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Original Article

Lipoprotein(a): A New Intensive Care Unit Admission Predictor in Coronavirus Disease 2019 Patients

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Abstract

OBJECTIVE: Endothelium-related events in patients with coronavirus disease 2019 are linked to a poor prognosis. Lipoprotein(a) plays a role in vascular endothelial cell dysfunction. This research aims to investigate whether baseline serum lipoprotein(a) levels could be a predictor for intensive care unit admission and related clinical parameters in coronavirus disease 2019 patients.

MATERIAL AND METHODS: The research covers 126 patients who were hospitalized in intensive care unit or the non-intensive care unit in our hospital. This prospective cohort study was conducted from January 2021 to June 2021. The patients who were positive for severe acute respiratory syndrome coronavirus 2 according to real-time polymerase chain reaction test results were included in the study. Two groups were created according to the status of intensive care unit admission. Lipoprotein(a) was studied from blood samples taken at the time of hospital admission.

RESULTS: According to the results of the first clinical evaluation, 46 patients were admitted to the intensive care unit and 80 patients were admitted to non-intensive care unit in the hospital. Patients with intensive care unit admission had significantly higher serum lipoprotein(a) levels than patients without intensive care unit admission (40.9 ng/mL and 17.4 ng/mL, $P < .001$, respectively). The regression analysis revealed that serum lipoprotein(a) levels were independently related to intensive care unit admission (odds ratio 1.242, 95% CI 1.109-1.391, $P < .001$). In receiver operating characteristic curve analysis, lipoprotein(a) level ≥31.42 ng/mL had 82.6% sensitivity and 72.5% specificity in predicting intensive care unit admission. The risk of intensive care unit admission was seen to be 12.522-fold higher in cases with lipoprotein(a) level ≥31.42.

CONCLUSION: Lipoprotein(a) could be used as a useful biomarker for the triage of coronavirus disease 2019 patients. Baseline serum lipoprotein(a) levels may serve as a useful prognostic biomarker in patients hospitalized for coronavirus disease 2019.

KEYWORDS: COVID-19, mortality, clinical outcome, lipoprotein(a)
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first named and identified by WHO on February 11, 2020.[1] Various clinical outcomes can be seen in the course of the COVID-19 disease, ranging from asymptomatic to death.[2] Clinical symptoms such as coughing, high fever, and dyspnea are frequently observed in patients, while embolic and vascular pathologies are also seen in some patients.[3,4]

During severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infectious disease, lipid and lipoprotein metabolisms can change, and these changes can be easily identified by biochemical tests. A virus exploits the host organism to satisfy its need to reproduce and can alter lipid and lipoprotein levels.[5,6]

Lipoprotein(a), which is a prothrombotic and anti-fibrinolytic lipoprotein, consists of low-density lipoprotein particles attached to apolipoprotein(a).[7,8] Lipoprotein(a) levels are mainly determined by genetics; however, they may temporarily increase during acute inflammatory episodes.[9] Lipoprotein(a) is an important acute phase reactant in endothelium-related events such as cardiac and non-cardiac clinical situations.[10,11] Our knowledge of how Lp(a) levels change in COVID-19 patients and the clinical use of this change are limited. We know from previous publications that endothelial-related events trigger worse clinical scenarios in COVID-19 patients.[12]

We hypothesized that Lp(a) may be associated with intensive care unit (ICU) admission in COVID-19 disease. The aim of our study was to investigate the relationship between Lp(a) levels at the time of hospitalization and the status of ICU admission in COVID-19 patients.

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MATERIAL AND METHODS

Study Population

Our prospective cohort study was conducted in a single center and included patients who applied to our tertiary health center between January 2021 and June 2021. The Ministry of Health of the Republic of Turkey and the ethics committee of Çanakkale Onsekiz Mart University approved the study (09.12.2020, 2011-KAEK-27/2020-E.2000175652). Our research was carried out in line with the decisions of the Declaration of Helsinki. Both verbal and written informed consent were obtained from the participants.

Our study consisted of 126 patients who were hospitalized and monitored in the clinics of cardiology, infectious diseases, and clinical microbiology and who were positive for COVID-19 according to clinical, laboratory, radiological, and real-time polymerase chain reaction (RT-PCR) tests.

Combined throat/nose swab samples were taken, and SARS-CoV-2 RT-PCR tests were performed in accordance with the guidelines of the Ministry of Health of the Republic of Turkey and the World Health Organization (WHO). Non-ICU and ICU admissions were made in line with the recommendations of the scientific committee in our country.[13]

Patients were hospitalized if any of the following symptoms were present:

1. Moderate/severe pneumonia (patients with bilateral widespread pneumonia findings on their chest x-ray or tomography).
2. Hypotension (<90/60 mmHg) and tachypnea (≥30/min) or an arterial oxygen saturation value (<93%) without supplemental oxygen.
3. Severe laboratory parameters [C-reactive protein (CRP) >40 mg/dL (high sensitivity), lymphopenia, or >1000 ng/mL ferritin] despite unilateral infiltration of the lung.

The patients were admitted to the ICU if any of the following symptoms were present:

1. A respiratory rate of ≥30/min.
2. Oxygen saturation of <90% and partial oxygen of 70 mmHg despite nasal oxygen supplement of >5 L/min.
3. Heart rate >100 beats/min and systolic blood pressure (bp) <90 mmHg or mean arterial bp <65 mmHg.
4. Arterial oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ≤300.
5. Lactate levels >2 mmol/L.

MAIN POINTS

- Laboratory parameter abnormalities on admission are common in coronavirus disease 2019 patients.
- Lipoprotein(a) could be used as a useful biomarker for the triage of coronavirus disease 2019 patients.
- Baseline serum lipoprotein(a) levels may serve as a useful prognostic biomarker in patients hospitalized for coronavirus disease 2019.

Patients with renal disease [estimated glomerular filtration rate (eGFR) <30 (mL/min/1.73 m^2)] and heart failure with reduced left ventricular function (left ventricular ejection fraction of 40% or less), thromboprophylaxis contraindications, malignant disease, abnormal liver dysfunction (ALT and AST >3x the upper limit of normal), cerebrovascular disease, chronic atrial fibrillation, a history of heart attack, a history of coronary artery bypass surgery, use of cholesterol-lowering drugs, systemic lupus erythematosus, rheumatoid arthritis, current use of oral contraceptives, steroids or monoclonal antibody drugs, and those with endocrine diseases such as familial hypercholesterolemia that may affect Lp(a) levels were excluded from the study.

Biochemical and hemogram parameters were acquired from peripheral blood samples taken at the time of hospitalization using standard laboratory techniques. Body temperatures were determined as ≥38°C. The recommendations of the WHO were applied in categorizing the patients according to the severity of the disease.[14]

Serum Lipoprotein(a) Measurements

Human Lp(a) test samples and 10 mL peripheral venous blood samples were taken from patients at the time of hospital admission (at the time of initial diagnosis and before starting treatments such as steroids). Blood samples were centrifuged at approximately 1000×g for 20 minutes, and the obtained serum samples were stored at −80°C before further analysis. ELK1564 enzyme linked-immunosorbent assay kits [ELK (Wuhan) Biotechnology CO., Ltd., Hubei, P.R.C] were used for measuring Lp(a) levels. The kit has a sensitivity of 1.48 ng/mL and a detection range of 3.13-200 ng/mL. The inter- and intra-assay variation coefficients are both less than 10% and 8%, respectively, for this test.

Statistical Analysis

The Kolmogorov-Smirnov test was used for the distribution analysis of variables. The data are presented as median and percentiles (25th and 75th percentiles) for continuous variables. Categorical data are expressed in percentages and numbers. The probability values of categorical data were compared using the chi-square test. The Mann–Whitney *U*-test was used to compare non-normally distributed data variables between the groups. The Spearman rank correlation coefficient was used for detecting the correlations between Lp(a) and the variables. The impact of Lp(a) and other factors on ICU admission were investigated using logistic regression analysis. To determine whether Lp(a) could be used as a predictor of ICU admission in COVID-19 patients, a receiver operating characteristic curve was used, and the area under the curve (AUC) was calculated. Data were considered statistically significant in the presence of *P*-values less than .05.

RESULTS

Characteristics of Study Subjects

Our study consisted of a total of 126 patients hospitalized with the diagnosis of COVID-19; 46 of the patients (19 men, 27 women) were admitted to the intensive care unit. The median age of the ICU admission group was 60 (53-73),

and the median age of the non-ICU admission group was 58 (44-67). The basic characteristics of the patients are given in Table 1. Oxygen saturation was lower [88 (86.7-92) vs. 92.5 (91-94), $P < .001$, respectively], and Lp(a) values were higher [40.9 (34.48-48.11) vs. 17.4 (9.18-30.91), $P < .001$, respectively] in patients with ICU admission compared to non-ICU admission group (Table 1).

Antibiotic treatment was added to the standard treatment in 16 patients (34.8%) in the ICU admission group and in only 8 patients (10%) in the non-ICU admission group. Twenty (43.5) patients in the ICU admission group required high-flow oxygen nasal cannula treatment, while only 14 (17.5%) patients in the non-ICU admission group needed it. In the ICU admission group, 23 (50%) patients required invasive mechanical ventilation. There was no need for invasive mechanical ventilation in the non-ICU admission group. There was a significant difference in Lp(a) levels between patients who received and did not receive high-flow oxygen nasal cannula treatment [35.28 (17.34-42.96) vs. 26.11 (12.92-35.81), $P = .016$]. Among the participants in our study, no one had a pulmonary embolism diagnosis.

It was discovered that Lp(a) and C-reactive protein are correlated ($r = 0.479$, $P < .001$) (Table 2).

The duration of treatment and hospital stay was observed to be longer in the ICU admission group compared to the non-ICU admission group [14 (9-15) vs. 8 (7-12) days, respectively, $P < .001$; Table 3]. In the study, 46 of the patients were admitted to the ICU following the initial evaluations and a total of 18 patients died (Table 3).

According to regression analysis, serum Lp(a) levels were independently related to the ICU admission [odds ratio (OR) 1.242, 95% CI 1.109-1.391, $P < .001$] (Table 4).

Table 1. Demographic and Laboratory Findings of the Patients

	ICU Admission		
	Without (n = 80)	**With (n = 46)**	***P***
Age	58 (44-67)	60 (53-73)	.127
Sex (male/female)	42/38	19/27	.226
SaO_2 (%)	92.5 (91-94)	88 (86.7-92)	<.001
SBP (mm Hg)	131 (128-135)	132 (128-136)	.667
DBP (mmHg)	67 (65-77)	67 (65-71.7)	.253
Heart rate (bpm)	90 (89-101)	90 (78-127)	.959
Smokers, n (%)	18 (22.5)	16 (34.8)	.135
Hypertension, n (%)	23 (28.8)	11 (23.9)	.556
Diabetes mellitus, n (%)	9 (11.3)	4 (8.7)	.767
COPD, n (%)	12 (15)	5 (10.9)	.514
Glucose (mg/dL)	116 (100.2-137.7)	109.5 (90-135.2)	.104
Creatinine (mg/dL)	0.77 (0.65-0.83)	0.72 (0.64-0.81)	.355
ALT (U/L)	26 (19-39)	30 (22-43)	.239
AST (U/L)	27.5 (22.2-38)	27 (19-41)	.980
TSH (uIU/mL)	0.63 (0.31-1.27)	0.86 (0.53-1.65)	.134
LDL-C (mg/dL)	96.5 (83-116)	87 (80-103)	.155
Total protein (g/dL)	6.84 (6.68-7.11)	6.8 (6.43-7.13)	.417
Albumin (g/dL)	4 (3.8-4.28)	4 (3-4.2)	.083
WBC ($\times 10^3$ /uL)	6.76 (4.72-8.48)	6.66 (4.77-11.96)	.182
Hemoglobin (g/dL)	12.95 (11.9-14.1)	12.5 (11.3-14)	.190
Neutrophil count ($\times 10^3$/uL)	4.84 (2.66-6.32)	4.95 (2.61-9.84)	.202
Lymphocyte count ($\times 10^3$/uL)	1.19 (0.88-1.76)	1.45 (0.93-1.71)	.602
CRP (mg/dL)	5.67 (2-13.75)	12 (4.84-15)	.012
Fibrinogen (mg/dL)	575 (385-764)	547 (385-792)	.953
D-Dimer (ugFEU/mL)	190 (130-299)	210 (110-521)	.794
Hs-TnT, ng/L	7.69 (6.1-10.3)	6.88 (4.9-9.36)	.672
Lp(a) (ng/mL)	17.40 (9.18-30.91)	40.90 (34.48-48.11)	<.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; FEU, fibrinogen equivalent units; Hs-TnT, high-sensitivity troponin T; ICU, intensive care unit; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SaO_2, arterial saturation; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone; WBC, white blood cells.

Table 2. Correlations Between Lipoprotein(a) and Laboratory Findings

		Age	Hs-TnT	D-Dimer	Fibrinogen	CRP	Albumin	LDL-C
Lipoprotein(a)	Correlation coefficient (*r*)	−0.72	−0.009	0.030	0.013	0.479	−0.126	−0.043
	P	.421	.923	.743	.884	<.001	.159	.634

CRP, C-reactive protein; Hs-TnT, high-sensitivity troponin T; LDL-C, low-density lipoprotein cholesterol.

Receiver operating characteristic curve analysis was performed to evaluate Lp(a) usability in predicting ICU admission. The cutoff value of Lp(a) was 31.42 (AUC: 0.815, 95% CI 0.738-0.891, $P < .001$, with 82.6% sensitivity and 72.5% specificity) (Figure 1). The risk of ICU admission was seen to be 12.522-fold higher in cases with Lp(a) level ≥31.42.

DISCUSSION

In our study, when investigating whether the Lp(a) levels are associated with ICU admission and related clinical parameters in COVID-19 patients, a significant relationship was found between baseline Lp(a) levels and ICU admission. We found that Lp(a) levels were independent predictors of ICU admission in COVID-19 patients. Lp(a) level ≥31.42 ng/mL had 82.6% sensitivity and 72.5% specificity in predicting ICU admission.

Severe acute respiratory syndrome coronavirus 2 causes vascular endothelial damage by stimulating the renin-angiotensin-aldosterone pathway. Endothelial injury decreases the antithrombotic function of cells, making them more prone to thrombus formation.[15,16] Increased fibrinogen levels, platelet activation, and hypoxia cause increased coagulation and complement activation in COVID-19 patients. As a result of all these factors, thrombosis can be triggered, and the dissemination of thrombosis can be accelerated by inflammation.[17] Patients who died from COVID-19 had widespread microthrombi in the peripheral capillaries and arterioles of several organs including the lungs and heart according to autopsy studies,[18] nevertheless, an autopsy is not possible for all of them. Early diagnosis of patients who may have a clinically serious and insidious course is important in reducing undesirable clinical outcomes.

Endothelial damage can be directly caused by SARS-CoV-2 or indirectly by the host's inflammatory response in many organs and by the interleukin-6 (IL-6) secreted by endothelial cells to defend against virus attack.[19] Increases in IL-6 levels can upregulate hepatic apo(a) synthesis, resulting in improved Lp(a) particle assembly and release into the circulation.[20] In addition, due to the increase in IL-6 levels in

Table 3. Clinical Outcomes of Patients

	ICU Admission			
Clinical outcomes	**All (n = 126)**	**With (n = 46)**	**Without (n = 80)**	***P***
ICU admission, n (%)	46 (36.5)	46 (100)	0	<.001
In-hospital mortality, n (%)	18 (14.3)	18 (39.1)	0	<.001
Hospital stay duration (days)	9 (7-14)	14 (9-15)	8 (7-12)	<.001

ICU, Intensive care unit.

Table 4. The Effect of Variables on ICU Admission

Variables	***P***	**Exp(B) Odds Ratio**	**95% CI Lower-Upper**
Age	.069	1.071	0.995-1.154
Hypertension	.055	1.284	0.558-2.952
Diabetes mellitus	.810	1.167	0.331-4.109
COPD	.515	1.447	0.475-4.404
SaO_2	.206	0.850	0.661-1.093
CRP	.706	0.970	0.827-1.137
Fibrinogen	.502	1.001	0.998-1.005
D-Dimer	.520	0.999	0.998-1.001
Hs-TnT	.541	1.016	0.965-1.070
Albumin	.728	0.719	0.112-4.621
LDL-C	.885	0.998	0.964-1.032
Lp(a)	< .001	1.242	1.109-1.391

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; Hs-TnT, high-sensitivity troponin T; ICU, intensive care unit; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SaO_2, arterial saturation.

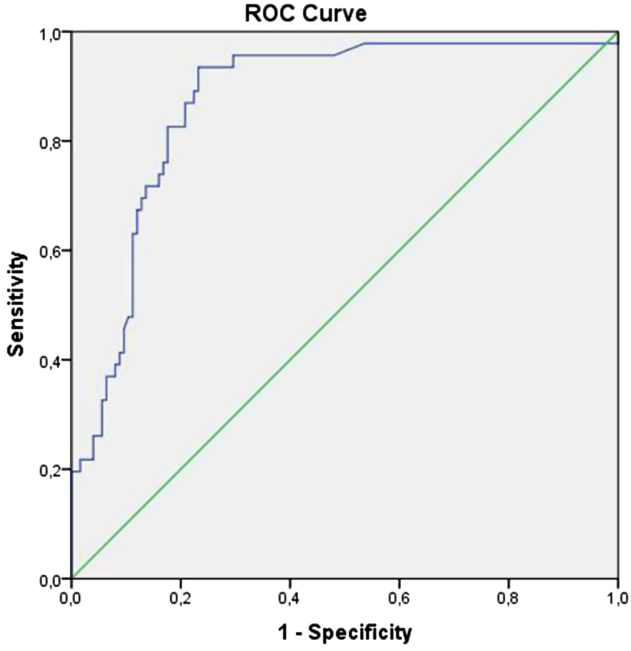

Figure 1. Receiver operating characteristic curve of lipoprotein(a) for ICU admission of Coronavirus Disease 2019 patients.

SARS-CoV-2 infection, an increase in CRP levels, which is an acute phase reactant, is observed secondarily in the liver.[21] Systemic inflammation with cytokine storm may cause vascular damage, causing disruptions in lipid transport.[22] In light of the above information, we think that both increased Lp(a) levels and impaired metabolism of Lp(a) are the main causes of poor clinical outcomes in COVID-19 patients. In our study, a positive correlation was observed between CRP and significantly higher Lp(a) levels in the ICU admission group. In addition, higher Lp(a) levels were detected in those who needed high-flow oxygen nasal cannula therapy.

D-Dimer has been shown to be a predictor of poor clinical outcomes including ICU admission and death in patients with COVID-19.[23] In another study, Huang et al[24] found that D-dimer levels were significantly higher in the ICU admission group than in non-ICU admission patients with COVID-19. However, in a recent study, researchers reported that D-dimer may have a lower accuracy than CRP for prognosis in patients with COVID-19.[25] In another recent study, it was reported that normal or slightly increased D-dimer and fibrinogen levels could be found. Obtaining different results from studies in the literature in terms of the main role of leukocytes in the thrombo-inflammatory process during bacterial infections shows that the main role of platelets in COVID-19 is not clear.[26] It is possible to see this difference in laboratory parameters. As seen in our study, no differences were observed between the groups in D-dimer and fibrinogen levels, which indicates that COVID-19 has a unique coagulopathy. However, Lp(a) levels were found to be significantly different between the groups in our study.

Lipoprotein(a) levels are not a simple acute phase reactant but are also likely to be an indirect indicator of complications that may develop in COVID-19 patients.[27] In light of all this information, it is expected that the risk of developing vascular events is higher in individuals with SARS-CoV-2 infection. The direct or indirect effect of the SARS-CoV-2 virus may contribute to endothelial cell damage, and poor clinical outcomes may be seen in COVID-19 patients as a result of endothelial damage. When our study results are evaluated, we believe that basal serum Lp(a) levels will provide clinicians with important information about the prognosis of patients hospitalized with the diagnosis of COVID-19.

In a recent study, it was shown that, despite a significant cardiac biomarker increase in COVID-19 survivors without known cardiovascular disease, mild deterioration in cardiac function may occur although cardiac biomarker increase has no effect on patient management or short-term prognosis.[28] As seen in our study, the results we obtained with cardiac troponin between both groups support the findings in the literature.

There were some limitations of our research. Considering our study results and current literature studies, it is not known how effective medical treatment that can impact Lp(a) levels may be in ICU admission. Serum Lp(a) samples were obtained from each patient at the first admission, and 1-time measurements were made. Therefore, we do not know whether there are dynamic changes in Lp(a) levels. However, the lack of a relationship between the time from the onset of symptoms to the time of diagnosis and Lp(a) levels is an important advantage of our study. We do not know how long it will take to change Lp(a) levels in recovering patients who have been discharged and how much higher Lp(a) levels may be associated with future COVID-19-related clinical conditions in this patient group compared to the control group. Multicenter studies are needed to support our study results and eliminate deficiencies.

Lipoprotein(a) can assist the clinician in the triage of COVID-19 patients. In line with these results, Lp(a) levels measured at hospital admission will provide clinicians with important information about which COVID-19 patients will require close monitoring.

Ethics Committee Approval: This study was approved by Ethics committee of Çanakkale Onsekiz Mart University University (Approval No: 2011-KAEK-27/2020-E.2000175652, Date: December 9, 2020).

Informed Consent: Both verbal and written informed consents were obtained from the participants.

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Declaration of Interests: The authors have no conflict of interest to declare.

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