to an increase of serum lactate level.

Hyperlactatemia can result from several processes (1), settling its interpretation challenging (6,7). An injured liver may itself be a source of lactate synthesis (8). In cardiac arrest, both absence of blood flow and consequent ischemia-reperfusion inflammation may lead to an increase in lactate levels (9); specifically in children (10) in post cardiac arrest situations, its effective clearance is associated with a better outcome (11,12). In trauma patients with important blood loss, some authors have suggested lactate levels might help detect hypoperfusion while normal vital signs are still present (13) and foresee worst outcomes in patients with occult hypoperfusion (14). Deviation from the transient pattern of lactate increase in seizures may lead clinicians to consider different or concomitant etiologies (15). Excessive muscle activity, either from heavy exercise (16) or respiratory failure, muscle fatigue (17) and asthma exacerbations (18), also seem to activate anaerobic metabolism, leading to excess lactate production (19). Other causes of hyperlactatemia include: regional ischemia, abdominal acute diseases or different types of tissue necrosis (20,21); severe burns (22) and smoke inhalation, due to carbon monoxide poisoning (23); diabetic ketoacidosis (24) and thiamine deficiency (an essential cofactor for carbohydrate aerobic metabolism) (25); and malignancy, usually leukemia or lymphoma with liver involvement (26). It may also result from numerous pharmacologic agents, toxins(27) and alcohols, whose association with elevated lactate is still controversial (28). Finally, inborn errors of metabolism have grater relevance in the pediatric population as a cause of hyperlactatemia (29).

Most investigations use 2.0 to 2.5 mmol/L as the upper limit for "normal" lactate, but an universal cut-off to define "elevated" lactate blood levels does not exist. A "high" lactate level has been suggested when its concentrations exceed 4mmol/L (14,24,30).

In critically ill patients, an increase in lactate concentration is commonly accepted as a marker of hypoperfusion (31), regardless of the underlying cause of hyperlactatemia (32), (1) and infection status (32,33). It is used as a good predictor of mortality and outcome at

discharge (34,35). The Surviving Sepsis Campaign (30) included the serum lactate concentration measurement into their guidelines, emphasizing the importance of performing the measurement within the first three hours from diagnosis. They propose that in the absence of $ScvO_2$ (central venous oxygen saturation), lactate normalization is a feasible option in detecting the patient with severe sepsis-induced tissue hypoperfusion. These guidelines suggest crystalloid administration for patients presenting with hypotension or lactate ≥4 mmol/L. Similarly, current trauma guidelines recommended risk stratifying patients and guiding fluid administration using lactate levels (36,37). Similar approaches and managements have been validated in pediatric critical patients (2,38).

Investigators have determined cut-off values for lactate kinetics capable of predicting short and/or long-term mortality (39), that serve as endpoints for resuscitation and as markers of therapeutic response. Though consensus hasn't been achieved, the results look promising (34,39–41). Recently, J. Pan and colleagues tested the usefulness of lactate clearance as a specific indicator of resuscitation outcome. Their results suggest lactate clearance, alone, is superior to $ScvO_2$, alone, during a standard resuscitation, although an optimal rate remains debatable (42). Yusuke H. *at all* compared 23 different lactate-related indices for in-hospital mortality prediction and concluded that the ROC-AUC (area under the ROC curve) of maximum lactate at 24 hours after admission was superior to other indices, as comparable with APACHE III (Acute Physiology & Chronic Health Evaluation III) score(43).

As seen, many have theorized and investigated the value of lactate kinetics or lactate clearance rate on the first hours of admission for predicting short and long term outcomes in critical care. In adults, several studies support this hypothesis (40,44–46), while the research regarding pediatric patients is scarce.

METHODS

We conducted an exploratory study, with retrospective data collection of patients admitted to Pediatric Intensive Care Unit (PICU) for a period of four years, from January 1st 2016 to December 31st 2019. All patients included had at least one lactate measurement in D1 (day 1) and another in D2 (day 2). Exclusion criteria included neonatal period, post-operative admissions or length of stay shorter than 48 hours.

Pediatric index of mortality-3 (PIM3) score was calculated within 24 hours of admission. Lactate measurements through blood gas analysis did not follow any specific protocol, as they were performed according to the doctor's assessment of the patient.

Demographic and clinical data were collected from a restricted access database including age, gender, length of PICU stay, diagnosis on admission, PIM-3, comorbidities, maximum lactate concentration in D1 and D2, number of days until lactate normalization, procalcitonin (PCT) levels (at admission, maximum level registered and time until normalization), need for invasive mechanical ventilation (IMV), ventilation-free-days, associated infection (timing, type of infection and use of antibiotics), acute kidney injury (AKI) - alongside renal replacement therapy and diuretics use -, use of vasoactive drugs and its length, death during PICU stay, destination after discharge and death until 28 days.

The difference between the maximum lactate concentration in D1 and in D2 was used to calculate delta-lactate (ΔL). We considered lactate to be elevated when ≥2 mmol/L and the day of lactate normalization when three consecutive lactate measurements were normal (<2 mmol/L). We considered PCT to be normal when its concentration was <0.5 ng/dL. Infections were considered 'at admission' when known at admission or diagnosed in the first 48 hours of PICU stay; they were expressed as 'hospital acquired infection' when the diagnostic was made after this period.

Ventilation-free-days were calculated according to the following rules: zero was attributed to patients who died and to surviving patients ventilated for ≥28 days; 28 was considered in patients free of ventilation for ≥28 days; 28 minus the total days of ventilation was calculated in the remaining.

The Youden Index was used to calculate an optimal cut-off (higher specificity and sensibility) to predict mortality in this sample. For comparative analysis between a lower and a higher mortality risk populations, two groups were considered based on the calculated cut-off value: "low mortality risk" - LMR (higher decrease in lactate level) and "high mortality risk" - HMR (increase in lactate levels or a smaller decrease).

Demographic and clinical variables were used to compare both groups. Correction for disease severity was considered given demographic data similarity, as shown in the next section. Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviations or medians and inter-quartile ranges,

for variables with non-normal distribution. Normal distribution was checked using Shapiro-Wilk Test or skewness and kurtosis. Chi-square test or Fisher Exact test were applied to compare qualitative variables; Mann-Whitney test was used to compare quantitative variables. The area under the curve from a ROC curve was analyzed to predict mortality.

Analysis was performed using SPSS® (Statistical Package for the Social Sciences), version 25. All reported *p* values were two-tailed, with a *p*-value of 0.05 indicating statistical significance.

RESULTS

Considering the exclusion criteria, from the 1564 constitutive cases of the database, our study included 249 patients, older than 28 days and younger than 18 years old (Table 1). In this sample, 60.6% were males and the median age was 5.6 years [IQR0.87-13.74]. Forty point six percent (40.6%) of these patients had between 10 and 18 years old and 28.1% were infants (Figure A). The median length of stay was 7.0 days [IQR3.0-11.0]. The most frequent diagnoses on admission were respiratory disorders (33.7%), followed by trauma (15.7%) and shock (15.3%). The median PIM3 score was 3.10 [IQR1.14-6.85]. Comorbidities were present in 55.8% of the patients: 14.5% of the patients (n=36) had cancer, 10.8% (n=27) had malformations or syndromic/hereditary disorders and a chronic heart disease was present in 8.8% (n=22).

The median of maximum lactate levels in D1 and in D2 were 1.6 mmol/L [IQR1.0-2.5] and 1.2 mmol/L [IQR0.8-1.8], respectively. Day 2.0 [IQR 2.0-3.0] was the median day of lactate values normalization.

An infection was diagnosed in 146 (58.6%) patients, with 17.8% (n=26) being hospital acquired infections. Amongst those, the majority (46.2%, n=12) were systemic, followed by respiratory (24.6%, n=9) and urinary tract (11.5%, n=3) infections. One hundred and forty patients (56.2%) needed invasive mechanic ventilation, with a median ventilation-free-days of 23.0 days [IQR17.0-26.0]. AKI was diagnosed in 17.7% (n=44) of the patients; it was already present at admission in 22.7% (n=10) of those. Renal replacement therapy was initiated in 19 patients (7.6%) and diuretics were administered in 141 (56.6%). Ninety-one patients needed vasoactive drugs (36.5%), for a median length of 4.0 days [IQR2.0-6.8].

Mortality rate during PICU stay was 7.2% (n=18) and two more children died on the 28 days' period after onset. In total, 20 patients (8.0%) died. The highest percentage of deaths occurred in children aged between 12 months and 10 years old (Figure A).

The median of maximum lactate in D1 of the patients who died during PICU stay was higher than in those who survived (3.0mmol/L [IQR1.3-9.7], *vs.* 1.5mmol/L [IQR1.0-2.4], p=0.006). Similarly, patients who died during PICU stay had a higher maximum median lactate level in D2 - 2.4mmol/L [IQR1.3-10.0], *versus* 1.1mmol/L [IQR0.8-1.7] in those who survived (p<0.001). Considering the mortality at 28 days, the median of maximum lactate was higher in the group of patients who died, both in D1 (2.9mmol/L [IQR1.3-9.3] *versus* 1.5mmol/L [1.0-2.4], p=0.010) and in D2 (2.4mmol/L [IQR1.4-8.6] *vs.* 1.1mmol/L [IQR0.8-1.7], p<0.001) respectively.

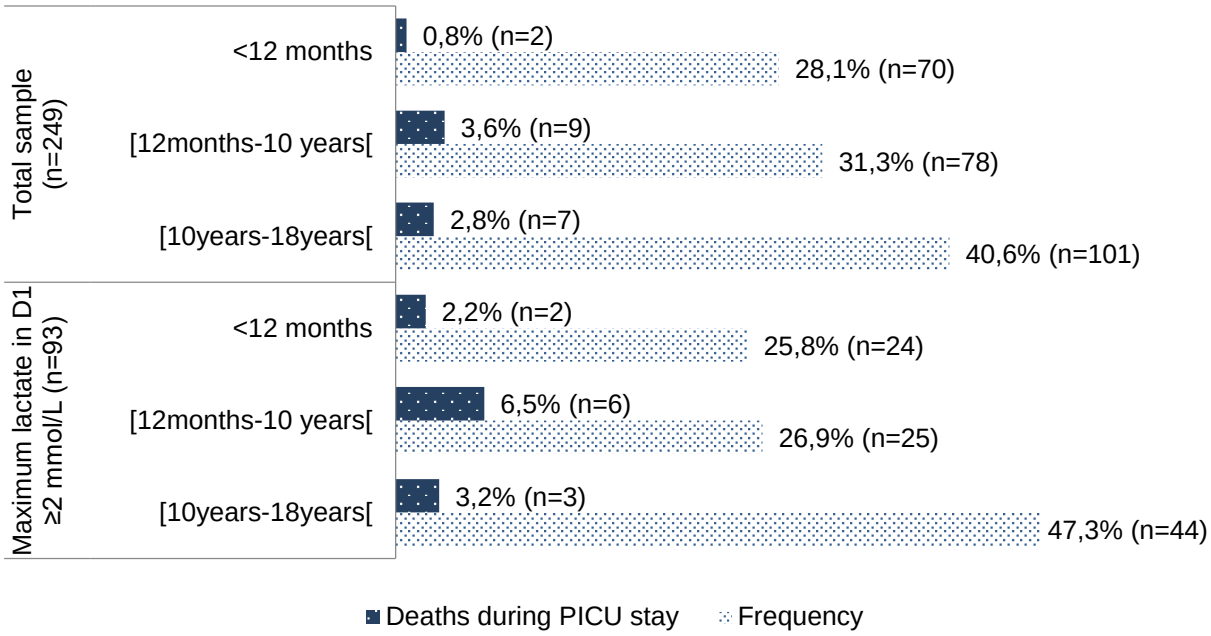
Table 1 | Demographic and clinical characteristics of the sample (n=249)

	Median or n	IQR or %		Median or n	IQR or %
Age at admission (years)	5.6	[0.9-13.7]	**PIM3 score** (pts)	3.1 0	[1.14-6.85]
Male gender	151	60.6%	**Max. lactate in D1** (mmol/L)	1.6	[1.0-2.5]
Admission diagnosis group			**Max. lactate in D2** (mmol/L)	1.2	[0.8-1.8]
Respiratory disease	84	33.7%	**Lactate normalization day**	2.0	[2.0-3.0]
Trauma	39	15.7%	**PCT at admission** (mmol/L)	1.35	[0.2-7.9]
Shock	38	15.3%	**Max. PCT registered** (mmol/L)	2.59	[0.4-15.1]
Neurologic disease	30	12.0%	**Infection**		
Renal disease	17	6.8%	**No infection**	103	41.4%
Cardiac disease	12	4.8%	**At admission**	120	48.2%
GI disease	12	4.8%	**Hospital acquired infection**	26	10.4%
Other	17	6.8%	**Systemic infection**	12	46.2%
Comorbidities			**Respiratory infection**	9	24.6%
No comorbidities	110	44.2%	**Urinary tract infection**	3	11.5%
Active cancer disease	36	14.5%	**Other**	2	7.7%
Syndrome/ Malformation	27	10.4%	**AKI**		
Chronic heart disease	22	8.8%	**No AKI**	205	83.3%
Chronic neurological disease	14	5.6%	**At admission**	10	4.0%
Chronic GI disease	10	4.0%	**During PICU stay**	34	13.7%
Prematurity	9	3.6%	**Renal replacement therapy**	19	7.6%
Chronic respiratory disease	9	3.6%	**IMV**	140	56.2%
Chronic endocrine disease	7	2.8%	**Ventilation-free-days** (days)	23.0	[17.0-26.0]
Other	5	2.0%	**Diuretic drugs**	141	56.6%
Discharge			**Vasoactive drugs**	91	36.5%
To another ward/ hospital	215	86.3%	**Length of vasoactive drugs** (days)	4.0	[2.0-6.8]
Home	16	6.4%	**Mortality during PICU stay**	18	7.2%
PICU length of stay (days)	7.0	[3.0-11.0]	**Mortality at 28 days**	20	8.0%

IQR inter-quartile range, *GI* gastro-intestinal; *PICU* pediatric intensive care unit; *PIM3* pediatric index of mortality-3; *Max*. maximum; *PCT* procalcitonin; *AKI* acute kidney injury; *IMV* invasive mechanic ventilation;

In table 2, we present the characteristics of the ninety-three patients (37.3%) who had a maximum lactate level of ≥2.0 mmol/L in D1. Amongst those, 64.5% were males and the median age at admission was 9.3 years [IQR0.9-14.1]. The majority of the patients belonged to the [10years-18years[age group (47.3%) and 25.8% were infants (Figure A). Trauma was the most frequent admission diagnosis (26.9%), followed by shock (24.7%) and respiratory disorders (18.9%). The median PIM3 was 3.50 [IQR1.35-7.12], not significantly higher than the value obtained for the total sample of 249 patients (p=0.065). In this group of patients, there were 11 deaths (11.8%) during PICU stay, and one more patient died until 28 days, leading to a total mortality rate of 12.9%. These mortality rates are, respectively, 1.7 times (p=0.030) and 1.6 (p=0.029) times higher than the correspondent rate in the initial group of 249 patients.

Figure A | Different age groups frequency and death rate



In these 93 patients, for optimal sensitivity (0.636) and specificity (0.890), death was predicted when lactate values either increased or decreased slightly (less than 0.05mmol/L) from D1 to D2. The area under the ROC curve was 0.698 [CI 95% 0.47; 0.93]**.** Based on the calculated cut-off, 17.2% (n=16) of patients were included in the HMR group, while 82.8% (n=77) were included in the LMR group.

The age group between [10-18[years old was the most representative in both groups, as presented in Figure B. Female gender prevailed in the HMR group, without statistical significance (*p*=0.056).

In both groups, shock and trauma were the most frequent diagnoses at admission. Comorbidities were reported in 37.5% of the HMR patients (18.8% had active cancer disease) and in 51.9% of the LMR patients, from which 11.7% had malformations or syndromic/hereditary disorders.

In both groups the median age was similar (8.8 years [IQR0.5-14.1] *vs.* 9.3 years [IQR1.0-14.1], *p*=0.895). HMR group scored significantly higher median PIM3: 15.28 [IQR3.56-63.58] *versus* 3.30 [IQR1.21-5.82] (*p*=0.002). There was no difference in length of PICU stay between groups (*p*=0.834). In HMR group no patients were discharged home (*vs.* 5.3% in the LMR group).

During PICU stay, seven patients of the HMR group died *versus* four patients in the LMR group: mortality rate was more than eight times higher in the HMR group (43.8% *vs.*

5.2%, p<0.001). At 28 days, one more patient from the LMR group died. Considering the different age groups (Figure B), in LMR patients, death during PICU stay was only reported in the [12months-10years[age group - trauma (n=2), respiratory disease (n=1) and shock (n=1) were their causes of admission to PICU. The highest number of deaths in HMR patients occurred in the [10years-18years[age group, from which 66.7% (n=2) had trauma as the admission diagnosis.

Both median of maximum lactate levels in D1 (p=0.359) and in D2 (p<0.001) were higher in the HMR group. Day 2.0 was the median day of lactatemia normalization in both groups (p=0.168). The median of PCT value on admission was slightly higher in the LMR group, without statistically significant difference between groups (4.4mmol/L [IQR0.5-18.9] *vs.* 2.0mmol/L [IQR1.1-32.0], p=0.520). Serum PCT normalization occurred, in median, in day 5.5 [IQR0.0-11.3] in LMR group, *versus* day 3.0 [IQR0.0-5.0] in HMR group (p=0.272). There was no difference between the maximum PCT during PICU stay in both groups (HMR 7.0 [IQR1.9-43.0] *vs.* LMR 6.4 [IQR1.1-27.9], p=0.740).

AKI was diagnosed in 31.3% (n=5) of patients in the HMR group - in one of them (6.3%) it was present at admission -, *versus* 23.4% in the LMR group, being it present at admission in four patients (5.2%). HMR patients needed renal replacement therapies more often (p=0.020). Diuretics were used similarly frequently in both groups (50.0 *vs.* 58.4%, p=0.535).

Vasoactive drugs were used in 75.0% of HMR patients and 54.5% of the LMR group of patients, (p=0.131); the median day of initiation was day 1.0 in both (p=0.296); the median amount of days with administration of vasoactive drugs was 4.5 days [IQR3.0-6.8] in the HMR group and 4.0 days [IQR3.0-8.0] in the LMR group (p=0.983).

Regarding ventilation assistance, 75.0% of patients from HMR group underwent IMV (*vs.* 68.8% of the LMR patients, p=0.769). The median of IMV initiation was day 1.0 [IQR1.0-1.0] in both groups, (p=0.638). The median of ventilation-free-days was lower in the HMR patients (0.0 days [IQR0.0-22.0] *vs.* 21.0 days [IQR15.0-24.5], p=0.011).

At some point, an infection was diagnosed in 54.5% (n=42) of the LMR patients and 50.0% (n=8) of the HMR patients; amongst those, respectively, 26.2% (n=11) and 25.0% (n=2) corresponded to hospital acquired infections. Finally, systemic and respiratory tract infections represented the majority of in-hospital infections, both in the LMR (45%, each) and HMR groups (50%, each).

Table 2 | Characteristics of patients of LMR and HMR groups

	All patients (n=93)		LMR Group[1] (n=77)		HMR Group[2] (n=16)		
	Median or n	IQR or %	Median or n	IQR or %	Median or n	IQR or %	*p* value
Age at admission (years)	9.3	[0.9-14.1]	9.3	[1.0-14.1]	8.8	[0.5-14.1]	0.895
Male gender	60	64.5%	53	68.8%	7	43.8%	0.056
Diagnosis at admission							
Trauma	25	26.9%	20	26.0%	5	31.3%	
Shock	23	24.7%	18	23.4%	5	31.3%	
Respiratory disease	18	19.4%	17	22.1%	1	6.3%	
Neurologic disease	9	9.7%	8	10.4%	1	6.3%	
Cardiac disease	7	7.5%	6	7.8%	1	6.3%	
Renal disease	6	6.5%	4	5.2%	2	12.5%	
GI disease	1	1.1%	1	1.3 %	0	0.0%	
Other	4	4.3%	3	3.9%	1	6.3%	
Comorbidities							
No comorbidities	49	56.7%	39	50.6%	10	62.5%	0.388
Active cancer disease	10	10.8%	7	9.1%	3	18.8%	
Syndrome/ Malformation	10	10.8%	9	11.7%	1	6.3%	
Chronic heart disease	8	8.7%	8	10.4%	0	0.0%	
Chronic endocrine disease	4	4.3%	3	3.9%	1	6.3%	
Chronic neurological disease	4	4.3%	4	5.2%	0	0.0%	
Chronic GI disease	3	3.2%	3	3.9%	0	0.0%	
Prematurity	2	2.2%	2	2.6%	0	0.0%	
Chronic respiratory disease	1	1.1%	1	1.3%	0	0.0%	
Other	2	2.2%	1	1.3%	1	6.3%	
PICU length of stay (days)	8.0	[4.0-13. 0]	8.0	[4.0-13.0]	7.5	[3.3-12.5]	0.834
Discharge							
To another ward/ hospital	78	83.9%	69	90.8%	9	64.3%	
Home	4	4.3%	4	5.3%	0	0.0%	
PIM3 score (pts)	3.5 0	[1.35-7.12]	3.30	[1.21-5.82]	15.28	[3.56-63.58]	0.002**
Max. lactate in D1 (mmol/L)	3.2	[2.4-6.15]	3.2	[2.4-6.0]	3.5	[2.6-8.8]	0.359
Max. lactate in D2 (mmol/L)	1.9	[1.2-3.2]	1.6	[1.1-2.4]	5.6	[3.1-10.7]	<0.001***
Lactate normalization day	2.0	[2.0-3.0]	2.0	[2.0-3.0]	2.0	[2.0-5.0]	0.168
PCT at admission (mmol/L)	4.3	[0.8-20.1]	4.4	[0.5-18.9]	2.0	[1.1-32.0]	0.520
Max. PCT registered (mmol/L)	6.4	[1.2-33.5]	6.4	[1.1-27.9]	7.0	[1.9-43.0]	0.740
Infection							
No infection	43	46.2%	35	45.5%	8	50.0%	
At admission	37	74.0%	31	73.8%	6	75.0%	1.000
Hospital acquired infection	13	26.0%	11	26.2%	2	25.0%	
Respiratory infections	6	42.2%	5	45.5%	1	50.0%	
Systemic infection	5	38.5%	5	45.5%	1	50.0%	
Urinary tract infection	1	7.7%	1	9.1%	0	0.0%	
Other	1	7.7%	0	0.0%	0	0.0%	
AKI							
No AKI	70	75.3%	59	76.6%	11	68.8%	
At admission	5	5.4%	4	5.2%	1	6.3%	1.000
During PICU stay	18	19.4%	14	18.2%	4	25.0%	
Renal replacement therapy	11	11.8%	6	7.8%	5	31.3%	0.020*
IMV	65	69.9%	53	68.8%	12	75.0%	0.769
Ventilation-free-days (days)	21.0	[9.5-24.0]	21.0	[15.0-24.5]	0.0	[0.0-22.0]	0.011*
Diuretic drugs	53	57.0%	45	58.4%	8	50.0%	0.535
Vasoactive drugs	54	58.1%	42	54.5%	12	75.0%	0.131
Length of vasoactive drugs(days)	4.0	[3.0-8.0]	4.0	[3.0-8.0]	4.5	[3.0-6.8]	0.983
Mortality during PICU stay	11	11.8%	4	5.2%	7	43.8%	<0.001***
Mortality at 28 days	12	12.9%	5	6.5%	7	43.8%	0.001***

[1]Decrease in lactate levels of ≥0.05mmol/L); *HMR* high mortality risk, [2]Increase or small decrease (<0.5mmol/L) in lactate levels*; IQR* inter-quartile range; *GI* gastro-intestinal; *PICU* pediatric intensive care unit; *PIM3* pediatric index of mortality-3; *Max.* maximum*; PCT* procalcitonin*; AKI* acute kidney injury; *IMV* invasive mechanic ventilation; *(*)(**)(**\)*levels ≤0.05, ≤0.01, and ≤0.001 of statistical significance, respectively.

Figure B | Different age groups frequency and death rate in LMR and HMR groups of patients

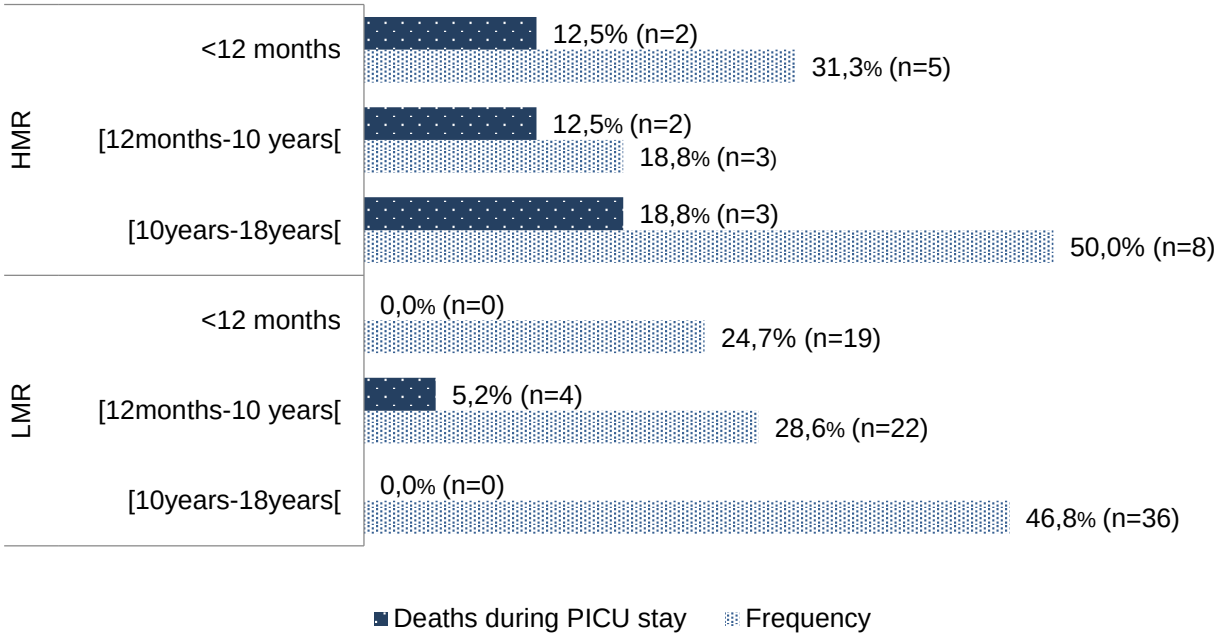
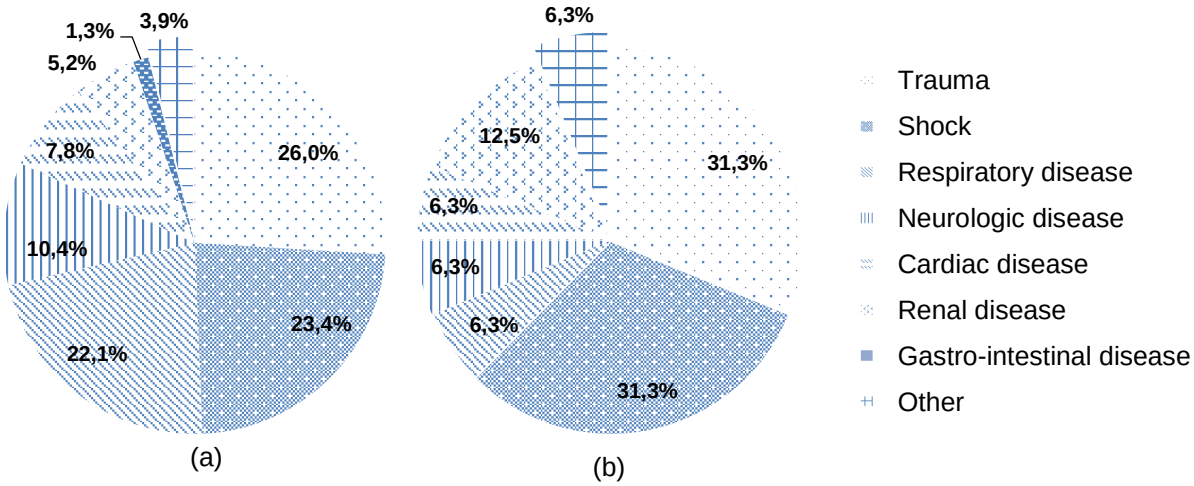


Figure C | Diagnosis at admission of LMR group (a) and HMR group (b) of patients



DISCUSSION

Firstly, this study proved that higher serum lactate levels in the first hours of admission to PICU, regardless of any normal range or limit, are associated with higher short-term mortality rates: considering the sample, the median of maximum lactate levels in D1 and in D2 were 2.0 and 2.2 times higher in patients who died during PICU stay, comparing to those who survived.

Secondly, resembling the existing literature (2,39,47), we established an increased lactate at admission to PICU as a good predictor of short-term mortality. When an upper limit of normality was considered for maximum lactate value in D1 (2mmol/L), the narrowed sample had a higher mortality rate, comparing to the initial 249 patients.

Thirdly, we acknowledged the importance of lactate´s trend over time in predicting mortality, rather than considering its absolute values, alone. The usefulness of a cut-off value for lactate concentrations and/or for its clearance rate in predicting therapeutic approach for critical patients is widely spread, in the adult population (40). However, the term “clearance” has been used to refer elimination, despite the need for radiolabeled lactate intravenous injection to directly measure its clearance (48). Nevertheless, a consensual cut-off has not been established. Recently, Masyuk M and colleagues showed that a lower rate than 19% decrease in lactate levels on the first 24 hours of admission was robustly associated with an adverse outcome (46). A cut-off of at least 36% lactate clearance in six hours was suggested by Walker C and colleagues (49).

Our study provided a ΔL´s cut-off of 0.05 mmol/L, valuable for clinical guidance concerning short-term mortality risk, in a pediatric sample of critically ill patients. Higher mortality during PICU stay was associated with an increase or decrease of lesser than 0.5 mmol/L in the maximum serum lactate values (ΔL <0.05 mmol/L), from D1 (the first 24 hours after admission) to D2 (the period from 24 to 48 hours after admission).

According to that same cut-off, based on mortality risk, patients with elevated maximum lactate on D1 were divided into two groups. The comparison of the two groups showed no significant difference in what concerned age, gender, length of PICU stay or the presence of known comorbidities, proving a similarity in demographic data between them.

In LMR and HMR groups, shock and trauma were the most frequent diagnoses reported at admission to PICU. These results come to reinforce the importance of serum lactate concentration measurements being incorporated into guidelines for the management of shock patients, as in The Surviving Sepsis Campaign (30), previously mentioned. The results also validate the usefulness of lactate levels in recent trauma guidelines, for risk stratifying patients and guiding fluid administration (36,37).

In the LMR group of patients, mortality during PICU stay was exclusively reported in the [12months-10years[, while in HMR patients, the highest mortality rate during PICU stay

was registered in patients aged between 10 and 18 years. Trauma was, again, an important cause of mortality in both of these age groups.

The similarity between both groups' median of maximum lactate levels in D1, in contrast to the difference seen in the median of D2 maximum lactate levels, reinforces the idea that variations in lactate levels are clinically more significant than isolated lactate concentrations. These results might also suggest that the period from 24 to 48 hours after admission is the best period to evaluate the patients and reliably estimate their clinical course. Baysan M, *at all* recently advocated the added predictive value of lactate at 24 hours after admission to the Acute Physiology and Chronic Health Evaluation IV model for in-hospital mortality in critically ill patients with sepsis (50).

As expected, HMR patients scored higher PIM3, reflecting the higher severity of their diagnosis at admission (51). The fact that no patients in the HMR group were discharged home suggest that either their cause of admission to PICU itself, or the resulting sequelae, unstated the need for longer hospital care (52,53).

AKI diagnosis was similar in both groups; however, patients in the HMR needed renal replacement therapy more often. Severity of renal function impairment and renal replacement therapy techniques can influence lactate's clearance in those patients (54).

Lesser ventilation-free-days suggest the unfavorable evolution of HMR patients. This group of patients reach clinical and laboratory criteria for ventilator weaning later than ones with more favorable outcome (55), and additionally are susceptible to the potential consequences of prolonged immobilization and sedation (56).

The need, timing and duration of the other different supportive therapies instituted - IMV, diuretics and vasoactive drugs - were similar in both groups. Other variables, including day of lactate normalization, serum PCT at admission and its maximum value during PICU stay or presence of infection showed no difference between the two groups and hence do not seem related to a higher risk of mortality.

For all mentioned above, our study highlights the usefulness of ΔL as a good predictor of outcome and stratification method in critically ill children: the need for longer hospital care, renal replacement therapies and lesser ventilation-free-days seem to be related to a slow decrease or an increase of lactate in the HMR group.

The heterogeneity of the sample, albeit exclusion criteria defined, might imply the need for further studies, with homogenized samples. Other potential limitations aroused during the study's course. The data were collected without some confounding variables being gathered: amongst others, the selection of a more severe diagnosis or comorbidity to the detriment of concomitant, but less determinant, diagnoses or comorbidities, based only on the authors' perspective (57). Given its retrospective nature, an insufficient number of lactate

measurements, or registrations of blood gas analysis results, led to a decrease in the number of cases included. Also, in a large amount of patients, it was seen that a normal first blood gas analysis did not motivate a second one, precluding the lactate kinetics interpretation and reducing our sample. The short follow-up period did not allow long-term mortality prediction or sequelae. Lastly, our prognosis analysis only contemplated mortality; possible sequelae from the acute illness that motivated admission to PICU were not included in our study.

For further future investigation on the subject, we suggest that a larger sample should be obtained in a controlled prospective collection analysis. A specific protocol should guide blood sample collection for blood lactate, namely the frequency per day or interval between measurements (30). Finally, a constellation of sequelae, recently referred as intensive care syndrome, including prolonged immobility, altered cognition, and the development of psychotic manifestations (58) should be considered in prognosis analysis, particularly in children (59).

CONCLUSION

This study highlights the clinical relevance of lactate serum levels in the first two days of admission, and its clearance rate, to predict the outcome of pediatric critically ill patients. While similar studies have been conducted in adults, the literature is scarce in the pediatric population.

It appears that ΔL is a hasty and reliable stratification parameter, predicting mortality when an increase or a small decrease of <0.05 mmol/L occurs from D1 to D2. The association between ΔL and the short-term outcome of this group of children may not only suggest ΔL as a promising risk predictor, but also pinpoint its relevance in assessing the therapy established and an adjusted urgently clinical response.

A promising improvement on critically ill patients' prognosis, through an approach based on lactate absolute serum concentrations and, further, its kinetics on the first hours of admission, emerges. Our results should therefore motivate further investigation: prospective and controlled studies comparing ΔL with short and long term prognosis, as well as the reliability of lactate kinetics in assessing the response to different therapies.

The complexity of lactate production, metabolism and elimination should be kept in mind, exhaustively pursuing the cause of hyperlactatemia.

AGRADECIMENTOS

À Dr.ª Andrea, por ensinar, por orientar e guiar este projeto.
À Dr.ª Joana Chagas e Drª Joana Andrade, pelo trabalho de equipa.
Ao Serviço de Cuidados Intensivos do Hospital Pediátrico de Coimbra.
À Prof.ª Doutora Guiomar Oliveira e a todos os que, como ela, inspiram o amanhã da medicina.

Aos ombros amigos, por brindarem conquistas e derrotas na mesma medida.
À família, mais perto ou mais longe, pelo colo de sempre.
Ao Daniel, por estar nas 25 horas do meu dia.

REFERENCES

1. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. Mayo Clinic Proceedings. 2013.
2. Bai Z, Zhu X, Li M, Hua J, Li Y, Pan J, et al. Effectiveness of predicting in-hospital mortality in critically ill children by assessing blood lactate levels at admission. BMC Pediatr. 2014;
3. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. Lancet. 1999.
4. McCarter FD, Nierman SR, James JH, Wang L, King JK, Friend LA, et al. Role of skeletal muscle Na+-K+. ATPase activity in increased lactate production in sub-acute sepsis. Life Sci. 2002;
5. Jeppesen JB, Mortensen C, Bendtsen F, Møller S. Lactate metabolism in chronic liver disease. Scand J Clin Lab Invest. 2013;
6. Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med. 2019;
7. Bakker J, Nijsten MWN, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care. 2013;
8. Mizock BA. The hepatosplanchnic area and hyperlactatemia: A tale of two lactates. Critical Care Medicine. 2001.
9. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Coun. Resuscitation. 2008;
10. Topjian AA, De Caen A, Wainwright MS, Abella BS, Abend NS, Atkins DL, et al. Pediatric Post-Cardiac Arrest Care: A Scientific Statement from the American Heart Association. Circulation. 2019.
11. Donnino MW, Miller J, Goyal N, Loomba M, Sankey SS, Dolcourt B, et al. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. Resuscitation. 2007;
12. Donnino MW, Andersen LW, Giberson T, Gaieski DF, Abella BS, Peberdy MA, et al. Initial lactate and lactate change in post-cardiac arrest: A multicenter validation study. Crit Care Med. 2014;
13. Blow O, Magliore L, Claridge JA, Butler K, Young JS. The golden hour and the silver day: Detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. In: Journal of Trauma - Injury, Infection and Critical Care. 1999.

14. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. Intensive Care Med. 2007;
15. Lipka K, Bülow HH. Lactic acidosis following convulsions. Acta Anaesthesiol Scand. 2003;
16. Cerretelli P, Samaja M. Acid-base balance at exercise in normoxia and in chronic hypoxia. Revisiting the “lactate paradox.” European Journal of Applied Physiology. 2003.
17. Roussos C. Function and fatigue of respiratory muscles. Chest. 1985.
18. Meert KL, McCaulley L, Sarnaik AP. Mechanism of lactic acidosis in children with acute severe asthma. Pediatr Crit Care Med. 2012;
19. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. Emerg Med J. 2005;
20. Demir IE, Ceyhan GO, Friess H. Beyond lactate: Is there a role for serum lactate measurement in diagnosing acute mesenteric ischemia? Digestive Surgery. 2012.
21. Martinschek A, Evers B, Lampl L, Gerngroß H, Schmidt R, Sparwasser C. Prognostic aspects, survival rate, and predisposing risk factors in patients with Fournier’s gangrene and necrotizing soft tissue infections: Evaluation of clinical outcome of 55 patients. Urol Int. 2012;
22. Jeng JC, Jablonski K, Bridgeman A, Jordan MH. Serum lactate, not base deficit, rapidly predicts survival after major burns. Burns. 2002;
23. Moon JM, Shin MH, Chun BJ. The value of initial lactate in patients with carbon monoxide intoxication: In the emergency department. Hum Exp Toxicol. 2011;
24. Cox K, Cocchi MN, Salciccioli JD, Carney E, Howell M, Donnino MW. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. J Crit Care. 2012;
25. A. F-V, M. R, R. M, H. T-A, A. K, B.-A. S, et al. Outbreak of life-threatening thiamine deficiency in infants in Israel caused by a defective soy-based formula. Pediatrics. 2005;
26. Suganuma K, Miwa H, Imai N, Shikami M, Gotou M, Goto M, et al. Energy metabolism of leukemia cells: Glycolysis versus oxidative phosphorylation. Leuk Lymphoma. 2010;
27. Smith ZR, Horng M, Rech MA. Medication-Induced Hyperlactatemia and Lactic Acidosis: A Systematic Review of the Literature. Pharmacotherapy. 2019.
28. Zehtabchi S, Sinert R, Baron BJ, Paladino L, Yadav K. Does ethanol explain the acidosis commonly seen in ethanol-intoxicated patients? J Toxicol - Clin Toxicol. 2005;
29. Mak CM, Lee HCH, Chan AYW, Lam CW. Inborn errors of metabolism and expanded newborn screening: Review and update. Critical Reviews in Clinical Laboratory Sciences. 2013.
30. Dellinger RP, Levy M, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock:

2012. Crit Care Med. 2013;
31. Broder G, Weil MH. Excess lactate: An index of reversibility of shock in human patients. Science (80-). 1964;
32. Oedorf K, Day DE, Lior Y, Novack V, Sanchez LD, Wolfe RE, et al. Serum lactate predicts adverse outcomes in emergency department patients with and without infection. West J Emerg Med. 2017;
33. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah C V., et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med. 2009;
34. Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. In: American Journal of Surgery. 2003.
35. Gladden LB. Lactate metabolism: A new paradigm for the third millennium. Journal of Physiology. 2004.
36. Tisherman SA, Barie P, Bokhari F, Bonadies J, Daley B, Diebel L, et al. Clinical practice guideline: Endpoints of resuscitation. Journal of Trauma - Injury, Infection and Critical Care. 2004.
37. Antonelli M, Levy M, Andrews PJD, Chastre J, Hudson LD, Manthous C, et al. Hemodynamic monitoring in shock and implications for management. Intensive Care Med. 2007;
38. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. In: Pediatric Critical Care Medicine. 2005.
39. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009 Jul;32(1):35–9.
40. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. JAMA - J Am Med Assoc. 2010;
41. Ghneim MH, Regner JL, Jupiter DC, Kang F, Bonner GL, Bready MS, et al. Goal directed fluid resuscitation decreases time for lactate clearance and facilitates early fascial closure in damage control surgery. Am J Surg. 2013;
42. Pan J, Peng M, Liao C, Hu X, Wang A, Li X. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: A meta-analysis. Medicine (Baltimore). 2019;
43. Nichol A, Bailey M, Egi M, Pettila V, French C, Stachowski E, et al. Dynamic lactate indices as predictors of outcome in critically ill patients. Crit Care. 2011;
44. Puskarich MA, Trzeciak S, Shapiro NI, Arnold RC, Heffner AC, Kline JA, et al.

Prognostic value and agreement of achieving lactate clearance or central venous oxygen saturation goals during early sepsis resuscitation. Acad Emerg Med. 2012;

45. H.B. N, W.S. K, M. B, P. S, M. M, C.-H. L, et al. Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: A multi-national evaluation. Critical Care. 2011.
46. Masyuk M, Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig JM, et al. Prognostic relevance of serum lactate kinetics in critically ill patients. Intensive Care Med. 2019;
47. Datta D, Walker C, Gray AJ, Graham C. Arterial lactate levels in an emergency department are associated with mortality: A prospective observational cohort study. Emerg Med J. 2015;
48. Zhang Z, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically Ill patients: A systematic review and meta-analysis. Critical Care Medicine. 2014.
49. Walker CA, Griffith DM, Gray AJ, Datta D, Hay AW. Early lactate clearance in septic patients with elevated lactate levels admitted from the emergency department to intensive care: Time to aim higher? J Crit Care. 2013;
50. Baysan M, Baroni GD, van Boekel AM, Steyerberg EW, Arbous MS, van der Bom JG. The Added Value of Lactate and Lactate Clearance in Prediction of In-Hospital Mortality in Critically Ill Patients With Sepsis. Crit Care Explor. 2020;
51. Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J, et al. Paediatric index of mortality 3: An updated model for predicting mortality in pediatric intensive care. Pediatr Crit Care Med. 2013;
52. Hermans G, Van den Berghe G. Clinical review: Intensive care unit acquired weakness. Critical Care. 2015.
53. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit Care Med. 2012;
54. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: A multinational, multicenter study. J Am Med Assoc. 2005;
55. Jansen TC, Van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, Van Der Klooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;
56. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;
57. Brookhart MA, Stürmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: Challenges and potential approaches. Medical Care.

2010.
58. Bryant SE, McNabb K. Postintensive Care Syndrome. Critical Care Nursing Clinics of North America. 2019.
59. Knoester H, Grootenhuis MA, Bos AP. Outcome of paediatric intensive care survivors. European Journal of Pediatrics. 2007.