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# An investigation to find the correlation between lupus anticoagulant and coagulation abnormalities in COVID-19 patients; a narrative review

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## ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19) which is associated with nonspecific respiratory syndromes, varying from mild symptoms of upper airway to required mechanical ventilation hypoxemia. A unique feature of this disease is COVID-19-associated coagulopathy (CAC) that linked with disease severity and hospital mortality. These patients have a profound hypercoagulable state and in patients with severe type arterial and venous thrombotic events are frequent. Abnormal coagulation parameters such as activated partial thromboplastin time (aPTT) were observed in patients with COVID-19. Regarding the above finding it could be considered as a reason to avoid anticoagulation at the both doses of therapeutic and prophylactic. A prolonged aPTT may indicate a coagulation factor deficiency or inhibitor of coagulation, which can be specific (antibody to factor VIII) or nonspecific (lupus anticoagulant, LA). LA can affect laboratory tests of blood coagulation, but is not usually associated with bleeding; however, it can be associated with thrombotic risk as a part of the antiphospholipid syndrome. In a phospholipid concentration-dependent manner LA recognizes a type of antiphospholipid antibodies (aPLs) that prolong clotting tests. In patients with antiphospholipid syndrome (APS) LA is considered as one of the laboratory criteria representing a significant risk factor of both thrombosis and pregnancy morbidity. Similarities between some of the pathophysiological features of COVID-19 and APS has been focused in several reports particularly in the most severe form, catastrophic APS. This study aimed to evaluate the effect of LA on the incidence of thrombophilia in patients with COVID-19, as well as its impact on the inflammation and finally the mortality final rate.

*Implication for health policy/practice/research/medical education:*
There are similarities between some of the pathophysiological features of COVID-19 and antiphospholipid antibody syndrome. Presence of lupus anticoagulants (LAs) in patients with antiphospholipid antibody syndrome represents a significant risk factor for thrombosis. It seems that LA is a vital clinical biomarker for the diagnosis and prediction the prognosis of thromboembolism disorder in COVID-19 patients.

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## Introduction

Coronavirus 2019 (COVID-19) is a respiratory illness caused by the coronavirus severe acute respiratory syndrome 2 (SARS-CoV-2) and characterized by nonspecific respiratory syndromes ranging from moderate upper respiratory symptoms to hypoxemia needing mechanical ventilator assistance. COVID-19 is known for its coagulopathy, linked to illness severity and hospital mortality. Despite pharmacological thromboprophylaxis, reports of venous thromboembolism (VTE) and arterial thrombosis are rising. Both macro-thrombosis (particularly pulmonary embolism [PE]) and micro-thrombosis in the lungs have been extensively documented. In COVID-19, micro-thrombosis may be caused by vascular damage.

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Review

There is a link between coagulopathy and severity and/or fatality of the disease. Antiphospholipid syndrome (APS) is an acquired thrombophilia that requires lifelong anticoagulation. A clinical course (thrombosis or pregnancy complications) and at least one persistent positive test for antiphospholipid antibodies (APAs), including lupus anticoagulant (LA) IgG and/or IgM, anti-cardiolipin antibodies (aCL) and beta-2 antibody glycoprotein 1 is required for the diagnosis of APS (aB2GP1). Antiphospholipid antibodies and phospholipid-binding proteins such as anti-prothrombin (aPT), anti-cardiolipin antibodies (aCL), or Beta-2 glycoprotein 1 antibody (aB2GP1) are implicated in leukocyte and endothelial activation, as well as VTE and arterial induction. Patients with high risk for thrombosis may be identified using a combination of positive APA profile tests, particularly triple positivity (LA, aCL, aB2GP1, same isotype). This allows for a more accurate diagnosis of APS. Furthermore, most triple-positive individuals have antiphosphatidylserine/prothrombin (aPS/PT) antibodies (tetra-positive patients), which puts them at a greater risk of thromboembolic events than patients with a normal APA profile. Furthermore, APAs are not exclusive to APS and may be seen in healthy people and clinical situations, including autoimmune diseases, medicines and infections. During other viral infections APA have largely been described and their pathogenicity in these contexts is still under discussion (1).

Several cases of a possible relationship between APA and thrombotic events have been recorded during the COVID-19 pandemic. In previous investigations, positive rates of LA ranged from 45% to 88% in various cohorts of medical wards and/or critical care units (ICUs). Only one laboratory study showed that APA positivity could be prothrombotic in COVID-19 patients, but the LA test was not evaluated. To the best of our knowledge, no substantial cohort has detailed a thorough LA and APA-related screening. Furthermore, with COVID-19, the link between APA and VTE or hospital mortality is still debatable (2).

Although systemic inflammation and procoagulant state play a substantial pathophysiological role in the severe kinds and are highly correlated with illness severity and mortality (1), it is not clear if the procoagulant profile is directly resulted from infection or the outcome of inflammation (3). This review study aims to look at the correlation between LA antibody and hyper coagulate state in COVID-19 patients.

## COVID-19 and coagulopathy

SARS-CoV-1, which was first identified as the source of SARS in 2002, has been associated with a prolonged activated partial thromboplastin time (aPTT) (63%), thrombocytopenia (55%) and thrombocytosis (49%) but not with significant bleeding (4,5). Deep vein thrombosis developed in 20.5% of patients in the case of SARS-CoV-1 infection, and clinical evidence of PE have seen in11.4% (3). The virus that causes COVID-19, SARS-CoV-2, may have a similar ability to cause thrombotic problems (6). In severe cases of acute respiratory distress syndrome (ARDS), a coagulation predominant-kind of coagulopathy can be detected (7).

The principal targets of SARS-CoV-2 are pulmonary epithelial cells, lymphocytes and vascular endothelial cells, which leads to ARDS, shock, and coagulopathy that present the clinical features of severe COVID-19 (8).

COVID-19 is thought to stimulate several complement pathways that produce microvascular damage and thrombotic events in those who are procoagulant (9). Coagulation dysfunction, ranging from COVID-19-associated coagulopathy to diffuse intravascular coagulation, seems to be one of the primary causes of death in these individuals. Poor prognosis is linked to abnormal coagulation parameters, such as D-dimer augmentation and fibrinolysis products (6). However, there are few published data on LAs in critical patients and the existed data has led to a variety of results so far (10).

Thromboembolism is caused by a viral infection that causes an inflammatory procoagulant condition. Coagulation parameter changes were linked to poor patient outcomes and death. COVID-19 individuals with intra-alveolar fibrin deposition have been known to have coagulopathy, which may lead to catastrophic respiratory failure. Coagulopathy affects practically every component of the coagulation cascade, including procoagulant, anticoagulant, fibrinolytic and anti-fibrinolytic proteins (6).

In reality, SARS-CoV-2 infection begins in the lungs; however, it quickly spreads to the vascular system, producing platelet alterations and irregular blood clotting, as well as a significant incidence of cardiovascular events and VTE, particularly in critical patients (10% to 34%) (1). According to the previous data, endothelial damage may play a significant role in procoagulant situations related to COVID-19. In both healthy males and patients with cardiovascular disease and recurrent VTE, elevated soluble intercellular adhesion molecule-1 (sICAM-1) predicts cardiovascular events (3). The severity of the illness and the incidence of VTE are linked. As a result, this marker should be investigated further to predict prognosis in COVID-19 patients. The preventive dosage of low-molecular weight heparin showed no impact on indicators of endothelial dysfunction in research by Falcinelli et al, which is consistent with minimal clinical effectiveness in avoiding VTE in COVID-19 patients (11). However, early therapy may reduce COVID-19-associated endothelial

damage, according to new research examining the impact of anticoagulation at the therapeutic dosage given to COVID-19 patients before hospitalization on endothelial injury evaluated by circulating endothelial cells. As a result, in high-risk individuals, increased sICAM-1 may be utilized as a signal to adjust the therapeutic dosage of heparin (11).

According to recent findings, patients manifest with more severe coagulopathy and disseminated intravascular coagulation (DIC). As a result, coagulation tests are thought to help distinguish severe COVID-19 patients. The most prevalent symptom of coagulopathy caused by COVID-19 is limb impairment, with uncommon hemorrhagic episodes. Furthermore, the coagulopathic character of mass fibrin production is evidenced by changes in hemostatic indicators such as increased D-dimer and fibrinogen/fibrin breakdown products. Reduced antithrombin activity is less prevalent, and thrombocytopenia is unusual in COVID-19 compared to DIC/coagulopathy related to bacterial sepsis (8).

Patients with COVID-19, have a more significant chance of thrombotic problems than those not infected and the prognosis is less promising if thrombosis starts. According to current standards, all patients with COVID-19 may be categorized as having a thrombotic risk and depending on their risk, given basic preventative maintenance medication (if not a therapeutic dosage). Patients may need more anticoagulation targets than usual after being diagnosed with thrombosis (12). Other therapeutic approaches, including plasma exchange, intravenous immunoglobulin and immunosuppression, have been recommended to address the safety-related consequences of thrombotic microangiopathies (TMA). There are several accessible clinical studies in this regard (4,7,11,13).

## Mechanisms of coagulation activation

A propensity to bleed, a modest reduction in platelets, a rise in plasma fibrinogen levels and the discovery of SARS-CoV-2 and complement components in thrombotic microangiopathy regions are all important defining aspects of COVID-19-associated coagulopathy (CAC). Direct viral invasion of endothelial cells through the angiotensin 2 converting enzyme receptor causes endothelial damage. The immobility related to hospitalization of COVID-19 will increase the chance of venous stasis. Ultimately, hypercoagulability has been indicted to a LA associated prolonged aPTT. Increased factor VIII and von Willebrand antigen activity has been seen, presumably owing to endothelial cell injury. VTEs develop in one-third of critically ill COVID-19 patients, even with prophylactic anticoagulation regimen. It has also been reported arterial thrombosis, including stroke and acute limb ischemia. In one study, macrovascular thrombosis, which involves leukocytes, fibrin, platelets, erythrocytes and microvascular thrombosis, which involves platelet-fibrin micro-thrombosis in venules, arterioles and capillaries of all major organs, were studied in patients with COVID-19. According to the results of this study, widespread small vessel blockage and TMA is mediated by complement and begins by immunity in COVID-19 patients (7).

Finally, it has been shown that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) cause significant lymphocyte apoptosis, resulting in severe lymphoid depletion in lymph nodes, on the other hand, lymphopenia, which is a frequent observation in SARS-CoV-1 and SARS-CoV-2. The expression of tissue factors in monocytes/macrophages and vascular endothelial cells is stimulated when the immune system is activated. The tissue factor on the cell surface is the primary initiator of the coagulation cascade (13).

## Lupus anticoagulant

The LA is a heterogeneous antibody that attacks negatively charged phospholipids in combination with proteins such as prothrombin and Beta2-glycoprotein I (aβ2-GP-I) (2,14). LA increases clotting time in the internal pathway and a lesser amount in the external pathway by blocking the prothrombinase complex (5). In the past, LA was diagnosed in preoperative screening by a prolonged aPTT in the coagulation tests in those who did not have a coagulation factor deficit. The need for LA-insensitive aPTT reagents arose as a result of this situation. However, it was quickly discovered that specific LA-positive individuals were at a higher risk of thrombosis and/or pregnancy problems. A thrombosis (venous, artery, or both) and/or pregnancy problems are linked to the existence of LA. LA is one of the three laboratory criteria for determining of APS. Anti-cardiolipin (aCL) or Beta2-glycoprotein I (aβ2-GP-I) antibodies are the other two criteria that identify APS. According to the International Society for Thrombosis and Hemostasis (ISTH) recommendations, APS is defined when the same patient has at least one clinical event (i.e. venous/arterial thrombosis or pregnancy complications) and LA positivity or the presence of moderately elevated titers of aCL or concomitant aβ2-GP-ICH (1,15).

## False-positive lupus anticoagulant

In the recent studies, the frequency of LA positive with dRVVT was raised both in thrombosis patients (by altering the quantity of C-reactive protein) (6) and in individuals without thrombosis in the trials including patients with COVID-19 (5). The findings of these studies, which met the ISTH criteria for LA positivity, demonstrate that the

presence of this protein is genuine and not an artifact (13).

C-reactive protein has a strong affinity to phospholipids, particularly phosphatidylcholine, false-positive LA tests are predicted in COVID-19 patients (16). LA analysis was conducted in their patient cohort as indicated by ISTH (4), using two tests: first, dRVTT (Hemosil dRVTT Werfen), then aPTT-sensitive assays employing confirmation/screening of hemosIL silica clotting time (Werfen). The results of the study by Harzallah et al were not influenced by CRP since all of the patients were positive for dRVVT (13).

Due to the widespread administration of low-molecular weight heparin and unfractionated heparin for thromboprophylaxis in patients hospitalized with COVID-19, false-positive findings due to anticoagulant interaction may be a necessary consequence of the high positive LA rate reported. According to the manufacturer's recommendations, blood should be obtained 12 hours after the last dosage of low-molecular weight heparin and 24 hours after the last dose of rivaroxaban (17).

Some drugs cause induced lupus and are used in COVID-19; this means the immune system attacks healthy tissue by mistake due to a reaction to some medicines. The most well-known drugs that cause drug-induced lupus erythematous are isoniazid, hydralazine, procainamide, tumor necrosis factor alpha (TNF-alpha) inhibitors, minocycline, interferon-alpha, and quinidine. Other, less commonly used medications could be to blame. Examples are anti-seizure medications, such as chlorpromazine, methyldopa, sulfasalazine and levamisole, while some of these drugs are administered in COVID-19. Interferon-alpha, tipiracil, and perampanel are examples of this use. However, these agents are less commonly used in COVID-19 patients (18-20).

## Lupus anticoagulant and COVID-19

The common finding of LA in COVID-19 has led researchers to survey the role of this antibody in viral infection. Antiphospholipid antibodies were found in admitted patients for COVID-19 and their role in thrombotic risk was suggested accordingly (21,22). Despite the high prevalence of LA, which ranged from 35.5 to 45 percent in severe COVID-19 (10,11), no other studies have found a link between LA and thromboembolic events (6). LA can signal the presence of autoimmune clinical findings like immune thrombocytopenia, autoimmune anemia, or both (6). Finally, despite the high prevalence of LA in COVID-19 patients, no increase in anticardiolipin (aCL) or antibacterial 2-glycoprotein I (aβ2HPI) antibodies was observed (13).

The significant relationship between cardiac troponin, oxygen saturation and LA could be of clinical significance, since it predicts a poor course of pneumonia with thrombotic complications and death (3).

Despite a significant increase in factor VIII, which shortens the aPTT, prolongation of the aPTT was observed in COVID-19 patients. aPTT prolongation should not be a barrier to the anticoagulation therapy in COVID-19 patients to prevent and treat venous thrombosis (9).

Micro-thrombosis, VTE and arterial thrombotic complications are linked to coagulopathy caused by COVID-19. Karahan et al was the first who looked at APAs in a large group of suspected COVID-19 patients, including both confirmed and unconfirmed cases. This research looked into the significance of common and uncommon APS markers during COVID-19 hospitalization to see if they play a role in the disease's prognosis. In their study, the high prevalence of LA in COVID-19 patients contrasted with the low-prevalence of anti-aCL IgG and IgM antibodies and anti-aB2GP1 IgM and also IgG antibodies. Higher inflammatory biomarkers such as fibrinogen and CRP, rather than interleukin-6 or ferritin, were significantly associated with LA positivity in COVID-19 patients. The differences in inflammatory markers and their relationship to LA positivity in COVID-19 suggested that these markers were not equally important. More research is needed to determine the role of inflammatory proteins in COVID-19 intensity and/or their role in COVID-19-related coagulopathy.

High levels of CRP and fibrinogen can lead to false-positive results; therefore, LA testing is not recommended in acute-phase inflammatory conditions (15). Zhang et al described three critical COVID-19 cases without heading details early in the outbreak, characterized by the absence of LA and the presence of IgG and IgA antibodies against aB2GP1 and also IgA antibodies against aCL. Ischemic events caused by multifocal thrombosis occurred in three patients. APA can be temporarily positive in patients with infectious diseases and these antibodies are only rarely linked to thrombotic events, which explains why this link is unreliable in critically ill patients. The relationship between IgG aCL level and COVID-19 intensity without a positive LA test was investigated in a study on 56 COVID-19 patients (20). Only one study found that APA positivity in mice could be pro-thrombotic and accelerates venous thrombosis *in vitro* and *in vivo* after the injection of purified IgG from the serum of APA-positive COVID-19 patients. However, the lack of APA specificity of purified IgG antibodies from COVID-19 patients was one of the significant drawbacks of this study. LA test was not considered in this recent study (21). APA can be temporarily positive in patients with infectious diseases, and these antibodies are only rarely linked to thrombotic events, which explains why this link is unreliable in critically ill patients. It is unknown if APA in COVID-19 is related to APA found in other

infectious diseases like hepatitis C virus, hepatitis B virus, and human immunodeficiency virus (HIV) (22).

Lupus anticoagulant positivity in COVID-19 patients was not linked to the increased VTE, mainly PE, or a worse prognosis, according to the study of Gendron et al (2). Their findings were in line with earlier publications from smaller cohorts that found no link between APA and the severity of COVID-19 and/or VTE. The high frequency of stroke or VTE in COVID-19, mainly PE, is not usual and has been documented very infrequently in other viral infections such as influenza virus (2).

Recent studies showed COVID-19 patients have always had moderate to low-APA titers. In the study of Teuwen et al, APA test was conducted during the acute phase, while the guidelines advise against due to possible interference and accordingly, it is recommended to repeat the test after three months to avoid over diagnosis by grading transient APA positivity (23). It is discouraged in the guidelines that APA testing was performed during the acute phase due to the potential interference and it is also recommended to retest after three months to avoid over-diagnosis by classifying the APA transient positivity (16). It is noteworthy that heparin therapy was not an issue in the protocol of Teuwen et al for LA testing due to used reagents contained heparin neutralizers and anti-FXa activities, since LA testing were lower in anti-coagulated patients with heparin than the cut-off. Despite the limited sample sizes of both groups and the heterogeneity of the non-COVID-19 control group, recent research found that COVID-19 had a greater incidence of LA positive than any other acute infectious inflammatory illness; however, the latter was associated with increased VTE and/or death. During the acute phase of COVID-19, similar to the other viral infections, LA and APA tests are not advised and should not be conducted. On the other hand, biological validation should be required upon recovery (23).

In LA positive COVID-19 patients a significant higher risk of thrombotic events was existed, emphasizing the necessity of early identification for the improved management (24).

When it comes to the partial thromboplastin time (PTT), which a raise in COVID-19 patients, this might suggest the existence of LA. C-reactive protein (CRP) levels are high in most COVID-19 patients, and CRP has been reported to interact with PTT LA-based diagnostics such as the hexagonal phase phospholipid neutralization assay (STACLOT-LA) (25).

According to the research by Harzallah et al, 25 of 56 COVID-19 patients in a French cohort tested were positive for LA (13). Meanwhile, a young woman with an abrupt stroke who was later diagnosed with COVID-19 tested positive for LA was reported by Gemcioglu et al (24). They concluded that LA might be synergistically engaged in the incidence of thromboembolic events in this COVID-19 patient, with an elevated risk of thrombosis during the infection (24).

A trial research in which LA test was conducted on 262 patients hospitalized with COVID-19 in ten wards at the university of Strasbourg, 56 tested case were positive. During follow-up, five patients were excluded owing to direct oral anticoagulant medication. The follow-up appointment took 144 days (range from 129 to 179) following the COVID-19 diagnosis, which showed only three patients tested positive for LA (12).

Furthermore, the significant reduction in VWF: antigen ratio in some patients demonstrates that, the recovery from acute endothelial injury following acute COVID-19, indicating that thrombosis did not develop during follow-up (11).

Yarlagadda et al presented the case of a 31-year-old man hospitalized with COVID-19, complicated by co-bacterial empyema and requiring thoracoscopic surgery with decortication and prolonged prothrombin time in preoperative laboratories that was not corrected through mixing studies. More workup found positive LA and anti-cardiolipin IgM along with a change in the levels of other clotting factors. The patient received fresh frozen plasma and vitamin K treatment preoperatively and prophylactic-dose of low molecular weight heparin for VTE prophylaxis because of an uneventful surgical course and no thrombotic events was experienced while hospitalization. His prolonged aPTT was attributed to positive LA and anti-cardiolipin antibody that cause no bleeding but it may increase the risk of thrombosis (10).

On the other hand, the presence of venous and arterial thrombosis, observed in 3.7% of COVID-19 patients may alert the clinician to secondary aPL syndrome in these individuals (24).

Harzallah et al tested 56 COVID-19 patients for LA using PTT and dRVVT tests during the current COVID-19 epidemic in Malchus, France. Only five of the 50 patients (10 percent, three LA-related cases) tested positive for aCL or aB2GPI utilizing immunoglobulin G and immunoglobulin M detection, whereas twenty-five cases (45%) tested positive for LA (13).

Another related project introduced an 89-year-old man with history of advanced prostate cancer, hypertension and type 2 diabetes admitted with generalized weakness and COVID-19 positive test without symptoms. It was found a prolonged aPTT secondary to both a high titre of factor VIII inhibitor and positivity of LA. While most severe cases of COVID-19 are associated with raised factor VIII, CAC, DIC, or APAs, this report is a case of coagulopathy associated with COVID-19, which presented with a prolonged PTT, an LA and a high titer of factor VIII inhibitor. As we know, this is the first reported

case of the co-presence of factor VIII inhibitors and LA in COVID-19 (7).

In research by Gendron et al, 249 patients were admitted for suspected COVID-19, 154 cases with confirmed COVID-19. They showed a considerable increase in LA. These patients had higher level of fibrinogen and C-reactive protein. However, no association between LA positivity and increasing risk of VTE or nosocomial mortality was reported in the mentioned study (2).

On the other hand, in Bowles et al., Most COVID-19 patients hospitalized with increased aPTT were positive for LA (91%) and often had an associated factor XII deficiency (4).

Zhang et al reported three occurrences of ischemic stroke in COVID-19 patients without a history of APS with APA detected by anticardiolipin (aCL) and β 2 Glycoprotein I (B2GP1) (20). In addition, Harzallah et al reported 25 positive cases for LA and 5 for aCL or aB2GP1 in a French cohort of 56 COVID-19 patients (13). Unfortunately, no LA nor APAb were reported. Transient LA or APA positivity without clinical signs is occasionally related to acute infections. Generally, in symptomatic COVID-19 patients, LA discovery with or without aCL or aB2GP1 is associated with a considerable increase in the risk of thromboembolic events, highlighting the significance of early diagnosis for improving therapeutic management (21).

The pathophysiological mechanisms underlying diffuse micro thrombosis at the endothelial level, chronic reactive endothelium, the release of von Vwf and coagulopathy as symptoms of severe COVID-19, primarily with pro coagulation status with d-dimer value and thrombin, are well understood. All SARS-CoV-2 genetic variants have a strong thrombogenic potential, particularly in older individuals, measuring the rise in D-dimer and thrombin levels has predictive relevance (26).

vWF activity levels were randomly determined as more than 200 % in 17 patients in the restricted sample of Lopez Reboiro et al's study, which included 35 patients with severe SARS-CoV-2 pneumonia (upper limit of normal is 150%) (27). This discovery was consistent with Falcinelli et al.'s findings (11). The LA test was done, and the results in patients needing non-invasive mechanical ventilation were only marginally higher than those in patients requiring traditional oxygen treatment. LA levels larger than 1.1 IU were found in eight patients, four of whom needed noninvasive mechanical ventilation, whereas no patient with LA less than 1.1 IU required ventilatory assistance. These findings imply that, in addition to vWF and other thrombogenic molecules, including fibrinogen, thrombin, and beta-2-glycoprotein I (beta2-GPI), LA plays an essential role in SARS-CoV-2-induced thrombogenesis (11). Beta-2 GPI enhances LA activity and platelet adhesion, aggregation, tissue factor release, and coagulation cascade activation, resulting in hypercoagulation, which is typically irreversible in later stages (7). By directly interacting with the etiology of thrombosis in COVID-19, cytokine storms may improve the thrombotic response of platelets by boosting platelet production and inducing widespread micro thrombosis in diverse parts of the vascular network. High LA levels are linked to an increased risk of prothrombotic events, progression, the requirement for mechanical ventilation, and poor clinical outcomes. The combination of vWF and LA characteristics is a powerful tool for predicting hospitalization risk and determining whether patients are candidates for mechanical ventilation and even mortality risk (27).

## Autoimmune disease and LA effect in COVID-19

It was suggested an autoimmune mechanism by antiphospholipid antibodies to explain procoagulant status in SARS-CoV-2 disease (28). The high onset of ANA (antinuclear antibodies), along with other autoimmune markers, shows the involvement of autoimmune mechanisms in SARS-CoV-2 disease (29). Gazzaruso et al speculated on the significance of autoimmune processes in SARS-CoV pneumonia requiring hospitalization and therapy (3). LA might be a sign of an autoimmune disorder. Antinuclear antibodies seem to be identified often, and clinical indications of autoimmunity such as immune thrombocytopenia, autoimmune anemia, or both are common (16).

In these severe forms, systemic inflammation and procoagulant state are key pathophysiological factors that correlate well with disease severity and mortality. It is unclear if the procoagulant profile is caused by infection or as a result of infection. Autoimmune illnesses are marked by inflammation and, in some instances, a procoagulant state; in addition, viruses play a role in their progression. Antiphospholipid antibodies have been hypothesized as a mechanism to explain the status of procoagulants in SARS-CoV-2 illness (14).

The significant incidence of ANA and other autoimmune markers suggest that autoimmune processes are involved in SARS-CoV-2 illness. Furthermore, LAs may be linked to an elevated thrombotic risk characterized by cardiac involvement, pulmonary difficulties, and mortality in a substantial percentage of patients. On the other hand, it is not impossible that the LA limit readings discovered early in the hospitalization may be positive soon after. C-reactive protein, D-dimer, PT, and aPTT did not vary significantly between individuals with and without ANA or LA. The absence of a difference in d-dimer between individuals with and without LA is unexpected, but it might be due to two factors: inflammation influences D-dimer readings

and our study's cohort is small. A significant relationship between cardiac troponin and oxygen error and LA will be of clinical importance since it predicts a worsening course of pneumonia, marked by thrombotic complications and mortality. Specific research, however, is required to support this idea (3,28).

## Conclusion

In this review article, the authors tried to explain the role of inflammation in the pathogenesis of COVID-19 and their interactive impact and the increase in the incidence of thrombotic events in this pathological condition. Furthermore, various tests that can be used for determining the risk of thrombotic events in this situation was discussed. Among these, LA, as a factor than can be act as a sign of autoimmune diseases and introduced as a probable mechanism to explain the procoagulant state was surveyed. It seems that LA is an invaluable clinical biomarker for the diagnosis and prediction the prognosis of thromboembolism disorder in COVID-19 patients. However, Poor standardization, challenging interpretation of results, and frequently prescribed medication combinations impact LA detection, making laboratory diagnosis problematic. The dRVVT test, for example, may result in false-positive LA detection. furthermore, because there is no unique test for detecting LA, laboratory diagnosis is based on coagulation tests and diagnostic criteria. On the other hands, the assays for detecting LA are sensitive to the presence of CRP, which is increased in patients with systemic or pulmonary inflammatory disorders and is a limiting factor in this test in acute inflammatory illnesses. As a final result, there is a need for more cohort studies that include in this review study in order to judge more accurately about the role of LA in the prognosis prediction of thrombotic disorders.

## Authors' contribution

Conceptualization: AM.
Methodology: MM, AA.
Validation: FS.
Investigation: MM, AA.
Resources: MM, AA.
Data curation: MM, AA.
Writing-original draft preparation: MM, AA.
Writing-review and editing: FSH.
Supervision: MM, AA.
Project Administration: AM.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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