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Original Article

Internal Medicine Section

Correlation of Lactate Dehydrogenase Level with Severity of Disease and In-hospital Outcome in Individuals Diagnosed with COVID-19: A Retrospective Study

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ABSTRACT

Introduction: The presence of tissue damage in the lungs, kidneys, heart, or other organs can be detected by monitoring the level of Lactate Dehydrogenase (LDH) in the blood and considered a reliable biomarker in early prediction of patients' prognosis.

Aim: To determine extent of correlation between LDH level with the spectrum and in-hospital outcome of Coronavirus Disease-2019 (COVID-19) infected patients.

Materials and Methods: This retrospective research was undertaken during March 2020 to May 2020, based on the data of 205 COVID-19 infected patients, reported at Dammam Medical Complex, Dammam, Eastern Province, Saudi Arabia. Patients' records were retrieved and the following data were recorded-age, gender, nationality, co-morbidities, lactate dehydrogenase level, number of days since the patient tested positive (upto 7,14 and >14 days), COVID-19 symptoms [mild, moderate, or severe as per British Thoracic Society guidelines (CURB (Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure)-65)]. The data was collected and tabulated as mean±SD, frequency and percentages. Analysis was carried out using specialised software of Statistical Package for Social Sciences (SPSS) version 20.0.

Results: On analysis of the collected data of all 205 included patients, the LDH level was found significantly high among males, 46-60 years old, and among non Saudi patients. The severity of COVID-19 symptoms and LDH levels were found to have a strong relationship (p-value <0.001). Patients between the ages of 46 and 60 were more likely (4.3 times) to have poor outcomes, and diabetes mellitus was predicted to be 2.32 times more likely to be associated with poor COVID-19 outcomes. Raised LDH levels were >5 times more likely to lead to in-hospital poor outcomes compared to those with borderline LDH levels.

Conclusion: The LDH level is a reliable predictor for the cause of COVID-19. The results of the present study suggest that patients aged 46-60 years, diabetic patients, or those suffering from severe symptoms of COVID-19 have raised levels of LDH.

Keywords: Biomarkers, Coronavirus disease-2019, Co-morbidities, Liver

INTRODUCTION

Monitoring the level of LDH in the blood helps to determine if there is any tissue damage in the lungs, kidneys, heart, and other organs [1]. Therefore, LDH has been considered a reliable biomarker in early prediction of outcome and prognosis of critically ill patients in Intensive Care Unit (ICU) suspected to have bacterial sepsis, Systemic Inflammatory Response Syndrome (SIRS) and respiratory distress syndrome [2]. LDH was studied among other serum or clinical factors, trying to find out some potential prognostic markers [3-4].

The recent pandemic of the novel coronavirus COVID-19 has appeared as an urgent challenge for frontline clinicians to effectively triage COVID-19 patients as an infectious disease that can cause severe respiratory illness and develop co-morbidities, which can lead to irreversible organ damage and, eventually, death [5,6]. The accuracy and reliability of the established early risk scores, such as the Sequential Organ Failure Assessment (SOFA) and the Modified Early Warning Score (MEWS) (MEWS), in predicting COVID-19 severity have been questioned [7-9].

The levels of lactate dehydrogenase (LDH), ferritin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) have shown changes among those with a severe disease [10]. LDH among three biochemical parameters has shown highest sensitivity (75%) with positive predictive value of 71.6% and diagnostic accuracy of 65.3% (AUC=0.65) in relation to RT-PCR gold standard test [11,12]. The use of a combination of common laboratory biomarkers (C-reactive Protein (CRP), LDH, and ferritin D dimer) to predict the diagnosis of COVID-19 having an established sensitivity and specificity may provide accurate diagnosis [13,14].

As the COVID-19 disease progresses (>7 days after the onset of symptoms), lymphopenia gets worse while neutrophil count, C-reactive protein levels, and lactate dehydrogenase levels rise [15]. Significant relationships were reported between hospitalisation in intensive care unit and LDH, lymphocyte count, LDH/lymphocyte ratio, CRP, highest D-dimer, initial Interleukin (IL)-6, neutrophil/lymphocyte ratio, and highest IL-6 values [16,17]. In a meta-analysis based on 264 records, LDH levels were significantly lower in the group of survivors than who died in-hospital, and lower LDH levels were observed in non severe groups compared to severe course of COVID-19 [18].

The present study was planned to determine the extent of correlation of serum LDH with the severity of COVID-19 disease among the patients admitted in ICU to demonstrate a strong correlation between elevated LDH level in relation to poor outcome of patients. LDH might be viewed as the ideal biomarker because it is affordable, reproducible, and simple to obtain in any laboratory.

MATERIALS AND METHODS

This retrospective study was undertaken at Dammam Medical Complex Hospital, Dammam, Eastern Province, Saudi Arabia, during

March 2020 to May 2020. Ethical approval was taken from the Institutional Review Board (IRB), [reference No. IRB-D-2020-5]. Data of 205 suspected patients of COVID-19 infection were recorded.

Inclusion criteria: Confirmed case of COVID-19 on a polymerase chain reaction (PCR) test positive, either gender, or age greater than 14 years were included.

Exclusion criteria: Patients with haemoglobinopathies and/or malignancies were excluded from the study. Incomplete data records or patient's Leaving Against Medical Advice (LAMA) were also excluded from the study.

As per the routine protocol, the patient's signed a consent statement having the description of all pros and cons of the procedures prior to being performed along with a Terms of Reference (TOR).

Study Procedure

Variables extracted from patients' medical records were age, gender, nationality, co-morbidities, lactate dehydrogenase level, COVID-19 severity, and the number of days since the patient tested positive (upto 7,14 and >14 days). LDH was classified into three categories i.e. normal upto 200 U/L, borderline 200-500 U/L, and raised >500 U/L [12]. At the time of admission, COVID-19 patients' severity was determined by using the following criteria (Saudi MoH protocol version 2.1;2020) [19]:

1 **Mild COVID-19 disease:** If chest radiography or chest Computed Tomography (CT) findings revealed only mild pneumonia or no evidence of pneumonia at all;

2 **Moderate COVID-19 disease:** If within 24-48 hours there was dyspnoea, respiratory rate less than 30 breaths per minute, blood oxygen saturation less than 93%, PaO_2/FiO_2 ratio less than 300, and/or lung infiltrates greater than 50%.; and

3 **Severe COVID-19 infection:** If there was respiratory failure, septic shock, and/or multiple organ dysfunction or failure.

STATISTICAL ANALYSIS

Statistical data testing was carried out using specialised software of Statistical Package for Social Sciences (SPSS) version 20.0. An International Business Management (IBM) product from Chicago (USA). Numeric type data variables (e.g. age) were presented as mean±SD. Frequencies and percentages were used to present qualitative variables, for instance gender, nationality, co-morbidities, lactate dehydrogenase level, symptoms, course of disease, and in-hospital outcome of patients. All these qualitative variables were compared by using a Chi-square test in relation to lactate dehydrogenase levels (LDH). To evaluate the predictors of COVID-19 outcome, logistic regression analysis was performed by taking COVID-19 in-hospital outcome as the dependent variable; the panel of independent covariates consisted of gender, age, nationality, co-morbidity, and COVID-19 severity. If a p-value ≤0.05, it reveals a significant result and non significant elsewhere.

RESULTS

Amongst total 205 COVID-19 confirmed cases, male preponderance (90.2%) was evident (M:F ratio=9.3:1). The mean age was 45.4±13.0 years (range from 18-89 years), and majority were non Saudi patients (79.5%). The LDH was normal in 37 (18.1%), borderline in 138 (67.3%), and raised in 30 (14.6%) patients. A significantly higher proportion of male patients 132 (95.7%) had borderline, and 25 (83.3%) had raised LDH levels (p=0.001). The age group of 46-60 years was found to be significantly affected (p=0.005), with borderline and raised LDH levels of 46.4% and 46.7%, respectively. Significantly higher proportions of the patients with borderline (82.6%) and raised (86.7%) LDH levels were non Saudis (p=0.014) as detailed in [Table/Fig-1].

Around two-thirds of the COVID-19 patients had no co-morbidities (64.4%). However, the proportions of patients with atleast one co-morbid condition were 39.9% and 36.7% of those with borderline and raised LDH levels, respectively. There was a significantly higher proportion of patients with raised LDH levels who had moderate and severe symptoms of COVID-19 disease. It revealed a significant association between the severity of disease symptoms and raised LDH level (p<0.001). A remarkably greater proportion of patients with borderline LDH had a course of disease of 7-14 days (52.5%) and those with raised LDH levels (33.3%) had a >14-day course of disease (p=0.004) as presented in [Table/Fig-2].

Patient's characteristics	Total (n=205)	Lactate dehydrogenase level			p-value
		Normal (n=37)	Borderline (n=138)	Raised (n=30)	
Gender					
Male	185 (90.2)	28 (75.7)	132 (95.7)	25 (83.3)	**0.001**
Female	20 (9.8)	9 (24.3)	6 (4.3)	5 (16.7)	
Age (in years)					
18-30	25 (12.2)	5 (13.5)	14 (10.1)	6 (20.0)	**0.005**
31-45	78 (38.0)	20 (54.1)	50 (36.2)	8 (26.7)	
46-60	83 (40.5)	5 (13.5)	64 (46.4)	14 (46.7)	
Above 60	19 (9.3)	7 (18.9)	10 (7.2)	2 (6.7)	
Nationality					
Saudi	42 (20.5)	14 (37.8)	24 (17.4)	4 (13.3)	**0.014**
Non Saudi	163 (79.5)	23 (62.2)	114 (82.6)	26 (86.7)	

[Table/Fig-1]: Association of Lactate Dehydrogenase (LDH) level with the demographic characteristics.

Associated characteristics	Total (n=205)	Lactate dehydrogenase level			p-value
		Normal (n=37)	Borderline (n=138)	Raised (n=30)	
Co-morbidity					
Without co-morbidity	132 (64.4)	30 (81.1)	83 (60.1)	19 (63.3)	0.061
With co-morbidity	73 (35.6)	7 (18.9)	55 (39.9)	11 (36.7)	
Diabetes mellitus	53 (25.9)	3 (8.1)	42 (30.4)	8 (26.7)	
Hypertension	39 (19.0)	5 (13.5)	27 (19.6)	7 (23.3)	
Ischaemic heart disease	9 (4.4)	2 (5.4)	4 (2.9)	3 (10.0)	
Chronic kidney diseases	4 (2.0)	1 (2.7)	3 (2.2)	0	
Others	17 (8.3)	3 (8.1)	11 (8.0)	3 (10.0)	
Symptoms					
Mild	154 (75.1)	35 (94.6)	106 (76.8)	13 (43.3)	**<0.001**
Moderate	37 (18.1)	2 (5.4)	23 (16.7)	12 (40.0)	
Severity	14 (6.8)	0 (0)	9 (6.5)	5 (16.7)	
Number of days after onset of disease					
<7 days	71 (34.6)	21 (56.8)	44 (31.9)	6 (20.0)	**0.004**
7-14 days	98 (47.8)	12 (32.4)	72 (52.2)	14 (46.7)	
>14 days	36 (17.6)	4 (10.8)	22 (15.9)	10 (33.3)	

[Table/Fig-2]: Association of LDH level with severity of COVID-19. Shows there were more than one co-morbidity in one patient

Patients with COVID-19 disease who had a raised LDH level (>500 U/L) had a higher mortality rate (26.7%), and admitted to Intensive Care Unit (ICU) (10%), revealed a significant correlation of in-hospital poor outcomes of patients with an increased LDH level (p=0.001) presented in [Table/Fig-3].

A panel of 12 covariates was selected to detect the predictors of COVID-19 severity and in-hospital mortality. According to regression analysis, patients between the ages of 46 and 60 years were more likely (4.3 times) to have poor outcomes, and diabetes mellitus was predicted to be 2.32 times more likely to be associated with poor COVID-19 outcomes. Raised LDH levels were >5 times more likely to lead to in-hospital poor outcomes compared to those with borderline LDH levels [Table/Fig-4].

Severity of disease	Total (n=205)	Lactate dehydrogenase level (U/L)				p-value
		Normal (n=37)	Borderline (n=138)	Raised (n=30)	Mean±SD	
Recovered	176 (85.9)	36 (97.3)	121 (87.7)	19 (63.3)	295.7±117.6	<0.001
ICU admission	13 (6.3)	0	10 (7.2)	3 (10.0)	423.6±105.1	
Deceased	16 (7.8)	1 (2.7)	7 (5.1)	8 (26.7)	468.1±166.9	

[Table/Fig-3]: Association of LDH level with the in-hospital outcome of patients.
LDH reference ranges: Normal below 200 U/L, Borderline 200-500 U/L and Raised >500 U/L;
ICU: Intensive care unit

Factors	In-hospital outcome		Crude Odd ratio OR (95% CI)	p-value
	Poor (ICU/Died) (n=29)	Good (Recovered) (n=176)		
Gender (Male)	28 (96.6)	157 (89.2)	3.39 (0.44-26.3)	0.243
Age (31-45 years)	6 (20.7)	72 (40.9)	2.62 (0.54-12.7)	0.232
Age (46-60 years)	15 (51.7)*	68 (38.6)	4.29 (1.15-16.0)	**0.030**
Age (above 60 years)	5 (17.2)	14 (8.0)	1.62 (0.51-5.12)	0.417
Non Saudi nationality	22 (75.9)	141 (80.1)	0.78 (0.31-1.97)	0.599
Co-morbid (yes)	15 (51.7)	58 (33.0)	2.18 (0.99-2.82)	0.054
Diabetes mellitus	12 (41.4)*	41 (23.3)	2.32 (1.03-5.26)	**0.043**
Hypertension	9 (31.0)	30 (17.0)	2.19 (0.91-5.28)	0.081
Moderate symptoms	10 (34.5)*	27 (15.3)	4.81 (1.86-12.4)	**0.001**
Severe symptoms	8 (27.6)*	6 (3.4)	17.3 (5.10-58.9)	**<0.001**
Course of disease (>14 days)	14 (48.3)	22 (12.5)	6.89 (2.36-20.1)	**<0.001**
Raised LDH level	11 (37.9)*	19 (10.8)	5.55 (2.42-12.7)	**<0.001**

[Table/Fig-4]: Predictors of in-hospital poor outcome related to severity of COVID-19 disease.
ICU: Intensive care unit; Values given in parentheses in 2nd and 3rd columns are percentages.
*Shows significantly higher proportions at 5% level of significance

DISCUSSION

The results of the present study confirmed a significant correlation between the in-hospital poor outcome of patients with an increased lactate dehydrogenase level (LDH) among tested positive cases. It also indicated that LDH levels were significantly high among males (46-60 years old), and among non Saudi patients. In addition, elderly people are at high-risk of getting infected [20,21], and the results of the present study showed the same too. It was found that those aged between 46 and 60 years old had the highest proportion of borderline or raised levels of LDH.

Henry BM et al., reported LDH as a strong predictor of the outcome of COVID-19 disease. They evaluated that LDH level increases the odds of developing the severity of the disease by a 6-fold and a 16-fold increase in odds of mortality in patients with COVID-19 [22]. Other studies have also reported LDH as one of the predictors of the progression of the disease (COVID-19), alongside the patients' demographics and other co-morbidities [23,24].

The proportion of males were high in which most of them were non Saudis. This finding is quite obvious as there is majority of male expatriates than females in Saudi Arabia [25]. Hence, it could be possible reason high proportion of cases among non Saudi males compare to others.

Statistical analysis revealed that the relationship between LDH level and severity of disease was significant, that is, symptoms were severe as the LDH level increased. It was also observed that an increase in the number of days after testing positive for COVID-19 had a significant association with an increase in LDH level. The release of LDH is directly associated with tissue damage and is involved in various pathological processes. Wu MY et al., demonstrated that monitoring LDH levels could aid in determining the progression or improvement of COVID-19, and they concluded that the time to normalise the LDH level is directly related to radiographic absorption [26]. Furthermore, COVID-19 infected patients with high LDH levels at the time of hospitalisation are more likely to develop Acute Respiratory Distress Syndrome (ARDS) [27].

The linear association between symptom severity and LDH level supports the hypothesis of the present study. Hence, regular monitoring of the LDH level could help to find the course of the disease. Furthermore, early detection of the course of the disease, can help to take necessary and preventive measures early. It was also found that COVID-19 patients with diabetes mellitus were 2.32 times more exposed to a poor outcome. Fang L et al., hypothesised that diabetic patients who were using ACE-stimulating drugs had a high-risk of developing severe symptoms of COVID-19 [28]. However, Guan W et al., [29] and Zhang JJ et al., [30] reported that 16.2% and 12% of their sampled COVID-19 patients had diabetes mellitus, respectively.

Limitation(s)

The duration of the planned study was very short, i.e., three months, because there was a general impression that the pandemic would be controlled in a short span of time by the enforcement of complete lockdown and strict precautionary measures. Two major factors related to the patient's data, i.e., occupation and standard of living, that could be associated with a greater risk of COVID-19 infection, especially in expatriate male workers, were neglected in the present study.

CONCLUSION(S)

Hence, it is concluded that monitoring LDH level is a reliable predictor for the cause of COVID-19. The results of the present study suggest that patients aged 46-60 years, diabetic patients, or those suffering from severe symptoms of COVID-19 have raised levels of LDH. Early measurements could be taken to control the increase in LDH level, which ultimately reduces the chances of severe symptoms endangering a patient facing the worst outcome of COVID-19.

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