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ORIGINAL ARTICLE

The Relationship between Basal Serum Lipoprotein(a) Levels and the Pulmonary Artery to Ascending Aorta Ratio in COVID-19 Survivors

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Abstract

Background: Coronavirus disease (COVID-19) can cause permanent damage to vascular structures by directly or indirectly affecting the cardiopulmonary system. Lipoprotein(a) [Lp(a)] is an important identified risk factor for vascular endothelial cell dysfunction.

Objective: The aim of this study was to reveal the relationship between Lp(a) levels measured at the time of COVID-19 diagnosis and the pulmonary artery (PA) to the ascending aorta (Ao) ratio (PA:Ao ratio) in survivors evaluated by transthoracic echocardiography (TTE).

Methods: The study sample consisted of 100 patients who recovered from COVID-19 in the past 3 to 6 months. The relationship between the change in the PA:Ao ratio (ΔPA:Ao) and the Lp(a) levels measured at the time of diagnosis was evaluated. Diameter measurements at baseline and follow-up were evaluated with TTE.

Results: A significant increase was found in PA, Ao, and epicardial adipose tissue (EAT) thickness in TTE ($p< 0.001$ for all). There was a weak correlation between D-dimer and high-sensitivity cardiac troponin measured at the time of diagnosis and ΔPA:Ao and ΔEAT in survivors. However, a positive and strong correlation was observed between Lp(a) levels and ΔPa:Ao ($r = 0.628$, $p< 0.001$) and ΔEAT ($r = 0.633$, $p< 0.001$).

Conclusion: There may be dysfunction in vascular structures due to COVID-19. For the first time in the literature, a strong correlation was shown between the Lp(a) levels measured at the time of diagnosis and ΔPA:Ao and ΔEAT values in patients with COVID-19.

Keywords: Lipoprotein(a); COVID-19; Pulmonary Artery; Aorta, Thoracic; Echocardiography.

Introduction

Coronavirus disease (COVID-19) has recently been added to the medical literature and has affected millions of people.[1] Although COVID-19 was identified as a respiratory system disease in the early stages of the pandemic, it is now considered a multisystem disease.[2] Various clinical manifestations related to endothelial cell dysfunction, autonomic nervous system damage, and microvascular and lung tissue damage can be observed in the early or late stages of COVID-19.[3] A recent study showed that endothelial cell damage may result in impaired arterial wall function and consequently reduced or impaired aortic elasticity within 3 to 6 months in COVID-19 survivors.[4] Another recent study showed that impaired cardiac performance can be seen as a result of loss of endothelial and vascular function due to COVID-19.[5]

Lipoprotein(a) [Lp(a)] consists of low-density lipoprotein particles.[6] Lp(a) is present in humans at low and stable levels and may increase during infections due to cytokine storm and various mechanisms.[7] Lp(a) can cause oxidized phospholipids to accumulate in the arterial wall, causing inflammation and resulting in loss of function in endothelial cells.[8] The pulmonary artery (PA) to ascending aorta (Ao) ratio (PA:Ao ratio) has been analyzed by various imaging modalities such as cardiac magnetic resonance and computed tomography (CT).[9,10]

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Central Illustration: The Relationship between Basal Serum Lipoprotein(a) Levels and the Pulmonary Artery to Ascending Aorta Ratio in COVID-19 Survivors

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Serum lipoprotein(a) levels and the pulmonary artery to ascending aorta ratio

100 patients with COVID-19 survivors

	Basal echocardiographic measurements	Control echocardiographic measurements	P value
Pa (mm)	23.35±2.51	25.55±2.51	<0.001
Ao (mm)	30.02±2.53	31.92±2.53	<0.001
Pa:Po	0.77±0.05	0.80±0.04	<0.001

	ΔPA		ΔAo		ΔPA:Ao	
	r value	P	r value	P	r value	P
Lp (a)	0.231	0.021	0.214	0.032	0.628	<0.001

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COVID-19 can cause adverse changes in the vascular walls. A strong correlation was shown between the Lp (a) levels measured at the time of diagnosis and ΔPA, ΔAo and ΔPA:Ao values in COVID-19 patients. PA: pulmonary artery; Ao: ascending aorta; PA:Ao: pulmonary artery to ascending aorta ratio; Lp(a): lipoprotein(a).

The PA:Ao ratio has been shown to be associated with various clinical conditions such as the presence and severity of pulmonary hypertension,[11] right ventricular outflow tract arrhythmias,[12] and prognosis of advanced heart failure.[13] Additionally, the PA:Ao ratio has been shown to be correlated with clinical outcomes in patients with COVID-19.[14]

There are no studies in the literature examining the relationship between the Lp(a) levels measured at the time of diagnosis and the PA:Ao ratio in survivors of COVID-19 within 3 to 6 months. Therefore, the aim of this study was to investigate whether this relationship exists.

Methods

This study was conducted in a tertiary health center, and it included 100 patients who recovered from COVID-19 in the past 3 to 6 months. Patients with positive polymerase chain reaction (PCR) test for COVID-19 were included in the study. Combined throat/nose swabs were taken for PCR tests in accordance with the instructions of the Turkish Ministry of Health and the World Health Organization. Patients infected with SARS-CoV-2 confirmed by PCR were followed up in the intensive care unit (ICU) or general care (outside ICU).[15]

After receiving written informed consent, biochemical and hemogram parameters were acquired from peripheral blood samples taken at the time of hospitalization using standard laboratory techniques.

Patients with any of the following criteria were excluded: renal disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2); heart failure with reduced left ventricular function (left ventricular ejection fraction ≤ 40%); contraindications for thromboprophylaxis; malignant disease; abnormal liver dysfunction (alanine aminotransferase and aspartate aminotransferase > 3 times the upper limit of normal); cerebrovascular disease; chronic atrial fibrillation or atrial flutter; history of heart attack; history of coronary artery bypass surgery; moderate or severe heart valve stenosis or insufficiency; connective tissue diseases; ascending Ao > 40 mm; prosthetic heart valves; bicuspid aortic valve; using cholesterol-lowering drugs; systemic lupus erythematosus; rheumatoid arthritis; using oral

contraceptives, steroids, or monoclonal antibody drugs; endocrine diseases that may affect Lp(a) levels, such as familial hypercholesterolemia; pulmonary hypertension; chronic thromboembolic pulmonary hypertension; presence of congenital heart defect; younger than 18 years of age; and poor echocardiographic window.

The study received approval from the Ethics Committee (Decision no: 2022-YÖNP-0068). The study was performed in accordance with the Declaration of Helsinki.

Echocardiographic Imaging Protocol

Transthoracic echocardiography (TTE) was performed using a Philips EPIQ 7 Ultrasound Device (Philips EPIQ 7 Cardiac Ultrasound, Bothell, WA, USA). Before echocardiographic imaging, each patient's blood pressure (BP) was measured in a quiet environment in the echocardiography laboratory. Measurements were made twice in the right and left arm with an oscillometric sphygmomanometer at 5 -minute intervals after resting for 15 minutes. The arithmetic average of systolic BP (SBP) and diastolic BP (DBP) values was used for analysis. Echocardiographic examinations were performed following BP measurements. Measurements of the left and right heart chambers were made in accordance with imaging guidelines.[16] Following the standard 2D measurements of the right and left heart cavities, PA diameter, Ao diameter, and epicardial adipose tissue (EAT) thickness were measured. Ascending Ao diameter measurement was made 3 cm from the aortic valve in the parasternal long axis. The largest diameter of the main PA at the bifurcation level on parasternal short- axis images was taken as the PA diameter. EA T thickness was obtained by taking the average of 3 cardiac cycles perpendicularly between the echo-dense pericardium layer and the echo-lucent space on the right ventricular free wall at the end of systole in the parasternal long- axis view. The aortic annulus was taken as reference. The arithmetic average of 5 consecutive heartbeats was used for the measurements.

Echocardiographic measurements of the patients were performed twice as basal (within the first 2 weeks following the positive PCR test) and control (within the first 3 to 6 months following the positive PCR test). Calculation of the PA:Ao ratio is shown in Figure 1.

Serum Lp(a) and Laboratory Measurements

Human Lp(a) test samples and 10-mL peripheral venous blood samples were collected from patients at the time of hospital admission. Blood samples were centrifuged at approximately 1000 × g for 20 minutes, and the obtained serum samples were stored at −80°C before further analysis. The human Lp(a) (ELK Biotech ELK1564) enzyme linked-immunosorbent assay kit (ELK [Wuhan] Biotechnology Co. Ltd., Hubei, PRC) was used for measuring Lp(a) levels. The kit has a sensitivity of 1.48 ng/mL and a sensing range of 3.13–200 ng/mL. The inter- and intra-assay coefficients of variation were both less than 10% and 8%, respectively.

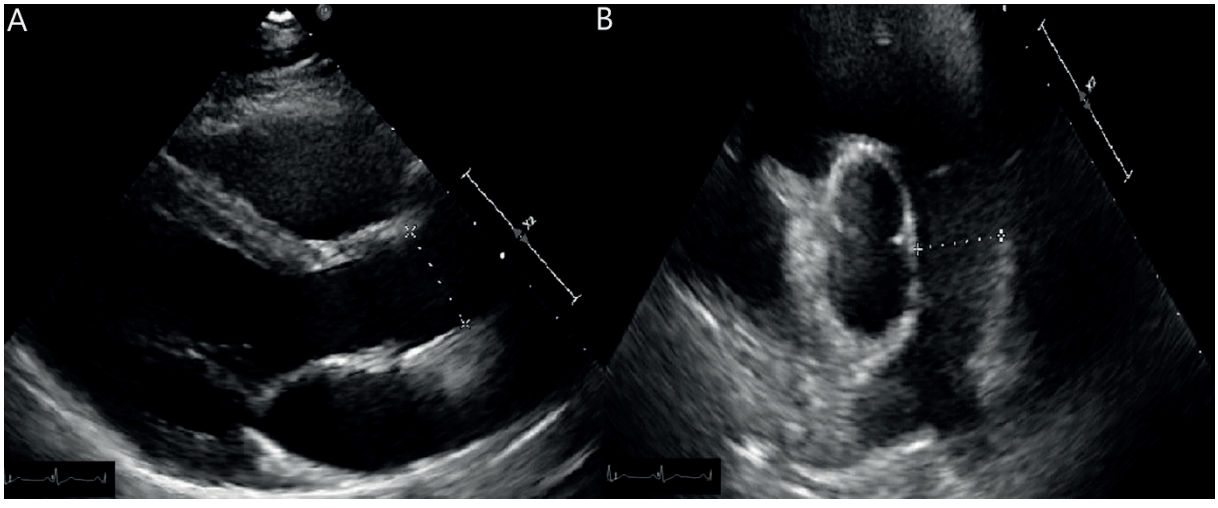

Figure 1 – Measurement of ascending Ao (panel A) and PA (panel B) diameters by TTE.

Statistical Analysis

Statistical data were analyzed using the SPSS 20.0 (SPSS Inc, Chicago, IL, USA) program. The one-sample Kolmogorov-Smirnov test was used to evaluate the distribution of numerical variables. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as percentages and numbers. Data are presented as median (interquartile range) for continuous variables. The paired sample t test was used to investigate the difference between the pretest and posttest scores of the groups. The Pearson and Spearman tests were used for correlation analysis. P values below 0.05 were considered statistically significant.

Reproducibility

Twenty patients were randomly selected, and the measurements were repeated under the same basal conditions. The reproducibility of the echocardiographic imaging parameters obtained by TTE was assessed with the coefficient of variation between the measurements. Intra- and inter-assay coefficients of variation were 4% and 2%, respectively.

Results

The study consisted of 100 COVID-19 survivors (52 men and 48 women). The mean age of the patients was 56.01 ± 13.85 years (Table 1).

All patients needed nasal oxygen support. In 15 patients, oxygen support was provided by non-invasive mechanical ventilation or high-flow nasal cannula. Oxygen support was provided by orotracheal intubation in 2 patients, and 8 patients were admitted to the ICU (Table 2).

Table 3 shows the patients' baseline and follow-up control echocardiographic parameters. When the baseline and follow-up echocardiographic parameters were analyzed, a significant difference was found in the values of PA (23.35 ± 2.51 mm and 25.55 ± 2.51 mm, $p < 0.001$), Ao (30.02 ± 2.53 mm and 31.92 ± 2.53 mm, $p < 0.001$), EAT (5.23 ± 0.82 and 6.10 ± 0.79, $p < 0.001$), and the PA:Ao ratio (0.77 ± 0.05 and 0.80 ± 00.4, $p < 0.001$).

While no relationship was found between ΔEAT, ΔPA, ΔAo, ΔPA:Ao ratio, and age and time elapsed since COVID-19 diagnosis, these variables were correlated with D-dimer, high-sensitivity cardiac troponin, and Lp(a). In particular, a strong correlation was observed between Lp(a), ΔPA:Ao ratio ($r = 0.628$, $p < 0.001$), and ΔEAT ($r = 0.633$, $p < 0.001$) (Table 4). The main findings are summarized in the Central Illustration.

Table 1 – Demographic and laboratory findings of patients with COVID-19

	COVID-19 (n = 100)
Age (years)	56.01 ± 13.85
Sex (n)	
Male	52
Female	48
Smoking (%)	26
Hypertension (%)	25
Diabetes mellitus (%)	8
BMI (kg/m²)	25.45 ± 1.24
Heart rate (bpm)	96.30 ± 17.29
SBP (mmHg)	129.03 ± 10.15
DBP (mmHg)	69.22 ± 8.12
Glucose (mg/dl)	115 (94-139.75)
Creatinine (mg/dl)	0.76 ± 0.18
Hemoglobin (g/dl)	12.83 ± 1.64
TSH (uIU/mL)	1.05 ± 0.96
LDL (mg/dl)	98.87 ± 23.49
HDL (mg/dl)	55.13 ± 14.65
Triglyceride (mg/dl)	132.67 ± 61.45
D-dimer (ugFEU/mL)	220 (130-495)
Hs-TnT (ng/L)	7 (5.31-9.41)
Lp(a) (ng/mL)	25.6 (10.2-36.4)

BMI: body mass index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; Hs-TnT: high-sensitivity cardiac troponin T; LDL: low-density lipoprotein; Lp(a): lipoprotein(a); SBP: systolic blood pressure; TSH: thyroid-stimulating hormone.

Discussion

The key findings of the present study were: (1) There was an increase in pulmonary and aortic diameters and EAT thickness in survivors of COVID-19; (2) A strong correlation was found between Lp(a) values measured at the time of COVID-19 diagnosis and ΔPA:Ao and ΔEAT obtained by echocardiographic imaging.

Table 2 – Clinical characteristics of COVID-19 patients

Signs and symptoms, n	COVID-19 (n = 100)
Fever	33
Cough	22
Myalgia	19
HFNC/NIMV	15
ICU admission	8
Invasive mechanical ventilation	2
Hospital stay (days)	9.7 ± 3.9

HFNC: high-flow nasal cannula; ICU: intensive care unit; NIMV: non-invasive mechanic ventilation.

Although the respiratory system is the main target of SARS-CoV-2, deaths may be related to multiple organ damage including the heart, nervous system, and kidneys.[17] The spike proteins found on the envelope of SARS-CoV-2 are the specific receptor of angiotensin converting enzyme-2 (ACE-2) in the host cell.[18] High levels of ACE-2 expression have been detected in cardiac and vascular tissues, and the increase in ACE-2 expression plays a key role in facilitating virus entry into cells and subsequent cellular damage.[19] Detection of diffuse thrombosis and intracellular virions in lung tissues in autopsy studies has been associated with severe endothelial damage.[20] Thromboembolic events such as myocardial infarction and deep vein thrombosis have been reported in patients with COVID-19 and are serious clinical

Table 3 – Echocardiographic parameters of the study population

	Basal echocardiographic measurements	Control echocardiographic measurements	P
LVEDD (mm)	44.19 ± 2.99	44.36 ± 2.92	0.183
LVESD (mm)	27.24 ± 2.13	27.26 ± 2.02	0.834
Left ventricle			
LVEF (%)	58.26 ± 2.02	58.30 ± 1.98	0.450
GLS (%)	-20.77 ± 1.20	-20.75 ± 1.16	0.750
IVS thickness (mm)	10.77 ± 1.20	10.77 ± 1.12	0.886
PW thickness (mm)	8.51 ± 1.17	8.59 ± 1.18	0.158
LA diameter (mm)	30.04 ± 2.52	30.03 ± 2.53	0.783
Right ventricle			
RA diameter (mm)	30.99 ± 2.64	30.77 ± 2.48	0.175
RV diameter (mm)	28.90 ± 3.11	29.75 ± 3.05	0.067
TAPSE (mm)	18.92 ± 2.47	19.04 ± 2.52	0.068
SPAP (mmHg)	20.30 ± 2.46	20.40 ± 2.52	0.279
TR Vmax, m/s	3.04 ± 0.17	3.08 ± 0.15	0.119
S', m/s	12.09 ± 1.18	12.04 ± 1.16	0.290
GLS (%)	-18.67 ± 1.25	-18.65 ± 1.21	0.750
EAT (mm)	5.23 ± 0.82	6.10 ± 0.79	<0.001
PA (mm)	23.35 ± 2.51	25.55 ± 2.51	<0.001
Ao (mm)	30.02 ± 2.53	31.92 ± 2.53	<0.001
PA:Ao	0.77 ± 0.05	0.80 ± 0.04	<0.001

Ao: ascending aorta; EAT: epicardial adipose tissue thickness; GLS: global longitudinal strain; IVS: interventricular septum; LA: left atrium; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic dimension; PA: pulmonary artery; PA:Ao: pulmonary artery to ascending aorta ratio; PW: posterior wall; RA: right atrium; RV: right ventricle; SPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; Vmax: maximal velocity.

Table 4 – Correlation of variables with PA to ascending Ao ratio in patients with COVID-19

	ΔPA		ΔAo		ΔPA:Ao		ΔEAT	
	r value	P	r value	P	r value	P	r value	P
Age	0.148	0.142	0.037	0.716	0.075	0.459	0.068	0.499
Time after first diagnosis [a]	0.102	0.315	0.016	0.873	0.043	0.668	0.020	0.841
Time after first diagnosis [b]	0.086	0.393	0.037	0.713	0.095	0.348	0.057	0.572
D-dimer	0.318	0.001	0.196	0.050	0.335	0.001	0.260	0.009
Hs-TnT	0.222	0.026	0.150	0.136	0.252	0.012	0.202	0.004
Lp (a)	0.231	0.021	0.214	0.032	0.628	<0.001	0.633	<0.001

Ao: ascending aorta; EAT: epicardial adipose tissue thickness; Hs-TnT: high-sensitivity cardiac troponin T; Lp(a): lipoprotein(a); PA: pulmonary artery; PA:Ao: pulmonary artery to ascending aorta ratio. a: First 2 weeks after positive PCR test; b: within the first 3 to 6 months following the positive PCR test.

endpoints of endothelial damage.[21] Since the inner surfaces of blood vessels are covered with endothelial cells, these findings suggest that COVID-19 may directly or indirectly cause endothelial dysfunction. Endothelial damage can occur directly due to SARS-CoV-2 itself or secondary to the inflammatory process.[22] Increased levels of interleukin-6 during the disease increase hepatic apo(a) synthesis, resulting in increased circulating Lp(a) levels.[23] It has been reported that Lp(a) may be an indicator of clinical outcomes in patients with COVID-19, as seen in previous studies.[24] This is the first such study in the literature, and it provides important information about the relationship between Lp(a) levels at the time of diagnosis and changes in PA and Ao diameters in patients with COVID-19.

PA dilatation is associated with poor prognosis in various lung diseases, such as interstitial lung fibrosis and chronic obstructive pulmonary diseases.[25,26] In a recent study, PA diameter measurements were made after hospitalization in patients with COVID-19 with CT, and it was reported that the increase in PA diameter could be a prognostic marker used to detect severe cases.[27] The present study showed that a specific cardiovascular risk marker such as Lp(a), especially during the disease, may be associated with PA diameter change in the long term in survivors of COVID-19. Previous studies have shown that approximately half of patients with COVID-19 have increased Ao diameter secondary to heart damage and severe inflammation. The studies have also stated that this may be due to the vascular endothelial damage triggered by COVID-19.[28] These findings suggest that increased PA and Ao diameters are associated with poor prognosis in patients with COVID-19. One of the key aspects of the present study is that it showed differences in PA and Ao diameters and the PA:Ao ratio in the long term among patients who survived COVID-19, and the relationship of these values with Lp(a) measured at the time of diagnosis was further investigated. It has been shown that PA diameter of 48 mm and above is a predictor of both unexpected death and all-cause mortality in patients with pulmonary hypertension.[29] Several studies have reported an association between PA:Ao ratio of 1.0 or greater with adverse events in patients with pulmonary hypertension.[30,31] However, the cut-off value obtained may not be accurate due to the fact that various factors such as ethnicity, age, and lifestyle, may differ between patient groups and studies. In fact, in a recent study, the PA: Ao ratio in COVID-19 patients was higher in those who lost their lives in the hospital compared to those who were discharged, but the ratio was found to be below 1.[32] As seen in the present study, a higher PA:Ao ratio was obtained in a certain number of patients after discharge.

EAT is an important known risk factor associated with vascular structures, and it has been shown to be associated with aortic elasticity independent of blood sugar in diabetic patients.[33] In another study, increased EAT volume was shown to be associated with abdominal aortic aneurysm.[34] In a recent study,

EAT was shown to be an independent risk factor for disease severity and mortality in patients with COVID-19, independent of obesity.[35] In the present study, in addition to the correlation between the PA: Ao ratio and Lp(a), there was also an increase in EAT thickness and this increase was found to be correlated with Lp(a). When these results are taken into consideration, baseline Lp(a) levels can be used as a predictor in the assessment of cardiopulmonary risk in COVID-19 survivors.

Limitations to the study

There are certain limitations of this study. The sample size was relatively small due to exclusion criteria, and the study was conducted in a single center. Although Lp(a) levels measured at the time of diagnosis in patients with COVID-19 were found to be associated with changes in echocardiographic parameters predictive of important cardiovascular diseases during follow-up, we do not know whether Lp(a) levels change during follow-up. This study was conducted over a relatively short follow-up period of 6 months and can guide further studies with longer follow-up periods to investigate cardiac and pulmonary complications.

Conclusions

The pathogenesis of the effects of COVID-19 on the cardiopulmonary system is unclear, and there are serious adverse effects. COVID-19 can cause adverse changes in the aortic and pulmonary vascular walls. This is the first study in the literature to show a strong correlation between Lp(a) levels at diagnosis and ΔPA:Ao and ΔEAT in COVID-19 survivors.

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Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, obtaining financing, writing of the manuscript, critical revision of the manuscript for intellectual content: Küçük U, Kirilmaz B.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee under the protocol number 2022-YÖNP-0068. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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