

Review Article

Role of Nasopharyngeal lactate dehydrogenase as a possible economical mass screening test for the detection and segregation of SARS-CoV-2 (COVID-19) cases in India

Mukul Arvind Gharote

Department of Medical Oncology, Mukta Cancer Clinic, MF-70, Sundarban Colony, Nashik, Maharashtra, India.



***Corresponding author:**

Mukul Arvind Gharote,
Department of Medical
Oncology, Mukta Cancer
Clinic, MF-70, Sundarban
Colony, Near Bhujbhal Farm
Road, Near Deccan Petrol
Pump, Nashik - 422009,
Maharashtra, India.

mukul.gharote@gmail.com

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ABSTRACT

COVID-19 pandemic is affecting almost every country in the world. Every country must test all the individuals with suspected clinical presentation of COVID-19. Unfortunately, the symptoms are mild and often the incubation period is 5–7 days. Hence, the detection of COVID-19 takes time and is costly even, many resource-constrained nations are not testing their citizens due to cost incurred. That is why we need an economical mass screening test to detect and help the health-care system to segregate cases needing their attention. Nasopharyngeal lactate dehydrogenase (LDH) is raised in viral upper respiratory infections, it can be easily tested and raised serum LDH in addition to nasopharyngeal LDH can predict stormy outcome of disease. Such prediction will help health-care system for effective resource allocation.

Keywords: COVID-19, SARS-Cov-2, Coronavirus, Nasopharyngeal lactate dehydrogenase

INTRODUCTION

Lactate dehydrogenase (LDH) is a membrane associated enzyme and is released in extracellular environment during inflammation as a result of cellular injury.^[1] Few studies established direct correlation between concentrations of LDH and acute-phase cytokines. LDH is a reliable biomarker of acute inflammatory injury associated with upper respiratory infections (URI). Unlike LDH, these cytokines in themselves do not directly represent cellular injury – the acute-phase cytokines are the mediators of inflammation, whereas LDH is the product of inflammatory injury.^[2] LDH is enzyme released in the bronchoalveolar space on damage of cytoplasmic cell membrane. Elevated LDH is also indicator of underlying lung injury and inflammation.^[3]

In fact, LDH is one of the four serological markers for diagnosis of pneumocystis pneumonia. Age, initial neutrophil count, and LDH were independently associated with poor prognosis in SARS outbreak at Hongkong in 2003.^[4]

Hence, LDH is raised in any nasopharyngeal or bronchial injury due to any source, i.e., malignancy, viral pneumonia, viral URI, or bacterial or mycoplasma infection.^[5] Elevated LDH and neutrophil count were also indicator of heavy viral load.^[4] Virus-induced cytolysis of tissue macrophage results in delayed clearance of enzymes like LDH,^[1] thus resulting in elevated plasma LDH. LDH is raised in almost 75% of the cases affected by novel coronavirus (SARS-CoV-2).^[6]

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Serum LDH elevation had direct links to prognosis in this outbreak as well. Cohort of 138 cases of COVID-19 reported LDH elevation in 38% which had 4% mortality^[7] whereas cohort of 99 cases reported having LDH elevation in 75% which had 11% mortality. Elevated LDH in the previous studies also was reported to be associated with bad prognosis as was seen in 2003 outbreak.^[4]

NASOPHARYNGEAL LDH, VIRAL URI, AND COVID-19

Above discussion makes one thing clear that elevated LDH is a marker of viral cytolysis and poor prognosis. Now coming to viral URI and elevated LDH, in a study done on pediatric cases, elevated LDH in nasopharyngeal sample was associated with increased chances of acute otitis media (AOM). LDH was indicator of nasopharyngeal injury and inflammation, leading to Eustachian tube damage which resulted in AOM.^[2]

COVID-19 starts as URI and in majority presents with same complaints few progresses onto lung injury and eventually ARDS. COVID-19 can be screened by doing nasopharyngeal LDH, even we can predict poor outcome on the basis of nasopharyngeal LDH and serum LDH.

Both nasopharyngeal LDH and serum LDH are economical tests which can help our health-care personnel to segregate patient who can have stormy course of disease. Nasopharyngeal aspirate was used as a surrogate for the lower respiratory tract, as several studies confirm virus titers obtained in nasal washes correlate with disease activity in the lower airways.^[8] In fact, cytopathic effects of respiratory syncytial viruses are detected earlier and are economical than isolation of virus itself.^[9]

WHAT SHOULD BE THE IDEAL TECHNIQUE TO DETECT NASOPHARYNGEAL LDH?

Various techniques to detect nasopharyngeal LDH

<p>Spontaneous secretion Nose blowing or collection of secretions dripping out of the nose Suction and microsuction Nose blowing or suction following stimulation (methacholine and histamine) Dilution techniques Combined aspiration lavage Spray blow techniques Nasal pool lavage Standard lavage and sequential lavage Absorption techniques Cotton wool Filter paper strips or disks Cellular materials (polyurethane foam and surgical cellulose sponges)</p>
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Nasal secretions consist of inhomogeneous fluids and have considerable intra- and inter-individual variations in amount, composition, physical properties, biological activity, and cellular content. These characteristics may change rapidly in response to various stimuli. Moreover, nasal secretions reveal spontaneous diurnal fluctuations.

Airway epithelial lining fluids derive from four major sources:

1. Goblet cells
2. Submucous glands
3. Transepithelial ion and water transport
4. Plasma transudation.

Nasal fluid is admixed with lacrimal fluid and water condenses at the mucosal surface during expiration can make an additional contribution.

Nasal secretions contain minute amounts of cytokines and other inflammatory mediators expressed by various epithelial and non-epithelial cells. Because cytokines play a dominant role in the pathophysiology of airway disease, interest has focused on cytokine determinations in nasal secretions. Data on cytokine concentration obtained with different sampling techniques may differ by more than an order of magnitude.^[10]

Polyurethane foam sampler technique is one of the most reliable and easy methods of detecting nasopharyngeal LDH.^[11]

CAN WE DO MASS SCREENING FOR COVID-19 WITH NASOPHARYNGEAL LDH?

For a resource-constrained country like ours and considering the demography, the task of applying COVID-19 to all the residents of India will be a daunting task on health care workers, not only that but the cost of such herculean exercise will be exorbitant! Practically, it is impossible. Our nation is being feared of entering Stage III of pandemic, i.e., community spread is highly likely. In such phase contact, tracing may not be possible for health-care system to track. In this phase, it is advisable to test each and every suspected case and isolate them and treat.

In case of community transmission, doing COVID-19 antigen or antibody tests in every cases of URI in India, the exchequer will have to bear exorbitant cost. Each testing kit today costs around 2000 to 5000 rupees per test. Besides there can be exhaustion of kits for the genuine cases of COVID-19. If Nasopharyngeal LDH is done as a initial test, those with increased nasopharyngeal LDH can be tested for COVID-19 antigen/antibody tests. Cases with normal nasopharyngeal LDH can be kept in home isolation and recheck nasopharyngeal LDH if their symptoms persist. Hence, nasopharyngeal LDH can be measured, those with high LDH can be segregated and treated at the earliest, they are likely to have severe course of disease, they may likely

be COVID-19 positive as well. While others may be having seasonal flu, without much damage, they may be very well treated at home, of course in home isolation. This will save lot of exchequers money and help the health-care systems to identify potential patients needing health-care assistance and ventilator support as well. Nasopharyngeal LDH – a marker of tissue damage can help us in finding and segregating patients of COVID-19, at much lesser cost as would have been incurred, had the COVID-19 kits applied on every person with URI.

WHAT SHOULD BE THE CUTOFF OF NASOPHARYNGEAL LDH?

For any screening test to be effective, false-negative rate should be minimal. Based on the study done on nasopharyngeal secretion LDH and development of AOM, higher nasopharyngeal secretion LDH was associated with high chances of AOM, we suggest that LDH-3 and LDH-4 are higher in nasopharyngeal secretion.^[12] Furthermore, viral URI causes more rise in LDH as compared to bacterial.^[13]

Based on the study done by Ede Lin, 2013,^[2] nasopharyngeal LDH and its association with various viruses are mentioned in Table 1.

Table 1: Lactate dehydrogenase as a marker of nasopharyngeal inflammatory injury during viral URI.

Virus type	Number of patients	LDH concentration (mU/ml)	
		Mean (\pm SD)	Median
Adenovirus	42	4627 (5740)	2816
Coronavirus	8	4157 (2557)	4777
Enterovirus	24	2194 (3365)	1325
Influenza A	16	4177 (4675)	2111
hBoV	39	4458 (4778)	2869
hMPV	22	1696 (1438)	1395
Parainfluenza	22	3680 (4970)	1790
Rhinovirus	54	4128 (4401)	2402
RSV	34	3627 (6916)	1307
Mixed viruses	187	371 (4849)	2055
Virus negative	146	2858 (4975)	1305

hBoV: Human bocavirus, hMPV: Human metapneumovirus, LDH: Lactate dehydrogenase, RSV: Respiratory syncytial virus^[2]

If we study this Table 1 carefully then, you can find that the mean LDH and median LDH concentration in mU/ml was higher in coronavirus patients, we agree that the study population was small and hence is limitation but still given the severity of COVID-19, it is bound to have raised LDH at presentation.

Even the standard deviation is also lower, indicating that the Gaussian curve is steep in case of coronavirus as compared to other viruses.

CONCLUSION

Based on above discussion and evidences, we can apply nasopharyngeal LDH as economical option to do mass screening and it will also help us in segregation of cases requiring urgent health-care support. No study has been done on nasopharyngeal LDH and COVID-19.

Hence, we do not know the false negativity of such approach, but given the cost of applying COVID-19 test kit on each and every suspected URI cases in India, we can give a serious thought to nasopharyngeal LDH.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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