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The predictive value of the LDH-albumin ratio on poor clinical course and mortality in COVID-19 patients

A single-center study

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Abstract

There are studies evaluating the association of serum lactate dehydrogenase (LDH) and albumin levels with mortality in COVID-19 patients. The aim of our study was to evaluate the predictive effect of the LDH/albumin ratio (LAR) on mortality and poor clinical course in COVID-19 patients. A total of 2093 patients for whom LDH and albumin tests were available were included in the study. Demographic data, length of hospitalization, and signs of poor clinical course were recorded and compared with the LAR value at the time of hospitalization. The study included 1010 female (48.3%) and 1083 male (51.7%) patients. Notably, 1408 (67.3%) of the patients had at least 1 comorbidity. Oxygen was required in 860 patients (41.1%) and intensive care unit was required in 215 patients (10.3%). The mortality rate was 8.1% (n: 170). The median LAR value was 8.05. A positive correlation was observed between LAR and length of hospitalization. The LAR value was significantly higher in patients who died compared with those who survived, in patients who required intensive care compared with those who did not, and in patients who required oxygen compared to those who did not. The cutoff value for LAR in predicting mortality was calculated as 10.48. The sensitivity and specificity were determined as 73.5% and 73.7%. In conclusion, serum LAR at the time of admission is predictive of poor clinical course and mortality in COVID-19 patients. Patients with LAR values higher than the cutoff value should be closely monitored for poor clinical course.

Abbreviations: ARDS = acute respiratory distress syndrome, AUC = area under the curve, CI = confidence interval, COVID-19 = coronavirus disease-2019, CT = computed tomography, ICU = intensive care unit, IL = interleukin, LAR = LDH/albumin ratio, LDH = lactate dehydrogenase, ROC = receiver operating characteristic, RT-PCR = reverse transcription polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Keywords: COVID-19, LDH/albumin ratio, mortality, prognosis

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) is an infectious agent that emerged in Wuhan, China in December 2019 and can affect many tissues and organs, mainly the respiratory system, cardiovascular system, nervous system, and gastrointestinal system. Coronavirus disease-2019 (COVID-19) has caused a pandemic by spreading rapidly worldwide and leading to the deaths of millions of people in a short period of time.[1]

The health systems of many countries have struggled to cope with the pandemic from time to time. The emergence of different variants has made the pandemic more complex and difficult to resolve.[2] Despite the important information gained from the studies conducted since the beginning of the outbreak, many aspects of its pathogenesis, clinical involvement, and complications still remain unknown.

Although SARS-Cov-2 is mostly asymptomatic or causes flu-like symptoms, it can present with various clinical conditions including pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and sometimes death.[3,4] It most commonly causes nonspecific symptoms such as fever, cough, and myalgia. The mortality rate varies according to the severity of the disease. While the prognosis is generally good in patients

Informed consent was waived due to the retrospective design of the study, which relied on medical records.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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with mild infection, mortality rates can reach 50% in patients with severe involvement.[5,6] Several studies have shown that the main cause of mortality is macrophage activation syndrome caused by excessive cytokine production by the immune system against the virus.[7,8]

Early and rapid identification of patients with severe COVID-19, causing mortality, may ensure the optimal use of limited resources and reduce mortality.[9] Therefore, many studies have been conducted to identify critically ill patients at an early stage.[10,11] Many variables such as demographic characteristics, clinical complaints, radiological findings, laboratory parameters, and comorbidities can be used to determine the severity of the disease.[2] In this process, repeated radiological examinations in particular cause significant radiation and cost burden. For this reason, the importance of biomarkers that can be analyzed quickly and easily in peripheral blood has attracted attention.[9,12]

Many studies have shown that the lactate dehydrogenase (LDH) enzyme measured during hospitalization is elevated in COVID-19 patients.[13,14] LDH is one of the enzymes involved in glycolysis located in the cytoplasm and has been shown to be associated with systemic inflammatory response and cell damage.[15]

Albumin is known as a negative acute phase reactant. The increase in capillary permeability, particularly in infectious diseases, is thought to be responsible for the decrease in albumin levels.[16] Albumin levels have been shown to decrease in patients with COVID-19 in many studies.[17]

Both LDH and albumin levels can be affected by various factors such as malignancies, liver diseases, and malnutrition, in addition to infectious diseases. It is thought that LDH/albumin ratio (LAR) may be more useful than LDH and albumin in identifying critically ill patients.[18,19]

The aim of this study is to evaluate the predictive value of LAR, a blood parameter measured at the time of hospital admission, on mortality among patients admitted to the wards and intensive care units (ICUs) of our hospital since the beginning of the pandemic. Additionally, assessing the relationship of LAR with the length of hospital stay and poor prognosis criteria was among the secondary objectives.

2. Material and methods

Between March 11, 2020 and August 11, 2021, a total of 2451 patients aged 18 years and older, who were hospitalized with a diagnosis of COVID-19, were retrospectively analyzed. Of these, 2093 patients with available LDH and albumin test results within the first 48 hours of hospitalization were included in the study (Fig. 1). COVID-19 diagnosis was primarily confirmed using reverse transcription polymerase chain reaction (RT-PCR) tests in accordance with World Health Organization guidelines. In cases where RT-PCR results were negative, the diagnosis was established based on clinical, laboratory, and radiological findings.

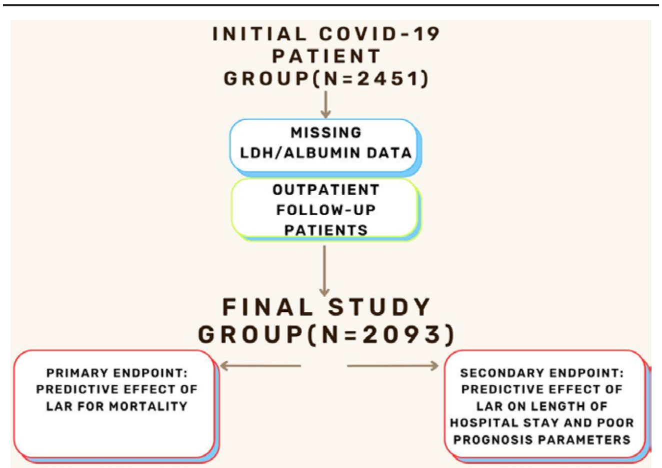

Figure 1. Flowchart depicting the patient selection process for the study.

The treatment modality was determined according to the guidelines published by the Ministry of Health of the Republic of Turkey, national and international publications, and clinical experience. At the beginning of the pandemic, patients were started on hydroxychloroquine and favipiravir followed by molnupiravir. As a result of the studies, steroid treatment was shown to be beneficial in patients in the hyperinflammatory phase, and 6 mg dexamethasone or equivalent corticosteroid was added to the treatment of especially hypoxic patients. In addition to these treatments, mini-pulse steroid and tocilizumab treatment was initiated in patients with macrophage activation syndrome.

All hospitalized patients were assessed for bleeding risk and all patients who were not at high risk of bleeding received thromboprophylaxis with low-molecular-weight heparin, standard heparin, or fondaparinux. In addition to COVID-19, patients with suspected bacterial infection based on clinical, radiological, and laboratory findings were started on empirical antibiotic treatment until culture results were obtained. Treatment was readjusted with culture results.

Patients' demographic data, duration of hospitalization, signs of poor clinical course (need for oxygen and/or intensive care), mortality status, serum LDH, and albumin levels at the time of hospitalization were recorded and the LAR value was calculated.

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All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago). Kolmogorov–Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as mean ± standard deviation or median (25–75 percentile), and categorical variables were expressed as counts (percentage). Comparisons of continuous variables between groups were performed using the Mann–Whitney Test. Comparisons of categorical variables between the groups were performed using the chi-square test. Correlation between variables was performed with Spearman correlation analysis. Diagnostic performance of LAR based on the receiver operating characteristic curve and positive and negative predictive values were defined. A 2-sided P value <.05 was considered statistically significant.

3. Results

The study included 1010 female (48.3%) and 1083 male (51.7%) patients. The median age of the included patients was 59 years. The median length of hospital stay was 5 days (min: 1, max: 80).

The RT-PCR test was positive in 712 (81.8%) patients. The test was negative in 381 patients and a high-probability diagnosis of COVID-19 was made based on clinical, radiological, and laboratory findings.

At least one comorbidity was present in 1408 patients (67.3%) and hypertension, diabetes mellitus, malignancy, and coronary artery disease were among the most common comorbidities. Demographic characteristics of the study population are shown in Table 1.

Oxygen requirement developed in 860 patients (41.1%) and ICU requirements developed in 215 patients (10.3%). During follow-up, 170 patients (8.1%) died (Table 2).

The median LAR of patients was 8.05 (25–75 percentile: 5.95–11.4). It was observed that there was a positive correlation between LAR value and age and length of hospitalization. A positive correlation was observed between LAR value and both age ($R = 0.27$, $P < .001$) and length of hospital stay ($R = 0.28$, $P < .001$) (Table 3).

The LAR value was significantly higher in patients who died compared with those who survived (14.4 vs 7.8, $P < .001$), in patients who required ICU compared with those who did not (15.5 vs 7.7, $P < .001$), and in patients who required oxygen compared with those who did not (10.7 vs 7.01, $P < .001$) (Table 4).

Receiver operating characteristic analysis was performed to evaluate the sensitivity and specificity of the LAR value in predicting mortality. The optimal cutoff value for LAR in predicting mortality was 10.48 (area under the curve [AUC]: 0.782, 95% confidence interval [CI]: 0.74–0.82; $P < .001$), with sensitivity and specificity values of 73.5% and 73.7%, respectively (Tables 5 and 6 and Fig. 2).

4. Discussion

This study showed that the LAR value was significantly higher in patients who required oxygen support, required intensive care, and died and that there was a correlation between serum LAR and length of hospital stay in COVID-19 patients followed and treated in hospital. Therefore, it was concluded that the LAR value can be used to predict a poor clinical prognosis.

The persistence of COVID-19 with emerging variants, such as Eris, underscores the importance of identifying patients at high risk for poor outcomes to optimize resource allocation and reduce mortality.[20] COVID-19's clinical presentations vary widely, from asymptomatic cases to severe, life-threatening conditions involving multiple organs, particularly the lungs.[21,22] Early identification and close monitoring of patients at high risk of deterioration are crucial to improve clinical outcomes.[17,23]

LDH is a soluble cytoplasmic enzyme that is widely produced in tissues that convert pyruvate to lactate when oxygen is reduced. Several studies have shown that serum LDH levels can be used as a prognostic factor in many diseases such as infections, sepsis, interstitial lung disease, ARDS, and malignancy.[24,25] Patients with high LDH levels generally have more infections and a worse prognosis. LDH elevation increases as a result of cell damage that can occur in various diseases and has low specificity. There are 5 known isoenzymes of the LDH enzyme and determining which isoenzyme is responsible for the increase in LDH can aid in the differential diagnosis.[15,26]

Many studies to date have shown that LDH level can be used as a determinant of disease severity and is a risk factor for mortality in COVID-19 patients.[14,27] In the study by Wu et al,[28] serum LDH value was found to be associated with the development of ARDS and mortality in patients with COVID-19. Thiruvengadam et al[29] showed a correlation between LDH levels and length of hospital stay. Similarly, Al Omair et al[27] reported that increased LDH level was an independent risk factor for prolonged hospitalization in COVID-19 patients. Bonetti et al[30] indicated that LDH level can be used as an early prognostic marker for myocardial involvement due to COVID-19. Masumoto et al[31] showed that in patients with COVID-19 and underlying cardiovascular comorbidities, elevated LDH on admission was associated with an increased risk of in-hospital mortality.

Albumin is the most abundant protein in plasma, closely related to nutritional status. It has very important functions such as regulation of osmotic pressure and capillary permeability, transport of many endogenous and exogenous substances, and keeping plasma pH within a certain range.[32] It is mainly synthesized in the liver and plasma levels can decrease in many diseases. It is thought to reflect the severity of systemic inflammation, particularly in infections.[33]

Several studies have shown that serum albumin levels are lower in patients with severe COVID-19. In the study by Li et al,[34] serum albumin levels were found to be low in all COVID-19 patients who died. Bonetti et al[30] reported that low albumin levels are an important biomarker in the assessment of poor prognosis and mortality. In the study by Al Omair et al,[27] low albumin levels were found to be an independent risk factor for in-hospital mortality and prolonged hospitalization.

High LAR value, which reflects the ratio of high LDH and low albumin, has been shown to be better than LDH and albumin in determining prognosis in sepsis, lower respiratory tract infections, esophageal and colorectal cancers.[18,35] In addition,

Table 1

Demographic characteristics of the study population (%).

Gender	Female	1010 (48.3%)
	Male	1083 (51.7%)
Covid-19 diagnosis	PCR+	1712 (81.8%)
	Clinically and radiologically diagnosed	381 (18.2%)
Comorbidity	(+)	1408 (67.3%)
	Hypertension	736 (35.2%)
	Diabetes mellitus	479 (22.6%)
	Coronary artery disease	175 (8.4)
	Congestive heart failure	86 (4.1%)
	Chronic kidney disease	128 (6.1%)
	Chronic obstructive pulmonary disease	95 (4.5%)
	Asthma	115 (5.5%)
	Malignancy	183 (8.7%)

PCR = polymerase chain reaction.

Table 2

Oxygen requirement, intensive care requirement, and mortality rates.

Clinical course	Oxygen requirement	860 (41.1%)
	Intensive care unit requirement	215 (10.3%)
	Mortality	170 (8.1%)

Table 3

Correlation analysis between LAR and age and length of hospitalization.

			Age	LAR	Length of hospitalization
Spearman ρ	Age	Correlation coefficient	1.000	0.274	0.221
		Significance (2-tailed)		0.000	0.000
		n	2093	2093	2093
	LAR	Correlation coefficient	0.274	1.000	0.284
		Significance (2-tailed)	**0.000**		**0.000**
		n	2093	2093	2093
	Length of hospitalization	Correlation coefficient	0.221	0.284	1.000
		Significance (2-tailed)	0.000	0.000	
		n	2093	2093	2093

Bold values indicate statistically significant results (P < .05).
LAR = LDH/albumin ratio, LDH = lactate dehydrogenase.

Table 4

Comparison of LAR with oxygen requirement, intensive care unit requirement, and mortality.

		LAR	*P*
Oxygen requirement	(+)	10.7	**.001**
	(–)	7.01	
Intensive care unit requirement	(+)	15.5	**.001**
	(–)	7.7	
Mortality	(+)	14.4	**.001**
	(–)	7.8	

Bold values indicate statistically significant results (P < .05).
LAR = LDH/albumin ratio, LDH = lactate dehydrogenase.

Table 5

ROC analysis of serum LAR value.

	Area under the curve	95% confidence interval	*P*
LAR	0.782	0.74–0.82	**.001**

Bold value indicates statistically significant results (P < .05).
LAR = LDH/albumin ratio, LDH = lactate dehydrogenase, ROC = receiver operating characteristic.

Table 6

Sensitivity and specificity of serum LAR value.

LAR	Sensitivity (%)	Specificity (%)
10.48	73.5	73.7

LAR = LDH/albumin ratio, LDH = lactate dehydrogenase.

the fact that LDH and albumin can be easily measured from peripheral blood is one of the major advantages.

While LDH and albumin levels are usually assessed separately in studies conducted in COVID-19 patients, there are a limited number of studies in which LAR is analyzed. In the study by Alizadeh et al, which included a total of 477 patients, the risk of mortality and the requirement of intensive care were found to increase by 7.78 and 4.78 times, respectively, when the group with LAR ≥ 148.78 was compared with the group with LAR < 101.46. In addition, it was reported that LAR ≥ 136 was the optimal cutoff value for predicting mortality with a sensitivity and specificity of 72% (95% CI: 62.1–80.5) and 70% (95% CI:64.9–74.4), respectively, and that the length of hospital stay was significantly increased in patients with high LAR. In this study, albumin value was measured as g/dL and in our study as g/L.[36] In the study by Altuntas et al, 206 patients over 65 years of age admitted to the emergency department were included and the optimal cutoff value of LAR for predicting mortality was found to be 9.6 (AUC: 0.815, sensitivity: 75.9%, specificity: 76.3%, *P* = .001) and the cutoff value for severe lung involvement on thorax CT was found to be 11.2 (AUC: 0.946, sensitivity: 93.6%, specificity: 87.4%, *P* = .001). Altuntas et al[37] reported that the LAR can be used to predict mortality and severity of lung involvement in elderly COVID-19 patients. In the study by Ergenc et al,[38] laboratory values of 90 patients followed up in the service and 90 patients followed up in the ICU were analyzed and the LAR value was found to be significantly higher in patients who died. Sipahioglu and Onuk[39] reported that LAR can be used as an independent prognostic factor for mortality in patients with severe ARDS caused by COVID-19 in their study of 351 COVID-19 patients. Shokr et al[23] found a high risk of mortality due to COVID-19 infection in patients with high LDH/albumin/urea ratio. Similarly, in our study, the cutoff value for LAR was calculated to be 10.48, and the sensitivity for LAR was found to be 73.5% and the specificity was 73.7%.

This study has some limitations. The first one is that the LAR value was assessed at the first hospitalization and no comparison was made with the values after treatment. Second, it was a retrospective and single-center observational study. However, despite these limitations, it stands out from other studies by including a larger number of patients and evaluating other poor clinical course parameters such as oxygen and ICU requirements in addition to mortality and length of hospitalization.

In conclusion, our study demonstrates that the LAR is a valuable biomarker for predicting poor clinical outcomes and mortality in hospitalized COVID-19 patients. The LAR is a simple,

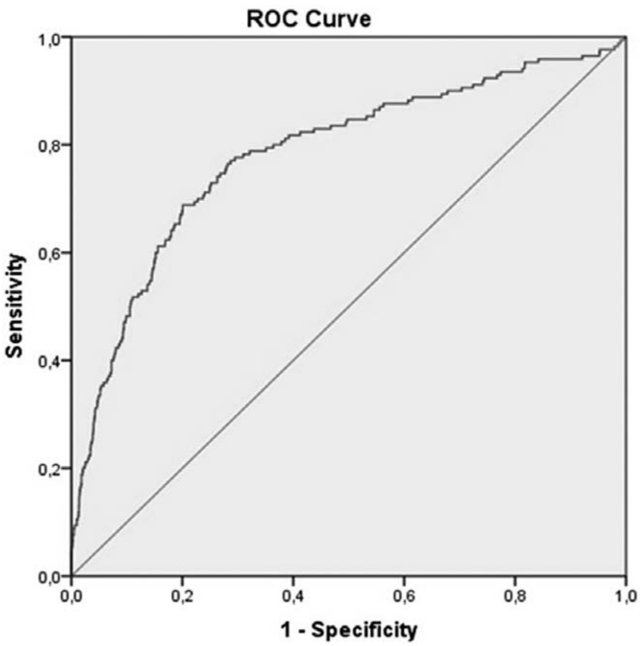

Figure 2. ROC analysis of LAR. LAR = LDH/albumin ratio, LDH = lactate dehydrogenase, ROC = receiver operating characteristic.

cost-effective, accessible, and easy-to-apply test. Our findings suggest that patients with values above the established cutoff should be closely monitored for adverse clinical outcomes and increased mortality risk. These results highlight the importance of incorporating this biomarker into routine clinical practice.

Author contributions

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