



Antiphospholipid syndrome in the era of COVID-19 – Two sides of a coin

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ABSTRACT

In addition to the respiratory symptoms associated with COVID-19, the disease has consistently been linked to many autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome (APS). APS in particular was of paramount significance due to its devastating clinical sequela. In fact, the hypercoagulable state seen in patients with acute COVID-19 and the critical role of anticoagulant treatment in affected individuals shed light on the possible relatedness between APS and COVID-19. Moreover, the role of autoimmunity in the assumed association is not less important especially with the accumulated data available regarding the autoimmunity-triggering effect of SARS-CoV-2 infection. This is furtherly strengthened at the time patients with COVID-19 manifested antiphospholipid antibodies of different types following infection. Additionally, the severe form of the APS spectrum, catastrophic APS (CAPS), was shown to have overlapping characteristics with severe COVID-19 such as cytokine storm and multi-organ failure. Interestingly, COVID vaccine-induced autoimmune phenomena described in the medical literature have pointed to an association with APS. Whether the antiphospholipid antibodies were present or de novo, COVID vaccine-induced vascular thrombosis in certain individuals necessitates further investigations regarding the possible mechanisms involved. In our current paper, we aimed to focus on the associations mentioned, their implications, importance, and consequences.

1. Introduction

In December 2019, a respiratory virus causing severe pneumonia with high morbidity and mortality led to an outbreak in China. Later on, the virus spread in a global fashion leading to a large-scale outbreak identified as the pandemic of severe acute respiratory syndrome. The causative agent, SARS-CoV-2 was designated as the responsible for the corona virus disease 2019 (COVID-19) [1]. The clinical presentation of COVID-19 has demonstrated great heterogenicity, ranging from asymptomatic infection to severe one with multi-organ failure [2]. With that mentioned, the most common presentation is flu-like symptoms such as fever, cough, dyspnea, and diarrhea to a lesser extent. Moreover, the clinical picture may escalate in some patients to acute respiratory distress syndrome (ARDS). The elderly showed greater mortality and risk of severe infection due to accompanying co-morbidities [3,4]. In addition, many patients developed a sequela of complications beyond the features of the disease, of importance are autoimmune-related ones. In some reports for instance, there were circulating autoantibodies in >50% of patients with moderate to severe COVID-19, pointing to a de

novo autoimmune sequela, such as antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) [5]. At the same time, the presence of autoimmune disease in patients infected with SARS-CoV-2 often worsened the course of the infection.

As of March 2020, the World Health Organization (WHO) declared the novel coronavirus disease to be a global pandemic urging countries into action [6]. By applying control means presented by quarantine and social distancing, the only promising plan was to develop an effective vaccine against the causative agent, SARS-CoV-2. Subsequently, according to the WHO, as of December 2020, 214 vaccine candidates were being developed, while 52 reached clinical trials [7]. Towards the end of the race, nine leading vaccines – manufactured by Pfizer-BioNTech [8], Moderna [9], Gamaleya [10], Novavax [11], Oxford-AstraZeneca [12], Sinopharm [13], Bharat Biotech [14], Johnson & Johnson [15], and Sinovac [13] – have been developed using viral S glycoprotein of the wild-type (WT) strain as the leading antigen. These vaccines more recently faced concerns of reduced effectiveness of neutralizing antibodies due to the emergence of 4 new variant of SARS-CoV-2, denoted as Alpha, Beta, Gamma, and Delta [16].

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Table 1
2023 ACR/EULAR antiphospholipid syndrome classification criteria.

Clinical criteria
1. Macrovascular (venous thromboembolism): including deep vein thrombosis of the legs/arms, pulmonary embolism, renal vein thrombosis, retinal vein thrombosis/occlusion, splanchnic thrombosis, and cerebral venous thrombosis.
2. Macrovascular (arterial thrombosis): including stroke, myocardial infarction (coronary artery disease), peripheral/splenic/retinal thrombosis, and other organ infarcts such as kidney, liver or spleen in the absence of visualized thrombus.
3. Microvascular: divided into:
A. <i>Suspected:</i> livedo racemose, livedoid vasculopathy lesions, antiphospholipid antibody (aPL) nephropathy, and pulmonary hemorrhage \geq confirmed by physical examination, or laboratory tests.
B. <i>Established:</i> livedoid vasculopathy, antiphospholipid antibody (aPL) nephropathy, pulmonary hemorrhage, adrenal hemorrhage or micro thrombosis, and myocardial disease (non-ST segment elevation MI with normal coronary angiogram, nonobstructive coronary arteries,) \geq confirmed by pathology report, imaging, or bronchoalveolar lavage for pulmonary hemorrhage.
4. Obstetric: pre-fetal death (preembryonic or embryonic loss), fetal death, preeclampsia with severe features (severe blood pressure elevation, visual disturbances, pulmonary edema, impaired liver function, renal dysfunction, thrombocytopenia), placental insufficiency with severe features (intrauterine fetal growth restriction, abnormal or non-reassuring fetal surveillance test, abnormal doppler flow velocimetry waveform analysis, severe intrauterine fetal growth restriction, oligohydramnios, or maternal vascular Mal perfusion on placental history).
5. Cardiac valve: valve thickening or vegetations.
6. Hematology: thrombocytopenia.
Laboratory criteria:
1. Lupus anticoagulant (LAC) assay: tested by coagulation based-functional assay.
• Two screening test systems: diluted Russel's viper venom time, and sensitive activated partial thromboplastin time.
• The LAC is considered positive if 1 of the 2 screening test systems is positive.
2. Anticardiolipin antibody (aCL), and anti-β_2-glycoprotein I antibody (anti-β_2 GPI): tested by solid-phased based assay.

Note: At least one clinical and one laboratory criteria is needed within 3 years of each other for the diagnosis.

Back to vaccines, the mRNA-1273 and BNT162b2 vaccines were developed by Moderna and Pfizer/BioNTech, respectively. These vaccines are nucleic acid-based ordering cells to produce a specific protein not the whole virus. Actually, no gene-based vaccines had been approved before the COVID-19 outbreak [17]. Interestingly, the mRNA is known for its instability and high innate immunogenicity, therefore, to counteract this shortcoming two proline subunits were added to one of the subunits. Another type is viral vector vaccines, those that use a virus molecule containing nucleic acid encoding an antigen to deliver target viral proteins. The viruses induce an immune reaction to the proteins without causing harm or infection. The following vaccines were developed using adenovirus vectors: AZD1222 or ChAdOx1 nCoV-19 by Oxford-AstraZeneca, Sputnik V by Gamaleya, and Ad26.COV2.S by Johnson & Johnson [18–20].

Following vaccination, the resultant humoral immunity successfully prevented severe COVID-19 presentation in the majority of vaccinated individuals [21]. Of course, vaccine related side effects such as localized pain [22] or fever and headache [23] were experienced by many patients upon mass vaccination programs. To notice, these adverse effects were prevalent in patients with autoimmune diseases [24]. Furthermore, several reports started pointing out the possible association of autoimmune disorders after vaccination such as vaccine induced immune thrombotic thrombocytopenia [25], IgA vasculitis [26], Guillain-Barre syndrome [27], lupus nephritis [28]. Such reactions affected women and younger adults more severely [29], in conjunction with the population most susceptible to autoimmune diseases such as SLE and APS [30].

2. Antiphospholipid syndrome

APS is an autoimmune multisystemic disorder characterized by the presence of antiphospholipid antibodies (aPL) including lupus anticoagulant, anticardiolipin, and anti-beta 2 glycoprotein I [31]. Although aPL are the hallmark of APS, they are seen in approximately 15% of healthy individuals and reaching up to 50% in elderlies with chronic diseases [32]. The syndrome is a common cause of acquired hypercoagulability and it frequently presents with pregnancy complications such as recurrent early miscarriages, and thrombotic events including arterial, venous, or microvascular thrombosis [33]. The risk of developing thrombotic or thromboembolic events is higher in patients with positive lupus anticoagulants (LA) antibodies, and it becomes much higher in patients with three antiphospholipid antibodies, a condition named “triple positivity” [34]. Although thrombosis is a lineament

feature of APS; around 10% of affected patients present with major bleeding. This percentage is increased when accompanied with several factors like renal impairment and increased age [35].

The diagnosis of APS, which was recently updated, is based on the 2023 ACR/EULAR antiphospholipid syndrome classification criteria including two components [36]. The first component is the laboratory criteria which includes positive lupus anticoagulant (LAC) confirmed by coagulation based functional assay, or positive IgM/IgG anticardiolipin antibody or IgM/IgG anti- β_2 -glycoprotein I antibody detected by solid-phase based assay. In addition, other antiphospholipid antibodies such as anti-phosphatidylserine/prothrombin, domain-specific anti-beta 2 glycoprotein I, annexin A5 and IgA isotopes are frequently seen in APS, but they are not included in the diagnostic criteria. The second component is the clinical criteria including 6 domains: Macrovascular (venous thromboembolism), macrovascular (arterial thromboembolism), microvascular, obstetric, cardiac valve, and hematological manifestations. The classification also requires the presence of clinical criteria within 3 years of the positive antiphospholipid antibodies.

The criteria for the diagnosis of APS are illustrated in Table 1.

3. COVID-19 versus APS

While the incidence of COVID-19 was rising throughout the pandemic, many manifestations other than the characteristic respiratory symptoms of COVID-19 began to appear. In terms of immune reactions, SARS-CoV-2 infection could overwhelm the immune system so host damage may occur throughout the cytokines produced, also known as cytokine storm with multiple organ failure (MOF) [37,38]. The damage may be also explained by the increased tendency of coagulation in reaction to the systemic inflammation [39]. It has been shown that the usage of coagulation parameters, such as D-dimer, in COVID-19 aids in determining the prognosis of patients. For instance, increased D-dimer and PT with decreased platelets and fibrinogen meeting the diagnostic criteria for disseminated intravascular coagulation (DIC) resulted in high mortality of COVID-19 patients [40]. Similarly, MOF occurred more often in patients with coagulopathy. Subsequently, anticoagulant treatment has been shown to reduce mortality in patients with COVID-19 [41,42]. Therefore, most clinicians agreed on using low molecular weight heparin (LMWH) in severe and critically ill COVID-19 patients. LMWH therapy has contributed to a decrease in mortality rates as well as evidence of anti-inflammatory and protective effects on the endothelium [43]. Importantly, around 20–50% of hospitalized COVID-19 patients showed abnormalities in coagulation tests (thrombocytopenia,

prolonged PT test, elevated D-dimer and low fibrinogen levels) presenting mostly as thrombotic events (specifically venous thromboembolism) rather than hemorrhagic ones [44]. The coagulopathy described in COVID-19 resembles to a great extent the abnormalities seen in APS, particularly higher incidence of venous thrombosis [45]. While thrombotic state does not indicate high platelet count; low platelet count reflects the severity of the coagulopathy caused by consumption and thrombin generation [46]. Thrombocytopenia was reported in 22–42% of APS patients, and in >35% of COVID-19 patients on admission [47,48]. Of importance, a decrease in platelet count was observed in all patients who later developed catastrophic APS. The main cause of thrombocytopenia was illustrated to be mostly caused by binding and activation rather than destruction of platelets [31]. In COVID-19, the systemic inflammation and cytokines were found to impair hematopoietic microenvironment causing thrombocytopenia. Other proposed mechanisms were direct viral invasion of hematopoietic stem cells and megakaryocytes, or antiviral antibodies cross reacting with hematopoietic cells and platelets [49].

In terms of coagulopathy, COVID-19 related hypercoagulability mostly resulted from SARS-CoV-2 infection activating many signaling pathways in immune cells eventually leading to cytokine release, complement and coagulation cascade activation, NETosis, TF secretion, fibrinolysis, and platelet recruitment [50–52]. Moreover, activation of endothelial cells to acquire a pro-thrombotic status could also result from direct viral activation or antiviral immune response. The detection of aPL in patients with COVID-19 further complicates the consequent condition by strengthening the linkage between inflammation and coagulation [53]. The latter is achieved by many mechanisms, the most important one is aPL adherence to monocytes and endothelial cells stimulating the expression of adhesion molecules and tissue factors, which play an important role in starting the coagulation cascade [54].

4. aPL in infection and vaccination

The detection of aPL in patients with various infections has drawn the attention to infectious agents as possible inducers of APS when genetic predisposition is present [55]. Molecular mimicry, the loss of immune system tolerance to body tissue during infection due to structural and sequential similarities between host and pathogenic peptides, is the main mechanism described in this regard. Molecular mimicry has been described as the mechanism of various autoimmune diseases other than APS such as Guillain-Barré syndrome (GBS), rheumatoid arthritis (RA), myocarditis, inflammatory bowel disease, and multiple sclerosis [56]. Among others, the most known infections associated with APS are rubella virus, toxoplasma, and HIV infections [57,58]. Interestingly, aCL, the most frequently encountered antibodies in viral infections especially HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV), are rarely associated with anti- β 2GPI and therefore have lower risk and incidence of thrombosis and other hematological manifestations of APS [59]. Recently the same correlation was reported in SARS-CoV-2 infection [54]. Following a paper reporting the presence of aPL in three COVID-19 patients with thrombotic events [60], many similar studies followed. According to published data, 5–71% of patients with COVID-19 had positive aPL with an incidence reaching up to 90% among ICU patients. Exclusion of aPL not included in the classification criteria of APS justified the variations in the prevalence of aPL among the studies [61–64]. Furthermore, results from studies analyzing aPL not included in the classification criteria, showed similar prevalence, with an even higher prevalence in some studies, of extra-criteria aPL compared to the ones used in the criteria [44]. LA had the highest incidence, seen in approximately 50% of patients, after which comes aCL and β 2GPI, whereas 25–50% of patients showed double positivity. Meanwhile, patients with double positivity were more prone to ischemic stroke.

In terms of pathogenesis, the presence of aPL in patients with COVID-19 was linked to two mechanisms: molecular mimicry and neopeptide formation, previously reported in medical literature [65]. Few studies

suggested that aPL in COVID-19 patients are different from the ones in APS patients. As an example, the domain I of β 2GPI, which is the main target of β 2GPI antibodies found in APS and highly related to the thrombotic events, is only detected in 5% of COVID-19 patients with aPL positivity. Furthermore, low levels of β 2GPI were more associated with ventilatory failure, sepsis, and mortality in the ICU [66]. The fact that the presence and persistence of aPL only rarely lead to thrombotic complications, suggests that the coexistence of inducing factors, mostly infections, malignancies or other procoagulant conditions, is crucial for the complications to take place [67].

Along with the same mechanism, vaccines against related infectious agents may be able to induce aPL. Some studies have detected aPL in individuals following vaccination against tetanus toxoid, seasonal influenza, and human papillomavirus [68–71]. Concomitantly, the administration of COVID-19 vaccine has been suspected through the same lens. Several months after the mass COVID-19 vaccination campaigns, concerns were raised as to a possible link between unexpected thromboembolic events and the vaccines [72]. More specifically, younger patients suffered from venous thrombosis, while older patients commonly had arterial thrombotic events [53]. This difference in correlations is indeed parallel to APS thrombotic presentations. The similarity of the thrombotic pattern may account for the blood clots after vaccination, in the presence of pre-existent or newly synthesized aPL. Although aPL have been detected in COVID-19 patients, their role in thrombogenesis is still being investigated [60,73,74]. Plausible hypotheses include molecular mimicry, especially known to the adenoviral vector-based vaccines [72]. The generation of antibodies directed against microbial epitopes may cross-react to be directed against self-epitopes, including protein-phospholipid complexes. Likewise, in asymptomatic patients having pre-existent aPL, infections may trigger pro-inflammatory cascades promoting the development of a full-blown APS [53]. Alongside, other suggested mechanisms were proposed for the incidences of thrombosis according to the type of COVID-19 vaccine. One hypothesis for both mRNA and adenoviral vaccines is the possibility of type I interferon production triggering aPL formation leading eventually to a thrombotic event after vaccination [75]. Of importance, adenoviral vector-based vaccines bind to platelets causing their destruction inducing thrombocytopenia along with platelet activation [72]. On March 2021 the EMA Safety Committee announced that the ChAdOx1-S vaccine manufactured by AstraZeneca may be associated with increased risk of thrombocytopenia and thrombosis. Throughout the European Union, several cases of blood clot development in unusual vascular districts, like the mesenteric vein or cerebral venous sinus, were reported in otherwise healthy individuals following the administration of the vaccine [76]. Interestingly, these events occurred in women <50 years of age [77]. Similarly, several rare blood clots formed in young females after the vaccination with the Johnson & Johnson adenoviral vector-based COVID-19 vaccine halted the vaccination campaign in the U.S. [78].

Although the clinical trials for mRNA type vaccines demonstrated no safety issues related to thrombotic events [9,79], extracellular RNA, no matter the type [80], has been associated with a procoagulant status, such as the high amounts of extracellular RNA in sepsis or cancer [81,82]. In one case report, a 66-year-old woman developed deep vein thrombosis 1 day after the second dose of the BNT162b2 mRNA vaccine [83]. Similarly, a 64-year-old female with history of several autoimmune diseases including Raynaud's disease and Sjogren's syndrome, developed severe fingertip necrosis following the first dose of BNT162b2 mRNA [84]. During investigations aPL directed against phosphatidylserine (aPL-PS) was detected in addition to cryoglobulins, and high antinuclear antibodies (ANA) titers making the authors conclude the development of SLE and APS in the presented patient. In a more severe case, a 27-year-old female developed acute renal failure and DIC 36 h after the first BNT162b2 vaccine dose [85]. Interestingly, this patient had a documented presence of aCL and anti- β 2GPI antibodies several years earlier. Finally, catastrophic APS (CAPS) was diagnosed based on the clinical

Table 2
Studies reported in medical literature pointing or concluding an association between COVID-19 and APS.

Author	Year	Study type	Aim of the study	No. of patients	Result
Liao et al. [46]	2020	R	Patients with coagulation imbalance in COVID-19	380	55 patients died; 30% of them had thrombotic embolic event.
Guan et al. [47]	2020	R	COVID-19 clinical lab values	1099	36.2% had thrombocytopenia
Bowles et al. [61]	2020	R	Lupus anticoagulant in COVID-19 patients	44	91% of patients with prolonged aPTT had lupus anticoagulant
Gazzaruso et al. [62]	2021	R	Lupus anticoagulant in hospitalized COVID-19 patients	192	49.5% had positive lupus anticoagulant
Siguret et al. [63]	2020	P	Antiphospholipid antibodies in critically ill COVID-19 patients	74	88% of patients had 1 or more of the antiphospholipid antibodies
Zuo et al. [64]	2020	R	Prothrombotic antibodies in hospitalized COVID-19 patients	172	52% were positive for at least 1 aPL antibodies 2/3 detected were moderate to high titers
Schrijver et al. [66]	2020	P	Beta-2-glycoprotein I as biomarker for sepsis in ICU	313	B2GPI levels were lower in sepsis patients than patients without sepsis
Hamadé et al. [73]	2021	R	Incidence of antiphospholipid antibodies in COVID-19 patients	41	17% tested positive for aPL
Harzallah et al. [74]	2020	R	Lupus anticoagulant in severe COVID-19 patients	56	45% were positive
Ott et al. [89]	2023	P	Antiphospholipid antibodies profile in APS patients after COVID-19 infection and/or vaccination	82	No increases in aPL in the total study population were detected.
Steinberg et al. [94]	2021	Case	PET/CT findings in SIRS after COVID-19 vaccine	1	Multiple pulmonary nodules, axillary, and splenic uptake with no malignancies or infections
Klok et al. [105]	2020	R	Incidence of thrombotic complications in critically ill ICU patient of COVID-19	184	31% incident of thrombotic complication in COVID-19 patient
Wright et al. [106]	2020	R	Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 patients	44	A complete lack of lysis of clot at 30 min was seen in 57% of patients; patients with no lysis of clot at 30 min and a d-dimer >2600 ng/mL had a venous thromboembolic event rate of 50%
Lippi et al. [108]	2020	R	Thrombocytopenia association with a more severe COVID-19 course	1779	The pooled analysis revealed that platelet count was significantly lower in patients with more severe COVID-19
Xu et al. [111]	2020	R	Suppressed T cell-mediated immunity in patients with COVID-19	187	a significant decrease of T lymphocyte subset is positively correlated with in-hospital death and severity of illness.
Su et al. [116]	2020	R	pathologic examination of kidney damage in critically ill patients with COVID-19	26	9 showed clinical signs of kidney injury that included increased serum creatinine and/or new-onset proteinuria

R: retrospective, P: prospective, APS: antiphospholipid syndrome, CAPS: Catastrophic APS, aPL: antiphospholipid antibodies, aPTT: activated partial thromboplastin time.

features and appropriate treatment resulted in recovery except for the kidneys. In addition, new onset SLE and secondary APS were reported in 42-year-old woman 2 weeks following the first dose of the BNT162b2 COVID-19 vaccine [30,86]. Furthermore, 4 patients with pre-existing APS developed thromboembolic events several days after the second dose and 1 after the first dose of BNT162b2 vaccine [87].

Actually, there are a couple of mechanisms by which RNAs can promote a pro-coagulant state. One of which, RNA can directly be a substrate for protease activation of coagulation factors XI and XII initiating the coagulation cascade [88]. Additionally, intact endothelium secretes RNases that help to prevent cascade activation by foreign or self RNA released during infections or cell damage [89]. The mRNA may also interact with pattern recognition receptors in the cytosol and endosomes triggering a type 1 IFN response [90]. This type of IFN signature has been related to primary and SLE-related APS [91]. Several reports showed the cytokine release effects after mRNA vaccination by detecting 18F-fluorodeoxyglucose activity on PET/CT in lymph nodes as well as systemically [92–94]. Therefore, the pro-inflammatory background may act as the “second hit” to asymptomatic patients with aPL, precipitating the development of APS.

5. CAPS and COVID-19

A life-threatening form of APS, catastrophic antiphospholipid syndrome (CAPS) is seen in approximately 1% of patients with APS, mostly females [31]. Although rare, it is associated with high mortality rates reaching up to 40%. CAPS is characterized by simultaneous multiorgan system thromboses [95]. This severe form of APS can be the initial presentation in 50% of patients with APS. Several studies analyzing patients with CAPS events stated that around 70% of the cases had

additional risk factors, most of which were infection, surgery, cancer, estrogen usage, pregnancy or postpartum, and active SLE [95,96]. Among various triggering factors, CAPS attacks have been consistently linked to infections, both bacterial and viral [97]. Infections, especially upper respiratory tract, have preceded CAPS in 6 out of 8 patients, one study reported [98]. Although cerebral involvement is the most common cause of death in CAPS; infections were also implicated as a cause of mortality in up to 17% of patients [99].

As CAPS is on the severe end of the spectrum of APS, COVID-19 has demonstrated heterogeneity with severe respiratory distress followed by multi-organ failure at its severe form as well. Thus, there seem to be a significant overlap in the clinical manifestations between CAPS and severe COVID-19 [54]. Actually, adjoining COVID-19 under the umbrella of hyperferritinemic syndrome beside CAPS, adult-onset Still's disease, macrophage activation syndrome, and sepsis supports the presented faces of the same coin [100]. Overall, CAPS possesses a pro-inflammatory state by releasing various cytokines leading to a pro-thrombotic state and severe inflammatory response syndrome (SIRS) similar to the cytokine storm seen in COVID-19 [101]. In terms of pathophysiology, CAPS was described as a “thrombotic storm” where multiple thrombi occur over a brief period resulting in predominantly macrovascular thrombosis [102,103]. Similarly, the pathophysiology of severe COVID-19 contains various microvascular and macrovascular thromboses [104,105]. It has been reported that the thrombotic risk in COVID-19 is due to the downregulation of fibrinolysis; however, increased fibrinogen levels were described as well in critically ill patients [106]. The latter findings along with the associated thrombocytopenia and elevated D-dimer levels encountered in severe COVID-19 patients [107,108], typically resemble the thrombotic microangiopathy in patients with CAPS [101,109]. The production of cytokines,

particularly TNF- α and IL-6, has been related to lymphopenia in addition to other mechanisms such as exhausting or directly infecting T-cells [110]. Some studies compared lymphocyte subsets in COVID-19 patients with mild ARDS and critically ill patients. The concerned papers illustrated lower CD4+ T-cells in severely ill patients [111,112], which are analogous to the CD4+ T-cell depletion documented in APS [113]. Another important manifestation reported in up to 7% of COVID-19 patients is acute kidney injury [114,115]. Meanwhile, three cases of 26-autopsy series in COVID-19 patients revealed fibrin thrombi within the glomerular capillaries along with ischemia [116], similar to autopsy findings described in CAPS [117].

Papers described in medical literature in correlation with COVID-19 and APS are presented in Table 2.

6. Conclusion

The hypercoagulability state SARS-CoV-2 infection induces and the need for anticoagulant treatment in patients with COVID-19 draws the attention to a possible link between APS and COVID-19. If viewed from pathophysiological aspects, the presence of antiphospholipid antibodies, of various types, in patients with COVID-19 makes this association stronger. Furthermore, similar features such as thrombocytopenia and multi-vessel thrombosis documented in severe COVID-19 overlap significantly with the severe form of APS, the CAPS. Whether aPL were present or not prior to infection, SARS-CoV-2 infection and COVID vaccines were able to produce aPL in certain individuals. The induction of aPL along with the characteristic symptoms of APS show a secondary APS in process. As vaccine-induced thrombosis mechanisms were previously reported, some vaccine programs were halted for further investigations. Although some vaccines showed several mechanisms of inducing thrombosis; others caused thrombosis by providing a proinflammatory environment. This second hit theory of inflammation with aPL could precipitate APS. While more in-depth investigations are needed to draw firmer conclusions; a presumed connection between COVID-19 and APS deserves clinical awareness in the time early detection, treatment and prevention are critical taking into consideration the deleterious consequences of APS and CAPS.

Declaration of competing interest

The authors declare no conflict of interests.

Data availability

No data was used for the research described in the article.

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