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The clinical significance of antiphospholipid antibodies in COVID-19 infection

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Abstract

Introduction: One of the factors that may aggravate the clinical presentation in COVID-19 is the increased level of antiphospholipid antibodies (aPLs) and thrombotic events that can be seen with the disease. In our retrospective study, we aimed to evaluate the effect of aPLs on the clinical findings in patients with a diagnosis of COVID-19.

Methodology: Seventy-three patients diagnosed with COVID-19 and examined for aPLs were included in the study. Patients were divided into two groups according to the test results of aPLs. Clinical and laboratory parameters were compared in both groups to reveal whether there was any difference between the groups.

Results: There were 15 patients with a positive aPLs test. Dyspnea, nausea, vomiting, myalgia, and abdominal pain were significantly higher in the aPLs positive group than those with negative aPLs. The duration of hospital stays and the need for oxygen therapy of the patients in the aPLs positive group were significantly higher than the aPLs negative group. However, no difference was found between the two groups in terms of mechanical ventilation need, intensive care admission rate, thrombosis and mortality. In terms of laboratory findings, those with positive aPLs have higher median C-reactive protein (CRP) and ferritin values than those with negative aPLs.

Conclusions: In our study group, we could not find a relationship between aPLs positivity and critical complications. According to our hypothesis, it may not be necessary to routinely examine aPLs in patients with a diagnosis of COVID-19 to determine the risk of thromboembolic complications.

Key words: COVID-19; antiphospholipid; antibodies; thrombosis.

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Introduction

Clinical presentation in coronavirus disease 2019 (COVID-19) disease may vary from asymptomatic disease to multiorgan failure. Morbidity and mortality generally occur as a result of respiratory distress, altered immune response and thromboinflammation [1].

Antiphospholipid antibodies (aPLs) are produced by B cells and by binding to the beta 2 glycoprotein initiate an autoimmune response targeting this protein [2]. With the activation of endothelial cells, complement cascade, platelets, neutrophils and monocytes, events leading to thromboembolism occur [2]. Tissue factor with neutrophil activation, neutrophil extracellular traps (NETosis) and interleukin release also play role in thrombosis associated with aPLs [3,4] antiphospholipid syndrome (APS) is the clinical picture in which aPLs and vascular thrombosis and/or pregnancy comorbidities coexist [5]. Not every aPLs positivity is clinically significant. Temporary aPLs positivity may be seen in healthy individuals and in various conditions such as malignancies, autoimmune diseases, hepatic diseases, and infections [2,6-8]. The hypercoagulation in COVID-19 infection has directed attention to aPLs and increased morbidity and mortality associated with hypercoagulability in COVID-19 have been reported [9-15]. Recently, it has been brought to attention that aPL antibodies may play a role in the pathogenesis of COVID-19-related thrombotic events [9]. Xiao *et al.* reported that aPL antibodies were detected in the sera of 31 of 66 COVID-19 patients (47%) with poor clinical condition while aPLs were detected in none of the 13 COVID-19 patients with good clinical condition [13]. In another study, Zuo *et al.* reported that 52% of 172 COVID-19 patients had aPL positivity [16].

In the present cross-sectional retrospective study, we evaluated if there was any difference between the COVID-19 patients who were aPLs-positive and those

who were aPLs-negative in terms of clinical characteristics, laboratory parameters and hospital admissions, duration of hospital stay, need for intensive care, duration of intensive care unit stay, and complications associated with COVID-19.

Methodology

After taking approval from the ethical committee of our institute (Number: E2-21-34), the medical records of the patients, whose reverse transcriptase polymerase chain reaction (RT-PCR) tests were positive and who received treatment for symptoms clinically consistent with COVID-19 were evaluated retrospectively. The records of the patients for whom aPLS was tested between April 1 and December 31, 2020 within one month after being diagnosed with COVID-19 at our hospital were examined. Serum anti cardiolipin (aCL) immunoglobulin (Ig)G and/or IgM, anti-beta 2 glycoprotein 1 (aB2GP1) IgG and/or IgM and lupus anticoagulant (LA) levels in the plasma. For LA, the dilute Russell viper venom test (DRVVT) and silica clotting time were used. For aCL antibodies (IgM, IgG) and aB2GP1 antibodies (IgM, IgG), a serological enzyme linked immunosorbent assay (ELISA) was used. According to the guidelines of the laboratory where the tests were performed, the upper limits for normal values were as follows: 12 U/mL for aCL IgG and IgM, 20 RU/mL for aB2GP1 IgG and IgM, DRVVT ratio 1.2 for LA. Patients who had positivity in any of the aPLs were grouped as aPLs positive. To exclude the false positivity in the aPL test results of patients who were taking warfarin and heparin, patients who had been taking these drugs for any reason before they were diagnosed with COVID-19 were excluded from the study [2,9]. Also, patients with a diagnosis of malignancy, patients who had undergone renal transplantation, hemodialysis patients, patients with a diagnosis of chronic hepatitis, lupus or other autoimmune disease, those taking quinidine, procainamide, hydralazine, and those who had been diagnosed with APS previously were excluded from the study.

COVID-19 was diagnosed using nasopharyngeal swab determined by RT-PCR assay. The following information was collected from medical files: age; sex; comorbidities; COVID-19 symptoms (fever, cough, dyspnea, arthralgia, myalgia, nausea, vomiting, diarrhea, abdominal pain, ageusia); duration of symptoms; laboratory parameters, tissue oxygen saturation (StO2); need for oxygen therapy and

Table 1. Comparison of clinical parameters of COVID-19 patients according to aPLs test results.

	aPLs positive patients (N = 15)	aPLs negative patients (N = 58)	*p*
Female sex, number (%)	9 (60)	33 (56.9)	0.828
Median age, years, (IQR)	54 (26)	51.5 (22)	0.548
COVID-19 symptoms, n (%)			
Cough	11 (73.3)	35 (60.3)	0.353
Fever	8 (53.3)	21 (36.2)	0.227
Dyspnea	12 (80)	26 (44.8)	**0.015**
Arthralgia	8 (53.3)	22 (37.9)	0.280
Myalgia	15 (100)	44 (75.9)	**0.034**
Nausea and vomiting	11 (73.3)	16 (27.6)	**0.001**
Diarrhea	4 (26.7)	9 (15.5)	0.314
Abdominal pain	5 (33.3)	6 (10.3)	**0.027**
Ageusia	3 (20)	19 (33.3)	0.319
Patients with ≥ 1 comorbidities, n (%)	10 (66.7)	36 (62.1)	0.742
Hypertension	8 (53.3)	27 (46.6)	0.639
Diabetes mellitus	6 (40)	19 (32.8)	0.598
Asthma	1 (6.7)	3 (5.2)	0.821
COPD	1 (6.7)	5 (8.6)	0.806
CHD	1 (6.7)	5 (8.6)	0.806
Outcomes			
Hospitalization, n (%)	13 (86.7)	45 (77.6)	0.438
Length of hospital stay, days, median (IQR)	12 (5)	8 (6)	**0.006**
Need to oxygen therapy, n (%)	12 (80)	23 (39.7)	**0.005**
Rate of mechanic ventilation, n (%)	1 (6.7)	1 (1.7)	0.296
Rate of intensive care unit admission, n (%)	1 (6.7)	5 (8.6)	1.000
Severe disease*, n (%)	12 (80)	27 (46.6)	**0.024**
Thrombosis, n (%)	2 (13.3)	1 (1.7)	0.105
Exitus, n (%)	1 (6.7)	1 (1.7)	0.296

*Disease severity assessed according to World Health Organization guidelines, COVID-19: coronavirus disease 2019, aPLs: antiphospholipid antibodies, IQR: interquartile range, CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, n: number

mechanical ventilation; need for intensive care unit (ICU) admission; thromboembolism, and mortality. We classified our patients by severity as per World Health Organization (WHO) guidelines as severe and non-severe [17]. All data were collected by the same physician.

Hospitalization, treatment, management, and discharge of the patients were decided according to the COVID-19 guidelines of the Turkish Ministry of Health [18]. All patients received standard of care comprising of hydroxychloroquine (HCQ), low molecular weight heparin (LMWH), acetylsalicylic acid, favipiravir, and additional anti-inflammatory treatment (steroids, anakinra etc.) when indicated according to the guidelines of the Turkish Ministry of Health about COVID-19 [18].

Statistical analysis was done by Statistical Package for the Social Sciences (SPSS) version 22. The normality of the data was tested by Shapiro-Wilk test. The distribution of measurable (quantitative) data were expressed as mean ± standard deviation. The variables that were not normally distributed were expressed with the median and minimum-maximum values. While t-test was used for the difference of normally distributed variables, the difference of variables without normal distribution were examined with Mann-Whitney U test. Chi-square test was used for categorical variables and expressed as percentage; p-values below 0.05 were considered to be statistically significant in all tests.

Results

Seventy-three patients with a confirmed COVID-19 diagnosis who had an aPLs test were included in the study. Median age (IQR) of the 15 patients (9 women, 6 men) who had an aPLs test with a positive result was 54 (26) and the median age (IQR) of the 58 patients (33 women, 25 men) whose aPLs test was negative was 51.5 (22). There was no statistically significant difference in terms of age, sex and comorbidity between the aPLs positive and negative patient groups. When compared in terms of clinical findings, dyspnea, nausea, vomiting, myalgia, and abdominal pain were found to be significantly more common in the aPLs positive group and 12 of 15 aPLs positive group (80%) admitted to hospital with serious symptoms according to WHO definition (Table 1).

Table 2. Distribution of aPLs positivity in COVID-19 patients.

	N (%)
Lupus anticoagulant	12 (80.0)
Anticardiolipin IgM	3 (20.0)
Anticardiolipin IgG	0 (0)
Beta 2 glicoprotein IgM	7 (46.7)
Beta 2 glicoprotein IgG	0 (0)
Double positive	3 (20)
Triple positive	2 (13.3)

COVID-19: coronavirus disease 2019; aPLs: antiphospholipid antibodies; Ig: immunoglobulin.

Median (IQR) duration of hospital stay (12 (5) vs 8 (6), p = 0.006) and need for oxygen therapy (12 (80) vs 23 (39.7), p = 0.005) were at a statistically significantly higher level in aPLs positive group. No difference was detected between the two groups in terms of the need for mechanical ventilation, rate of admission to intensive care, thrombosis diagnosis and mortality.

Of the 15 aPLs positive patients, two had positive LA, aCL IgM and aB2GP1 IgM antibodies, two had positive LA and aB2GP1 IgM antibodies, one had positive aCL IgM and aB2GP1 IgM antibodies. Two patients were positive for only aB2GP1 IgM antibodies

Table 3. Comparison of laboratory parameters of COVID-19 patients according to aPLs test results.

	Baseline		
	aPLs positive patients (N = 15)	aPLs negative patients (N = 58)	*p*
Creatinine [mg/dl]	0.71 (0.68)	0.90 (0.36)	0.628
AST [U/L]	34 (38)	28 (17.75)	0.405
ALT [U/L]	30 (42)	28.5 (23)	0.753
LDH [U/L]	324 (117)	257 (82.75)	0.074
CRP [mg/L]	66.0 (84)	30.5 (60.75)	**0.009**
ESR [mm/h]	39.5 (39.25)	24 (37)	0.173
Ferritin [µg/L]	388 (247)	163 (261)	**0.023**
WBC [10^9/L]	7.30 (4.46)	5.92 (2.70)	0.299
Lymphocyte [10^9/L]	0.88 (0.51)	1.165 (0.78)	0.052
Hgb [gr/dL]	12.7 (2)	13.45 (2.15)	0.137
Platelet [1/mm^3]	184,000 (109,000)	232,500 (92,000)	0.146
Fibrinogen [g/L]	5.65 (3.42)	4.42 (2.34)	0.062
D-dimer [µg/mL]	0.5 (2.12)	0.47 (1)	0.293
D-dimer > 1, N (%)	5 (33.3)	19 (32.8)	0.966

All values are presented in median (IQR); COVID-19: coronavirus disease 2019; aPLs: antiphospholipid antibodies; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood count; CK: creatinine kinase.

and 8 patients were only LA positive (Table 2). Two patients who were LA positive also had secondary bacterial infection accompanying COVID-19 infection. There was no growth in the blood culture of any aPLs positive patient. The patient who died had a single aPL positivity (LA positivity). Among patients who were admitted to the hospital and who had a positive result for the aPLs test, 8 (61.5%) had a single aPL positivity, 3 (23.1%) had double aPLs positivity and 2 (15.4%) had triple aPL positivity. Remaining two patients who were not admitted to the hospital had single aPL positivity.

When the baseline laboratory parameters of the COVID-19 patients who had been examined for aPLs were compared; median (IQR) C-reactive protein ; mg/l) and median (IQR) ferritin values of patients with a positive aPL test were higher than those with a negative aPL test 66 (84) vs 30.5 (60.75), p = 0.009; 388 (247) vs 163 (261), p = 0.023 (Table 3). No activated partial thromboplastin time (APTT) elevation was detected in any patient in the aPL positive patient group.

Discussion

In our study, aPLs positivity was detected in 20.54% of the COVID-19 patients who had been examined for aPLs. The most frequent aPLs positivity was LA with 80%. We also detected the positivity of the IgM parts of aCL and aB2GP1 antibodies. The duration of hospital stay and the need for oxygen therapy in aPLs positive patients were detected to be at a higher than the aPLs negative patients.

aPLs positivity rate is unclear in the general population [2]. However, in two different studies, aPL positivity rate was reported as 5-10% in 552 and 775 blood bank donors [19,20]. aPLs are generally checked in the investigations for thromboembolic events and rheumatic diseases. It has been reported that the frequency of aPLs is between 6-14% in patients with pregnancy comorbidity, stroke, myocardial infarction or deep vein thrombosis [21]. In another study conducted in our country, aPLs positivity was detected in about 25% of the 31 COVID patients in the ICU and this is similar to the ratio we found [22].

In our study, dyspnea, nausea and vomiting, myalgia, and abdominal pain were observed to be more prominent in the aPLs positive COVID-19 patient group when compared to the aPLs negative group. Our findings may be suggestive of a marked gastrointestinal vulnerability in the aPLs positive group. Although the comorbidity rates were similar in both groups, duration of hospital stay and need for oxygen therapy were detected to be at higher rates in the aPLs positive patient group. Clinical symptoms were more severe, duration of hospital stay was longer and the need for oxygen therapy was higher for the aPLs positive group which may be associated with the more pronounced inflammatory response in this group.

Ferritin and C-reactive protein (CRP) elevation in COVID-19 patients is important in representing the inflammatory response [23]. There is a complex relationship between infections, CRP elevation, and aPLs. There may be a temporary aPLs elevation predominantly of IgM besides CRP elevation during various infections [24-27]. Also, it has been reported that CRP elevation could lead to false aPLs positivity due to cross reaction [28]. Likewise, in our study CRP and ferritin values in the aPLs positive group were higher than those in the aPLs negative group. Presence of a positive correlation between inflammation and tendency to coagulation is also known [29,30]. Under the light of this information, possibility of CRP and aPLs elevation to pose a tendency to thrombus formation cannot be neglected [31].

D-dimer elevation in COVID-19 disease is an important parameter showing inflammation and hypercoagulability [1,13]. Hypercoagulation is considered to aggravate the clinical picture of the patients followed up in ICU due to COVID-19 [13,14]. No difference was found in patients between the two groups in terms of D-dimer elevation.

Since beta 2 glycoprotein 1 is a protein that inhibits the development of atherosclerosis, the antibodies that develop against it are considered capable of triggering atherosclerotic plates [32]. In a study, which included 59 (31 COVID-19 positive patients, 28 COVID-19 negative patients) intensive care patients, conducted in Turkey, while no aB2GP1 IgM and IgG antibodies were detected in any patient, aCL IgG positivity was detected in only 2 subjects in COVID-19 patient group [18]. In the antiphospholipid syndrome, IgG positivity has been seen to be more significantly associated with thrombotic events than IgM positivity [33,34]. In our study, IgG antibody (aCL or aB2GP1) positivity was detected in none of the aPLs positive patients. This may explain the small number of thrombotic events within the groups and the absence of differences in terms of thromboembolic events between the groups. Also, the possibility of the aPLs positivity being due to infection as well as the possibility of CRP elevation and LMWH prophylaxis causing false positivity should be kept in mind [35].

Acetylsalicylic acid, LMWH and HCQ treatment may have also had an impact on the similarity of the thromboembolic events in both groups.

Hydroxychloroquine (HCQ) is an antimalarial drug which had been used in the treatment of autoimmune rheumatic diseases for years due to its anti-inflammatory and immunomodulatory effects. The use of HCQ treatment have been discussed in COVID-19 due to its inhibitory influence on viral replication and immunomodulatory effects [36]. Although its mechanism of action is yet to be fully clarified, it is known that HCQ is useful in preventing the thrombotic events, accordingly, thrombotic events are less frequent in lupus patients who take HCQ treatment than the ones who do not [37,38]. In the studies conducted before the COVID-19 pandemic, it has been reported that HCQ treatment was effective in preventing the thrombotic events in patients with aPS [39,40]. Nuri *et al.* have detected that the aPLs titers were lower and thrombotic events were less frequent in the primary aPS patients taking HCQ treatment than those who were not taking [41]. According to the study of Sciascia *et al.*, it was found that pregnant women with aPL antibodies taking HCQ treatment had a higher incidence of live birth than those who were not [42].

There are studies that recommend LA screening in patients with prolonged APTT because of the correlation between them [9,43]. Bowles *et al.* have detected prolonged APTT in 43 of the 540 patients. LA positivity was detected in 11 (%25) of them [9]. However, Ocáriz *et al.* have detected prolonged APTT in only 1 of the 27 aPLs positive patients [44]. In our study, elevated APTT was detected in none of our patients.

Our study has some limitations. It is not a prospective study. We have concerns regarding the power of the study since there were only 15 patients with a positive aPLs test. Majority of the patients was examined for single or double aPLs, and aPLs values were investigated once and not followed-up. Another limitation is the probability that the LMWH prophylaxis have affected the aPLs test results. However, it should be kept in mind that aPLs results in 80% of the patients included in the study who all received LMWH prophylaxis were negative.

Conclusions

Prominence of clinical findings in the aPLs positive group in comparison to the negative group may be associated with the more pronounced inflammatory response in the former. Elevated CRP and ferritin values in this group are also a sign of the aggravated inflammatory response. In other words, the high acute phase reactants in aPLs positive patients may indicate that COVID-19 findings can be more prominent in this group. There is a need for multi-center prospective controlled studies to reveal the exact relation between COVID-19 infection, aPLs and thromboembolic events.

Authors' Contributions

E.A., A.E. and B.A. designed the study; E.A. collected all the data. A.E. made statistical analysis; S.C.G., I.A. contributed to the interpretation of the results; E.A, A.E. wrote the manuscript in consultation with A.O., O.K; All authors checked the data, discussed the results and commented on the manuscript.

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