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Lactate Dehydrogenase as a Biomarker for Assessment of COVID-19 Prognosis in Severe and Critically Ill Patients in Nepal: A Single-centered Retrospective Study

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ABSTRACT

Introduction: COVID-19 is an infectious disease caused by a corona virus. The level of serum LDH has been observed to be an important biomarker in predicting the extent of lung tissue damage. This study aimed to further investigate the predictive accuracy of LDH in estimating the prognosis of critically ill patients.

Methods: A retrospective study was conducted among COVID-19 patients, ≥ 18 years admitted to the intensive unit of Nepal APF Hospital from July 2020 to November 2021. Ethical approval was taken from NHRC and non-random sampling technique was done. The demographic, clinical and baseline LDH data was collected from the admission record files. The clinical status was investigated to look for discharge or death in the ICU. Those patients who were discharged or transferred to step-down were recorded as surviving patients. Data was entered in Microsoft Excel and analyzed using SPSS v16.

Results: Out of 190 patients 63% were males. The mean age noted was 56.59 ± 15.706 years. The duration of ICU stay was 9.13 ± 5.392 days. Among them 103 died and 87 of them survived. The cut-off value of LDH as a prognostic marker for mortality was observed to be 450 IU/L. On ICU admission, 164 patients had high LDH. Higher mortality was observed in the high LDH group (56%) as compared to the low LDH group (42.3%).

Conclusions: LDH is a useful biomarker for predicting in-hospital mortality in severe and critically ill COVID-19 patients and can guide the treating physicians to approach and plan the clinical management of patients with severe disease.

Keywords: *COVID-19; Lactate dehydrogenase; Nepal; Prognostic Value.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a type of coronavirus.[1] COVID-19 was first noticed as a series of atypical respiratory infections that spread from the seafood market in Wuhan City China in December 2019.[2] This virus spreads primarily via respiratory droplets and contact routes.[1,3] It was declared a pandemic on March 11, 2020.[4] Globally, as of 30 November 2023, there have been 77,20,52,752 confirmed cases of COVID-19, including 69,85,278 deaths, reported to WHO.[5] In Nepal, this disease infected 10,03,450 and 12,031 have succumbed to this disease.[6]

After entry into host cells, the virus multiplies leading to impaired O2/CO2 exchange and rise in cytokines producing hyperinflammation ultimately leading to widespread multiple organ damage. This increases the levels of various inflammatory markers like CRP, ESR, interleukins, and LDH.[7] LDH is a hydrogen transfer

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cytoplasmatic enzyme that catalyzes the final reaction in the anaerobic glycolysis.[8] The increase of LDH reflects cell and tissue destruction and is regarded as a common sign of tissue damage.[9] As COVID-19 affects multiple organs, any injury to these organs can lead to a rise in LDH.[10]

Few studies have identified the role of LDH in predicting severity and prognosis. Researches have also found that plasma LDH levels are important in predicting in-hospital mortality.[11,12] Other biomarkers which can be used are d-dimer, CRP, AST, ALT, lymphocytes, and albumin.[13] We aimed to further investigate the predictive accuracy of LDH, measured during ICU admission, in the prognosis of severe and critically ill COVID-19 patients in a developing country like Nepal.

METHODS

An observational, retrospective analytical single center, hospital-based study from July 2020 to November 2021 (17 months) was done which investigated data records of all admitted patients in COVID ICU of Nepal Armed Police Force Hospital. Inclusion and exclusion criteria were as follows:

Study Population

All SARS-CoV-2 positive COVID-19 patients of age more than 18 years confirmed by real time RT-PCR with severe and critical disease as per WHO living guidelines[14]and admitted to Nepal APF hospital COVID ICU from 1st July 2020 to 20th November 2021 were included in the study.

All patients admitted with 'suspected' or 'probable' COVID-19 status or diagnosed by Rapid Diagnostic Tests (RDT) only or whose serum LDH test at ICU admission was not done or not recorded or missing demographic or laboratory data were excluded from the study. All cases without definitive outcomes (Brought dead patients and Left Against Medical Advice) and with presence of any other condition in which serum LDH was raised such as recent myocardial infarction (MI) or stroke (in last 1 month), decompensated heart failure, hemolytic disorders, active hepatitis, chronic kidney disease, and pancreatitis were also excluded.

According to WHO 'Clinical management of COVID-19: living guidance' **severe disease** includes "adolescents or adults with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air." **Critical disease/ illness** includes "patients with ARDS (Acute Respiratory Distress Syndrome) or sepsis or septic shock or acute thrombosis or MIS-C (Multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19)".[14]

Sample size was calculated using Buderer methodology

n based on sensitivity,

$$= [Z^2_{(1-\alpha)/2} \times S_N X (1-S_N)] / L^2 \times Prevalence$$

n based on specificity,

$$= [Z^2_{(1-\alpha)/2} \times S_P X (1-S_P)] / L^2 \times (1-Prevalence)$$

where n = required sample size,

S_N = anticipated sensitivity,

S_p = anticipated specificity,

α = size of the critical region (1 – α is the confidence level),

$z_{1-\alpha/2}$ = standard normal deviate corresponding to the specified size of the critical region (α), and

L = absolute precision desired on either side (half-width of the confidence interval) of sensitivity or specificity.

Prevalence = In this study 'mortality rate' is taken as the prevalence

The expected sensitivity and specificity of 74% and 69% respectively, has been taken from a systematic review and meta-analysis.[15]The mortality rate has been taken as 40.5% in critically ill patients infected with COIVD-19 as described in systematic review and meta-analysis conducted by Macedo et al.[16] The precision and confidence interval are fixed at 10% and 95% respectively. The estimated sample size for sensitivity and specificity is calculated to be 183 and 139 respectively, and the larger value of 183 is selected.

Non-random sampling technique was done. The clinical and laboratory data of all admitted patients in COVID ICU was searched for and extracted as per the defined study objectives. Serum LDH level of all the admitted patients were measured using Fully Automated Biochemistry Analyser (DIATRON PICTUS 500) in the laboratory of Nepal APF Hospital.

Independent variables recorded were patient's demographics, LDH, and co-morbidities. Dependent variables were duration of ICU stay and outcome of patients in terms of survival and mortality

A thorough search for all past records of COVID-19 patients admitted in the hospital during the defined period was performed. The demographic and clinical data including age, gender, duration of ICU stay and known co-morbidities was collected. The baseline laboratory data of LDH on patient admission records along with their record files were utilized for data collection. All the data was independently reviewed by a team of three physicians/researchers and entered into the computer database software (MS-Excel which was encrypted with password) by two researchers.

The confidentiality and anonymity was maintained at each step of the research including data collection, data entry in encrypted database software, data analysis, and reporting of results. The hard copies of patient files were kept safe in the medical record section by trained personnels in the restricted section designated

for patient record keeping. The digital copies were kept in an encrypted filing system by the same set of researchers. Anonymity was maintained by including only the unique case ID of the patients. Personal details such as name, address, telephone number and/or any other details that could link to patient identification were not included. Ethical approval was taken from the National Health Research Council (Ref N0. 1576).

All the collected data was entered in Microsoft Excel by researchers under supervision of principal investigator and then analyzed using Microsoft Excel as well as International Business Machine Software Statistical Package for the Social Sciences (SPSS) version 16 for windows.

RESULTS

Total of 190 patients were included in the study. The following table shows the baseline characteristics of the patients.

Table 1. Table showing baseline patient characteristics

	Survival (n = 87)	Mortality (n = 103)
Age (in years)	22 – 93 (53.17 ± 16.012)	27 – 87 (59.48 ± 14.918)
Sex (M:F)	53:34	67:36
Comorbidities (n)	85	80
LDH (<450): low	15	11
LDH (>450): high	72	92
Duration of stay (days)	2 – 22 (9.76 ± 4.425)	1 – 33 (8.59 ± 6.061)

Age =Range (mean ± SD), Sex = Male : Female, Comorbidities = total number of patients with comorbidities, Duration of stay =Range (mean ± SD) in days

Overall mean age of the patients was 56.59 ± 15.706 years. As shown in figure 1, majority of the patients were males.

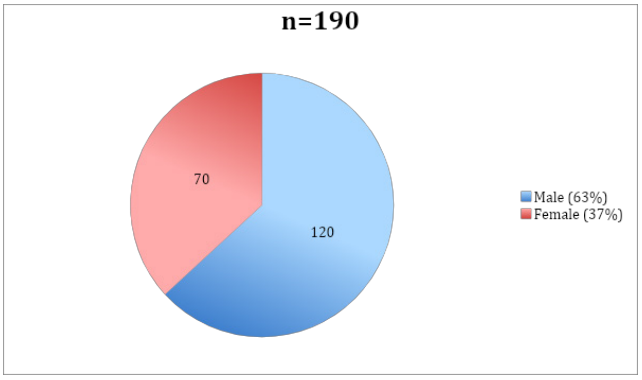

Figure 1. Pie chart showing male-female distribution

Regarding age group distribution of the patients, most of the patients were more than 60 years of age, which is shown in figure 2.

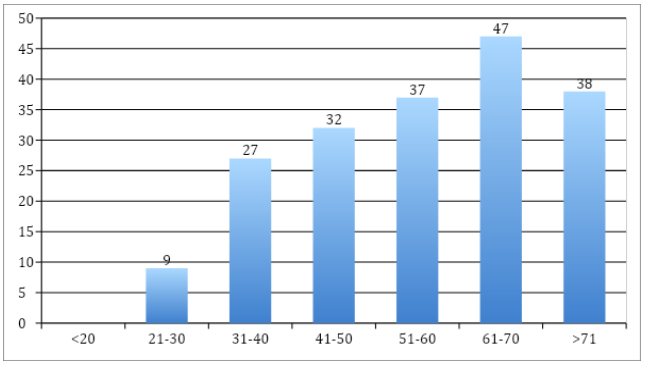

Figure 2. Bar diagram showing age group distribution

Most common comorbidity noted was hypertension. Other comorbidities observed were atrial fibrillation, benign prostrate hypertrophy, coronary artery disease, congestive heart failure, chronic liver disease and seizure disorders. Bar diagram in figure 3 shows the distribution of the most frequent comorbidities.

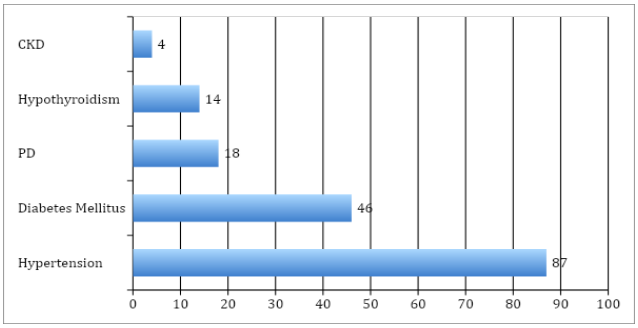

Figure 3. Diagram showing comorbidity distribution

The overall length of stay of the patients was 9.13 ± 5.392 days. Out of 190 patients, 103 died and 87 of the patients were transferred to step-down ward or referred to another center. According to the cut-off value of the lab reports of LDH, 450 IU/l was the cut-off point for high mortality prognosis. Among all, 164 patients had high LDH on ICU admission. There was higher mortality in the high LDH group as shown in the figure 4. The mortality percentage in high LDH and low LDH group was 56% and 42.3% respectively.

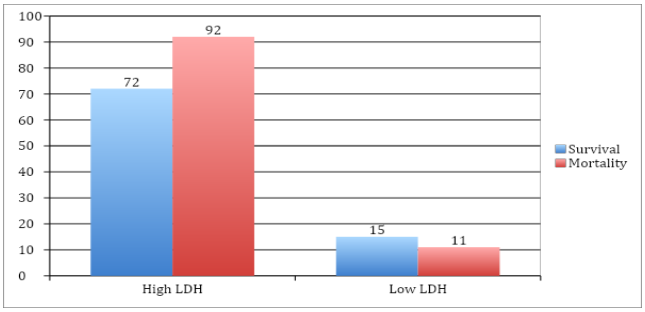

Figure 4. Bar diagram showing survival and mortality in high and low LDH group

DISCUSSION

The majority (63%) of the patients admitted in our study were males. Similar other types of studies also showed that majority of the patients were males with more than 70% of the patients being male.[17]

Majority of patients (47) were in the 61 – 70 years age group and 44.73% patients were older than 60 years. The overall mean age noted was 56.59 ± 15.706 years. In a study conducted in Tongji Hospital, China, the mean age noted was 58.83 ± 16.46, which is comparable to our study. [9] Patients in the survival group were younger than in the mortality group. Mean age in the survival group was 53.17 ± 16.012 years whereas in the mortality group it was 59.48 ± 14.918 years. In a multicenter retrospective cohort study done in Mexico, survivors (41.8 ± 22.7 years) were younger than non-survivors (46.72 ± 25.7 years).[17]

On average, the comorbidity profile was almost similar in both the groups as 85 of the survivors and 80 patients in the mortality group had comorbidities. Hypertension was the most commonly reported comorbidity followed by diabetes mellitus. A total of 87 (44.73%) had hypertension and 46 (24.21%) patients had diabetes. A similar finding was noted in a systematic review and meta-analysis, with hypertension followed by diabetes as the most commonly reported comorbidity.[15]

As per laboratory reports, the cut-off value of LDH was observed to be 450 IU/l for higher mortality prognosis. Among all patients 164 (86.31%) had high LDH on admission. The mortality in high LDH group was 56% in comparison to the low LDH group, which was 42.3%. The overall mortality in severe COVID-19 patients admitted to the intensive care unit of Nepal APF Hospital was 54.21%. Similar results were noted in the study conducted in Wuhan, China.[11]

Duration of hospital of stay was almost equal in both survival and mortality groups, which were 9.76 and 8.59 days respectively. However, in one of the similar retrospective studies conducted in Wuhan, China, the average length of stay was 17 days.[18]

This study had few limitations. This was a single centered retrospective study with small sample size. A large scale, multi-centered prospective study including other inflammatory markers such as d-dimer, CRP, ESR along with other laboratory parameters and the clinical manifestations of the patients would be needed in order to further clarify patient profile and provide deeper insights into the value of LDH as a prognostic marker in COVID-19 patients.

CONCLUSIONS

LDH is a useful biomarker for predicting in-hospital mortality in severe and critically ill COVID-19 patients. The test is easily available and can guide the treating physicians and intensive care specialists to approach and plan the clinical management of patients with severe disease. The resources can be prioritized and appropriate treatment can be initiated early, for better patient outcomes, thus, minimizing morbidity and mortality.

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CONFLICT OF INTEREST

None

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