J ONE HEALTH RES

Journal of One Health Research

Original Article

J One Health Res 2023;1(1): 7-14

DOI: 10.5281/zenodo.7521677

Role of Lactate Dehydrogenase in COVID-19 pneumonia: a single tertiary care center follow-up experience of 1000 cases in India

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Please cite this article as: Patil S,Bhadake M, Narwade G, Acharya A.Role of lactate dehydrogenase in COVID19 pneumonia: a single tertiary care center follow-up experienceof 1000 cases in India.J One Health Res 2023;1(1):7-14.

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Received Date: 04.12.2022
Revision Date: 08 .12.2022
Accepted Date: 10.12.2022
Published online: 2.01.2023

ABSTRACT

Objective: The role of various inflammatory markers has been documented during the evaluation of COVID-19 pneumonia. In the present study, the role of lactate dehydrogenase (LDH) in COVID-19 pneumonia in predicting severity, oxygenation status and confirming response to interventions and final radiological outcome was examined.

Methods: This observational study included 1000 PCR-confirmed COVID-19 cases. All cases were assessed with lung involvement documented and categorized on thorax computer tomography, oxygen saturation, inflammatory marker as LDH at the entry point and follow-up. Age, gender, comorbidity and use of bi-level positive airway pressure/noninvasive ventilation (BPAP/NIV) and outcome as with or without lung fibrosis as per tomography severity were observed.

Results: In the study of 1000 COVID-19 pneumonia cases. Tomography severity score at the entry point has significantly associated with LDH level ($p<0.001$). LDH level has a significant association with the duration of illness and oxygen saturation at the entry point ($p<0.001$). BPAP/NIV requirement during the course of hospitalization has a significant association with LDH level ($p<0.001$). Follow-up LDH titer during hospitalization as compared to entry point abnormal LDH has a significant association in post-covid lung fibrosis ($p<0.001$). Follow-up LDH titer during hospitalization as compared to entry point normal LDH has a significant association in post-covid lung fibrosis ($p<0.001$).

Conclusion: LDH has documented a important role in COVID-19 pneumonia in predicting the severity of illness and progression of pneumonia. Sequential LDH titers will help assess response to treatment during hospitalization and analyse post-covid lung fibrosis.

Keywords: COVID-19, pneumonia, lactate dehydrogenase

INTRODUCTION

COVID-19 pneumonia is the first global pandemic in the history of mankind.[1,2] COVID-19 is primarily affecting lung parenchyma and secondarily affects airways, pulmonary vasculature and interstitium. Variable pulmonary manifestations are seen in individual cases of COVID-19, such as pneumonia, microvascular thrombosis and interstitial lung disease. In some patients, extra-pulmonary manifestations have been documented resulting from exaggerated inflammatory response resulting into a 'cytokine storm', which is reported in this pandemic. Pathophysiological pathways involved in disproportionate pulmonary and extra-pulmonary manifestations immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extra-pulmonary tissues. Identification of laboratory predictors of progression towards severity and fatality is needed for the efficient management of patients with coronavirus disease 2019 (COVID-19). In this effect, several biochemical analytes that show abnormal values in severely affected patients have been proposed as disease biomarkers, including, among others, serum or nasopharyngeal lactate dehydrogenase (LDH) activity.[3-7]

In the last few decades, LDH has been analyzed as a prognostic marker in haematology and oncology, in hemolytic anaemia, megaloblastic anaemias, Hodgkin disease and non-Hodgkin lymphoma and leukaemias.[8-10] Severe infections, including interstitial pneumonia or acute respiratory distress syndrome (ARDS), may cause tissue damage induced by cytokine production with subsequent release of LDH into the bloodstream.[7-9]

As 5 % of COVID-19 pneumonia cases require intensive care unit treatment, including mechanical ventilation, these patients are at high risk of death.[10,11] Therefore, markers with high positive predictive value for early prediction of ARDS will help in decreasing mortality. In inflammatory panel evaluation, LDH has a very well association with direct lung damage and significantly raised in more widespread tissue injury. A recently published study on a large case series of COVID-19 patients documented that high serum concentrations of LDH were associated with more chance of death due to pneumonia.[12]

The aim of this study was to evaluate the association between LDH level and post-covid fibrosis.

METHOD

This observational study was conducted from July 2020 to May 2021 in two centers, Pulmonary Medicine, MIMSR Medical College and Venkatesh Hospital Latur India. The study included 1000 PCR-confirmed COVID-19. All COVID-19 pneumonia cases above 18-year age, admitted in the indoor unit, have been enrolled in the study. COVID-19 pneumonia cases not willing to participate in the study, cases not willing to undergo follow-up LDH analysis, COVID-19 pneumonia cases who want discharge against medical advice before clinical recovery from the hospital and COVID-19 pneumonia below 18 years of age were excluded from the study (Figure 1).

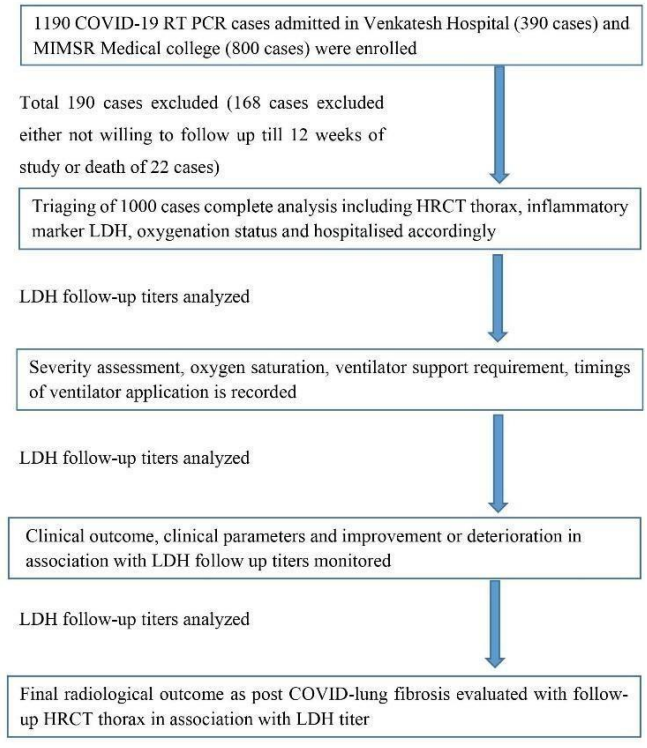

Figure 1: Flow of the study

All of the COVID-19 cases were confirmed with PCR tests performed on nasopharyngeal samples collected with all standard institutional infection control policies. Thorax computer tomography (CT) was applied to assess the severity of lung involvement and categorized as mild if the score

was <7, moderated if the score was 8-15 and severe if the score was >15 or 15-25.[4-6] Clinical assessment and routine biochemistry and hematological workup with viral inflammatory markers such as CRP, Ferritin, LDH, and IL-6 titers.

Entry point LDH titer was utilized as an assessment tool of the severity of illness with clinical parameters. If LDH analysis was normal at the entry point, then LDH titer was repeated on the day of discharge from the hospital or done during hospitalization if the clinical course deteriorated. LDH level was considered normal up to 470 mg/L. A two-fold raised LDH level was classified as significant positive; a four-fold raised LDH level was classified as highly significant. A value raised or decreased in two-to-four-fold change during follow-up was considered significant. If LDH analysis was abnormal at the entry point, we repeated it every 72 hours as the follow-up to assess the severity, progression of illness and also titer level utilized to assess response to medical treatment. Follow-up CT was done after twelve weeks or 3 months of discharge from the hospital for analysis of post covid lung fibrosis in selected cases with abnormal LDH levels at discharge and required bi-level positive airway pressure/noninvasive ventilation (BPAP/NIV) during hospitalization and cases that required oxygen supplementation at home.

Statistical analysis was performed with R-3.4 software. Frequency and percentage were used as descriptive statistics. Chi-square test was used in the analysis of categorical data. A p value was considered significant if it was below 0.05.

RESULTS

A total of 1000 COVID-19 pneumonia cases PCR confirmed COVID-19 cases were included in the study. Six hundred and fifty (65.0%) of cases were male, and 600 (60.0%) of the case were ≥50 years of age. The sociodemographic features according to LDH levels are summarized in Table 1.

A significant difference was found between patients with normal and abnormal LDH levels in terms of CT severity score, duration of illness, oxygen saturation level and BIPAP/NIV requirement ($p<0.001$, $p<0.001$, $p<0.001$ and $p<0.001$, respectively).

The severity of computer CT at diagnosis according to LDH level in COVID-19 cases is summarized in Table 2. On the other hand, the timing of BIPAP/NIV during the course of COVID-19 pneumonia in a critical care setting has a significant association with LDH level ($p<0.001$). BIPAP/NIV onset time according to LDH level in COVID-19 pneumonia cases in summarized in Table 3.

Follow-up LDH titer during hospitalization as compared to entry point abnormal LDH has a significant association in post-covid lung fibrosis ($p<0.001$). Follow-up LDH titer during hospitalization as compared to entry point normal LDH has a significant association in post- COVID lung fibrosis ($p<0.001$). The frequency of post COVID pulmonary fibrosis according to LDH level groups at the time of diagnosis and follow- up are summarized Table 4 and Table 5.

DISCUSSION

We have documented CT severity can be considered the best visual marker of the severity of COVID-19 pneumonia, which can be correlated with inflammatory markers such as LDH, and it will help in triaging cases in casualty and help in targeting interventions in indoor units accordingly to have successful treatment outcome. In many studies, it was documented that LDH level help in predicting the extent of lung involvement, its significantly raised value indicates more lung damage, and resultant hypoxia is the trigger for raised levels due to increased anaerobic metabolism.[13-18]

It was found that COVID-19 pneumonia cases who has <7 days disease duration and cases with >15 days disease duration were having normal LDH levels, while cases between 7-14 days disease duration time had abnormal or raised LDH levels. As the duration of illness in COVID-19 pneumonia cases increases, lung inflammation and tissue necrosis increase with the worsening of hypoxia resulting in high LDH levels.[19,20]

Table 1: Sociodemographic features according to LDH levels

		LDH level normal (n=320)	LDH level abnormal (n=680)	P*
Age groups	≥50 years <50 years	140 (43.7) 180 (56.3)	460 (67.6) 220 (32.4)	**<0.001**
Gender	Male Female	190 (59.4) 130 (40.6)	460 (67.6) 220 (32.4)	**<0.001**
Diabetes mellitus	Yes No	150 (46.8) 170 (53.2)	450 (66.2) 230 (33.8)	**<0.001**
Hypertension	Yes No	160 (50.0) 160 (50.0)	50 (7.4) 630 (92.6)	**<0.001**
COPD	Yes No	100 (31.2) 220 (68.8)	50 (7.4) 630 (92.6)	**<0.001**
IHD	Yes No	110 (34.3) 210 (65.7)	90 (13.2) 590 (86.8)	**<0.001**
Obesity	Yes No	20 (66.6) 300 (33.4)	140 (20.6) 540 (79.4)	<0.001

*COPD: Chronic obstructive pulmonary disease; IHD: Ischemic heart disease; LDH: Lactate dehydrogenase *Chi-squared test*

Table 2: The severity of computer tomography at diagnosis according to LDH level in COVID-19 cases

		Normal LDH (n=320)(%)	Abnormal LDH (n=680) (%)	*p
CT severity score	<8 points 9-15 points >15 points	190 (59.3) 90 (28.1) 40 (12.6)	110 (16.1) 210 (30.8) 360 (53.1)	<0.001
Duration of illness	<7 days 8-15 days >15 days	30 (9.3) 160 (50.0) 130 (40.7)	310 (45.5) 300 (44.1) 70 (10.4)	<0.001
Oxygen saturation	≥90% 75-89% ≤74%	110 (34.3) 150 (46.8) 60 (18.9)	100 (14.7) 340 (50.0) 240 (35.3)	<0.001
BIPAP/NIV requirement	Required Not required	155 (48.4) 165 (51.6)	445 (65.4) 235 (34.6)	<0.001

BIPAP/NIV: Bilevel positive airway pressure/non-invasive ventilation; CT: Computer tomography; LDH: Lactate dehydrogenase
**Chi-squared test.*

Table 3: BIPAP/NIV onset time according to LDH level in COVID-19 pneumonia cases

Onset time	Abnormal LDH (n=290) (%)	Four-fold raised LDH (n=210) (%)	*p
<1 days	110 (37.9)	70 (22.5)	<0.001
3- 7 days	150 (51.7)	160 (51.6)	
After 7 days	30 (10.4)	80 (25.9)	

*BIPAP/NIV: Bilevel positive airway pressure/non-invasive ventilation; LDH: Lactate dehydrogenase *Chi-squared test.*

Table 4: Frequency of post-covid pulmonary fibrosis according to LDH level groups at the time of diagnosis and follow-up

Pulmonary fibrosis	LDH titer increased/abnormal at the entry point (n=400) (%)	LDH titer fourfold increased during follow up (n=280) (%)	*p
Present	40 (10.0)	170 (60.7)	<0.001
Absent	360 (90.0)	110 (38.3)	

*LDH: Lactate dehydrogenase *Chi-squared test.*

Table 5: Frequency of post-covid pulmonary fibrosis according to LDH level groups at the time of diagnosis and follow-up

Post-covid pulmonary fibrosis	Normal LDH at the entry point and remained less than fourfold (n=120) (%)	LDH titer fourfold increased during follow up (n=200) (%)	*p
Present	5 (4.2)	35 (17.5)	**<0.004**
Absent	115 (95.8)	165 (82.5)	

*LDH: Lactate dehydrogenase. *Chi-squared test.*

In the present study, we have documented that LDH level has a positive correlation with the requirement of BIPAP/NIV, high-flow nasal cannula oxygen supplementation and invasive mechanical ventilation in the critical care setting. In two different studies documented the prognostic role of LDH in predicting severity and mentioned that increased LDH levels were associated with about a 6-fold increase in odds of developing severe/critical disease.[21,22] Wang et al observed that elevated neutrophil count, D-Dimer, BUN, creatinine and LDH are predictors of poor outcomes and the maximum patient who require mechanical ventilation in intensive care units and are associated with mortality.[23]

In the present study, LDH level has a significant association with oxygen saturation in COVID-19 pneumonia cases. It was observed that a higher proportion of patients with elevated LDH have significant hypoxia at the entry point, and we have anticoagulation and corticosteroid with protocolized interventions in intensive care units resulting in decreased hypoxia, inflammation and LDH levels during follow-up.[24,25] Xu Zet al. mentioned that postmortem examination of advanced COVID-19 patients as diffuse alveolar damage and hyaline membrane formation, and increased LDH in the blood may be because of diffuse alveolar damage resulting from hypoxia-induced cell necrosis and cytokine-induced lung injury.[26]

In the present study, the timing of BIPAP/NIV requirement during the course of COVID-19 pneumonia in critical care setting has a significant association with LDH level; cases received BIPAP/NIV at entry point <1 day, 3-7 days and after 7 days of hospitalization were documented significance in four-fold raised LDH level in 110/70,150/160 and 30/80 cases, respectively. Rational for similar observation would be, as LDH is involved in the anaerobic metabolism of glucose, up-regulated when oxygen supplies are limited, and its levels are increased in patients with advanced COVID-19 pneumonia requiring ventilatory support.[27-31]

We have documented that serial measurement of LDH during hospitalization, irrespective of entry point abnormal level, has a very well correlation with the requirement of interventions in indoor and intensive care units such as high flow nasal cannula, BIPAP/NIV, and invasive mechanical ventilation. We have observed the usefulness of LDH as markers for evaluating clinical severity and monitoring treatment response in COVID-19 pneumonia. Serial titer will be helpful in assessing the improvement or progression of the disease; persistently high level or rising trends indicates nonspecific responses to hypoxia, tissue injury, and necrosis, indicating underlying radiological progression, which is the earliest predictor of lung fibrosis in these cases.[32-34]

We have documented that normal LDH is a predictor of good clinical and radiological outcomes, and serial measurement of LDH during hospitalization, irrespective of entry point level, has a very well correlation with underlying lung pathology. We have observed that LDH rising trends would help in predicting exaggerated underlying lung parenchymal damage secondary to cytokine-induced lung necrosis and cytokine-induced acute lung injury (ALI)/ARDS. These insults as necrosis or ALI/ARDS, are considered an early marker of future lung fibrosis. We have observed that a small proportion of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, we recommend that all healthcare institutions should also pay close attention to mild patients, identify progressors early, and provide appropriate treatment to reduce mortality. Yan et al. in a retrospective analysis in Wuhan, China, documented similar observations in their study.[30]

In the present study, the age of the patient and gender of included cases has a significant association in COVID-19 cases with normal and abnormal LDH level. It is parallel to other studies.[35-37] In the present study, comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, ischemic heart disease, hypertension, and obesity have a significant association in COVID-19 cases with LDH levels.[36-37]

CONCLUSION

LDH is an easily available, sensitive, reliable, cost-effective, and universally acceptable inflammatory marker in the COVID-19 pandemic. Correlating LDH with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at the entry point is important to have a satisfactory treatment outcome.

LDH follow-up titer has significant associations in predicting the progression of pneumonia, as a proportionate number of pneumonia cases with mild variety on CT thorax and normal initial LDH has progressed to critical illness, which was documented with the help of rising titers, and we have documented follow-up rising titers has played a crucial role with other inflammatory markers like CRP & ferritin in the intensive care setting.

LDH rising titers in the second week of illness indicate nosocomial bacterial infection and target therapy accordingly, and decreasing LDH titers has very well correlated with improved oxygenation status, excellent response to treatment and decreased underlying inflammation. LDH sequential titer also guides in predicting the risk of progression of COVID-19 pneumonia and post covid lung fibrosis irrespective of entry point titer.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study had received no financial support.

Ethics Committee Approval: The research was approved by the Venkatesh Hospital and Critical care Center Ethics Committee (Approval date: July 19 2020, and Approval number: VCC/48-2020-2021). Verbal consent was obtained from all participants.

Authorship Contributions: Concept-OO, SK, HA, SH; Design – SP, MB, GN, AA; Materials – SP, MB, GN, AA; Data collection and/or processing – SP, MB, GN, AA; Analysis and/or Interpretation-SP, MB, GN, AA; Writing-SP, MB, GN, AA; Critical review – SP, MB, GN, AA.

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