RESEARCH ARTICLE / *Araştırma Makalesi*

The Role of Atherogenic Index Of Plasma in The Diagnosis of Long COVID

Aterojenik Plazma Indeksinin Uzamış COVID Tanısındaki Rolü

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Öz

Objectives — One of the well-known prolonged effects of coronavirus disease 2019 (COVID-19) is the gradual loss of pulmonary functions, known as 'long COVID'. Due to the importance of this deleterious condition, several studies have been conducted to investigate predictors of long COVID throughout hospital admission and after hospital discharge. Recently introduced, the atherogenic index of plasma (AIP) has a better predictive value for the prediction of adverse events in COVID-19 patients compared to other biomarkers. This study aimed to explore the role of AIP in the prediction of long COVID among COVID-19 survivors.

Methods — We evaluated 52 eligible patients with a diagnosis of long COVID and 80 healthy control subjects with a prior history of COVID-19. To confirm long COVID diagnosis, all subjects underwent a standardized questionnaire which recount the presence or absence of COVID-19-related complaints. All participants' past medical records and clinical, and demographic characteristics were scanned and underwent comprehensive physical examination and echocardiographic assessment

Results — According to our study, body surface area, Troponin T, NT-pro-BNP, and AIP were the independent predictors of long COVID. AIP was the best predictor of long COVID among the aforementioned parameters (p=0.005). To determine the AIP cut-off value for predicting long COVID, the receiver operating characteristic (ROC) curve was drawn and the best cut-off value was determined as 0.113 by using the Youden index, (AUC:0.658, 95% CI:0.556-0.760, P=0.002).

Conclusions — Our data indicate that AIP is an independent predictor of long COVID.

Key words — Atherogenic index of plasma; COVID-19; Long COVID

Abstract

Amaç — *Koronavirüs 2019 hastalığının (COVID-19) iyi bilinen uzun süreli etkilerinden biri, 'uzamış KOVİD' olarak bilinen solunum fonksiyonlarının kademeli kaybıdır. Mevcut durumun önemi nedeniyle, hastaneye yatış süresince ve hastaneden taburcu olduktan sonra uzamış COVID öngörücüleri üzerine çeşitli çalışmalar yapılmıştır. Yakın zamanda klinik kullanıma giren aterojenik plazma indeksi (APİ), diğer biyobelirteçlere kıyasla COVID-19hastalarında advers olayların öngörülmesinde daha iyi bir prediktif değere sahiptir. Bu çalışmada, COVID-19 geçirmiş hastalarda gelişebilen uzamış COVID tahmininde APİ'nin rolünü araştırmayı amaçladık.*

Yöntemler — *Uzamış KOVİD tanısı almış 52 uygun hastayı ve geçirilmiş COVID-19 öyküsü olan 80 sağlıklı kontrol hastasının verilerini inceledik. Uzamış COVİD teşhisini doğrulamak için tüm deneklere COVİD-19 ile ilgili şikayetlerin varlığını veya yokluğunu değerlendiren standart bir anket uygulandı. Tüm katılımcıların geçmiş tıbbi kayıtları ile klinik ve demografik özellikleri tarandı ve kapsamlı fizik muayene ve ekokardiyografik değerlendirme yapıldı.*

Bulgular — *Çalışmamıza göre vücut yüzey alanı, Troponin T, NT-pro-BNP ve APİ, uzamış KOVİD'in bağımsız öngörücüleri olarak ön plana çıkmaktadır. APİ, mevcut parametreler arasında uzamış COVİD'in en iyi prediktörü olarak ön plana çıkmaktadır (p=0,005). Uzamış KOVİD tahmini için APİ prediktif değerini belirlemek için alıcı çalışma karakteristiği (ROC) eğrisi çizildi ve Youden endeksi kullanılarak en iyi kesme değeri 0.113 olarak belirlendi (AUC:0.658, %95 CI:0.556). -0.760, P=0.002).*

Sonuç — *Verilerimiz, APİ'nin uzamış KOVİD'in bağımsız bir öngörücüsü olduğunu göstermektedir.*

Anahtar Kelimeler — *Aterojenik plazma indeksi; COVİD-19; Uzamış COVİD*

INTRODUCTION

Since the emergence and rapid spread of coronavirus disease 2019 (COVID-19), there have been several studies reporting persistent and prolonged effects of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on multiple organs in the human body[1]. One of the well-known prolonged effects of COVID-19 disease is the gradual loss of pulmonary functions, known as 'long COVID'[2,3]. According to the currently available data, epithelial and endothelial cell damage owing to an accelerated immune response to viral infection, direct viral toxicity, and impairment of the intra-alveolar diffusion provoked by activation of thrombotic pathways play important roles in the development of the long COVID[4-7]. Due to the importance of this deleterious condition, several studies have been conducted to investigate clinical, laboratory, and radiological predictors of long COVID throughout hospital admission and after hospital discharge. Yet, there is still no consensus among healthcare professionals on how to identify high-risk patients who are more likely to develop long COVID following SARS-CoV-2 infection.

Recently introduced, the atherogenic index of plasma (AIP) has been established for the evaluation of plasma atherogenicity and is strongly associated with various cardiovascular and respiratory conditions such as coronary artery disease, chronic obstructive pulmonary disease, type II diabetes mellitus, and metabolic syndrome[8-12]. In addition, this index has a better predictive value for the prediction of adverse events in COVID-19 patients compared to other atherogenic biomarkers or individual lipoprotein indices[13,14]. However, no relevant research has investigated the association between AIP and long COVID. Therefore, this study aimed to explore the role of AIP in the prediction of long COVID among COVID-19 survivors.

MATERIAL and METHODS

Study population

In this study, subjects were selected from the patients who were referred to our COVID-19 outpatient clinic for long COVID symptoms including, cough, fever, dyspnea, musculoskeletal, and gastrointestinal complaints. To be included, those identified patients had to be hospitalized for laboratory-confirmed COVID-19 at least one year ago and the persistent complaints could not be attributed to alternative diagnoses. In order to confirm long COVID diagnosis, all subjects underwent a standardized questionnaire which recount the presence or absence of COVID-19-related complaints during the acute phase of infection and whether these symptoms persisted at the time of the study enrollment. Patients; having moderate to severe valve pathologies, ejection fraction less than %55, New York Heart Association functional status ≥2, chronic obstructive pulmonary disease, pulmonary thromboembolism history, atrial fibrillation, malignancy, acute or chronic renal failure, pregnancy, and patients who were on statin therapy during the index hospitalization were excluded. All participants' past medical records and clinical, and demographic characteristics were scanned and underwent comprehensive physical examination and echocardiographic assessment. After applying exclusion criteria, eligible patients were included in the study as a study group. Healthy individuals who were hospitalized with COVID-19 at least one year ago and feel fully recovered after being discharged were also included in the study as a control group. Informed consent of all participants was taken and approval was obtained from the local ethics committee of our hospital, (approval number: 09-12/01.09.2022).

Echocardiographic assessment

Transthoracic echocardiographic evaluation was performed in the standard left lateral decubitus position with a GE Vingmed Vivid S5 echocardiography device (GE Vingmed Ultrasound, Horten, Norway) by an experienced cardiologist who was blinded to the patient data. After continuous single-lead ECG monitoring, standard 2-dimensional and M-mode echocardiographic examinations with color-Doppler evaluations were performed. Left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were obtained using the modified Simpson's method.

In addition to basic echocardiographic measurements, other specialized echocardiographic parameters including, tricuspid annular plane systolic excursion (TAPSE), the tissue doppler of the free lateral wall S'measurement (Sm), estimated systolic pulmonary artery pressure (sPAP), and RV fraction area change (FAC) were measured. TAPSE was obtained from an M-mode study through the lateral tricuspid annular plane by measuring the amount of longitudinal motion of the annulus at peak systole. RV fraction area change (FAC) was estimated as the [(RV end-diastolic area – end-systolic area)/end-diastolic area] ×100, sPAP was calculated by adding the Doppler-determined trans-tricuspid gradient to the estimated right atrial pressure, as evaluated by the inspiratory collapse of the inferior vena cava. To perform tissue Doppler imaging (TDI)-derived tricuspid lateral annular systolic velocity Sm measurement, apical 4-chamber windows were utilized with a tissue Doppler mode region of interest displaying the RV free wall. The tricuspid annulus peak systolic velocity was obtained either on the tricuspid annular line or in the middle of the basal segment of the RV free wall. The velocity Sm stood for the highest systolic velocity. All the Doppler measurements were obtained at a sweep speed of 50–100 mm/s with a simultaneous superimposed ECG. All measurements were performed according to the American Echocardiography Society criteria[15].

Blood Collection

A comprehensive metabolic panel was conducted to measure complete blood cell counts, liver and kidney functions, and serum lipid concentrations. From each patient after overnight fasting, blood samples without anticoagulant were taken during the index hospitalization. Complete blood count parameters, including platelet, neutrophil, and lymphocyte, were evaluated with an automated analyzer. An automatic hematology analyzer (Sysmex, XT-2000i) was used for whole blood counts. The AIP was calculated with the formula, AIP= log [triglyceride (TG)¬/ high-density lipoprotein (HDL-C)],[16].

Statistical Analysis

Data were analyzed with the SPSS software version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). In this study, data are expressed as mean ± standard deviation (SD) for normal distribution and as median (25th-75th percentiles) for abnormal distribution. The Kolmogorov-Smirnov's test was used to evaluate the distribution of continuous variables. The $\chi 2$ test and Fisher's exact test were used to analyze categorical variables. The Student's t-test was used for continuous variables with normal distribution and the values were presented as mean ± SD. The comparison of intergroup continuous variables without normal distribution was analyzed using Mann-Whitney U-test. The effect of various variables on long COVID was calculated by univariate regression analysis. In these analyses, variables with unadjusted $p<0.1$ were identified as confounding factors and were included in multivariate regression analyses to determine the independent predictors of long COVID. A p-value of <0.05 was considered statistically significant during the study. The area under the receiver operating characteristic (ROC) curves (AUCs) was used to assess the predictive value of the AIP for the development of long COVID. The Youden index was also used to determine the best cut-off value for the AIP for predicting long COVID.

RESULTS

Over the period from January 2021 to June 2022, 52 eligible patients with a diagnosis of long COVID and 80 healthy control subjects were included in this study. Of the total patients, 40.9% of them were male and the mean age was 50.8±12.6 years. Baseline demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. There was no statistically significant difference between the two groups in terms of demographic and clinical characteristics. On the other hand, the estimated body surface area was significantly higher in patients with long COVID compared to healthy control subjects (1.94±0.17 m2 vs 1.83±0.18 m2, $p<0.05$). Regarding baseline laboratory values, serum low-density lipoprotein cholesterol (LDL-C) level [2.52 (1.89–3.24) mmol/L vs

2.56 (2.01–3.14) mmol/L, p<0.05], serum high-density lipoprotein cholesterol (HDL-C) level [1.03 (0.88–1.19) mmol/L vs 1.07 (0.91–1.28) mmol/L, p<0.05], and serum triglyceride level [1.15 (0.86–1.57) mmol/L vs 1.31 (0.95–1.84) mmol/L, p<0.05] were significantly lower in patients with long COVID compared to healthy control subjects. On the other hand, serum non-HDL-C level [3.11 (2.49–3.91) mmol/L vs 2.99 (2.37–3.61) mmol/L, p<0.05] was significantly higher in patients with long COVID compared to healthy control subjects. In addition, patients with long COVID had significantly higher levels of serum Troponin T, D-dimer, and NT-pro-BNP than healthy control subjects, [9.50 (3.90-17.20) pg/mL vs 4.50 (3.10-6.70) pg/mL, 0.46 (0.33-1.25) ug/mL vs 0.25 (0.19-0.44) ug/mL, 249 (162-505) pg/mL vs 45 (22-70) pg/mL, p<0.05 respectively).

The echocardiographic findings of both groups are shown in Table 2. According to our study, both groups had similar echocardiographic properties (p>0.05). On the other hand, calculated left ventricular end-diastolic diameter, left atrial diameter, and TAPSE was significantly higher among patients with long COVID compared to healthy control subjects (48.40±4.80 mm vs 46.10±3.50 mm, 37.90±4.90 mm vs 33.30±3.60 mm, 23.30±0.26 mm vs 20.8±0.20 mm, p<0.05 respectively). Additionally, estimated RV FAC measurement was significantly lower among patients with long COVID compared to healthy control subjects [40 (37-42) % vs 43 (40-47) %, p<0.01].

To identify the prognostic indicators of long COVID, several variables were included in the univariate Cox regression analysis. After the exclusion of variables that showed no impact on the development of long COVID in univariate analysis, Cox multivariate regression analysis was performed, which identified body surface area, Troponin T, NT-pro-BNP, and AIP as the independent predictors of long COVID, (Table 3). According to our data, AIP was the best predictor of long COVID among the aforementioned parameters (p=0.005). To determine the AIP cut-off value for predicting long COVID, the ROC curve was drawn and the best cut-off value was determined as 0.113 by using the Youden index, (AUC:0.658, 95% CI:0.556-0.760, P=0.002). Above this cut-off value, long COVID could be detected with a sensitivity of 78.6% and a specificity of 69.2%.

Table 1. Baseline demographic, clinical, and laboratory characteristics of the study population

	All Patients (N=132)	Control subjects (n=80)	Patients with long COVID (n=52)	P-value
Age, years	50.8±12.6	49.0±12.3	53.6±12.8	0.149
Male, n (%)	54 (40.9%)	28 (35.0%)	26 (50.0%)	0.226
Weight, kg	80.5±14.4	76.9±12.8	86.0±15.2	0.010
Height, cm	165±8	163±8	167±7	0.058
Body mass index, kg/m2	29.6±4.6	28.8±3.8	30.9±5.4	0.066
Body surface area, m2	1.87±0.18	1.83±0.18	1.94±0.17	0.013
Hypertension, n (%)	56 (42.4%)	32 (40.0%)	24 (46.2%)	0.621
Diabetes mellitus, n (%)	38 (28.8%)	20 (25.0%)	18 (34.6%)	0.399
Hemoglobin, g/dL	13.3±1.7	13.4±1.5	13.1±2.1	0.437
Platelet, 10^3/uL	265±64	275±58	249±71	0.115
Neutrophil, 10^3/uL	4.52±1.50	4.78±1.63	4.10±1.18	0.078
Lymphocyte, 10^3/uL	2.34±0.70	2.45±0.65	2.16±0.75	0.114
Glucose, mg/dL	102 (92-117)	100 (91-112)	109 (92-139)	0.102
Creatinine, mg/dL	0.72 (0.61-0.84)	0.68 (0.60-0.82)	0.75 (0.63-0.97)	0.194
Uric acid, mg/dL	5.04±1.58	4.87±1.26	5.31±1.97	0.294
LDL-C, mmol/L	2.54 (2.01–3.13)	2.56 (2.01–3.14)	2.52 (1.89–3.24)	0.011
HDL-C, mmol/L	1.06 (0.91–1.28)	1.07 (0.91–1.28)	1.03 (0.88–1.19)	0.021
Triglyceride, mmol/L	1.28 (0.92–1.78)	1.31 (0.95–1.84)	1.15 (0.86–1.57)	0.001
Non-HDL-C, mmol/L	2.99 (2.39–3.63)	2.99 (2.37–3.61)	3.11 (2.49–3.91)	0.003
Total-C, mmol/L	4.12 (3.46–4.78)	4.11 (3.46–4.76)	4.19 (3.48–5.09)	0.077
Troponin T, pg/mL	5.5 (3.3-9.7)	4.5 (3.1-6.7)	9.5 (3.9-17.2)	0.008
High Troponin T, n (%)	18 (13.6%)	4 (5.0%)	14 (26.9%)	0.023
D-dimer, ug/mL	0.23 (0.31-0.49)	0.25 (0.19-0.44)	0.46 (0.33-1.25)	<0.001
High D-dimer, n (%)	30 (22.7%)	8 (10.0%)	22 (42.3%)	0.002
Fibrinogen, mg/dL	385 (345-454)	384 (344-443)	399 (345-487)	0.338
NT-pro-BNP, pg/mL	73 (30-195)	45 (22-70)	249 (162-505)	<0.001
AIP	0.08(−0.09 - 0.27)	0.04(−0.09 - 0.18)	0.09(−0.10 - 0.27)	<0.001

Data are presented as percentage, mean ± standard deviation, or median (interquartile range). HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, NT-proBNP: N-terminal pro-brain natriuretic peptide, Total-C: total cholesterol, AIP: atherogenic index of plasma.

Table 3. Univariable and multivariable logistic regression analysis of the variables for long COVID

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.030 (0.989-1.074)	0.153		
Male	1.600 (0.583-4.392)	0.362		
Body mass index	1.061 (0.950-1.185)	0.290		
Body surface area, m2	6.517 (0.800-53.089)	0.080	2.295 (0.139-38.012)	0.562
Diabetes mellitus	2.370 (0.797-7.047)	0.121		
Hemoglobin	0.850 (0.632-1.143)	0.282		
Platelet	0.999 (0.991-1.007)	0.883		
Neutrophil	1.064 (0.756-1.497)	0.723		
Lymphocyte	1.602 (0.763-3.365)	0.213		
Glucose	1.006 (0.997-1.015)	0.202		
Creatinine	1.878 (0.684-5.154)	0.221		
Uric acid	1.340 (0.930-1.930)	0.116		
LDL-C	1.008 (0.992-1.024)	0.343		
HDL-C	0.974 (0.938-1.012)	0.174		
Triglyceride	1.000 (0.660-0.900)	0.903		
AIP	7.556 (2.467-23.142)	<0.001	5.732 (1.709-19.223)	0.005
Troponin T	4.000 (0.900-17.772)	0.068	1.451 (0.209-10.060)	0.706
NT-pro-BNP	3.281 (0.998-10.789)	0.048	1.535 (0.385-6.122)	0.544
Fibrinogen	1.005 (0.998-1.011)	0.183		
D-dimer	1.028 (0.989-1.068)	0.160		
LVEDD	1.004 (0.961-1.050)	0.853		
TAPSE	1.031 (0.984-1.080)	0.198		
RV FAC	1.060 (0.984-1.142)	0.124		
sPAP	1.024 (0.956-1.096)	0.500		
RV ejection fraction	0.972 (0.907-1.042)	0.419		
LV ejection fraction	1.030 (0.989-1.072)	0.157		

OR: odds ratio, CI: confidence interval, AIP: atherogenic index of plasma, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, LV: left ventricle, LVEDD, left ventricular end-diastolic diameter, RV: right ventricle, RV FAC: Right ventricular fractional area change, sPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion

DISCUSSION

In the present study, we investigated the association between the AIP and the development of long COVID among COVID-19 survivors. Our results demonstrate that there is a significantly higher level of AIP values among patients with long COVID compared to healthy control subjects which indicates the strong relationship between plasma atherogenicity and impairment of pulmonary functions.

It has been shown in a number of studies that COVID-19 is associated with serious health complications not only in the acute phase of the disease but also in the long-term sequelae1. The absence of post-infection immunity and the ability of SARS-CoV-2 to rapidly change surface spike proteins are major determinants of long-term adverse effects[17,18]. Therefore, recent COVID-19 research has focused more on the regulation of viral transmembrane molecular trafficking and features related to virus binding to the host cell membrane. Based on these studies membrane lipid components are found to play a key role in this process. According to those studies, alteration in lipid metabolism among patients with COVID-19 was identified as an in-

dicator of disease severity and hypermetabolic state[19-21]. Yet, due to the very recent emergence of the disease, data on SARS-CoV-2 and its effects on lipid metabolism are quite scarce. On the other hand, studies investigating the effect of HIV, which is also an RNA virus, demonstrated that HIV-positive patients had lower total cholesterol and LDL-C and higher triglyceride values[22,23]. In addition, previous reports revealed an increased level of reactive oxygen species production triggered by lipoprotein peroxidation and decreased level of lipoprotein lipase activities which result in decreased triglyceride clearance and impaired lipid metabolism in HIV-positive patients. Since cholesterol and fatty acids are essential components of viral membranes and envelopes, these studies also revealed a significant relationship between altered lipid metabolism and higher viral load[24,25].

In our study, we observed altered lipid metabolism in patients with long COVID compared to healthy control subjects. According to our study, serum LDL-C, HDL-C, and triglyceride levels were significantly lower in patients with long COVID compared to healthy control subjects ($p<0.05$). On the other hand, serum non-HDL-C level was significantly higher in patients with long COVID compared to healthy control subjects ($p<0.05$). Additionally, echocardiographic measures of RV functions including TAPSE and RV FAC were found to be worse in patients with long COVID compared to healthy control subjects. We also observed significantly higher levels of AIP values in long COVID patients compared to healthy control subjects ($p<0.05$). Our results are in line with the previous reports demonstrating varying degrees of lower triglycerides and HDL-C levels among patients with COVID-19 as a result of lipoprotein modifications[20,21].

Similar results were also obtained from a study conducted by Masana et al. that revealed baseline AIP level during hospitalization was not only considered a high-risk marker for COVID-19 but also associated with a worse prognosis of COVID-1914. They speculated that intermittent hypoxemia accompanied by sympathetic bursts in association with increased viral load may contribute to lower levels of HDL-C and higher levels of triglyceride. In this context, an impaired lipid profile was recognized as an indicator of increased viral load. Confirming the current results, in our study, high AIP levels and impaired RV functions were detected in patients with long COVID symptoms due to increased viral load. The strong relationship between the higher viral load and overall worse prognosis was also reported during the 2002 SARS-CoV epidemic[26-28]. Based on these results, we suggest that elevated AIP may be associated with increased viral load and an indicator of the prolonged adverse effects of COVID-19.

Limitations

There are some limitations of our study. First, this is a single-center retrospective study with a limited number of patients. Second, owing to a lack of continuous measurement of blood tests in this study, AIP values were measured at a one-time point, and fluctuation of AIP values was not considered. Follow-up monitoring may provide additional predictive value. Third, we did not compare the measurements of the AIP values with other hematological and biochemical markers.

Conclusion

Our data indicate that AIP is an independent predictor of long COVID. Due to the limited treatment options and identification of risk factors related to long COVID, early detection and identifying risky patients who need a close follow-up are crucial. In this context, the AIP might be a convenient method for early prediction of long COVID among COVID-19 survivors.

Author contributions

Concept- M.D., M.B.Ö., E.K., Design-M.D., M.B.Ö., E.K., Supervision – M.D., M.B.Ö., Resource – M.D., E.K., Materials – M.D., E.K., Data Collection and/or Processing - M.D., E.K., Analysis and/or Interpretation – M.D., E.K., Literature Search – M.D.,M.B.Ö., Writing – M.D., Critical

Reviews – E.K., M.B.Ö.

Ethics Approval

Ethics committee approval of the study was obtained from the ethics committee of Health Sciences University Konya State Hospital on 01/09/2022 with the approval number 09-12.

The Conflict of interest statement

The authors declare that there is no conflicts of interest.

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