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Original article

Value of Serum Level of Lactate Dehydrogenase (LDH) as a Factor for Assessment of Severity and Mortality in Children with COVID-19

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Abstract

Background: Lactate dehydrogenase (LDH) is an enzyme found inside most of body cells and has an important role in generation of energy via the inter conversion of pyruvate and lactate. LDH is elevated in severe infectious or inflammatory diseases including patients with COVID-19 infection. **Aim and objectives:** to assess value of serum level of LDH as a predictor of severity and mortality in children infected with SARS COV 2 virus. **Subjects and methods:** This cross-sectional analysis encompassed a sample of 81 pediatric patients admitted to Benha Children Hospital, who were categorized into two distinct cohorts: those exhibiting severe symptoms and those with non-severe manifestations. LDH concentrations were quantified across both groups and their associations with CBC, D-dimer levels, hepatic function markers, and serum ferritin were evaluated. Additionally, these clinical indicators were assessed in context of hospital stay duration, necessity for invasive respiratory support, cardiac intervention, and overall patient outcomes. The classification of "severe disease" was based on clinical requirements for inotropic support, meeting criteria for acute respiratory distress syndrome, dependence on mechanical ventilation, or the need for admission to ICU. **Results:** LDH levels were elevated in severe group. Causes of admission, length of stay, and treatment strategies varied between two groups. A significant correlation was found between LDH levels and liver function, D-dimer, and serum ferritin. Additionally higher LDH levels were correlated with need for invasive ventilation, cardiac support and adverse clinical outcomes.**Conclusion:** LDH could be identified as a predictive factor for severity and mortality in children with COVID-19.

Keywords: Lactate Dehydrogenase (LDH), Mortality, COVID-19

Introduction

In late 2019, a previously unknown coronavirus, subsequently designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was pinpointed as the etiological agent behind a series of pneumonia cases that emerged in Wuhan, a metropolitan hub in China's Hubei province. The virus exhibited rapid transmissibility, leading to its global dissemination and the subsequent declaration of a pandemic by the WHO, which termed the associated illness as coronavirus disease 2019 (COVID-19) [1].

During the initial phase of the COVID-19 pandemic, the incidence of confirmed cases among pediatric populations was comparatively low, leading to the early assumption that children were infrequently impacted by this virus [2]. Emerging research has consistently demonstrated that children and adolescents are indeed vulnerable to SARS-CoV-2 infection. However, a major proportion of pediatric cases present as either asymptomatic or pre-symptomatic, leading to an underestimation of the actual infection rate, which is compounded by the relatively low frequency of testing within this demographic [3].

Severe manifestations of COVID-19 are marked by an intense inflammatory response that can progress to multi-organ failure and potentially culminate in patient mortality. Numerous biomarkers are presently being explored for their potential utility in prognostic assessment of COVID-19 patients [4].

LDH has garnered attention as a biomarker of particular interest, largely due to its historical association with poor clinical outcomes in patients afflicted by other viral infections, where elevated LDH levels have been linked to more severe disease progression [5]. The correlation between inflammatory mediators, including IL-6 and LDH, with severe disease presentations implies that an overwhelming inflammatory response is a pivotal factor contributing to adverse clinical outcomes [6].

LDH exhibits an early elevation in myocardial infarction and hemolytic conditions, given its prominent enzymatic activity across vital organs such as the liver, striated muscles, myocardium, kidneys, lungs, brain, and erythrocytes. Upon cellular insult, LDH is liberated from intracellular compartments, leading to a marked increase in its serum concentration and enzymatic activity. Elevated serum LDH activity is recognized as an unfavorable prognostic indicator in such pathological states. Moreover, LDH serves as a critical biomarker for a diverse array of inflammatory pathologies, including infectious diseases, neoplasms, myocardial infarction, sepsis, and cardiopulmonary dysfunction [5].

This work aimed to study the value of lactate dehydrogenase (LDH) in predicting severity and outcome in children with COVID-19.

Patients and Methods

This cross-sectional observational study included 81 patients all Children with various presentations of COVID-19 infection admitted to Benha Children Hospital isolation department from March 2022 to March 2023.

Inclusion criteria

All pediatric patients, aged between 1 month and 16 years, presenting with probable, suspected, or confirmed COVID-19 infection and admitted to the isolation department of Benha Children Hospital were included in the study.

Suspected case [7]:

A) Clinical **AND** Epidemiological Criteria:

-Acute onset of fever and cough OR
≥ 3 of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/ vomiting, diarrhea, altered mental status

And 1 of the following within 14 days of symptom onset*:

Residing or working in an area with high risk of transmission*	Residing or travel to an area with community transmission	Working in a healthcare setting

OR: B

Patients with severe acute respiratory infections (SARI) defined as acute respiratory infection with symptoms within 10 days of presentation, cough, fever, and hospitalization.

Probable case:

A patient who meets clinical criteria AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster with at least one confirmed case.
OR
Suspect case with chest imaging showing findings suggestive of COVID-19 disease*
OR
Recent onset of loss of smell or taste in the absence of any other identified cause
OR
Unexplained death in an adult with respiratory distress who was a contact of a probable or confirmed case or epidemiologically linked to a cluster with at least 1 confirmed case

*Hazy opacities with peripheral and lower lung distribution on chest radiography; multiple bilateral ground glass opacities with peripheral and lower lung distribution on chest CT; or thickened pleural lines, B lines, or consolidative patterns on lung ultrasound.

Confirmed case:

A patient with laboratory-confirmed COVID-19 infection, regardless of the presence or absence of clinical manifestations.

Exclusion criteria

Patients less than one month, and more than Sixteen years old or Patients with another etiologic cause elevated LDH e.g: oncological disorders.

Then, they were divided based on the following classification [10] into: -

Group A (Non-Severe): Mild / Moderate Cases

Group B (Severe): Severe / Critically-ill Cases.

Mild: Mild clinical Symptoms, No pneumonia on lung CT.

Moderate: Fever, cough, [O2 saturation >93 % at rest]

Lung CT with Pneumonia.

Severe: Respiratory distress (RR> 30/ min, O2 saturation ≤ 93 % at rest), and ratio PaO2 / FiO2 ≤ 300 mmol)

Critically ill: criteria of respiratory failure receiving mechanical ventilation (RR> 30/Min, O2 saturation < 93 %, PaO2/FiO2 <300) and \ or

- Multi Organ failure.
- ICU hospitalization.

Methods:

All patients were systematically subjected to the following evaluations: -

- **Detailed History Taking:** This included personal history, history of present illness, past medical history of systemic diseases, and past surgical history.
- **Clinical Examination:**
  - **General Examination:** Comprehensive assessment of overall health and symptoms.
  - **Local Examination:** Focused assessment of cardiovascular, chest and GIT systems
  - **Local CNS Examination:** Neurological evaluation.
- **Investigations:**
  - **Laboratory Investigations:** CBC, CRP, arterial blood gases (ABG), liver function tests (LFTs - AST, ALT), kidney function tests (KFTs - urea, creatinine), blood culture, D-dimer, serum ferritin, nasopharyngeal swab for COVID-19, and serum LDH. LDH levels were measured within the first 24 hours of admission in COVID-19 children.
  - **Radiological Investigations:** X-ray and CT scans of the chest were performed to confirm the diagnosis.
- **Data Collection on Morbidity and Mortality:** Information was gathered on the **duration** of hospital stay, need for **assisted**

ventilation, inotropic support requirements, and mortality outcomes (survival or non-survival).

Ethical consideration

Informed written consent was secured from the parents of all participants. The research protocol received approval from the Benha Faculty of Medicine's ethics committee for human subject's research. All data collected from participants were treated with strict confidentiality. Participants' identities were anonymized in any related reports or publications. Prior to enrollment, the study's purpose, scope, and a thorough risk-benefit analysis were clearly communicated to the participants and their guardians.

Approval code: (MS 3-6-2022)

Statistical analysis

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant. Spearman correlation was done to estimate the degree of correlation between two quantitative variables. The overall diagnostic performance of each test was assessed by ROC curve analysis. The area under the curve (AUC) evaluates the overall test performance.

Results

Eighty-one patients were involved in our study and classified into server and non-severe:

- Non-severe(n=33)
- Severe(n=48)

Clinical presentation of MISC was significantly higher among severe group (p<0.001), While fever, Chest and GIT symptoms were more frequent among non-severe group (p=0.03, 0.002 and 0.02 respectively). Table 1, Figure 1.

IVIG and solumedrol were **more frequently used** in severe group.

Regarding ABG This table examines ABG differences between "Not severe" and "Severe" study groups. Significant variations in pH, PCO2, and HCO3 levels (p<0.05) highlight potential respiratory and metabolic distinctions linked to severity. **Table 2.**

Regarding LDH this table shows that LDH was statistically significantly higher among severe group (p<0.001). **Table 2.**

There was statistically significant positive correlation between LDH, AST, ALT, D-dimer and S. ferritin. **Table 3.**

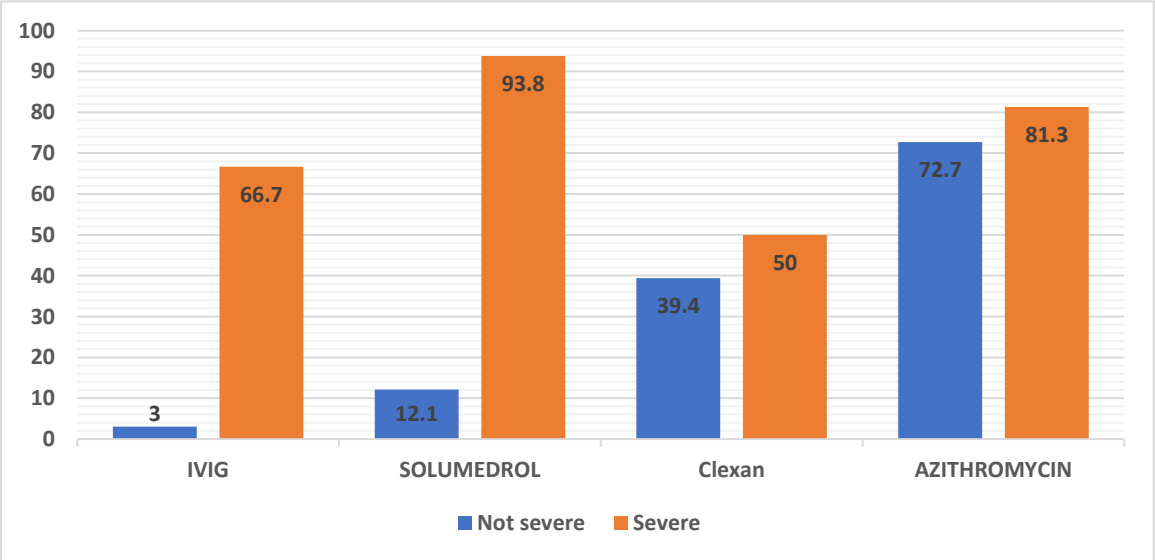
LDH was statistically significantly higher among non-survivors' group (p<0.001). **Table 4, Figure 2.**

Our study showed that LDH was fair test for detection of severity with 75% sensitivity and 66.7 % specificity. **Table 5, Figure 3.**

Table (1): Comparison of study groups regarding clinical presentation

	Not severe (n=33)		Severe (n=48)		X^2/FET	p-value
	No.	%	No.	%		
Chest	17	51.5%	13	27.1%	5.01	0.03*
MIS-C	0	0.0%	33	68.8%	33.6	<0.001*
GIT	9	27.3%	1	2.1%	9.3	0.002*
Fever	5	15.2%	0	0.0%	5.4	0.02*
Neurological	2	6.1%	0	0.0%	0.9	0.3
Kawasaki	0	0.0%	1	2.1%	0.7	0.4

(MIS-C: Multi System Inflammatory Syndrome)



Bar Chart Figure (1): Study groups regarding treatment

Table (2): Comparison of study groups regarding ABG and LDH.

Characteristics	Not severe (n=33)		Severe (n=48)		T	p-value
	mean	± SD	mean	± SD		
pH	7.34	0.07	7.28	0.12	2.3	0.02*
PCO2 (mmHg)	40.01	8.67	32.94	13.01	2.4	0.02*
HCO3 (mEq/L)	21.13	3.79	17.17	4.84	3.5	<0.001*
Characteristics	**Not severe (n=33)**		**Severe (n=48)**		**U**	**p-value**
	Mean	**± SD**	**mean**	**± SD**		
LDH (IU/L)	3860.30	1940.62	6910.19	6120.87	30.3	<00.001*

Arterial blood gas (ABG), Lactate Dehydrogenase (LDH)

Table (3): Correlation between LDH and lab data

	LDH (IU/L) R	p-value
TLC (cells/µL)	-0.003	0.981
Lymphocytes (%)	-0.094	0.413
HB (g/dL)	0.109	0.338
Platelets (cells/µL)	0.077	0.496
AST (IU/L)	0.566	<0.001*
ALT (IU/L)	0.641	<0.001*
Urea (mg/dL)	0.045	0.698
Creatinine (mg/dL)	-0.001	0.992
pH	0.033	0.790
PCO2 (mmHg)	0.030	0.812
HCO3 (mEq/L)	0.018	0.884
D-dimer (µg/L)	0.547	<0.001*
S. ferritin (ng/mL)	0.251	0.031*

AST: Aspartate transaminase, ALT: Alanine transaminase

Table (4): Comparison of LDH level regarding outcome

Characteristics	**Non-Survivors (n=15)**		**Survivors (n=66)**		**U**	**p-value**
	mean	**± SD**	**mean**	**± SD**		
LDH (IU/L)	8270.87	4710.92	5070.68	5000.96	30.6	<0.001*

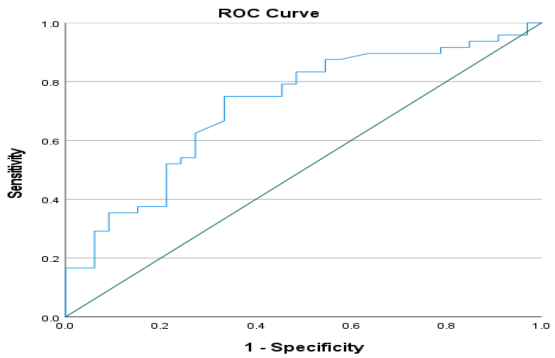


Figure 2: ROC curve for assessing value of LDH for prediction of severity in Covid 19 patients

Table (5): Area under the Curve

Area	p-value	95% Confidence Interval Lower Bound	Upper Bound
0.7	0.001*	0.6	0.8

Fair test for detection of severity with Cut-off = 406 IU/L

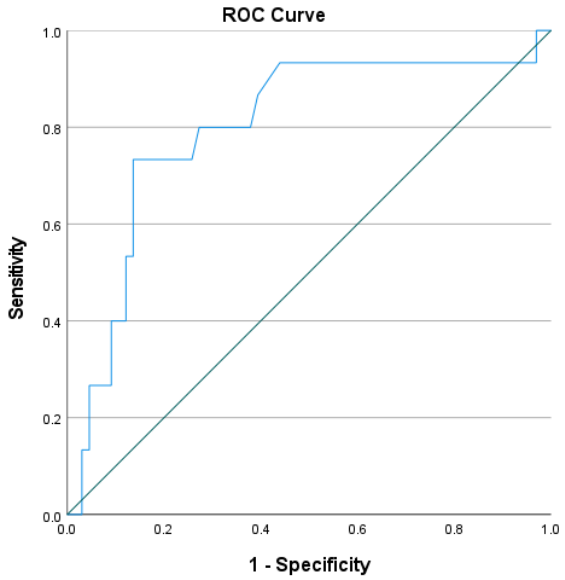


Figure 3: ROC curve for assessing value of LDH for prediction of outcome in Covid 19 patients

Discussion

The coronavirus disease 2019 (COVID-19) pandemic has emerged as a profound global public health crisis, imposing substantial economic burdens on numerous nations. Despite extensive research, the SARS-CoV-2 virus and its mechanism of causing disease remain only partially understood, with many aspects still under investigation [8, 9]. Our results reveal a higher occurrence of MIS C within the severe group ($p<0.001$), while chest symptoms, gastrointestinal manifestations, and fever were significantly more prevalent in the non-severe group ($p=0.03$, 0.002, and 0.02, respectively).

These results align with Zayed et al. [10], who observed a statistically significant difference between groups regarding GIT (diarrhea-anorexia) and chest (COPD-Bronchial asthma), but differed from our findings on fever, where no statistically significant difference was reported ($p= 0.79$). Contrary to our results, Marcos et al. [11] found no variation between the studied groups in terms of fever and GIT (peptic ulcer), while they did find a significant difference in cardiac (CHF-arrhythmia) and neurological causes.

Additionally, our research showed a significantly higher usage of IVIG and SOLUMEDROL in severe cases ($p<0.001$ for both), while Clexan and AZITHROMYCIN usage did not differ significantly between the groups. Ergenc et al. [12] supported these findings, noting that methylprednisolone was more frequently used in the severe group ($p = 0.016$), while azithromycin and enoxaparin usage remained similar between the groups.

We also identified significant variations in pH, PCO2, and HCO3 levels between the severe and non-severe groups ($p<0.05$), indicating potential respiratory and metabolic

distinctions linked to disease severity. Severe acid-base imbalances, often resulting from COVID-19's impact on the lungs and kidneys, can lead to serious multi-organ consequences, including respiratory symptoms like arterial hypoxia and pulmonary issues affecting blood acid-base balance. This aspect of our study is supported by Zayed et al. [10], who also found significant differences in pH, PCO2, and HCO3 levels ($p<0.05$), though it contrasts with the findings of Marcos et al. [11], who reported no significant difference in bicarbonate levels ($p= 0.101$).

Moreover, our research demonstrated that serum levels of D-dimer and ferritin were significantly elevated in the severe group, consistent with the hypercoagulable state often observed in COVID-19 patients. Elevated D-dimer levels, for example, have been associated with ischemic stroke cases. Furthermore, LDH was found to be statistically significantly higher in the severe group ($p<0.001$), a finding corroborated by Han et al. [13], who reported that LDH levels positively correlate with the severity of pneumonia as quantified on initial computed tomography (CT) in COVID-19 patients. Although high LDH levels are linked to increased lung injury, studies suggest that LDH is not necessarily associated with poor prognosis [14].

Our study also revealed a statistically significant positive correlation between LDH, AST, ALT, D-dimer, and s. ferritin, in line with Kaftan et al. [15], who found a non-significant positive correlation between these markers. LDH levels were notably elevated in patients requiring invasive ventilation and cardiac support, consistent with Zeng et al. [16], who reported that patients with elevated LDH levels had significantly higher rates of mechanical ventilation.

In addition, LDH was statistically significantly higher among ICU patients ($p=0.004$). Gopaul et al. [17] agreed with this finding, suggesting that laboratory parameters like LDH could be vital in predicting COVID-19 severity, particularly in the context of limited ICU resources. Our findings also showed that LDH was significantly elevated in the non-survivor group ($p<0.001$), a result consistent with Fialek et al. [8], who found that LDH levels were significantly lower in survivors compared to patients who died in the hospital. Henry et al. [5] further demonstrated a significant association between elevated LDH levels and increased odds of mortality in COVID-19 patients.

Finally, our study demonstrated that LDH, with a cut-off of 406 IU/L, was a fair test for detecting severity in Covid 19 children with 75% sensitivity and 66.7% specificity. At a cut-off of 501 IU/L, LDH was a good predictor of outcomes with 80% sensitivity and 72.7% specificity. Similar findings were reported by Eid et al. [18], who identified LDH as a predictor of lung involvement severity with a sensitivity of 75% and specificity of 60.1% at a cut-off of 395 U/L. Likewise, Magdy et al. [19] showed that serum LDH

levels at a cut-off point ≥ 386 U/L could predict the severity and clinical outcomes of COVID-19 patients with high accuracy.

Furthermore, Han et al. [13] found that an LDH level above 344.5 U/L had high specificity (96.9%) and sensitivity (68.8%) for predicting severe conditions in COVID-19 patients, demonstrating the robustness of LDH as a predictive marker.

Conclusion

Higher level of LDH was detected in individuals with severe disease. There was an association between LDH and need for Invasive ventilation, Cardiac support and outcome, so LDH could be identified as a predictor for severity and mortality in pediatric COVID-19. Larger studies are needed to confirm these findings.

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