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TANAFFOS

Evaluation of Antiphospholipid Antibodies in COVID-19 Patients with Coagulopathy

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Background: Due to the importance of recent published studies regarding the thrombotic events in COVID-19 patients, the purpose of this study was to evaluate the frequency of antiphospholipid antibodies in COVID-19 patients with coagulopathy.

Materials and Methods: The present cross-sectional study was conducted on COVID-19 patients with coagulopathy admitted to Imam Khomeini Hospital in Sari, Iran, between June and September in 2020. Later on, the levels of anti-phospholipid antibodies (aPL-ab) and biochemical factors were measured.

Results: This study was performed on 40 patients. Individuals who were positive for at least one of the aPL-ab were classified in the group of aPL-ab positive; according to which 29 patients (72.5%) had no positive aPL-ab and 11 patients (27.5%) had at least one positive aPL-ab. 8 patients were only positive for lupus anticoagulant (LA) assay, one patient had B2GPI- IgM, one patient had aCL- IgG and only one patient had two positive simultaneous tests for LA and aCL- IgG. Thrombotic events have been found in 7 patients (17.5%) of which, three patients with deep vein thrombosis, one patient with pulmonary embolism, two patients with stroke, and one patient with myocardial infarction. The values of aPTT for the screening of Lupus anticoagulant assay were significantly different between the two groups, although there was no significant difference between the two groups in the co-morbidities, disease severity, death and laboratory tests (P> 0.05).

Conclusion: Despite the high incidence of thrombotic complications reported in COVID-19 patients in the current study, the levels of antiphospholipid antibodies had no significant correlation with the occurrence of thromboembolic events and disease outcome in COVID-19 patients with coagulopathy.

Key words: COVID-19; Coagulopathy; Anti-phospholipid syndrome

INTRODUCTION

Coronaviruses are zoonotic pathogens. In late 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia. In February 2020, the World Health Organization named COVID-19, which stands for Coronavirus 2019 (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes COVID-19, formerly known as 2019n-CoV (2). More than 200 million people worldwide have been confirmed to be infected with COVID-19; with the number increasing daily (3). Infections with coronavirus vary in severity. The spectrum of symptomatic infections varies from mild to critical, and most infections are not severe (4-10). A specific report from the Chinese Center for Disease

Control and Prevention reported about 44,500 confirmed infections with estimated disease severity, including mild infection (no or mild pneumonia) in 81%, severe illness (such as shortness of breath, hypoxia, or lung involvement> 50% on imaging during 24-48 hours) in 14%, critical illness (such as with respiratory failure, multiple organ dysfunction or shock) in 5%, and an overall mortality rate of 2.3%, with non-critical cases showing no mortality (11).

According to laboratory findings, the patients with COVID-19 exhibited a change in white blood cell count as leukopenia, leukocytosis, and lymphopenia, with a higher prevalence of lymphopenia (6-8, 12). The pathogenesis of hypercoagulability in COVID-19 is ill-defined. All three components of Virchow's triad appear to be involved, including endothelial injury, stasis, and hypercoagulable state. Endothelial injury is evident from the direct invasion of endothelial cells by SARS-CoV-2 (13). High levels of D-dimer and more severe lymphopenia are also associated with higher mortality (7). Specific laboratory findings with worse consequences that require more attention include lymphopenia, elevated activity of liver enzymes, increased activity of lactate dehydrogenase, elevated levels of inflammatory markers (such as CRP and ferritin), elevated levels of D-dimer (> 1 µg / ml), prolonged prothrombin time (PT), enhanced levels of troponin and creatine phosphokinase, and acute renal failure (14-16).

One of the complications of COVID-19 that is still under investigation is coagulopathy and the possibility of positive anti-phospholipid antibodies in such patients. On the other hand, COVID-19 may predispose patients to venous and arterial thromboembolism due to hyper inflammation, hypoxia, immobility, and disseminated intravascular coagulation (17).

Antiphospholipid Antibody Syndrome (APS) is a systemic autoimmune disorder characterized by venous and arterial thrombosis or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (18). APS occurs as a primary disease or in the presence of systemic lupus erythematosus or another autoimmune disease. Infectious agents are the major initiators of the synthesis of antiphospholipid antibodies (19). Therefore, the occurrence of coagulopathy and the positivity of antiphospholipid antibodies are not far from what is expected to be the possible outcomes of COVID-19. The antiphospholipid antibodies are a heterogeneous group of antibodies directly used against membrane phospholipids (20). The appearance of antiphospholipid antibodies and antigen-antibody reaction on the surface of different cells leads to a wide range of clinical symptoms such as arterial and venous thrombosis, recurrent pregnancy loss, thrombocytopenia, neurological disorders and stroke, transient ischemic attacks accompanied by blurry vision, cardiovascular disorders, pulmonary hypertension, lower limb gangrene, etc. in patients with APS (19). Criteria for classifying a patient as a person with APS has been revealed according to both clinical and laboratory parameters. The patients are diagnosed with the APS, who have at least one of the clinical criteria (presence of vascular thrombosis and pregnancy complications) and at least one of the laboratory criteria (21).

COVID-19 patients have severe hypercoagulability disorders that are prone to thrombotic complications. On the other hand, in some patients, aPTT disorder is seen. The reason for the increase in PTT is either a decrease in coagulation factor or the presence of a coagulation inhibitor, the non-specific type of which is LA (22). The development of acute respiratory syndrome and thromboembolic episodes that may lead to diffuse intravascular coagulation (DIC) is the leading cause of death during COVID-19 infection. Evidence suggests that thrombotic diathesis is due to a disorder of the coagulation system, including an increase in D-dimer, which is inversely related to survival. Thromboembolic events due to COVID-19 may indicate APS (23).

Given the importance of reports published in recent studies of thrombotic events and in situ thrombosis in COVID-19 patients and also inconsistency as a result of studies and failure to investigate this issue in Iran, this

study was conducted with the aim of evaluation of antiphospholipid antibodies in COVID-19 patients with coagulopathy.

MATERIALS AND METHODS

The present cross-sectional study was conducted on the COVID-19 patients with coagulopathy admitted to Imam Khomeini Hospital in Sari, Iran, in 2020. The sample size included 40 patients who were selected by the census. Inclusion criteria included patients admitted with COVID-19 based on RT-PCR or typical chest computed tomography manifestations along with one of the paraclinical evidence of prolonged PTT, hemolytic anemia, thrombocytopenia, and evidence of deep vein thrombosis or pulmonary embolism. Exclusion criteria also included patients who, in addition to COVID-19 had Systemic lupus erythematosus, leukemia, and lymphoma, heparin-induced thrombocytopenia (HIT), and disseminated intravascular coagulation (DIC).

This research was approved by the Ethics Committee of Mazandaran University of Medical Sciences with the code of ethics of No.7619. In line with the ethical considerations and confidentiality, all participants in the study were informed about the principles and objectives of the research, the confidentiality of the data, and the anonymity of the checklists. In addition, they were free to refuse to participate. To collect information in this study, after obtaining the informed consent of the patients, demographic data, clinical and laboratory parameters of the patients were extracted and recorded from the patients' medical records with the help of designed checklists. Patients were admitted to the study with inclusion criteria and after recording clinical findings, blood samples were collected from them. Serum and plasma samples were isolated from each patient and then the levels of D-dimer, FDP, fibrinogen, lupus anticoagulant, anticardiolipin IgM, IgG, B2 glycoprotein I IgG, IgM with the kits of STAGO, MahsaYaran (21_FI_021, Iran, Tehran), AESKU, Wendelsheim, Germany and UROIMMUNE Lübeck, Germany were measured by latex agglutination, coagulation, and ELISA methods. Also CBC, PT, PTT were performed for all patients.

The test results were interpreted as the normal range of anticardiolipin IgG or IgM antibodies and anti-β2-glycoprotein I IgG or IgM antibodies less than 20 units, and more than 20 units as the positive cases.

Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. Data were analyzed by SPSS version 20 software using t-test for quantitative variables and chi-square, Pearson correlation and Fisher's exact tests for qualitative variables at a significance level of P-value<0.05.

RESULTS

The present study was conducted on 40 patients with a mean age of 65.15±17.47 years, including 20 (50%) females and 20 (50%) males. The subjects with at least one positive antiphospholipid antibody were included in the group of antiphospholipid antibody-positive patients. According to which 29 patients (72.5%) had no positive antiphospholipid antibody and 11 patients (27.5%) had at least one positive antiphospholipid antibody. Eight patients were only positive for lupus anticoagulant assay, one patient had B2 GPI IgM, one patient had Anti cardio IgG, and only one patient had two positive simultaneous tests for lupus anticoagulant and Anti cardio IgG. The values of aPTT for the screening of Lupus anticoagulant assay were significantly different between the two groups (p=0.000). The mean age was 49.81±17.73 years in antiphospholipid antibody-negative patients, and 60.17±16.87 years in antiphospholipid antibody-positive patients; no significant difference in age was observed between the two groups (P=0.096). Of 29 antiphospholipid antibody-negative patients, 16 (55.2%) were male and 13 (44.8%) were female. Of 11 antiphospholipid antibody-positive patients, 4 (36.4%) were male and 7 (63.6%) were female and no significant difference in gender was observed between the two groups (P=0.480).

In this study, patients were evaluated based on ICU admission history, underlying diseases (diabetes and

hypertension), and disease severity, the results of which are reported in Table 1. Based on the severity of the disease, 9 patients (81%) of antiphospholipid antibody-positive patients had respiratory rate of >30 and SO2 level of <94% who were included in the group with severe disease. According to Table 1, there was no significant difference between the two groups in terms of ICU admission history, underlying diseases (diabetes and hypertension), and disease severity (P>0.05).

The results for the evaluation of clinical and laboratory parameters of patients including WBC, platelet count, CRP, D-dimer, fibrinogen level, fibrinogen degradation product, antibody-positive, and antiphospholipid antibody-negative groups are depicted in Table 2 (Figure 1). According to Table 2, WBC count, platelet count, CRP level, D-dimer level, and fibrinogen level were not significantly different between antiphospholipid antibody-negative and antiphospholipid antibody-positive groups (P>0.05).

Table 1. Demographic profile in antiphospholipid antibody-negative and antiphospholipid antibody-positive groups

Variables	Antiphospholipid antibody negative N=29	Antiphospholipid antibody positive N=11	Total N=40	p-value
Age (Mean±SD)year	60.17±16.87	49.81±17.73	65.15±17.47	0.096
	Number (%)	Number (%)	Number (%)	
Male	16(55.2%)	4(36.4%)	20(50%)	0.48
Female	13(44.8%)	7(63.6%)	20(50%)	
Inpatient department				
ICU	3 (10.3%)	4 (36.4%)	7 (17.5%)	0.075
General wards	26 (89.7%)	7 (63.6%)	33 (82.5%)	
Basic illness history				
Diabetes	12 (41.4%)	5 (45.5%)	17 (42.5%)	1.000
Hypertension	10 (34.5%)	4 (36.4%)	26 (65.0%)	
Severity of the disease				
Non-severe	13 (44.8%)	2 (18.2%)	15 (37.5%)	0.158
Severe	16 (55.2%)	9 (81.8%)	25 (62.5%)	
Thromboembolic events	4(13.8%)	3(27.3%)	7(17.5%)	0.369
Fibrinogen abnormality	17 (58.6%)	9 (81.8%)	26 (65.0%)	0.270
Disease outcome				
Recovery	24 (82.8%)	6 (54.5%)	30 (75.0%)	0.103
Died	5 (17.2%)	5 (45.5%)	10 (25.0%)	

Table 2. Laboratory findings in antiphospholipid antibody-negative and antiphospholipid antibody-positive groups

Variables	Antiphospholipid antibody negative Median(IQR)	Antiphospholipid antibody positive Median(IQR)	p-value
WBC	5300(3550-9700)	3900(3600-12600)	0.743
Platelet count	130(114-135)	148(118-225)	0.148
CRP	36.4(28.7-59)	35.9(22-70)	0.765
D-dimer	1347(459-4025)	4576(850-7395)	0.90
Fibrinogen Level	220(188-253)	230(230-330)	0.148
aPTT	38(35-39)	55(45-68)	0.000
Anti B2 GPI IgM	2.9(0.41-5.4)	3.2(0.4-7.4)	0.698
Anti B2 GPI IgG	2.1(1.66-2.48)	2.4(2.16-3.2)	0.116
Anti cardio IgM	0.66(0.35-1.1)	0.96(.054-1.29)	0.175
Anti cardio IgG	1.05(0.62-1.37)	1.22(0.8-8.94)	0.308

Moreover, 27% of patients with antiphospholipid antibodies had leukocytosis and 54% had leukopenia. In this study, 7 patients (17.5%) had thrombotic events including three patients with deep vein thrombosis (42%), one patient with pulmonary embolism (14.2%), two patients with stroke (28.5%), and one patient with myocardial infarction (14.2%), of which three patients (27.8%) were in the positive antiphospholipid antibody group. According to Table 1, no significant difference in the occurrence of thromboembolic events was observed between the two groups (P>0.05).

In this study, levels of antiphospholipid antibodies (including B2 GPI IgM, B2 GPI IgG, Anti cardio IgG, and Anti cardio IgM), D-dimer, and fibrinogen were evaluated for different severity stages of disease. Based on this study, no significant difference was observed between levels of antiphospholipid antibodies at different disease severity stages.

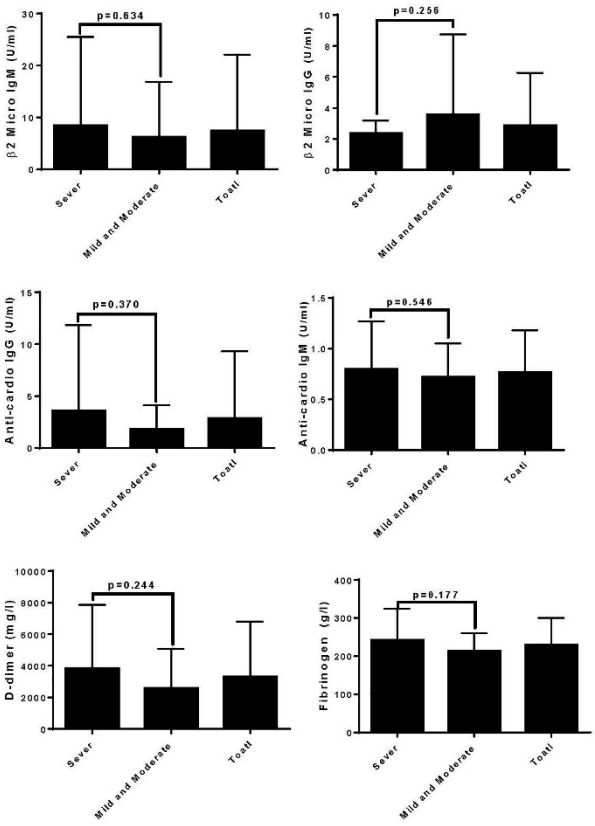

Figure 1. Levels of antiphospholipid antibodies, D-dimer and fibrinogen

DISCUSSION

In some cases, patients with COVID-19 have been reported to have coagulopathy, and high rates of thrombotic events have been observed in clinical and postmortem studies (24). This study aimed to evaluate antiphospholipid antibodies in COVID-19 patients with coagulopathy. There was no significant difference in ICU admission, underlying diseases (diabetes and hypertension), and disease severity between the two groups (P>0.05). Platelet count, WBC count, CRP, D-dimer, fibrinogen level, FDP, coagulopathy, and disease outcome were not significantly different between antiphospholipid antibody-negative and antiphospholipid antibody-positive groups (P>0.05). There was no significant difference in the levels of antiphospholipid antibodies (including B2 GPI IgM, B2 GPI IgG, Anti cardio IgG, and Anti cardio IgM), D-dimer, and fibrinogen in terms of SO2 level. Based on the results of this study, the difference of aPTT values for the screening of Lupus anticoagulant assay was significant between the two groups (P<0.05) but the levels of other antiphospholipid antibodies including B2 GPI IgM, B2 GPI IgG, Anti cardio IgG, and Anti cardio IgM showed no significant differences between the two groups and different disease severity stages. One plausible explanation for the significant difference of aPTT values for the screening of Lupus anticoagulant assay between the two groups can be noted as functional assays for LA may have been influenced by higher levels of CRP which was not evaluated in the current study and further investigations is required to clarify the plausible effect (25).

Recent studies have shown conflicting results regarding the association between positive lupus anticoagulant assay and COVID-19 thromboembolic complications. The Siguret et al. (26) study did not show a significant difference in the prevalence of positive lupus anticoagulant assay between patients with severe COVID-19 with and those without thrombotic complications, while Reyes Gil et al. (25) reported a higher percentage of thrombotic events in patients with positive lupus

anticoagulant assay. These conflicting results may be due to differences in age, disease severity stages, and interference from drugs used for anticoagulation and study design. Moreover, Positive Lupus anticoagulant assay may be transient in patients with COVID-19 devoid of any predictive power for thromboembolism.

In a study by Harzallah et al. in the population of patients with COVID-19 and lupus, the results showed that 25 patients were positive for lupus anticoagulants, while five patients had anti-cardiolipin antibodies or anti-β(2)-glycoprotein I (anti-β2 GPI) antibodies, and lupus anticoagulant was also positive simultaneously in three patients. In this study, it was revealed that the isotypes of anti-cardiolipin antibodies and anti-β2 GPI antibodies were IgG and IgM. They suggested that the presence of these antibodies should be used as evidence for primary anticoagulant therapy in severe COVID-19 patients with a risk factor for thrombosis (27). According to Zhang et al. case series, three COVID-19 patients with coagulopathy have been reported with thrombocytopenia, presence of IgA anticardiolipin antibodies and anti-β2 GPI antibodies, IgA and IgG antibodies in paraclinical evaluations, who experienced multiple cerebral infarctions (28). Antiphospholipid antibodies are common in the general population, especially during infection (29,30). Antiphospholipid antibodies abnormally target phospholipid proteins; the presence of these antibodies plays a key role in the diagnosis of antiphospholipid syndrome. However, these antibodies can also appear transiently in patients with critical illness and various infections (31). The presence of these antibodies can rarely lead to thrombotic events, which are difficult to distinguish from other causes of multifocal thrombosis in serious patients such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic microangiopathy (32). The fact that the IgA isotype alone, cited by Zhang et al, causes thrombosis remains controversial, with only high-titered IgG and IgM isotypes being considered diagnostic criteria for APS. The absence of IgG and/or IgM titers in this case series precludes any assessment of their role in the described thrombotic complications (28,33). Thrombosis is common during critical illness, and all patients in the case series of Zhang et al. have a history of cardiovascular disease, which increases the risk of developing arterial thrombosis. A key question remains whether COVID-19 patients experience arterial thrombotic events more rapidly than very severe patients without SARS-CoV-2. The findings presented by Zhang et al. could not confirm the anti-cardiolipin antibodies as the causative agent of arterial thrombosis observed in their case series (28).

Albeit the incidence of thrombotic events was not significantly different between the two groups in our study, in a study by Amezcua-Guerra et al., 57% of patients with severe COVID-19 had high levels of antiphospholipid antibodies. They noted that hyperinflammatory aPL antibodies are associated with very high levels of ferritin, CRP, and interleukin-6, and may also be associated with pulmonary thromboembolism. They also suggested that these antibodies may be transient during acute infection, thrombosis, or inflammation and that a COVID-19 patient with coagulopathy and aPL antibody should not be thought to have catastrophic antiphospholipid syndrome (32). In this regard, Borghi et al. reported a low prevalence of antiphospholipid antibodies and thrombotic events in patients with COVID-19. They also acknowledged that these antibodies are often B2 GPI, which have different epitope characteristics from antibodies in antiphospholipid syndrome. Moderately down-titrated antiphospholipid titers are consistently found in patients with COVID-19, whereas higher titers are seen in patients with antiphospholipid syndrome (34).

Although in our study, the levels of CRP, D-dimer, fibrinogen, FDP, and disease outcome were not significantly different between antiphospholipid antibody-negative and antiphospholipid antibody-positive groups, some studies have reported that COVID-19 develops a hypercoagulable state with increased fibrinogen and

minimally prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT); the exact mechanisms of coagulation infrastructure are unknown (35). In the evaluation of COVID-19-associated coagulopathy, it is important to evaluate the d-dimer for coagulation disorders in COVID-19. Although d-dimer is initially elevated, other routine coagulation laboratory tests, including PT, aPTT, and platelet counts, are often normal and are not useful indicators of thrombotic risk. Elevated factor VIII and von Willebrand factor (VWF) possibly the presence of antiphospholipid antibodies (28) and increased complement cascade have also been reported, however, the study of these biomarkers is not practical. The pathogenesis of coagulation in COVID-19 is complex, but COVID-19-associated coagulopathy can be detected by increased D-dimer, elevated fibrinogen levels, and VWF, but relatively normal PT, aPTT, and platelet count (36). In this study, 7 patients (17.5%) had thrombotic events, of which three patients (27.8%) were in the positive antiphospholipid antibody group and no significant difference in the occurrence of thromboembolic events was observed between the two groups (P>0.05). Although the ages were not significantly different between the two groups, patients with positive anticardiolipin antibodies were older by one decade than the other group.

Due to the inconsistency of the results of the current study with other published previous studies, it is suggested to conduct more extensive studies with the approach of the effect of COVID-19 on coagulation parameters and to elucidate the effect of positive Lupus anticoagulant assay on thromboembolic events and clarify intervening factors.

CONCLUSION

In the present study, considering the study limitations such as small sample size, despite the high incidence of thrombotic complications as reported previously in COVID-19 patients, the levels of antiphospholipid antibodies had no significant correlation with the occurrence of thromboembolic events, different disease severity stages, and disease outcome in COVID-19 patients with coagulopathy. However, to elucidate the effects of positive lupus anticoagulant assay and aPL antibodies on thromboembolic complications and disease outcome in COVID-19 patients, further studies in recommended.

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