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Original Article

Predictive value of serum lactate dehydrogenase in diagnosis of septic shock in critical pediatric patients: A cross−sectional study

HebatAllah Fadel Algebaly[1], Ahmed Abd−Elal[1], Rasha El Kaffas[2], Elshymaa Salah Ahmed[1✉]

[1]*Pediatric Critical Care Department, Cairo University School of Medicine, Egypt*

[2]*Department of Clinical and Chemical Pathology, Cairo University School of Medicine, Egypt*

ABSTRACT

Objectives: To determine the predictive value of lactate dehydrogenase (LDH) in the diagnosis of septic shock and its association with other prognostic scores in critical pediatric patients.
Methods: A cross-sectional study was performed at Children's Hospital of Cairo University between June 2019 and December 2019. A total of 200 pediatric patients were divided into the septic shock group [100 critically ill patients with septic shock from the pediatric intensive care unit (PICU)] and the control group (100 patients with only sepsis). LDH was determined in the first 24 hours of admission. The sensitivity and specificity of LDH in diagnosis of septic shock were assessed; the levels of related indicators of patients with different etiologies were compared; correlations between LDH, Paediatric Index of Mortality Ⅱ, and Pediatric Sequential Organ Failure Assessment (pSOFA) were analyzed.
Results: Median LDH was 512 μL (406.50-663.00) in the septic shock group and was significantly higher than that [190 μL (160.00-264.50)] in the control group (*P*<0.001). Besides, median LDH in children with chest infecion was higher than that in children with other diagnoses (*P*=0.047). A good positive correlation was found between pSOFA and LDH (*r*=0.503, *P*<0.001).
Conclusions: LDH could be a potential inflammatory marker in the diagnosis of septic shock and is valuable for PICU admission decisions.

KEYWORDS: Lactate dehydrogenase; Septic shock; pSOFA

1. Introduction

Many cascade reactions are involved in severe illness (*e.g.* sepsis) that always begin with the pro-inflammatory process[1]. Lactate dehydrogenase (LDH) is one of the anaerobic metabolic pathway enzymes. Its serum level is elevated in multiple conditions resulting from tissue damage[2]. Several studies recorded a significant increase in LDH serum levels very early in sepsis[3]. Also, LDH levels have been proposed as a marker for sepsis prognosis[4]. They showed that LDH was prognostically elevated in cases of severe sepsis and septic shock, and it is considered as an index to assess the extent to which the tissue was affected[5].

LDH was found associated with 28-day mortality in patients with severe sepsis[6]. Also, it has been shown that pH, LDH and heart rate were the most important factors to assess the progress and outcome of a septic patient[7]. LDH level was found to be a prognostic marker for severe illness in neonates (*e.g.* early neonatal sepsis)[8]. Others said that if the LDH levels were not improved within 48 h in patients with severe sepsis, patients will be more likely to die[4].

Recently, LDH is considered a valuable biomarker in the diagnosis and follow-up of SARS-Cov-2 infection. One study concluded that LDH was a useful biomarker in the evaluation of case severity and for monitoring its response to treatment[9]. Another recommendation is successive measurements of LDH, C-reactive protein (CRP), and procalcitonin (PCT) in pediatric patients with COVID-19 infection as they may help follow the course of the illness[10]. Although there are a lot of studies on LDH, they have not explained the relation between LDH and severity in pediatric patients with sepsis. Moreover, several prognostic scores such as Sequential Organ Failure Assessment (SOFA) score and Paediatric Index of Mortality

Ⅱ(PIMⅡ) score have been applied to assess the severity and predict the risk of death at PICU admission, which can be a guide for treatment and caring. PIMⅡ was first developed by Slater *et al*. in 1997, updated in 2003[11]. Also, the Sepsis-Related Organ Failure Assessment was developed initially to assess organ conditions in critically ill adults[12]. Recently, a pediatrics version of the SOFA score (pSOFA) was developed for critically ill children[13]. The score is composed of 6 variables for respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems, respectively[12]. This study aims to determine the predictive value of LDH in diagnosis of septic shock and its relationship with other proven prognostic scores.

2. Patients and methods

2.1. Study design

A cross-sectional, case-control study was performed at University Children Hospital from June 2019 till December 2019.

2.2. Ethical approval

The institutional review board at our institution approved our study with ethical approval No. I.101015.

2.3. Inclusion and exclusion criteria

We included patients with sepsis, severe sepsis, or septic shock who met the criteria of the American College of Critical Care Medicine[14]. The American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock 2012 defines septic shock by clinical signs, including hypothermia or hyperthermia, altered mental status, and peripheral vasodilatation (warm septic shock) or vasoconstriction with capillary refill time more than 2 seconds (cold septic shock) before hypotension occurs.

We excluded patients with lipid disorders, metabolic disorders, tumors, acute hemolytic anemia, chronic liver or kidney disease, and patients on steroid therapy.

2.4. Patients and grouping

Two hundred pediatric patients were grouped into the septic shock group (100 critically ill patients with septic shock from PICU) and the control group (100 patients with only sepsis).

2.5. Sample collection and assessments

The sample was taken for LDH assay as follows: 2 mL of whole blood were collected with plain tubes (BDO vacutaier). Samples were immediately centrifuged, and the serum was used for analysis through blood chemistry analyzer Dimension RXL M AX integrated

chemistry system from Siemens Health care S.A.E, Germany Ⅰ*. Principle of the enzymatic assay is that the reaction between pyruvate and Nicotinamide adenine dinucleotide dehydrogenase (NADH) is catalyzed by LDH to produce Nicotinamide adenine dinucleotide (NAD) and *L*-lactate: LDH+Pyruvate+NADH=*L*-lactate+NAD. The stronger the catalytic activity of LDH, the more NAD oxidation. It was estimated by measuring the decrease in absorbance at 340 nm.

Also, the PIMⅡ score at the time of admission was calculated. Ten items with yes or no answers for these variables scored as 1 or 0. These variables were entered into the system (www.sfar.org/scores2/pim22.html). The system calculates the mortality rate based on standard methods using logistic regression equations[11].

2.6. Statistical analysis

All data was analyzed using the Statistical Package Social Science (SPSS) version 16 and expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Differences in clinical and biochemical characteristics were analyzed by student's paired and unpaired *t*-test and Mann-Whitney *U* test. Areas under curves was used to assess the specificity and sensitivity of LDH in diagnosis of spetic shock. Correlation analysis were conducted to determine the association between LDH and different parameters in the septic shock group. Kruskall Wallis *H* test was applied to assess the differences among diagnoses of septic shock regarding laboratory and clinical criteria. The significant level of this study was set at α=0.05.

3. Results

CRP in the septic shock group was 46.3 (23.35-80.80) mg/L, which was significantly higher than that in the control group of 11.00 (1.60-24.00) mg/L (*P*<0.001). Serum glutamic-oxaloacetic transaminase (SGOT) in the septic shock group was 32.00 (22.00-56.50) μL, which was significantly higher than that in the control group of 23.00 (18.00-31.00) μL (*P*=0.001). Besides, LDH in the septic shock group was 512.00 (406.50-663.00) μL, which was significantly higher than that in the control group of 190.00 (160.00-264.50) μL (*P*<0.001) (Table 1). The cutoff point of 272 μL of LDH was a potential adjuvant for clinical evaluation and differentiation of septic shock from sepsis only with a sensitivity of 91% and specificity of 77% (Figure 1).

Also, our study revealed that there was a good positive correlation between LDH and liver enzyme (SGOT and SGPT) (*r*=0.581, *P*<0.001; *r*=0.491, *P*<0.001, respectively), and creatinine (*r*=0.202, *P*=0.043). Also, the higher the pSOFA score, the higher the LDH (*r*=0.503, *P*<0.001), unlike with other score systems as PIMⅡ (*r*=0.034, *P*=0.738) (Figure 2) (Table 2) .

The results showed that the median of LDH in chest infection was higher than that in other diagnoses (*P*=0.047) (Table 3).

Table 1. Comparison of the clinical and laboratory criteria of the two groups.
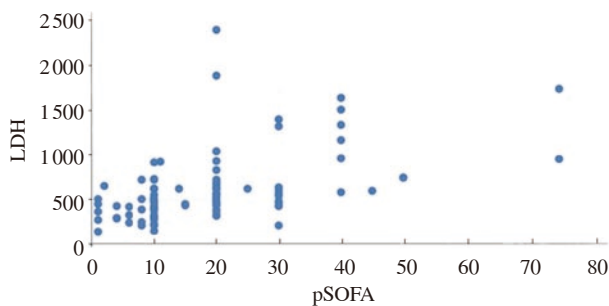
Variables	Control group	Septic shock group	t/U	P
Age (months)	24.00 (12.00-60.00)	24.00 (6.50-36.00)	1.914*	0.056
Base excess (mL/L)	0.00 (0.00-2.00)	−0.20 (−4.00-3.00)	2.261*	0.012*
Na (mmol/L)	135.27±4.61	139.03±6.95	4.512≠	<0.001*
K (mmol/L)	3.59±0.51	3.78±0.74	2.080≠	0.039
Creatinine (mg/dL)	0.60 (0.50-0.60)	0.50 (0.40-0.60)	1.227*	0.160
BUN (mg/dL)	13.28±4.19	11.40±3.29	3.529≠	0.001*
SGOT (μL)	23.00 (18.00-31.00)	32.00 (22.00-56.50)	5.011*	0.001*
SGPT (μL)	40.00 (35.00-58.00)	30.50 (22.00-52.00)	1.742*	0.083
Hemoglobin (g/dL)	10.43±1.75	9.95±1.54	2.049≠	0.042*
Platelets (×10⁹/L)	294.16±105.20	269.31±97.24	1.735≠	0.084
WBCs (×10⁹/L)	11.55 (8.20-13.90)	11.90 (9.75-15.20)	1.827*	0.069
Band cells (μL)	6.00 (4.00-8.00)	8.00 (3.00-12.00)	3.225*	<0.001*
Segmented cells (μL)	50.66±13.01	53.50±15.51	1.403≠	0.162
CRP (mg/L)	11.00 (1.60-24.00)	46.30 (23.35-80.80)	7.358*	<0.001*
LDH (μL)	190.00 (160.00-264.50)	512.00 (406.50-663.00)	10.001*	<0.001*

Data are expressed as mean ± SD or median (IQR); *: Mann-Whitney *U* test; ≠: Independent *t*-test; *: Significantly different; BUN: Blood urea nitrogen; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; SOFA: The Sequential Organ Failure Assessment; WBCs: White blood cells; CRP: C-reactive protein; LDH: Lactate dehydrogenase.
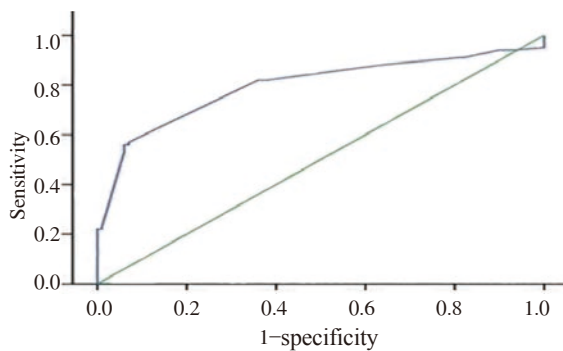
Figure 1. Sensitivity and specificity curve for serum lactate dehydrogenase level. The area under curves is 0.9; Sensitivity: 91%; Sepecificity:77%; Green line: Reference line; Blue line: lactate dehydrogenase (μL).

Table 2. Correlation between LDH and different parameters in the septic shock group (*n*=100).

Variables	R	P
SBP	−0.021	0.838
pSOFA	0.503	<0.001*
PIM II	0.034	0.738
Na	−0.062	0.543
K	0.047	0.642
Creatinine	0.202	0.043*
BUN	0.063	0.533
SGOT	0.581	<0.001*
SGPT	0.491	<0.001*
Hemoglobin	0.075	0.460
WBCs	0.077	0.444
CRP	−0.023	0.817

SBP: Systolic blood pressure; PSOFA: Pediatrics version of the SOFA score; PIM II : Paediatric Index of Mortality II ; BUN: Blood urea nitrogen; SGOT: Serum glutamic-oxaloacetic transaminase; WBCs: White blood cells; CRP: C-reactive protein.

Figure 2. Correlation between lactate dehydrogenase and Pediatrics version of the SOFA score. pSOFA: Pediatrics version of the SOFA score; LDH: Lactate dehydrogenase.

4. Discussion

Last decade, a lot of biomarkers and scores have been developed for early diagnosis and assessment of severe illness in the emergency department[15]. LDH is the cornerstone in the diagnosis of different illnesses[16]. Erez *et al.* recorded a significant increase in serum level of LDH at the onset of sepsis[2].

Table 3. Differences among diagnoses of septic shock regarding laboratory and clinical criteria.

Variables	Etiologies					H	P
	Cardiac cause	Chest infections	CNS infection	Abdominal infection	Unknown infection		
Age (year)	30.00 (24.00-48.00)	21.00 (6.00-25.00)	32.00 (7.00-48.00)	55.00 (24.00-60.00)	15.00 (4.00-30.00)	14.400	0.006*
PIM II	16.50 (13.70-18.40)	16.50 (13.84-18.10)	17.80 (14.50-21.70)	16.00 (14.23-17.50)	16.80 (13.63-20.18)	4.872	0.301
PSOFA	12.50 (10.00-30.00)	20.00 (10.00-25.00)	20.00 (10.00-30.00)	20.00 (10.00-30.00)	10.00 (10.00-20.00)	1.922	0.650
LDH (mL)	450.00 (415.00-530.00)	614.00 (495.00-662.00)	513.00 (311.00-928.00)	522.00 (314.00-612.00)	433.00 (377.00-611.00)	2.980	0.047*

Data are expressed as median (IQR); *: Significantly different; PIM II : Paediatric Index of Mortality II ; PSOFA: Pediatric Sequential Organ Failure Assessment; LDH: Lactate dehydrogenase; CNS: Central nervous system.

In our study, the median value of LDH in patients with severe sepsis/septic shock was 512 μL. A neonatal study by Ozkiraz *et al.* described the usefulness of LDH and lactate in deciding to refer neonates who suffer from transient tachypnea of new born to high-level neonatal care before the clinical situation deteriorates[17].

In our study, the cutoff value of 276 μL was a predictor for organ failure and the need for PICU admission with a sensitivity of 90% and specificity of 77% and was able to distinguish septic shock and severe sepsis from sepsis only. Karlsson *et al.* concluded that LDH might be of a significant value during the neonatal period, and its predictive value is more important than that of lactate. Preterm infants presented with a serum LDH level range of 500-700 μL with a cut-off of 600 μL were predicted to have a strong need for NICU admission[18].

Our study showed that LDH in chest infection was higher than that in other diagnoses (*P*=0.047). Another study shows LDH is a good biomarker for a limited list of diseases, mostly infections, particularly chest infection, tumor, liver metastases, and hematologic malignancies[19]. Hendya *et al.* showed in a case presented with community-acquired pneumonia, LDH, albumin, CRP, and neutrophils should be determined to give an idea about the course, prognosis, and complication[20]. Pleural fluid LDH is useful for assessing the severity of pediatric community-acquired pneumonia patients with mycoplasma pneumonia and fever lasting for >3 d had a high level of LDH and total leucocytic count[21]. LDH is usually used besides another marker and clinical criteria in the diagnosis of certain opportunistic infections, like pneumocystis crania pneumonia and toxoplasmosis[22], especially in patients suffering from AIDS[23]. Another report argued the specificity of LDH as it is highly increased within minutes of hypoxic-ischemic state occurring anywhere in the body[24]. However, we suggest its use in addition to other clinical signs of infection rather than to replace them to quantify sepsis severity.

Current study observed a good positive correlation between pSOFA and LDH, the higher the SOFA score, the higher the LDH (*r*=0.503, *P*<0.001). Similarly, García-Gigorro *et al.* concluded that SOFA and changes in the SOFA score over time are good tools for assessing and follow up critically ill patients in ICUs[25].

The high LDH level was associated with a bad outcome in the form of more admission days, a higher risk factor for in-hospital mortality[26]. Its level was not considered as a dependent risk factor for mortality in patients with sepsis[6]. The patients with serum LDH more than 1 000 μL also had a long hospital stay and multiple organ affection as evident by SOFA score[27]. Chkhaidze *et al.*, who found that SOFA scores are an excellent tool to assess the organ affection in critically ill patients while PIM Ⅱ gives a good rank for diagnosis risk rather than specific organ involvement[28].

All in all, LDH could be a potential inflammatory marker in conjunction with the other clinical criteria to discriminate against critically ill children with severe sepsis. This can guide the decision of PICU admission.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

H.A.F.A.: Creating idea of the work; A.A: Data collection; R.E.K.: Laboratory analysis; E.S.A.: Paper writing.

References

[1] Van Eijk LT, Dorresteijn MJ, Smits P, Van der Hoeven JG, Netea MG, Pickkers P. Gender differences in the innate immune response and vascular reactivity following the administration of endotoxin to human volunteers. *Crit Care Med* 2007; **35**(6): 1464-1469.

[2] Erez A, Shental O, Tchebiner JZ, Laufer-Perl M, Wasserman A, Sella T, et al. Diagnostic and prognostic value of very high serum lactate dehydrogenase in admitted medical patients. *Isr Med Assoc J* 2014; **16**(7): 439-443.

[3] Trepos E, Katodritou E, Roussou M. High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. *Eur J Haematol* 2010; **85**(2): 114-119.

[4] Joe GZ, Gregory LL, Maroun RN, Mohammed D, Gary TK. Prognostic significance of elevated serum lactate dehydrogenase (LDH) in patients with severe sepsis. *Chest* 2004; **126**(4): 873S.

[5] Bekhit OE, Algameel AA, Eldash HH. Application of pediatric index of mortality version 2: score in pediatric intensive care unit in an Africandeveloping country. *Pan Afr Med J* 2014; **17**: 185.

[6] Lu J, Wei ZH, Jiang H, Cheng L, Chen QH, Chen MQ, et al. Lactate dehydrogenase is associated with 28-day mortality in patients with sepsis: a retrospective observational study. *J Surg Res* 2018; **228**: 314-321.

[7] Duman A, Akoz A, Kapci M, Ture M, Orun S, Karaman K, et al. Prognostic value of neglected biomarker in sepsis patients with the old and new criteria: predictive role of lactate dehydrogenase. *Am J Emerg Med* 2016; **34**(11): 2167-2171.

[8] Anh TN, Hao TK, Hoang HH. The role of plasma lactate dehydrogenase testing in the prediction of severe conditions in newborn infants: A prospective study. *Res Rep Neonatol* 2020; **10**: 31-35.

[9] Wu MY, Yao L, Wang Y, Zhu XY, Wang XF, Tang PJ, et al. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia. *Respir Res* 2020; **21**(1): 171.

[10]Henry BM, Benoit SW, Santos de Oliveira MH, Hsieh WC, Benoit J, Ballout RA, et al. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. *Clin Biochem* 2020; **81**: 1-8.

[11]Slater A, Shann F, Pearson G. PIM Ⅱ: a revised version of the pediatric index of mortality. *Intensive Care Med* 2003; **29**(2): 278-285.

[12]Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D,

Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**(8): 801-810.

[13]Matics TJ, Sanchez-Pinto LN. Adaptation and validation of a Pediatric Sequential Organ Failure Assessment Score and evaluation of the Sepsis-3 definitions in critically ill children. *JAMA Pediatr* 2017; **171**(10): e17235.

[14]Dellinger RP, Levy MM, 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; **41**(2): 580-637.

[15]Biron BM, Ayala A, Lomas-Neira JL. Biomarkers for sepsis: What is and what might be? *Biomark Insights* 2015; **10s4**: 7-17.

[16]Khan AA, Allemailem KS, Alhumaydhi FA, Gowder SJT, Rahmani AH. The biochemical and clinical perspectives of lactate dehydrogenase: An enzyme of active metabolism. *Endocr Metab Immune Disord Drug Targets* 2020; **20**(6): 855-868.

[17]Ozkiraz S, Gokmen Z, Boke SB, Kilicdag H, Ozel D, Sert A. Lactate and lactate dehydrogenase in predicting the severity of transient tachypnea of the newborn. *J Matern Fetal Neonatal Med* 2013; **26**(12): 1245-1248.

[18]Karlsson M, Dung K, Thi TL, Borgström E, Jonstam K, Kasström, et al. Lactate dehydrogenase as an indicator of severe illness in neonatal intensive care patients: a longitudinal cohort study. *Acta Paediatr* 2012; **101**(12): 1225-1231 .

[19]Wasserman A, Shnell M, Boursi B. Prognostic significance of serum uric acid in patients admitted to the department of medicine. *AMJ Med Sci* 2010; **339**(1): 5-21.

[20]Hendya RM, Elawadyb MA, Abd EL Kareemc HM. Role of lactate dehydrogenase and other biomarkers inpredicting prognosis of community-acquired pneumonia. *Egypt J of Bronchol* 2020; **13**(4): 539-544.

[21]Jeong JE, Soh JE, Kwak JH, Jung HL, Shim JW, Kim DS, et al. Increased procalcitonin level is a risk factor for prolonged fever in children with *Mycoplasma pneumonia. Korean J Pediatr* 2018; **61**(8): 258-263.

[22]Butt AA, Michaels S, Kissinger P. The association of serum lactate dehydrogenase level with selected opportunistic infections and HIV progression. *Int J Infect Dis* 2002; **6**(3): 178-181.

[23]Deng C, Li Y, Li Y. Systemic review: the accuracy of lactic dehydrogenase in the diagnosis of pneumocystis pneumonia. *Zhonghua Wei Zhong Bing Ji Jiu Yi* 2018; **30**(4): 322-326.

[24]Helliksson F, Wernerman J, Wiklund L, Rosell J, Karlsson M. The combined use of three widely available biochemical markers as predictor of organ failurein critically ill patients. *Scand J Clin Lab Invest* 2016: **76**(6): 479-485.

[25]García-Gigorro R, Sáez-de la Fuente I, Marín Mateos H, Andrés-Esteban EM, Sanchez-Izquierdo JA, Montejo-González JC. Utility of SOFA and -SOFA scores for predicting outcome in critically ill patients from the emergency department. *Eur J Emerg Med* 2019; **26**(4): 309-310.

[26]Farah R, Makhoul N. Usefullness of various inflammatory markers to differentiate pulmonary edema from pneumonia. *Isr Med Assoc J* 2011: **13**(4): 225-229.

[27]Anand M, Radhakrishnan A, Rajendiran C, Kanagasabai V. Serum lactate dehydrogenase and C reactive protein levels in sepsis and itscorrelation with APACHE- Ⅱ score. [Online] Available from: http://repository-tnmgrmu.ac.in/6754/1/200100112anand.pdf. [Accessed on 20 January 2021].

[28]Chkhaidze MG, Kheladze ZS, Pruidze DR, Abelashvili DI, Gvetadze PR. Comparison of PIM and SOFA scoring systems for mortality risk prognosis in critically ill children with sepsis. *Georgian Med News* 2006; (131): 66-68.