Role of Initial and Follow-up LDH Titer in COVID-19 Pneumonia: A Single Center Experience of 2000 Cases in Tertiary Care Setting in India

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Abstract:

Introduction*: Robust data of LDH (Lactate dehydrogenase) is available in bacterial infection, and it can be utilized in this COVID-19 Pneumonia pandemic for initial assessment, planning of treatment in indoor setting in association with HRCT severity.*

Methods: *Prospective, observational, 12 weeks follow up study, included 2000 COVID-19cases confirmed with RT PCR. All cases were assessed with lung involvement documented and categorized on HRCT thorax, oxygen saturation, LDH at entry point and follow up. Age, gender, comorbidity and BIPAP/NIV use and outcome as with or without lung fibrosis as per CT severity. Statistical analysis is done by Chi square test.*

Results*: HRCT severity score at entry point has significant correlation with LDH titer [p<0.00001] LDH titer has significant association with duration of illness (Doi) [p<0.00001] Comorbidities has significant association with LDH titer. [p<0.00001] LDH titer has significant association with oxygen saturation [p<0.00001] BIPAP/NIV requirement during hospitalization has significant association with LDH titer. [p<0.00001] Timing of BIPAP/NIV requirement has significant association with LDH titer. [p<0.00001] Follow-up LDH titer during hospitalization as compared to entry point (initial) normal and abnormal LDH has significant association in post-covid lung fibrosis [p<0.00001]*

Conclusion: *LDH is easily available, and universally acceptable inflammatory marker in COVID-19 pandemic and documented very crucial role in covid-19 pneumonia in predicting severity of illness, assessing response to treatment and analyzing outcome during hospitalization.*

Key words: *COVID-19 pneumonia, LDH, Oxygen saturation, Inflammatory marker.*

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Introduction:

The current pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, originally emerged from 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.[1] Identification of laboratory predictors of progression towards severity and fatality is needed for an efficient management of patients with coronavirus disease 2019 (COVID-19).[2-3] In this effect, several biochemical analytes that show abnormal values in severely affected patients have been proposed as disease biomarkers, including among others serum.[4-10]

COVID-19 Pneumonia is a heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Although Lung is the primary target organ involvement in corona virus disease-19 (COVID-19), many patients were having pulmonary and extrapulmonary effects due to the immune

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activation pathway and direct virus induced lung damage. In COVID-19 Pneumonia pathophysiology constitutes different pathways like immune activation, inflammatory, thrombogenic and direct viral infection to lungs and extrapulmonary tissues

In last few decades, LDH has been analyzed as prognostic marker in hematology and oncology[11], in hemolytic anemia[12], in megaloblastic anemias, Hodgkin disease and non-Hodgkin lymphoma and leukemias[13] Elevated LDH levels are the product of enhanced glycolytic activity of the tumor and tumor necrosis due to hypoxia, the latter being associated with high tumor burden. LDH has many subtypes, 1-5 released by erythrocytes, heart and skeletal muscles, its isolation usually done as major component and subtyping is not routinely required.[14] Severe infections including interstitial pneumonia or ARDS (acute respiratory distress syndrome) may cause tissue damage induced by cytokine production with subsequent release of LDH into the bloodstream.[15-16] 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 prediction of ARDS will help in decreasing mortality.[17] In inflammatory panel evaluation, LDH has very good association with direct lung damage and significantly raised in more widespread tissue injury[18,19]. In a recently published study[20] on a large case-series of COVID-19patients, documented high serum concentrations of LDH was associated with more chance of death due to pneumonia.[20]

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

Materials and methods:

Data source:

Prospective, observational, 12 weeks follow up study, conducted during July 2020 to May 2021 in two centers, Pulmonary Medicine, MIMSR Medical College and Venkatesh Hospital Latur India, included 2000 COVID-19cases confirmed with RT PCR, to find out role of LDH in predicting severity of illness, assessing response to therapy and outcome as post-covid fibrosis is diagnosed COVID-19 Pneumonia cases admitted in critical care unit. Total 2000 cases were enrolled in study after IRB approval and written informed consent of all included cases were taken at respective centers of study in Venkatesh Hospital and MIMSR Medical college Latur.

Ethical Approval:

This study was approved by the Institutional Review Board/ Ethics Committee at Venkatesh Hospital and Critical Care Center Latur India and MIMSR Medical college Latur India, (Approval # VCC/19-2020-2021; Approval date 24/07/2020)

Inclusion criteria: COVID-19patients, confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, 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 CRP and not willing to remain in follow-up, and cases that died during hospitalization or before 12 weeks of discharge from hospital were excluded.

All study cases were undergone following assessment before enrolling in study:

COVID-19RT PCR test was performed on nasopharyngeal samples collected with all standard institutional infection control policies, if first test results were negative and radiological features clearly documenting pneumonia, we have repeated RT PCR test and enrolled all cases with positive COVID-19 RT-PCR test. 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. Clinical assessment and routine biochemistry and hematological workup with viral inflammatory markers as LDH, Ferritin, LDH, IL-6 titers. Entry point LDH titer was utilized as an assessment tool of severity of illness with clinical parameters. If LDH analysis was normal at entry point, then LDH titer was repeated on day of discharge from hospital or done during hospitalization if clinical course deteriorates. If LDH analysis was abnormal at entry point, we repeated it every 72 hours as follow up to assess severity, progression of illness and also titer level utilized to assess response to medical treatment. Follow-up HRCT thorax was done after twelve weeks or 3 months of discharge from hospital for analysis of post covid lung fibrosis in selected cases with abnormal LDH level at discharge and required BIPAP/NIV during hospitalization and cases requiring oxygen supplementation at home.

Study design:

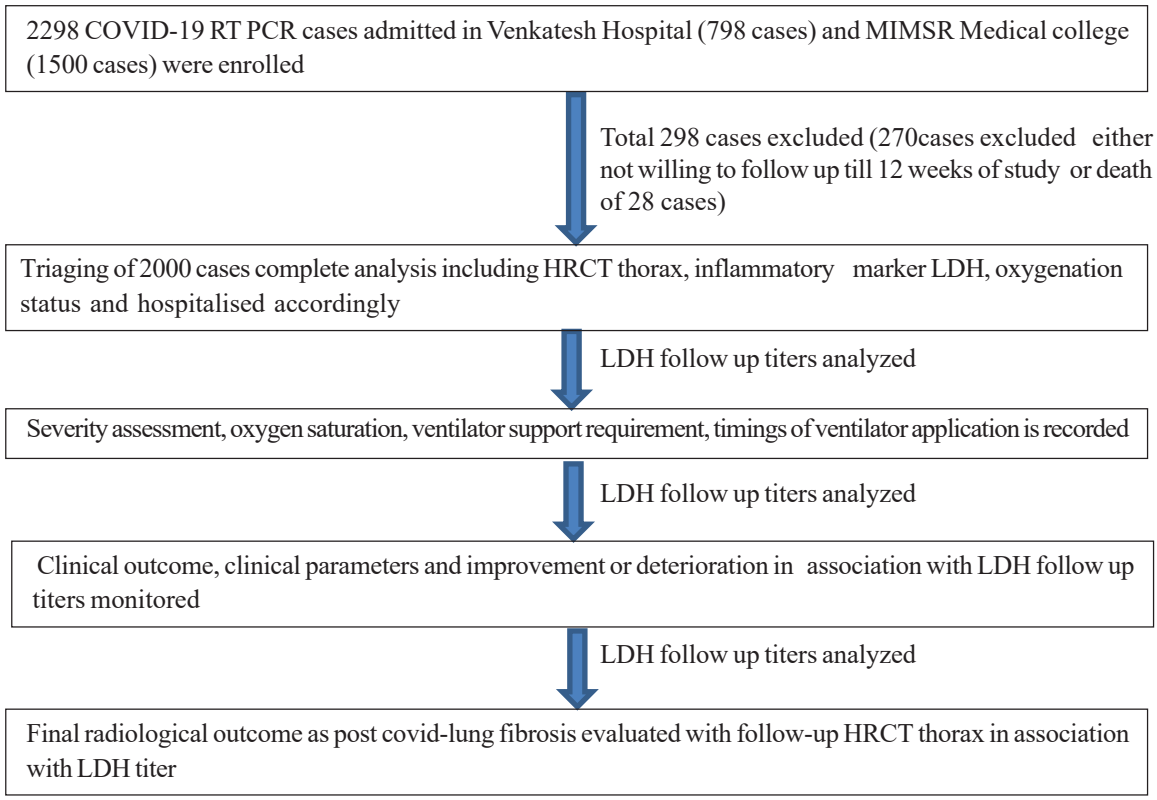

Figure 1. Flow of the study

Methodology of LDH titer assessment: Kinetic method, sample serum, quantitative method, kits prepared by Spinreact diagnostics and samples processed biochemistry analyzer by Roche.

Principle: Lactate to Pyruvate (NADH)

Normal values: 70-470 mg/dL

Interpretation of results:

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

Statistical Analysis:

The statistical analysis was done by using chi-square test in R-3.4 software. Significant values of ÷2 were seen from probability table for different degree of freedom required. *P* value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

Results:

In present study, 2000 COVID-19 pneumonia cases confirmed by COVID-19 RT PCR, males were 1300/2000 and females were 700/2000, age >50 were 1200 cases and age <50 were 800 cases. Significant association in LDH and COVID-19 pneumonia has been documented with variables like age, gender, diabetes mellitus, IHD, Hypertension, COPD, Obesity [p<0.00001] (Table 1).

Core observations

HRCT thorax severity score at entry point with LDH level has significant association in COVID-19 pneumonia cases [p<0.00001] (Table 2) LDH level has significant association with duration of illness in COVID-19 pneumonia cases [p<0.00001] (Table 3) LDH level has significant association with oxygen saturation in COVID-19 pneumonia cases [p<0.00001] (Table 4) BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with LDH level [p<0.00001] (Table 5) Timing of BIPAP/NIV requirement during course of COVID-19 Pneumonia in critical care setting has significant association with LDH level [p<0.00001] (Table 6) Follow-up LDH titer during hospitalization as compared to entry point abnormal LDH has significant association in post-covid lung fibrosis [p<0.00001] (Table 7) Follow-up LDH titer during hospitalization as compared to entry point normal LDH has significant association in post-covid lung fibrosis [p<0.00001. (Table 8).

Table 1. *Other variables and LDH level in COVID-19 Pneumonia cases (n=2000)*

COVID-19 RT PCR positive (n=2000)	CRP titer normal (n=640)	CRP titer abnormal (n=1360)	Analysis
Age >50 years (n=1200)	280	920	χ^2=51.77
Age <50 years (n=800)	360	440	p< 0.00001
Male gender (n=1300)	380	920	χ^2=6.5
Female gender (n=700)	260	440	p< 0.010
Diabetes mellitus (n=1200)	300	900	χ^2=33.77
Without diabetes (n=800)	340	460	p< 0.00001
Hypertension (n=420)	320	100	χ^2=238.55
Without Hypertension (n=1580)	320	1260	p< 0.00001
COPD (n=300)	200	100	χ^2=97.46x
Without COPD (n=1700)	440	1260	p< 0.00001
IHD (n=400)	220	180	χ^2=60.77
Without IHD (n=1600)	420	1180	p< 0.00001
Obesity (n=320)	40	280	χ^2=33.28
Without obesity (n=1680)	600	1080	p< 0.00001

Table 2. *Association of CT severity (at entry point) and LDH in COVID-19cases (n=2000)*

CT severity	Normal LDH (n=640)	Abnormal LDH titer (n=1360)	Analysis
<8 score (n=600)	380	220	χ^2=224.87
9-15 (n=600)	180	420	p<0.00001
>15 (n=800)	80	720	

Table 3. *Duration of illness (DOI) at entry point during hospitalization and LDH level in COVID-19 Pneumonia cases (n=2000)*

Duration of illness	Normal LDH(n=640)	Abnormal LDH (n=11360)	Analysis
<7 days (n=680)	60	620	χ^2=185.65
8-15 days (n=920)	320	600	p<0.00001
>15 days (n=400)	260	140	

Table 4. *Oxygen saturation at entry point and LDH level in COVID-19 Pneumonia cases (n=2000)*

Oxygen saturation	Normal LDH titer (n=640)	Abnormal LDH titer (n=1360)	Analysis
>90% (n=420)	220	200	χ^2=60.37
75-90% (n=980)	300	680	p<0.00001
<75% (n=600)	120	480	

Table 5. *Association of BIPAP use with LDH level in COVID-19 Pneumonia cases (n=2000)*

BIPAP/NIV	Normal LDH (n=640)	Abnormal LDH titer (n=1360)	Analysis
BIPAP/NIV required (n=1200)	310	890	χ^2=26.21
BIPAP/NIV not required (n=800)	330	470	p<0.00001

Table 6. *BIPAP/NIV initiation time at entry point and LDH level COVID-19 Pneumonia cases (n=1200)*

BIPAP used (n=1200) with duration of illness	Abnormal LDH titer (n=580)	Four-fold raised LDH titer (n=620)	Analysis
Entry point <1days (n=360)	220	140	χ^2=31.30
3- 7 days (n=620)	300	320	p<0.00001
After 7 days (n=220)	60	160	

Table 7. *Abnormal LDH titer at entry point (n=1360) and follow up and its correlation with post-covid lung fibrosis*

Post-Covid pneumonia lung fibrosis	LDH titer increased/ abnormal at entry point (n=800)	during follow up (n=560) LDH titer fourfold increased	Analysis
Pulmonary fibrosis present (n=420)	80	340	χ^2=198.45
Pulmonary fibrosis absent (n=940)	720	220	p<0.00001

Table 8. *Normal LDH titer (n=640) at entry point and follow up and its correlation with post-covid lung fibrosis*

Post-Covid pneumonia lung fibrosis	LDH normal at entry point and remained less than fourfold (n=240)	LDH titer fourfold increased during follow up (n=400)	Analysis
Pulmonary fibrosis present (n=80)	10	70	χ^2=12.19
Pulmonary fibrosis absent (n=560)	230	330	p<0.00048

Discussion:

In present study, CT severity score at entry point with LDH level has significant association in COVID-19 Pneumonia cases. [p<0.00001] CT severity is the best 'visual marker' of lung involvement and LDH titer increases in proportion with extent of lung parenchymal damage. Rationale for this would be related to hypoxia induced by lung parenchymal necrosis and resultant anaerobic metabolism. Author Magdy A.M et al [21], Huang C et al[22], Salvador P et al[23] Tao RJ et al[24], Tordjman M et al[26], Boldt M.J et al[27], Deng X et al[28], Xi et al[33] and Cho WH et al[34] documented similar observations in their studies.

In present study, LDH level has significant association with duration of illness in COVID-19 pneumonia cases. [p<0.00001] Although LDH is raised in COVID-19 pneumonia, we have documented that proportionate number of cases with duration of illness <1 week or 7 days and many cases with duration of illness > two weeks or 15 days were having normal LDH level, while pneumonia cases between 7-14 days of illness were having abnormal or raised LDH level. Rationale for observation is not known, maybe the inflammatory response pattern is different, and we have correlated LDH pattern with other inflammatory markers like LDH, IL-6 and D-dimer and documented that these two markers raised parallel to LDH. As duration of illness in COVID-19 Pneumonia cases increases, lung inflammation and tissue necrosis increase with worsening of hypoxia resulting in high LDH level. Authors, C.L. Liu et al[34] and Huang H et al[39] observed raised LDH with increased duration of illness due to more lung parenchymal involvement as disease duration progresses.

In present study, BIPAP/NIV requirement during course of COVID-19 Pneumonia in critical care setting has significant association with LDH level [p<0.00001]. Authors Henry et al.[7] and Lv et al[25] 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. D. Wang et al[36] observed Elevated neutrophil count, D-Dimer, BUN, creatinine and LDH are predictors of poor outcome and maximum patient required mechanical ventilation in intensive care units and associated with mortality. Various Researchers, Poggiali E et al[37] and Han Y et al[38] documented similar observations in their studies. 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 pneumonia requiring aggressive interventions.

In present study, LDH level has significant association with oxygen saturation in covid-19 pneumonia cases [p<0.00001] we have observed that higher proportion of patients with elevated LDH have significant hypoxia at entry point and we have with anticoagulation and corticosteroid with protocolized interventions in intensive care units resulted in decreased hypoxia, inflammation and LDH level during follow-up. Authors Fang X et al[40] and Li X et al[41] observed similar findings. Author, Xu Z et al[32] mentioned that postmortem examination of advanced COVID-19patients as diffuse alveolar damage and hyaline membrane formation, and increased LDH in blood may be because of diffuse alveolar damage resulted from hypoxia induced cell necrosis and cytokine induced lung injury.

In present study, Timing of BIPAP/NIV requirement during course of COVID-19 Pneumonia in critical care setting has significant association with LDH level [p<0.00001] Rational for similar observation would be, as LDH is involved in the anaerobic metabolism of glucose, upregulated when oxygen supplies are limited, and its levels are increased in patients with advanced COVID-19 Pneumonia requiring ventilatory support. Authors, Poggiali E et al[37], Wu C et al[46] and Goyal P et al[47], Booth CM et al[48], Li W et al[49] and Garcia-Gordillo JA et al[50] observed findings collaborating with our study.

In present study, Follow-up LDH titer during hospitalization as compared to entry point abnormal LDH has significant association in post-covid lung fibrosis [p<0.00001] We have observed usefulness of LDH as markers for evaluating clinical severity and monitoring treatment response in COVID-19pneumonia. Serial titer will be helpful in assessing improvement or progression of disease, persistent high level or rising trends indicates nonspecific responses to hypoxia, tissue injury, and necrosis, indicating underlying radiological progression which is earliest predictor lung fibrosis in these cases. Authors, M Wu et al[29] Chen N et al[30] and Li G et al[31] mentioned similar findings.

In present study, Follow-up LDH titer during hospitalization as compared to entry point normal LDH has significant association in post-covid lung fibrosis [p<0.00001] We have observed that, small proportion of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, we recommend that all health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality. Author Yan L A et al[49] in retrospective analysis in Wuhan, China documented similar observations in their study.

In present study, age of the patient i.e., <50 years and >50 years has significant association in COVID-19 cases with normal and abnormal LDH level [p<0.00001]. We have also documented the gender of included cases has significant association in COVID-19 cases with normal and abnormal LDH level. [p<0.010] Authors, Duan YN et al[42], Huang Y et al[43] and Gao Y et al[44] documented similar observations in their study. In present study, comorbidity as Diabetes mellitus, COPD, Hypertension, IHD and obesity has significant association in COVID-19 cases with normal and abnormal LDH level [p<0.00001]. Authors, Huang Y et al[43] and Gao Y et al[44] documented similar observations.

Conclusions:

LDH is an easily available, sensitive & reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pandemic. Correlating LDH with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome.LDH titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial LDH has progressed to critical course which were documented with help of rising titers and we have documented follow-up rising titers has played crucial role with other inflammatory markers like LDH & ferritin. LDH rising titers in the second week of illness indicates nosocomial bacterial infection and target therapy accordingly. Also decreasing LDH titers has been assessed and analyzed with improved oxygenation status and excellent response to treatment and decreased underlying inflammation.

LDH titer can help in predicting progression of COVID-19 pneumonia, and assessing risk of post covid lung fibrosis if LDH titer is persistently high in these cases and proportionate number of cases with normal or abnormal LDH at 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 follow-up post covid care setting.

Abbreviations:

RT PCR- real time reverse transcription polymerase chain, HRCT-high resolution computerised tomography, CRP C-reactive protein, SpO2 oxygen saturation, LDH lactate dehydrogenase, IL-6 Interleukin-6, CT-computerised tomography, SARS-CoV-2 severe acute respiratory syndrome-corona virus-2 BIPAP/NIV- bilevel positive airway pressure/non-invasive ventilation

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