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Evaluating Serial LDH (Lactate dehydrogenase) Monitoring as a Marker for Severity and Early Lung Fibrosis in COVID-19 Pneumonia: Insights from a Study in an Indian Tertiary Care Center

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A B S T R A C T

Background: COVID-19 pneumonia is a heterogeneous disease with variable effects on lung parenchyma, airways and vasculature, leading to long-term impacts on lung functions. Although Lung is the primary target organ involved in coronavirus disease-19 (COVID-19), many patients had pulmonary and extrapulmonary effects due to immune activation pathways and direct virus-induced lung damage.

Objective: Robust data on LDH is available as a prognostic marker in haematology, malignancy, and pneumocystis pneumonia, and we have analyzed its usefulness in COVID-19 pneumonia.

Methodology: Prospective, observational and interventional study included 1000 COVID-19 cases confirmed with RT PCR. All patients were assessed with lung involvement documented and categorized on HRCT thorax, oxygen saturation, inflammatory marker as LDH at the entry point and follow-up. Age, gender, Comorbidity use BIPAP/NIV and outcome with or without lung fibrosis as per CT severity were vital observations. Statistical analysis is done by using the Chi-square test.

Results: CT severity score at the entry point with LDH level has a significant association ($p<0.00001$). LDH level is significantly associated with illness duration ($p<0.00001$). Comorbidities were significantly associated with normal and abnormal LDH levels, respectively ($p<0.00001$). LDH level has a significant association with oxygen saturation ($p<0.00001$). BIPAP/NIV requirement during treatment in critical care settings has a significant association with LDH level ($p<0.00001$).

Conclusion: LDH is a readily available and universally acceptable inflammatory marker in the COVID-19 pandemic, and 'follow-up titers' have documented a crucial role in predicting the severity of illness and assessing response to treatment during hospitalization. 'Follow-up LDH titer' during hospitalization and discharge can be an early predictor of post-covid lung fibrosis.

Keywords: COVID-19 Pneumonia; LDH; Oxygen Saturation; Inflammatory Marker; Post Covid Lung Fibrosis

Introduction

The current pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, which initially emerged in China, has documented 274,628,461 confirmed cases and 5,358,978 deaths globally, and 34,752,164 confirmed cases, 478,007 deaths in India. Identification of laboratory predictors of progression towards severity and fatality is needed to efficiently manage 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.[1,2]

COVID-19 pneumonia is a heterogeneous disease with variable effects on lung parenchyma, airways and vasculature, leading to long-term impacts on lung functions. Although Lung is the primary target organ involved in coronavirus disease-19 (COVID-19), many patients had pulmonary and extrapulmonary effects due to immune activation pathways and direct virus-induced lung damage. In COVID-19, pneumonia pathophysiology constitutes different pathways like immune activation, inflammatory, thrombogenic and immediate viral affection to lungs and extrapulmonary tissues.

In the last few decades, LDH has been analyzed as a prognostic marker in haematology and oncology, in hemolytic anemia, in megaloblastic anaemias, Hodgkin disease and non-Hodgkin lymphoma and leukaemias. Elevated LDH levels are the product of enhanced glycolytic activity of the tumour and tumour necrosis due to hypoxia, the latter being associated with high tumour burden. LDH has many subtypes, released by erythrocytes, heart and skeletal muscles; its isolation is usually done as a significant component, and subtyping is not routinely required. Severe infections, including interstitial pneumonia or ARDS (acute respiratory distress syndrome), may cause tissue damage induced by cytokine production and subsequent LDH release into the bloodstream.[3-5]

As 5 % of COVID-19 pneumonia cases require intensive care unit treatment, including mechanical ventilation, and these patients are at high risk of death. Therefore, markers with high positive predictive value for early ARDS prediction will help decrease mortality. In inflammatory panel evaluation, LDH has a very sound correlation with direct lung damage and significantly raised in more widespread tissue injury. In a recently published study on a large case series of COVID-19 patients, documented high serum concentrations of LDH were associated with more chance of death due to pneumonia.[6,7]

In the present study, we have utilized LDH as a primary marker in a laboratory panel of all COVID-19 patients. We have analyzed it as a core marker with other inflammatory markers to assess response to therapy and its role in predicting post-covid fibrosis.

Objective

The present study was conducted to know the role of LDH as a prognostic marker in haematology, malignancy, and pneumocystis pneumonia, and we have analyzed its usefulness in COVID-19 pneumonia.

Methodology

The prospective, observational and interventional study, conducted from July 2020 to May 2021 in MIMSR Medical College and Venkatesh Hospital Latur India, included 1000 COVID-19 cases confirmed with RT PCR to find out the role of LDH in predicting severity of illness, assessing response to therapy and outcome as post-covid fibrosis in diagnosed covid-19 pneumonia cases admitted in critical care unit. A total of 1000 cases were enrolled in the study after IRB approval and written informed consent of the patient.

Inclusion criteria: Covid-19 patients, confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centres, including those with comorbidities and irrespective of severity and oxygen saturation, were included in the study.

Exclusion criteria: Those not willing to give consent, not able to perform LDH and not willing to remain in follow-up were excluded.

All study cases underwent the following assessment before enrolling in the study:

1. COVID-19 RT PCR test was performed in all cases; if the first test results were negative and radiological features clearly documented pneumonia, we repeated the RT PCR test. We enrolled all patients with positive COVID-19 RT-PCR tests.
2. HRCT Thorax to assess severity of lung involvement, and categorized as Mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25.
3. Clinical assessment as- vital parameters like heart rate, oxygen saturation, respiratory rate, blood pressure and documentation of respiratory adventitious sounds.
4. Laboratory parameters- haemoglobin, renal functions, blood sugar level, kidney functions, ECG.
5. Haematological parameters like Total white blood cell counts and platelet counts are repeated whenever required if initial documentation is abnormal. Normal and abnormal parameter readings were considered as per pathological laboratory standards.
6. Viral inflammatory markers like LDH, CRP, and IL-6 are assessed at the entry point and repeated whenever required during illness. Normal and abno-

rmal parameter readings were considered as per pathological laboratory standards.
7. Entry point LDH titer was utilized as an assessment tool of severity of illness with clinical parameters.
8. If LDH analysis was expected at the entry point, then LDH titer was repeated on the day of hospital discharge or during hospitalization if the clinical course deteriorated.
9. If LDH analysis was abnormal at the entry point, we repeated it every 72 hours as a follow-up to assess the severity, illness progression and titer level utilized to assess response to medical treatment.
10. Follow-up HRCT thorax 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. It required BIPAP/NIV during hospitalization and matters supplementation of oxygen needed at home.

Methodology of LDH titer assessment: Lactate to Pyruvate (NADH)

Typical values: Normal values 70-470 mg/dL

Interpretation of results:
1. Average: LDH value up to 470 mg/L
2. Positive: value above 470 mg/dL
3. Significant: two-fold raised LDH level
4. Highly effective: four-fold raised LDH level
5. Follow-up significance: values increased or decreased in two-to-four-fold change

The statistical analysis was done using the chi-squared test. Significant values of $\chi 2$ were seen from the probability table for different degrees of freedom required. P value was considered vital if it was below 0.05 and highly effective if it was less than 0.001.

Results

The present study included 1000 confirmed cases of COVID-19 pneumonia, ascertained through RT-PCR testing. The gender distribution was notably skewed, with males constituting 65% (n=650) of the cases and females 35% (n=350). Age distribution was similarly bifurcated, with 60% (n=600) of the cases being individuals over 50 and 40% (n=400) under 50 years. One of the main aspects of the present study was the investigation of the correlation between the CT severity score at the time of admission and the LDH levels in patients. The results indicated a highly significant correlation ($p<0.00001$), suggesting that higher LDH levels were associated with greater severity of lung involvement on CT scans in COVID-19 pneumonia cases. Further, the study delved into the relationship between LDH levels and the duration of illness. A considerable association was observed ($p<0.00001$), implying that LDH levels may serve as a prognostic indicator for the duration of COVID-19 pneumonia. The association of LDH levels with various comorbidities and demographic variables was also investigated. The study found a significant association between LDH levels and factors such as age, gender, diabetes mellitus, ischemic heart disease (IHD), hypertension, chronic obstructive pulmonary disease (COPD), and obesity ($p<0.00001$). This finding undersc-ores the multifaceted impact of LDH levels in the clinical trajectory of COVID-19 pneumonia. The study revealed a significant association between LDH levels and oxygen saturation in COVID-19 pneumonia cases ($p<0.00001$). This association underscores the potential of LDH as a marker of respiratory compromise (Table 1).

In the critical care setting, the need for Bilevel Positive Airway Pressure (BiPAP) or Non-Invasive Ventilation (NIV) was significantly associated with LDH levels ($p<0.00001$). This result suggests that higher LDH levels could predict the need for advanced respiratory support in critical COVID-19 pneumonia cases (Table 2).

Additionally, the timing of the requirement for BiPAP/NIV during the disease also showed a significant association with LDH levels ($p<0.00001$), further emphasizing the predictive value of LDH in managing severe cases (Table 3).

This study also explored the relationship between follow-up LDH titers during hospitalization and post-COVID lung fibrosis. A substantial association was found between abnormal LDH levels at the entry point and the development of lung fibrosis post-COVID ($p<0.00001$). Similarly, a significant association was observed when comparing normal entry-point LDH levels with post-COVID lung fibrosis ($p<0.00001$). This finding indicates the potential role of LDH as a biomarker for post-COVID pulmonary sequelae (Table 4).

Discussion

In the present study, CT severity score at the entry point with LDH level has a significant correlation in COVID-19 pneumonia cases; scores <8, 8-15 and >15 documented normal and abnormal LDH levels as in 190/110, 90/210 and 40/360 respectively of total 1000 study cases. Similar study also found in another study which documented correlation of CT severity score and LDH levels in mild to moderate points, and no statistical significance detected in CT severity score and LDH levels between severe and critically severe cases.[8] Some other studies showed that significant role of LDH over other laboratory markers like CRP, Lymphocyte count, and AST in predicting severity and outcome in COVID-19 pneumonia cases.[9-11] Some other researchers in their study observed the prognostic role of LDH in pneumocystis pneumonia and H1N1 pneumonia, respectively and used them as a predictor of mortality.[12,13] In another study Deng X et al. documented

Table 1a. Correlation of CT severity (at entry point) and LDH in covid-19 cases (n=1000)

CT severity	Normal LDH (n=320)	Abnormal LDH level (n=680)	Analysis
<8 score (n=300)	190	110	X^2=224.87, p<0.00001
9-15 (n=300)	90	210	
>15 (n=400)	40	360	
Duration of illness			
<7 days (n=340)	30	310	X^2=185.65, p<0.00001
8-15 days (n=460)	160	300	
>15 days (n=200)	130	70	
Age			
Age >50 years (n=600)	140	460	X^2=51.77, p< 0.00001
Age <50 years (n=400)	180	220	
Gender			
Male (n=650)	190	460	X^2=6.5, p< 0.010
Female (n=350)	130	220	
Diabetes Mellitus			
With Diabetes mellitus (n=600)	150	450	X^2=33.77, p< 0.00001
Without diabetes (n=400)			
Hypertension			
With Hypertension (n=210)	160	50	X^2=238.55, p< 0.00001
Without Hypertension (n=790)	160	630	

Table 1b. Correlation of CT severity (at entry point) and LDH in covid-19 cases (n=1000)

COPD			
COPD (n=150)	100	50	X^2=97.46, p< 0.00001
Without COPD (n=850)	220	630	
IHD			
With IHD (n=200)	110	90	X^2=60.77, p< 0.00001
Without IHD (n=800)	210	590	
Obesity			
Obesity (n=160)	20	140	X^2=33.28, p< 0.00001
Without obesity (n=840)	300	540	
Oxygen saturation			
>90% (n=210)	110	100	X^2=60.37, p<0.00001
75-90% (n=490)	150	340	
<75% (n=300)	60	240	
BIPAP/NIV			
BIPAP/NIV required (n=600)	155	445	X^2=26.21, p<0.00001
BIPAP/NIV not required (n=400)	165	235	

that LDH could also be a fascinating biological marker of COVID-19 pneumonia, which will help in predicting the extent of lung involvement; its significantly raised value indicates more lung damage, and hypoxia is triggered for increased levels during the conversion of lactate to pyruvate as a resultant effect of anaerobic metabolism.[14]

In the present study, LDH level has a significant association with duration of illness in COVID-19 pneumonia cases, Doi <7 days, 8-15 days and >15 days of onset of symptoms documented normal and abnormal LDH levels in 30/310, 160/300 and 130/70 cases respectively (p<0.00001) Although LDH is raised in covid-19 pneumonia, we have documented that a proportionate number of patients with duration of illness < 1 week or 7 days and many cases with course of disease> two weeks or 15 days were having average LDH level, while pneumonia cases between 7-14 days of infection were having abnormal or raised LDH level. The observation's rationale is unknown; it may be that the inflammatory response pattern is different, and we have correlated the LDH pattern with other inflammatory markers like CRP, IL-6 and D-dimer and documented that these two markers raised parallel to LDH.

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

Table 2. BIPAP/NIV initiation time at entry point and LDH level COVID-19 pneumonia cases (n=600)

BIPAP used (n=600) with duration of illness	Abnormal LDH level (n=290)	Four-fold raised LDH level (n=310)	Analysis
Entry point <1days (n=180)	110	70	X^2=31.30, p<0.00001
3- 7 days (n=310)	150	160	
After 7 days (n=110)	30	80	

LDH levels. Other inflammatory markers like CRP, IL-6, D-dimer and ferritin positively correlate with LDH and duration of illness. Thus, as the time of infection increases, it will reflect an inflammatory burden and help in aggressive interventions to be taken in these cases in intensive care units. C.L. Liu et al. documented that during an epidemic of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, elevated LDH in 58% of the patients at admission, which indicates lung damage secondary to the pneumonia process.[15]

Raised LDH after the second week of illness may indicate a worsening of COVID-19 pneumonia or secondary bacterial infection, which will help the clinician formulate antibiotics policy accordingly and indirectly guide in managing these cases by assessing follow-up titers. In their study, Huang H et al. showed that raised LDH is an indicator of underlying advanced disease, which is correlated with other parameters such as fast respiratory rate and elevated serum C-reactive protein level.[16] They specifically mentioned that the combination of two factors, rapid respiratory rate plus elevated LDH, could provide a high predictive value for severe symptom development.

In the present study, BIPAP/NIV requirement during COVID-19 pneumonia in a critical care setting has a significant association with LDH level; cases received BIPAP/NIV during hospitalization were documented as normal and abnormal LDH levels in 155/445, 165/235 points, respectively (p<0.00001). Some other researcher documented the prognostic role of LDH in predicting severity and mentioned that increased LDH levels were associated with a 6-fold increase in odds of developing severe/critical disease.[17,18] Some other studies observed Elevated neutrophil count, D-Dimer, BUN, creatinine and LDH are predictors of poor outcomes and maximum patient-required mechanical ventilation in intensive care units and are associated with mortality, high CRP and LDH levels correlate with PaO2/FiO2 values, suggesting a relationship between tissue damage and infective status, positive relationship between CRP, LDH and AST with APACHE II and SOFA scores. The present study revealed significantly higher LDH levels in severe cases requiring ventilatory support than in nonsevere patients, suggesting that the LDH level may be a biomarker of disease severity and progression in patients with COVID-19 requiring aggressive interventions.[19,20]

In the present study, LDH level has a significant association with oxygen saturation in COVID-19 pneumonia cases; cases with oxygen saturation >90%, 75-90%, and <75% were observed as normal and abnormal LDH levels in 110/100, 150/340 and 60/240 cases respectively (p<0.00001) we have observed that higher proportion of patients with elevated LDH have significant hypoxia at entry point. Anticoagulation and corticosteroid with

Table 3. Abnormal LDH level at entry point (n=680) and follow up and its correlation with post-covid lung fibrosis

Post-covid Covid pneumonia fibrosis	LDH titer increased/abnormal at entry point (n=400)	LDH titer fourfold increased during follow up (n=280)	Analysis
Pulmonary fibrosis present (n=210)	40	170	X^2=198.45, p<0.00001
Pulmonary fibrosis absent (n=470)	360	110	

protocolized interventions in intensive care units decreased hypoxia, inflammation and LDH levels during follow-up. Similar findings also observed in few other articles. They mentioned that corticosteroids may slow virus clearance due to their immunosuppressive effect. This may affect the disease course and biochemical indicators, including LDH; therefore, further research is needed to determine the effects of corticosteroids and anticoagulants on LDH in patients with COVID-19.[21,22]Xu Z et al. mentioned that overwhelming inflammation and cytokine-associated lung injury could be essential factors in initiating severe events in patients with COVID-19, which can be adequately analyzed by LDH level. They have also documented in postmortem evaluation of these patients as diffuse alveolar damage and hyaline membrane formation, and increased LDH in blood may be because of diffuse alveolar damage resulting from hypoxia-induced cell necrosis and cytokine-induced lung injury.[21]

In the present study, the Timing of BIPAP/NIV requirement during COVID-19 pneumonia in a 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 (p<0.00001). Few other researchers also observed associations between LDH concentrations and respiratory failure requiring mechanical ventilation and mentioned a five-fold more significant risk of acute respiratory distress syndrome (ARDS) in patients with high LDH level compared with those with lower LDH level and 50 documented that the biomarkers used in the COVID-IRS scores (respiratory rate, SaO2/FiO2 ratio, LDH, and either IL-6 or NLR) accurately represent relevant aspects of the clinical phenomena seen in severe COVID-19. LDH is involved in the anaerobic metabolism of glucose and, thus, is upregulated when oxygen supplies are limited. LDH levels are increased in patients with COVID-19 pneumonia, associated with adverse outcomes, and consistently included in COVID-19 severity scores.[20,22,23]

In the present study, Follow-up LDH titer during hospitalization as compared to entry point abnormal LDH has a significant association in post-covid lung fibrosis (p<0.00001), i.e., LDH at the entry point to four-fold raised cases in the presence or absence of pulmonary fibrosis were 40/170 and 360/110 cases respectively. Some studies validated LDH's potential usefulness in evaluating clinical severity and monitoring treatment response in COVID-19 pneumonia. Serial titer will help assess improvement or progression of the disease; persistent high-level or rising trends indicate underlying radiological progression, which is the earliest predictor of poor radiological outcome and, ultimately, lung fibrosis in these cases and mentioned various infective, inflammatory, malignancies and endocrinological disorders that can raise LDH levels. The inflammatory responses reflected the nonspecific responses to hypoxia, tissue injury, and necrosis, indicating a correlation between infectious cells, immune system and inflammatory response.

In the present study, Follow-up LDH titer during hospitalization as compared to entry point normal LDH has a significant association in post-covid lung fibrosis (p<0.00001), i.e., LDH at the entry point to four-fold raised cases in the presence or absence of pulmonary fibrosis were 5/35 and 115/165 cases respectively. We have observed that a small proportion of nonsevere patients developed severe issues in the first 2 weeks after symptom onset. Therefore, we recommend that all healthcare institutions pay close attention to mild patients, identify progressors early, and provide appropriate treatment to reduce mortality.

In the present study, the age of the patient, i.e., <50 years and >50 years, has a significant association in COVID-19 cases with normal and abnormal LDH levels (p<0.00001). We have also documented that the gender of included subjects has a significant association in COVID-19 cases with normal and abnormal LDH levels (p<0.010).

In the present study, Comorbidities such as Diabetes mellitus, COPD, Hypertension, IHD and obesity has a significant association in COVID-19 cases with normal and abnormal LDH level (p<0.00001).Different studies also documented significant risk factors of severe clinical course and outcomes of COVID-19 patients as elderly

Table 4. Normal LDH level (n=320) at entry point and follow up and its correlation with post-covid lung fibrosis

Post-covid Covid pneumonia fibrosis	LDH normal at entry point and remained less than fourfold (n=120)	LDH titer fourfold increased during follow up (n=200)	Analysis
Pulmonary fibrosis present (n=40)	5	35	X^2=12.19, p<0.00048
Pulmonary fibrosis absent (n=280)	115	165	

age, male gender, ethnicity, fever, dyspnea, gastrointestinal symptoms, preexisting hypertension, diabetes, obesity, COPD, ILD, tumour, immunodeficie-ncies, pregnancy, thromboembolism, coagulation disorders, leukocytosis, lymphopenia, eosinopenia, elevated serum levels of D-dimer, LDH, AST and ALT, BUN and creatine, CRP, PCT, IL-6, IL-1β, KL-6, ferritin, higher CT pneumonia score, high number of affected pulmonary lobes, and smoking.[25,26]

Conclusions

LDH is a readily 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 essential for a satisfactory treatment outcome.LDH titer has significant associations with 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 the critical course, which was documented with the help of rising titers. We have noted that follow-up rising titers have played a crucial role with other inflammatory markers like CRP & ferritin. LDH rising titers in the second week of illness indicate nosocomial bacterial infection and target therapy accordingly. Also, decreasing LDH titers has been very well assessed and analyzed with improved oxygenation status, excellent response to treatment and decreased underlying inflammation.

LDH titer can help predict the progression of COVID-19 pneumonia and assess the risk of post-lung fibrosis if LDH titer is persistently high in these cases. A proportionate number of patients with normal or abnormal LDH at the entry point were predicted with underlying fibrosis or ongoing inflammation and necrosis of lung parenchyma if LDH is persistently high. LDH titer can guide antifibrotic treatment response in a follow-up post-COVID care setting.

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