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PROGNOSTIC VALUE OF LACTATE DEHYDROGENASE IN COVID 19 PATIENTSAT TISHREEN UNIVERSITY HOSPITAL

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) has triggered a global health crisis that has affected populations and spread rapidly worldwide. **Aim:** The purpose of this study was to evaluate the role of lactate dehydrogenase LDHas a potential predictor for COVID-19 induced fatal clinical complications in hospitaliz ed patients. **Materials and Methods:** This was an Analytic Cohort study(Retrospective) involved 293 patients with proven diagnosis of COVID-19 admitted at quarantine unit, Tishreen University Hospital, Lattakia, during the period 2020- 2021. Patients were divided into two groups according to LDH: group 1 included patients with normal levels of LDH (15 patients), and group 2 included patients with elevated levels of LDH (278 patients). Morbidity and mortality were compared between two groups. **Results:** Out of 293 patients, 165 were male and 128 were female, with mean age of the patients was 62.4±15.1. There were no significant differences between two groups regarding of age, gender, and comorbidities ($p>0.05$). There were significant differen ces between two groups regarding laboratory investigations: lymphocytes levels whic h decreased significantly with increasing LDH and D-dimer which were higher in patie nts with higher levels of LDH($p<0.05$). High levels of LDH was associated with an indep endent risk for mortality (RR: 3.9[1.9-10.3], p:0.0001), admission in intensive unit care ICU (RR: 2.1[1.2-7.5], p:0.0001), need for non-invasive ventilation (RR: 2.6[1.1-7.6], p: 0.004), and longer duration of hospitalization (RR: 3.1[2.9-9.8], p:0.0001). **Conclusion:** The current study showed unfavorable results of elevated levels of LDH on final outcome regarding morbidity and mortality in COVID-19 patients.

KEYWORDS: COVID-19, lactate dehydrogenase, morbidity, mortality.

INTRODUCTION

Coronaviruses comprise a vast family of viruses that lead to respiratory infe ctions, which includes severe acute respiratory syndrome(SARS) that first origin ated in bats and transmitted to humans, middle east respiratory syndrome (ME RS) emerged in humans through intermediate host of camels and SARS-CoV-2(COVID-19).[1] SARS-CoV-2 was first reported in Wuhan, Hubei Province, China in late December 2019, and then disseminated rapidly across the world in a short span of time with declaration by world health organization(WHO) that it is as a global pandemic on March 2020[2,3] It has resulted in high morbidity and mortality, in which approximately 73 million cases and 1.5 million deaths have been reported worldwide.[4]

Clinical manifestations of COVID-19 are diverse and might vary from asymptomatic infection and mild upper respiratory tract symptoms to respiratory failure and death.[5] There are many factors that predispose to severe form which include; advanced age, presence of comorbidities, and obesity. In addition to, severe forms of disease showed laboratory changes including lymphopenia, elevate d levels of inflammatory markers and D-dimer.[5]

Lactate dehydrogenase(LDH) represents an important cytoplasmic enzyme of the anaerobic metabolic pathway, and elevated levels of serum LDH reflect the severity of tissue damage.[6] There is reprogramming of glucose metabolism in inflammatory conditions such as severe conditions of COVID-19 especially in glycolysis pathway.[7] Despite its lack of specificity, serum LDH can have prognostic significance, and many studies demonstrated that elevated levels of LDH is associated with severe disease and reflect cell injury induced by infection.[7] The pandemic continues to place a major strain on a country's resources and it is predicted that mortality and morbidity rates will become pronounced with rising spread among lower income countries, so that finding a simple, fast, a sensitive test is considered crucial to detect patients who are considered high risk for

COVID-19 complications.[8] Therefore, the objectives of the current study were to: 1- detect the prognostic value of elevated LDH levels in COVID-19 patients, 2-to determine the utility of LDH on admission for predicting mortality.

PATIENTS AND METHODS

This is an Analytic Cohort study of a group of patients attending Department of Pulmonary Medicine at Tishreen University Hospital in Lattakia-Syria during one-year period (January 2020 and January 2021). The inclusion criteria were: patients older than 15 years, males or females, with a positive PCR, and who didn't receive vaccination. The exclusion criteria were presence of one of the following: patients with diseases that lead to elevated levels of LDH such as; tumors, liver diseases (viral hepatitis, liver cirrhosis, autoimmune hepatitis), hematologic diseases (hemolytic anemia, sickle cell anemia), myocardial diseases (heart failure, myocardial infarction), muscular disease(rhabdomyolysis), and renal diseases (hemodialysis). Complete history, review of systems, physical examination, and laboratory investigations included white blood cell(WBC), C-reactive protein (CRP), lymphocyte(LYM), procalcitonin(PCT) were performed. Radiological investigation was performed, and laboratory confirmation of COVID-19 diagnosis was done based on using real-time PCR with a standard protocol. Patients were stratified according to the LDH levels into two groups: group I included COVID-19 patients with normal levels of LDH(15 cases), and group II included COVID-19 patients who with elevated levels of LDH(278 cases). Demographic variables, requirement to respiratory support and final outcome were compared between two groups.

Ethical consideration: All patients were provided a complete and clear informed consent after discussion about the study. This study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations(SD), Frequency and percentages. To examine the relationships and comparisons between the two group, chi-square test was used. Independent t student test was used to compare 2 independent groups. Multivariate logistic regression analysis was performed to estimate risks associated with high levels of LDH on prognosis. The receiver operating characteristics(ROC) curve was constructed, and the area under curve(AUC) was established to assess the ability of peak LDH in predicting progressive of disease and mortality. All the tests were considered significant at a 5% type I error rate($p<0.05$), β:20%, and power of the study:80%.

RESULTS

The study included a group of 293 patients with a diagnosis of COVID-19. The baseline characteristics of patients were as shown in Table (1). Age ranged from 19 to 95 years, with a mean age of 62.4±15.1 years. Males represented 56.3% and females 43.7% of the patients. Patients included for the analysis, presented some comorbidity as follow; hypertension in 135 cases (46.1%), diabetes mellitus in 88 cases (30%), cardiovascular diseases in 49 cases (16.7%), and COPD in 26 cases (8.9%). Patients were classified according to the LDH levels into four groups: <250(5.1%),250-500(33.8%), 500-1250(49.5%), and>1250(11.6%).

Table 1: Demographic Characteristics of the Study Population.

Variable	Result
Age(years)	62.4±15.1(19-95)
Gender Male	 165(56.3%)
Female	128(43.7%)
Comorbidities	
Hypertension	135(46.1%)
Diabetes mellitus	88(30%)
Cardiovascular diseases	49(16.7%)
COPD	26(8.9%)
Laboratory findings	
LDH	
<250	15(5.1%)
250-500	99(33.8%)
500-1250	145(49.5%)
>1250	34(11.6%)

Patients were classified according to the levels of LDH into two groups: group I (normal levels of LDH) included 15 cases and group II (elevated levels of LDH) included 278 cases. As shown in table (2), no significant difference was found between the two groups in terms of age, gender and presence of comorbidities ($p>0.05$). In group I, a mean age was 55.8±13.9 years versus 62.8±15.1 in group II, p:0.08. Males represented 66.7% and females 33.3% of the patients versus 55.8%,44.2% respectively in group II, p:0.4. Comorbidities that detected in group Iwere as follow; hypertension (53.3%), cardiovascular diseases (26.7%), diabetes mellitus (20%), and COPD (20%) versus 45.7%,30.2%,16.5% and 8.3% respectively.

Table 2: Demographic Characteristics of The Study Population by Comparison of The Two Groups.

	LDH		P- value Group IIElevatedGroup I Normal
			Variable
Age(years)	55.8±13.9	62.8±15.1	0.08
Gender			
Male	10(66.7%)	155(55.8%)	0.4
Female	5(33.3%)	123(44.2%)	
Comorbidities			
Hypertension	8(53.3%)	127(45.7%)	0.5
Diabetes mellitus	3(20%)	46(16.5%)	0.7
Cardiovascular diseases	4(26.7%)	84(30.2%)	0.7
COPD	3(20%)	23(8.3%)	0.1

As shown in table (3), there were significant differences in the mean values of LYM, D-Dimer in group I versus group II as follow; (766.6±475.6 versus 1064.5±965.2, p:0.04) and (1019.6±931.2 versus 3136.5±3530.4,p:0.02).

Table 3: Laboratory Parameters of The Study Population By Comparison of The Two GroUps.

Variable	LDH		P-value
	Group I Normal	Group II Elevated	
WBC	9552±5952.8	10763.6±5879.4	0.4
LYM	766.6±475.6	1064.5±965.2	0.04
CRP	101.5±85.1	110.7±86.9	0.6
D-Dimer	1019.6±931.2	3136.5±3530.4	0.02
PCT	1.39±4.6	4.41±30.9	0.7

During hospitalization, no patient required mechanical ventilation in group I versus 19 cases (6.8%) in group II, p:0.002. Admission to ICU was higher in patients with elevated levels of LDH (33.8% versus 13.3%, p:0.01). Recovery was occurr ed in 13(86.7%) patients in group I versus 130 cases (46.8%) in group II, and 13.3% of the patients died in group I versus 53.2% in group II, p:0.005. Duration of hospitalization was significantly longer in group II(8.16±8.1 versus5.53±4.6,p:0.001).

Table 4: Final outcome of the study population by comparison of the two groups.

Variable	LDH		P- value
	Group I Normal	Group II Elevated	
Mechanical ventilation			
Present	0(0%)	19(6.8%)	0.002
Absent	15(100%)	259(93.2%)	
Admission to intensive care unit (ICU)			
Present	2(13.3%)	94(33.8%)	0.01
Absent	13(86.7%)	184(66.2%)	
Outcome			
Recovery	13(86.7%)	130(46.8%)	0.01
Death	2(13.3%)	148(53.2%)	
Duration of hospitalization(day)	5.53±4.6 (1-17)	8.16±8.1 (1-54)	0.001

In the multivariate logistic regression analysis, elevated level of LDH was an ind ependent risk factor that associated significantly with occurrence of death (RR 3.9,95% CI 1.9-10.3, p=0.0001), need for mechanical ventilation (RR 2.6,95% CI 1.1-7.6, p=0.004), admission to ICU (RR 2.1,95% CI 1.2-7.5, p=0.0001), and longer duration of hospitalization (RR 3.1,95% CI 2.9-9.8, p=0.0001),

Table 5: Multivariate logistic regression analysis of LDH levels of the study population.

Variable	RR [CI 95%]	P value
Death	3.9[1.9-10.3]	0.001
Need for mechanical ventilation	2.6[1.1-7.6]	0.004
Admission at ICU	2.1[1.2-7.5]	0.0001
Duration of hospitalization	3.1[2.9-9.8]	0.0001

As shown in table (6), need for mechanical ventilation, admission to ICU, duration o f hospitalization and death were increased significantly with increasing LDH levels($p<0.05$).

Table 6: Outcome of the study population by comparison of LDH groups.

Variable	LDH			P value
	Mild (99)	Moderate (145)	Severe (34)	
Need for mechanical ventilation	3(3%)	11(7.6%)	5(14.7%)	0.0001
Admission to ICU	20(20.2%)	62(42.8%)	12(35.3%)	0.001
Duration of hospitalization	5.36±4.3	9.61±9.2	12.38±11.5	0.002
Death	36(36.4%)	73(50.3%)	21(61.8%)	0.01

Analysis of the ROC curve illustrated an 0.78 area under the curve (AUC) for LDH levels as a predictor of mortality (95% CI:0.65-0.92). The AUC of this biomarker indicated a high diagnostic value for mortality with the optimal threshold value being 342 with a sensitivity of 77.8% and specificity of 63.1%(figure 1).

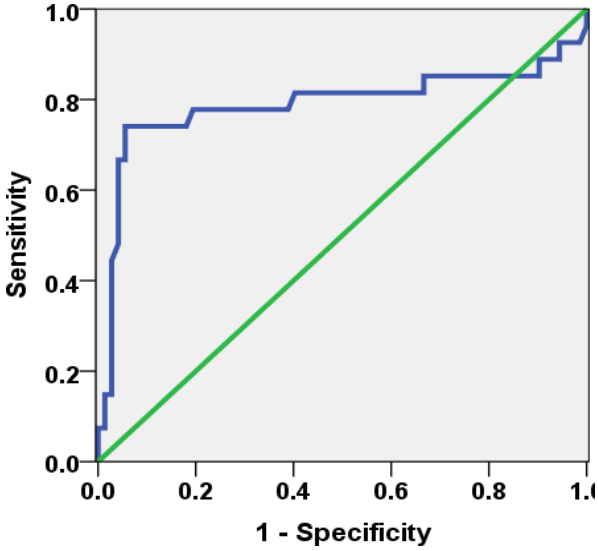

Fig. 1: Receiver operating curve of LDH: AUC 0.78[0.65-0.92]

DISCUSSION

The COVID-19 pandemic is a worldwide public health issue that has resulted in increased mortality with high rate of morbidity. To our knowledge, this study provides an empirical evidence of the impact of elevated levels of LDH on final outcome of COVID-19 patients. The result of the current study revealed that approximately 60% of the patients were males with presence of elevated levels of LDH in 94.9% of cases. The rate of mechanical ventilation and admission to ICU was significantly higher in patients with elevated levels of LDH. Duration of hospitalization was longer and the rate of recovery was lower in patients with elevated levels of LDH. Elevated levels of LDH was an independent risk factor that associated significantly with increased risk of mortality, need for mechanical ventilation, long duration of hospitalization, and admission to ICU. The cutoff of LDH 342 was the optimal value for accurate prediction of mortality with AUC of 0.78 and this value corresponded to sensitivity:77.8% and specificity:63.1%. These finding might be explained by inflammation and cell damage which play an important role in the pathological processes of pulmonary tissues and lead to elevated levels of LDH. The results of current study are consistent with the previousstudies.

Martha et al (2021) showed in an analytic study conducted in 10399 patients with COVID-19 that elevated levels of LDH were detected in 44%. Elevated levels of LDH was associated significantly with poor outcome(OR:5.33) and mortality(OR:4.22).[9]

Zeng et al (2020) demonstrated in a study included 317 patients with COVID-19 in China that LDH levels were increased significantly with increasing severity of disease; 234 U/L in moderate cases versus 496 U/L in severe cases, p:0.001. The level of LDH higher than 400 U/L was associated significantly with increasing the severity of disease.[10]

Poggiali et al (2020) showed in a study performed in 123 patients with COVID-19 in Italy that the cut-off of LDH 450 predicted moderate to severe disease with sensitivity 75% and specificity 70%. Respiratory performance represented by (PaO2/FiO2) showed a strong inverse correlation with LDH (r : 0.62, p: 0.0001).[11]

Dong et al (2020) demonstrated in a study conducted in 119 patients with COVID-19 that death was occurred in 54 cases, and the levels of LDH were significantly higher in non-survival patients (559.5 versus 228, p:0.0001). Elevated level of LDH was an independent risk factor for mortality (HR:5.9, p:0.01) and the cut-off of LDH 353 predicted in hospital-mortality with sensitivity 94% and specificity 89.2%.[12]

Fialek et al (2022) showed in an analytic study performed in COVID-19 patients that elevated levels of LDH were associated significantly with increasing severity of disease and the need for admission to ICU.[13]

In summary, elevated level of LDH on admission might be a prognostic marker in COVID-19 patients to detect high risk patients.

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