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Review

Anti-phospholipid syndrome and COVID-19 thrombosis: connecting the dots

Moon Ley Tung [1,2,*], Bryce Tan[3], Robin Cherian[2,4] and Bharatendu Chandra[2,5,*]

Abstract

As the coronavirus disease 2019 (COVID-19) pandemic, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is spreading rapidly worldwide, it has emerged as a leading cause of mortality, resulting in >1 million deaths over the past 10 months. The pathophysiology of COVID-19 remains unclear, posing a great challenge to the medical management of patients. Recent studies have reported an unusually high prevalence of thromboembolic events in COVID-19 patients, although the mechanism remains elusive. Several studies have reported the presence of aPLs in COVID-19 patients. We have noticed similarities between COVID-19 and APS, which is an autoimmune prothrombotic disease that is often associated with an infective aetiology. Molecular mimicry and endothelial dysfunction could plausibly explain the mechanism of thrombogenesis in acquired APS. In this review, we discuss the clinicopathological similarities between COVID-19 and APS, and the potential role of therapeutic targets based on the anti-phospholipid model for COVID-19 disease.

Key words: COVID-19, thrombosis, anti-phospholipid antibodies, anti-phospholipid syndrome, autoimmunity, molecular mimicry, oxidative stress, anticoagulation

Key messages

- There is an unusually high prevalence of thromboembolic events in COVID-19 patients, involving both the arterial and the venous circulation.
- Clinical and pathological features of COVID-19 thrombosis resemble APS.
- Acquired APS, via molecular mimicry and endothelial dysfunction, could plausibly explain thrombogenesis in COVID-19.

REVIEW

Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected 36 361 054 people worldwide, resulting in 1 056 186 deaths as of 9 October 2020 [1]. ARDS leading to multi-organ failure has been described as the major cause of mortality in COVID-19 [2, 3]. Recently, several studies have reported an unusually high incidence of thrombotic complications associated with COVID-19, implicating a potential role of thrombotic complications in mortality [4, 5]. However, the exact mechanism for thromboembolic manifestations in COVID-19 has yet to be elucidated.

The association of viral infections with the presence of aPLs is well described in the literature. Individuals infected with viruses such as HIV, HBV, HCV, EBV and Parvovirus B19 are commonly associated with this condition [6]. However, there have been limited data linking aPLs with coronavirus infections.

[1]Department of Hematology and Oncology, National University Cancer Institute, [2]Yong Loo Lin School of Medicine, National University of Singapore, [3]Department of Medicine, National University Hospital, [4]Department of Cardiology, National University Heart Centre Singapore and [5]Division of Neurology, Department of Medicine, National University Hospital, Singapore, Singapore

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Correspondence to: Moon Ley Tung, Department of Hematology and Oncology, National University Hospital, 1E Kent Ridge Road, NUHS Tower Block, Level 7, Singapore 119228, Singapore.
E-mail: moon_ley_tung@nuhs.edu.sg

*Moon Ley Tung and Bharatendu Chandra contributed equally to this study.

An earlier study reported the presence of aCL in convalescent severe acute respiratory syndrome (SARS), which is caused by SARS-CoV, in patients with osteonecrosis [7]. Regarding SARS-CoV-2, a study reported the presence of aPLs in three patients who presented with strokes [8]. Subsequently, three larger studies found LA positivity rates of 91%, 87.7% and 45% amongst 34, 57 and 56 COVID-19 patients, respectively [9–11]. A more recent study found aPLs in 52% of 172 COVID-19-positive samples and demonstrated the potential thrombogenicity of these antibodies using mouse models [12]. Although these studies have described the presence of aPLs in coronavirus infections, the exact mechanisms of antibody formation and associated pathogenicity remain unclear. Additionally, it is debatable whether the presence of aPLs is the cause or an epiphenomenon of thromboembolic events in COVID-19 patients.

In this review, we discuss the pathogenesis of thromboembolic manifestations in COVID-19 using an APS model, highlighting similarities in the clinical and pathological features of severe COVID-19 and catastrophic APS (CAPS), and its implication in the treatment of COVID-19.

APS and COVID-19

APS is an autoimmune prothrombotic disease characterized by persistently elevated aPLs, resulting in recurrent arterial and venous thromboembolic events [13]. In women, APS can be associated with pregnancy-related complications, such as eclampsia, pre-eclampsia and recurrent miscarriages [14]. APS is diagnosed by the presence of any of the clinical criteria described above along with a positive laboratory test for at least one specific antibody [14], which includes aCL, LA antibodies and anti-β_2-glycoprotein I antibodies [15]. LA antibodies are identified through a coagulation-based assay, where they demonstrate prolongation of a phospholipid-dependent clotting time [16]. aCLs and anti-β_2-glycoprotein I antibodies are detected by immunoassays that measure reactivity to cardiolipin, a phospholipid, and β_2-glycoprotein I, a phospholipid-binding protein, respectively [17].

Although aPLs are associated with APS, the prevalence of the presence of aPLs varies from 1–5% in healthy young individuals [18] to ~50% in elderly individuals with chronic diseases [19]. The pathogenesis of APS remains elusive owing to the marked heterogeneity in clinical manifestations. Some patients with aPLs remain asymptomatic, others may develop spontaneous thrombosis of large vessels affecting a single site, whereas a small proportion may develop rapidly progressive, life-threatening, multi-organ microvascular thromboses.

CAPS is a rare and severe form of APS. Initial descriptions of CAPS had ≤50% mortality rate; therefore, the prefix catastrophic was used for this form of APS [20]. The diagnostic criteria for CAPS include multiple organ dysfunction developing over a short span of time, histopathological evidence of multiple small vessel occlusions and high titres of aPLs [21]. Histopathological confirmation may not be possible in most CAPS patients owing to the severity of the illness and associated coagulopathy [22]. The international CAPS registry (https://ontocrf.grupocostaisa.com/web/caps/home) has played a pivotal role in the development of diagnostic algorithms, classification criteria and therapeutic guidelines for CAPS [21, 23, 24]. Nearly half of the cases in this registry reported bacterial or viral infections as the main inciting factor, followed by surgical procedures and malignancies [24].

Pathogenesis of aPLs in COVID-19

Coronaviruses have four structural proteins: spike (S), membrane (M), envelope (E) and nucleocapsid (N) [25]. The trimeric, transmembrane S glycoprotein, consisting of two subunits, determines the diversity of the virus and host tropism [26]. The S1 subunit is responsible for the attachment of the virus to the host cell receptor, and the S2 subunit assists in the fusion of the viral capsid with the host cell membrane [27]. Once bound to the receptor, the S protein undergoes host protease-mediated cleavage, resulting in endocytosis of the virus particle. Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor that allows the binding of SARS-CoV-2 to its host cells [28]. What is unique in SARS-CoV-2 compared with SARS-CoV is the presence of a furin-like cleavage site (^{682}RRAR/S^{686}) at the S1/S2 site, which allows complete separation from the viral capsid [29].

We postulate that the generation of aPLs in individuals infected with SARS-CoV-2 could be explained by two possible mechanisms that are not mutually exclusive: molecular mimicry and neoepitope formation. The first possibility is that the S1 and S2 subunits of S protein might form a phospholipid-like epitope that induces the generation of aPLs [30]. Antibodies generated against these phospholipid-like determinants of SARS-CoV-2 and other similar viruses can trigger an immunogenic response if those determinants are shared with native tissues [31]. The other possibility is that the conformation of β_2-glycoprotein I in host cells is changed owing to oxidative stress caused by SARS-CoV-2 [32, 33], creating a neoepitope for the antibody generation [34]. β_2-Glycoprotein I is a plasma protein that is crucial in maintaining haemostasis and is the most common target of pathogenic aPLs [35]. Various groups have demonstrated that oxidative stress is increased in APS [13, 36, 37], which can lead to a disulfide bond formation in domains I and V of β_2-glycoprotein I through the thiol exchange reaction [38]. As a result, the corresponding conformational change in the β_2-glycoprotein I exposes the crucial B cell epitope, making it immunogenic [13].

aPLs are not thrombogenic *per se*, as previously demonstrated in animal models [39], which indicates that if aPLs are a part of the pathogenic pathway, there must

be additional factors [40]. A similar two-hit hypothesis could possibly explain the activation of thrombogenesis in the context of SARS-CoV-2 infection [40]. The potential second hit might be triggered by endothelial injuries [41, 42] caused by SARS-CoV-2 infection that result in further disruption of the redox balance owing to increased production of reactive oxygen species by macrophages and endothelial cells [32, 33]. Pathologically, the virus downregulates the antioxidant pathway by inhibiting ACE2, nitric oxide and endothelial nitric oxide synthase pathways [32, 33]. The loss of these protective antioxidant pathways results in thrombus generation and activation of the coagulation cascade [39].

Mechanism of thrombosis in COVID-19 by anti-phospholipid model

aPLs in COVID-19 patients can cause thrombosis by several possible mechanisms (Fig. 1). First, they can induce the expression of adhesion molecules and tissue factor by binding to endothelial cells and monocytes [43]. Tissue factor is an inducible membrane glycoprotein that plays a major role in initiating the coagulation cascade [44] and fibrin deposition in immunological and inflammatory conditions [45]. These antibodies can also upregulate IL-6, IL-8 and VEGF and induce nitric oxide synthase [46]. Mechanistically, these processes are mediated by p38 mitogen-activated protein kinase (MAPK) phosphorylation and nuclear factor-κB activation [47].

Second, oxidative stress [13] and mitochondrial dysfunction [48] might have a major role in thrombogenesis in APS. aPLs can induce nitric oxide and superoxide production, resulting in increased production of a pro-oxidant molecule, peroxynitrite [49]. Concomitantly, these antibodies can result in reduced activity of paraoxonase, an antioxidant enzyme, culminating in oxidative damage to lipid and proteins [37]. The uptake of aPLs into the endosome activates NADPH oxidase and generates superoxide, which upregulates the expression of Toll-like receptors 7 and 8 and sensitizes the cells to these ligands [50]. The disruption of the redox balance through the production of reactive oxygen species by monocytes and neutrophils, accompanied by a reduction in the antioxidant capacity and the observed mitochondrial dysfunction, lead to pro-inflammatory and prothrombotic states in patients with APS [48].

Third, aPLs can also activate platelets, with increased expression of glycoprotein IIb–IIIa [51] and synthesis of thromboxane A2 [52]. This results in platelet aggregation through stimulation with suboptimal doses of adenosine diphosphate, thrombin, collagen or thrombin receptor agonist peptide [51]. Moreover, increased levels of thromboxane A2 can further promote platelet aggregation and vasoconstriction [53].

Fourth, anti-β_2-glycoprotein I autoantibodies can disrupt the annexin A5 shield, predisposing to vascular thrombosis and pregnancy loss in APS [54]. Annexin A5 is found in placental and vascular endothelium and functions as an anticoagulant protein [55].

Finally, aPLs can induce complement activation to generate complement split products that attract inflammatory cells to initiate thrombosis and further tissue injury. Activated complement fragments can induce a procoagulant phenotype by direct action through the C5b-9 (membrane attack complex) [56] or the C5a receptor-mediated effects [57].

CAPS and severe COVID-19

Pathological similarities

CAPS can present with features akin to severe sepsis because both these conditions exhibit a pro-inflammatory state represented by elevated levels of cytokines, such as TNF-α, IFN-γ and IL-1 [22]. This process leads to a prothrombotic state and the development of a systemic inflammatory response syndrome.

Occasionally, the term thrombotic storm is used to describe hypercoagulability in patients who progress from a single thrombosis to multiple thromboses at various sites over a short span of time [58]. The putative mechanism involves activation of the coagulation cascade with enhanced thrombin generation mediated by thromboplastic substances and procoagulant proteins released from injured tissues [58]. Concurrently, the downregulation of innate thrombin inhibitors and the fibrinolytic system culminates in further progression of thrombogenesis. Most patients with a thrombotic storm have raised ESR, CRP, fibrinogen and factor VIII levels, consistent with an acute inflammatory state [59]. The pathophysiology of CAPS is similar to that of thrombotic storm, indicating a disease continuum, whereby thrombotic storm predominantly results in macrovascular thrombosis [60]. The pathological features of severe COVID-19 encompass microvascular and macrovascular thromboses, suggesting a spectrum similar to CAPS and thrombotic storm [4, 5]. Additionally, it has been reported recently that the downregulation of fibrinolysis is a main contributor to thrombotic manifestations in severe COVID-19 [61].

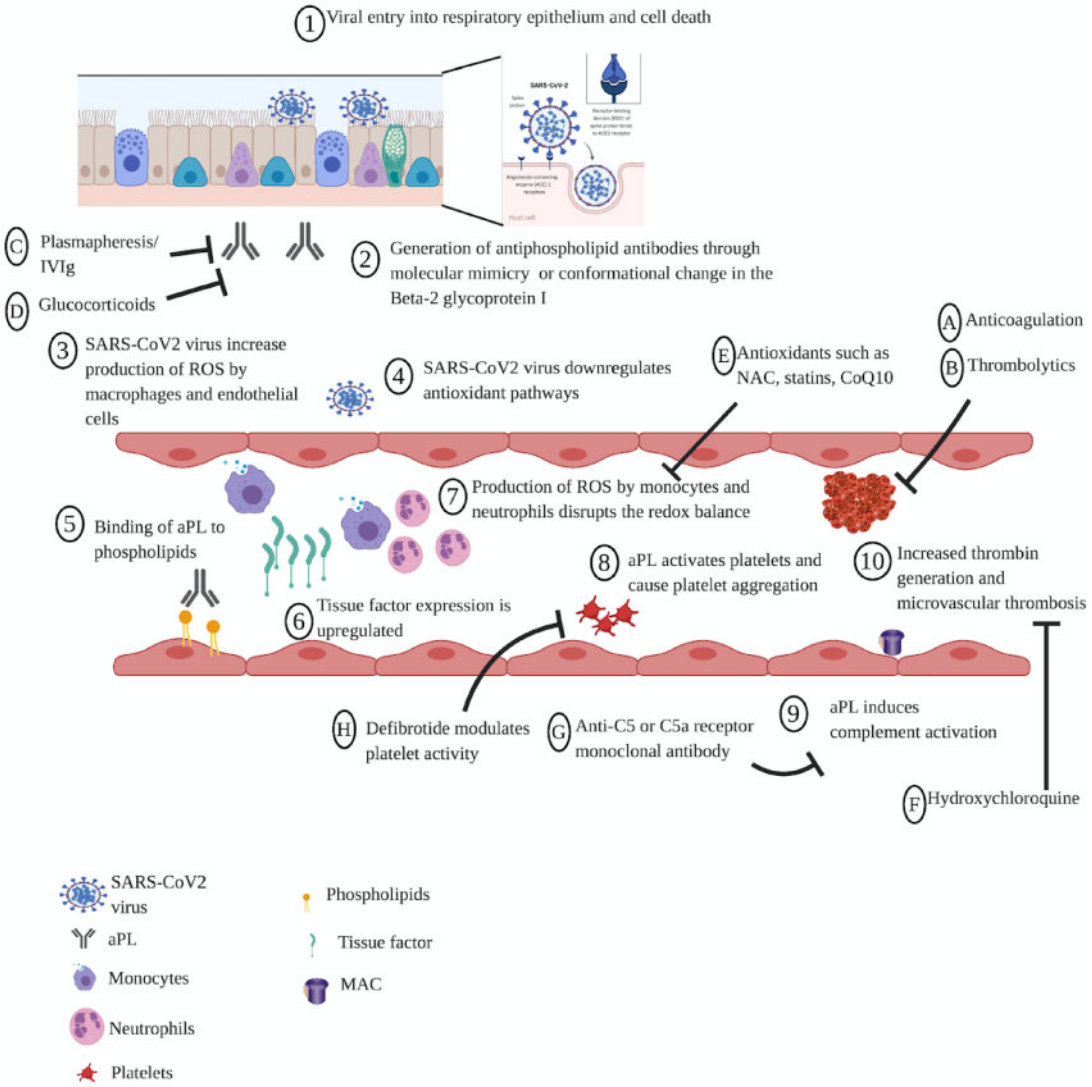
Clinical similarities

The myriad of clinical presentations seen in patients with severe COVID-19 bear uncanny resemblances to those of patients with CAPS. COVID-19 patients present with a range of clinical manifestations from asymptomatic to mild upper respiratory symptoms to severe respiratory distress, culminating in multi-organ failure. The significant overlap between clinical manifestations of severe COVID-19 and CAPS is summarized in Table 1.

Venous thromboembolism

The clinical features seen in COVID-19 respiratory failure mirror what would be expected of progressive *in situ* thrombosis in the lung [85, 86]. Observational studies revealed a very high incidence of pulmonary embolism in critically ill COVID-19 patients (87% in a cohort of 75 patients) [66], compared with previous reports of

Fig. 1 Proposed mechanisms of APS pathophysiology and potential therapeutic targets in coronavirus disease 2019



Pathophysiological mechanism of coronavirus disease 2019 (COVID-19). Viral infection of the respiratory epithelium results in endothelial damage, which triggers the production of aPLs, either through molecular mimicry of the SARS-CoV-2 with the innate β_2-glycoprotein I or with the generation of a neoepitope resulting from oxidative stress leading to a conformational change in the β_2-glycoprotein I. The SARS-CoV-2 induces the production of reactive oxygen species (ROS) by monocytes and endothelial cells and suppresses the antioxidant pathways at the same time. aPL binds to phospholipids and upregulates tissue factor expression, inducing monocytes and neutrophils to produce reactive oxygen species (ROS), which disrupt the redox balance and activate platelets, leading to platelet aggregation and increased thrombin generation. Proposed interventions include anticoagulation, plasmapheresis, IVIG, antioxidants, HCQ, anti-C5 or anti-C5a receptor mAb and defibrotide to reverse APS pathophysiology in COVID-19 patients. MAC, Membrane Attack Complex; NAC, *N*-acetylcysteine.

critically ill patients with influenza A virus subtype H1N1 and bacterial pneumonia [87]. Radiologically, perfusion defects seen on dual energy perfusion CT (DECT) scan and ventilation perfusion scan with proximal dilated vessels suggested *in situ* thrombosis [88, 89]. Indeed, autopsies consistently show diffuse microvascular thrombosis and marked right ventricular dilatation, suggesting acute pressure overload [90]. Likewise, several other studies reported a very high prevalence of pulmonary arterial thrombosis in autopsies of COVID-19 patients [42, 91–93].

These observations suggest that hypercoagulability is a unique pathophysiological mechanism in COVID-19, distinguishing it from other causes of ARDS. In addition, these manifestations appear to be shared with SARS, in whiche significant microvascular pulmonary embolism

Table 1 Clinical similarities between catastrophic APS and severe coronavirus disease 2019

Clinical features	CAPS registry (%)	Reference	Severe COVID-19 (%)	Reference
Renal disease	73	[22, 24]	78–89.1	[62, 63]
ARDS	36	[24]	28.8–85	[2, 64, 65]
Pulmonary emboli	26	[24]	23–87	[66, 67]
Cerebral disease	56	[24]	45.5	[68]
Headache	8	[24]	17	[68]
Cardiac disease	50	[22]	19.7–59.6	[69, 70]
Myocardial infarction	44	[22]	39.3	[71]
Skin manifestations	47	[22]	20.4–34	[72, 73]
Livedo reticularis	43	[24]	6	[74]
Elevated liver enzymes	63	[24]	15–93.4	[75, 76]
Venous thrombosis	69	[24]	46.1–79	[77, 78]
Laboratory findings				
Thrombocytopenia	67	[22]	57.7–71	[79, 80]
Hyperferritinaemia	71	[81]	63–96	[82, 83, 84]
Associated aPLs				
LA	83	[24]	45–91	[9, 10, 11]
aCL IgG	81	[24]	4.7	[12]
aCL IgM	49	[24]	23	[12]
Anti-β_2-glycoprotein I IgG	78	[24]	2.9	[12]
Anti-β_2-glycoprotein I IgM	40	[24]	5.2	[12]

CAPS: catastrophic APS; COVID-19: coronavirus disease 2019.

was noted in post-mortem studies [94, 95], suggesting that pulmonary embolism could be a common pathophysiological mechanism across beta-coronavirus infectious diseases. Interestingly, the prevalence of pulmonary embolism [67] and ARDS [2, 64] are similar to what have been described in the CAPS registry [24].

The incidence of deep vein thrombosis was reported to be ~1% of all severely ill COVID-19 patients in initial studies [5, 66]. However, a recent Chinese study showed that ≤46.1% of a cohort of 143 patients had developed deep vein thrombosis [77], despite one-third of them receiving thromboprophylaxis with low molecular weight heparin. This is rather unusual given the low rate of venous thromboembolism in a Chinese population [96] and raises the possibility that COVID-19 infection might be contributory to this phenomenon. Moreover, a French study demonstrated a prevalence of 79% for deep venous thrombosis in COVID-19 patients within 48 h of intensive care unit admission despite thrombophylaxis [78]. Based on the studies described above, the rate of venous thromboembolism reported in COVID-19 patients appears to be similar to that of the CAPS registry.

Immunological features

Immunological studies have been informative in understanding the pathophysiology of COVID-19, although these studies focused primarily on patients with severe disease [65, 97]. Patients with lymphopenia demonstrated decreased peripheral blood T cells with increased plasma levels of pro-inflammatory cytokines, including IL-6, IL-10, G-CSF, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 and TNF-α [65, 97]. Although these findings described above suggest similarities between COVID-19 and ARDS, there are differences in lymphocyte subsets between critically ill COVID-19 patients and ARDS patients. Small studies examining lymphocyte subsets in COVID-19 patients found lower $CD4^+$ T cells in critically ill patients than in mildly affected patients [98, 99], which parallels the $CD4^+$ T cell depletion observed in APS [100] and contrasts with $CD4^+$ T cell expansion observed in ARDS attributable to other infections [101, 102].

Thrombocytopenia

Thrombocytopenia has been observed in patients with severe COVID-19 [79], many hypotheses for which have been suggested but none has been proved definitively [103]. This feature is similar to CAPS, where 60–70% of patients develop thrombocytopenia [22]. Given the incidence of high D-dimer levels with thrombocytopenia in critically ill COVID-19 patients, it is plausible that this is secondary to disseminated intravascular coagulopathy and likely to represent a pre-terminal event [80, 104–106]. However, the increased fibrinogen levels in critically ill patients contradict the diagnosis of disseminated intravascular coagulopathy [107] and are more consistent with thrombotic microangiopathy seen in CAPS patients [22, 108].

Hyperferritinaemia

A study of 99 COVID-19 patients revealed that the incidence of elevated ferritin levels was as high as 60% [82], which was confirmed by other groups [83, 84]. These observations formed the basis of the use of

tocilizumab in an attempt to counteract this hyperinflammatory syndrome seen in severe COVID-19 [109]. Interestingly, hyperferritinaemia is a common pathological feature described in severe sepsis, macrophage activation syndrome, Still's disease and CAPS [110]. A previous study reported that hyperferritinaemia was observed in about two-thirds of all patients with CAPS, correlating with venous thrombosis and skin necrosis [81]. Ferritin plays a pivotal role in many biological pathways. Besides being a circulating acute phase reactant, ferritin also induces expression of pro-inflammatory mediators, such as IL-1β, inducible nitric oxide synthase, intercellular adhesion molecule 1, inhibitor κBα and T cell immunoglobulin-domain and mucin-domain 2, by activating the nuclear factor-κB signalling cascade [111]. Conversely, increased pro-inflammatory cytokines can stimulate further synthesis of ferritin by macrophages [112], thereby resulting in a cytokine storm. The unusually high incidence of hyperferritinaemia in COVID-19 is similar to what is observed in the CAPS registry [22, 81].

Cardiac and cerebral manifestations

Myocardial infarctions and valvular vegetations have been observed in patients with SARS and COVID-19 [95, 113], suggesting a common pathophysiological pathway with APS [114]. Two studies demonstrated that cardiac enzymes were elevated, signifying cardiac injury, in ∼20–30% of COVID-19 patients [69, 70]. Moreover, a recent study reported close to 40% of localized ST-elevation myocardial infarctions with no culprit lesion, which raises the possibility of other mechanisms of cardiac injury aside from coronary artery disease [71]. Likewise, most APS patients with myocardial infarctions have normal coronary angiography findings [115], suggesting a potential role of aPLs in the disease pathophysiology. This is further corroborated by raised titres of aPLs in a small but significant proportion of myocardial infarction patients [116].

Cerebral manifestations have been reported in 36.4% of COVID-19 patients in one study [68]. The study showed that patients with severe COVID-19 have a high incidence of neurological manifestations, such as acute cerebrovascular disease and impaired consciousness, in addition to skeletal muscle injury. Additionally, a recent case series of three patients reported the presence of anti-cardiolipin IgA, anti-β_2-glycoprotein I IgA and IgG with associated strokes [8]. In the CAPS registry, 56% of the reported cases developed cerebral manifestations, whereas microvascular thrombosis was observed in 48.9% of autopsies from this registry [22].

Renal manifestations

Approximately 3% [82, 117] to ∼7% [64] of COVID-19 patients in initial studies from China had acute renal injury. However, subsequent larger studies from the USA showed incidences ranging from 33.9% ($n = 850$) [62] to 36.6% ($n = 5449$) [63]. Approximately 90% of patients with severe COVID-19 requiring mechanical ventilation developed acute renal injury [63].

The pathophysiology of renal dysfunction in COVID-19 is unclear, and it is postulated to be attributable to direct cellular injury caused by SARS-CoV-2 or sepsis-related cytokine storm syndrome [118]. An autopsy series of 26 COVID-19 patients revealed the presence of spherical virus-like particles similar to coronavirus in the proximal tubular epithelium and podocytes, suggesting direct cytopathic effects of the SARS-CoV-2 [119]. Interestingly, the pattern of endothelial injury is consistent with the distribution of ACE2 expression. Three cases within this autopsy series also had fibrin thrombi within the glomerular capillary loops with evidence of glomerular ischaemia [119], which is similar to renal autopsy findings in CAPS [22, 24].

Liver dysfunction

Recent meta-analyses indicated elevated liver enzymes in ∼15–20% of COVID-19 patients [75, 76], with a higher incidence of liver injury in those with severe disease. The mechanism of liver injuries is thought to be attributable to the direct binding of SARS-CoV-2 to ACE2-expressing cholangiocytes and not to hepatocytes [120]. A recent autopsy series documented the presence of a central vein thrombosis with focal necrosis of the liver cells in a COVID-19 patient, suggesting a hypercoagulable state similar to that in CAPS [91].

Dermatological manifestations

Although dermatological manifestations of COVID-19 have not been well reported, there is emerging evidence of cutaneous manifestations in ∼20–30% of COVID-19 patients [72, 73], and some of these dermatological features are similar to those found in APS. A recent large, prospective study identified the presence of livedo reticularis in ∼6% of COVID-19 patients [74]. Likewise, a case series described acral ischaemia in young COVID-19 patients with mild or no symptoms [121]. Prominently, a significant time lapse was noted between the onset of COVID-19 symptoms and the onset of acral ischaemia, which suggests that the pathophysiological processes of acral ischaemia could be a secondary effect of COVID-19 rather than a consequence of viremia.

Obstetric manifestations of COVID-19 mirror APS

A systemic review revealed that preterm birth at <37 weeks of gestation occurred in 41.1% of pregnant women hospitalized for COVID-19, and the rate of perinatal death was 7% [122]. Moreover, it was noted that there were relatively increased rates of pre-eclampsia and cesarean delivery among these pregnant patients [122] The pathophysiological processes that explain these observations remain poorly understood. In a post-mortem study of the fetus in a COVID-19-positive primigravida patient with miscarriage, intervillous fibrin deposition and umbilical cord vasculitis were observed in the presence of detectable SARS-CoV-2 by PCR and

absence of concomitant bacterial infection [123]. These pathological findings were initially attributed to viral infection, although other secondary causes, including LA, were not investigated. However, the role of viral infection in placental vessel thrombosis is controversial; a case series of 19 COVID-19 patients with miscarriages found the presence of vascular thrombosis in the absence of placental SARS-CoV-2 S protein or viral particles. The emergence of aPLs and the possibility of APS as a cause of miscarriages in pregnant COVID-19 patients warrant further investigation. Nonetheless, pregnancy morbidity, including premature births at $<$34 weeks of gestation owing to pre-eclampsia and the presence of placental insufficiency, in pregnant COVID-19 patients is significant because pregnancy morbidity is considered a clinical criterion for diagnosis of APS. This similarity between COVID-19 and APS further strengthens our argument that aPLs play a major role in the pathophysiology of COVID-19 (Fig. 2).

Therapeutic implications

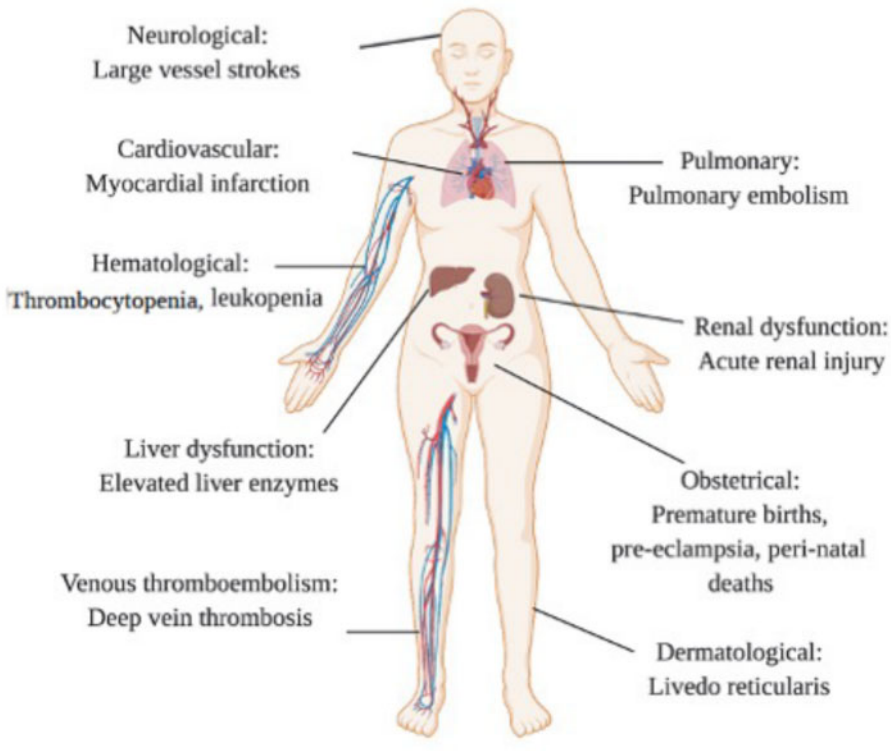
Antithrombotic and fibrinolytic therapy

Recent updates on the clinical data from COVID-19 patients suggest that the use of anticoagulant reduces mortality [124]. Case reports of COVID-19 patients improving clinically after administration of systemic [125] or atomized plasminogen [126] support the inference that hypofibrinolysis is a major driver of the procoagulant state. Hence, thrombolytic therapy might be warranted in order to interrupt the coagulation cascade, restore homeostasis and prevent potential cardiorespiratory compromise. There are two ongoing prospective studies evaluating the role of thrombolytics in with patients severe COVID-19 and ARDS (Table 2).

Glucocorticoids

Glucocorticoids are one of the commonest anti-inflammatory drugs used in the treatment for CAPS. Triple therapy with glucocorticoids, anticoagulation and plasma exchange, with or without IVIG, was associated with the lowest mortality rate compared with no treatment in the CAPS registry [127]. The use of glucocorticoids in patients with severe COVID-19 has recently been demonstrated to be effective in reducing mortality. The RECOVERY study, which randomized 2104 hospitalized COVID-19 patients to receive dexamethasone, found that the use of CSs reduced deaths by one-third in mechanically ventilated patients and by in one-fifth of patients receiving oxygen therapy [128]. Additional clinical trials are underway to evaluate the efficacy of this therapy.

Fig. 2 Overlapping features of APS and COVID-19



There is a significant overlap of dermatological, haematological, obstetric, pulmonary and neurological manifestations of APS with COVID-19.

Table 2 Therapeutic implications of CAPS in COVID-19

CAPS therapy	Potential role of target in COVID-19	Drug type	Drug name	Number of studies on Clinical Trials.gov[a]
Anticoagulation	Heparin exhibits ant-inflammatory properties and might also prevent the binding of aPLs to their targets on cell surfaces	Heparin	Enoxaparin Tinzaparin or UFH Heparin	7 1 1
Thrombolytic therapy	Fibrinolytic therapy	–	Alteplase	2
Glucocorticoids	Anti-inflammatory properties, inhibition of the pro-inflammatory transcription factors, such as nuclear factor-κB, in addition to reduction of aPL production	Glucocorticoids: methylprednisolone prednisone	Tocilizumab + methylprednisolone Siltuzimab + methylprednisolone Dexamethasone Prednisone/ hydrocortisone Hydrocortisone Methyprednisolone	3 5 2 6
Plasma exchange	Removal of aPLs and cytokines, in addition to the restoration of natural anticoagulants with the use of fresh frozen plasma as a volume replacement	N/A	Plasma exchange	1
IVIG	Inhibits pathological autoantibody development, with subsequent reduction in aPL titres and downregulation of regulatory T cells during a cytokine storm	IVIG	IVIG *vs* IST Human immunoglobulin Polyvalent immunoglobulin	3
CYC	Suppression of lymphoid tissues leads to a decreased level of aPLs and cytokine levels	–	N/A	N/A
Defibrotide	Exhibits haemostatic properties by increasing the release of prostacyclin and prostaglandin E_2, reduces levels of leukotriene B4 and modulates platelet activity	–	Defibrotide	2
Eculizumab	Inhibits the cleavage of C5 to C5a and reduces the chemoattractant function and formation of the membrane attack complex	Anti-C5 mAb Anti-human complement factor C5a mAb Synthetic macrocyclic peptide inhibitor of the terminal complement protein C5 Anti-C5a receptor antibody	Eculizumab Ravulizumab IFX-1 Zilucoplan Avdoralimab	3 2 1 1 1
N-Acetylcysteine	Inhibits reactive oxygen species-mediated thrombosis	Methylene Blue, vitamin C, *N*-acetyl cysteine	MCN *N*-Acetylcysteine	1 1
Coenzyme Q_{10}	Inhibits aPL-mediated reactive oxygen species generation	N/A	N/A	N/A
Statins	Upregulate endothelial nitric oxide synthase and inhibit thrombosis in a mouse model of tissue factor-dependent APS	–	Atorvastatin Simvastatin	2
HCQ	Inhibits anti-β_2-glycoprotein I disruption of the annexin A5 shield and TLR7 activation *in vitro* and reduces thrombosis in APS mouse models	–	Combination therapy including HCQ	90

[a]The respective clinical trial numbers are provided in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. COVID-19: coronavirus disease 2019; N/A: not assessed; IFX-1: Anti-C5a antibody(vilobelimab); IST: Immunosuppressive therapy; MCN: Methylene blue- vitamin C- N-acetyl Cysteine; TLR7: Toll-like receptor 7; UFH: Unfractionated heparin.

Plasmapheresis and IVIG

The successful trial of one patient [129] with severe COVID-19 using plasmapheresis and IVIG in averting mechanical ventilation suggests that removing inflammatory cytokines, stabilizing endothelial membranes and resetting the coagulation cascade could halt disease progression and prevent mortality [130, 131]. This modality for therapy is recommended for CAPS, and it merits further investigation in patients with severe COVID-19 not responding to standard therapies.

Complement cascade inhibitors

There have been a few case reports on the benefit of eculizumab, an anti-C5 mAb, in the treatment of refractory CAPS [132–134]. Given the increasing evidence of the role of the complement pathway in the pathogenesis of COVID-19 [135], eculizumab appears to be a promising option for severe COVID-19. Several studies are underway to evaluate other complement inhibitors in COVID-19 (Table 2).

Antioxidant therapy

Antioxidant therapies, including *N*-acetylcysteine [136], statins [137–141] and coenzyme Q_{10} [48], are proposed as adjunctive therapy for APS based on a few observational and animal model studies. A recent retrospective study reported a possible association between statin pretreatment and reduced mortality rate in COVID-19 patients [142]. The parallels in the role of oxidative stress in CAPS and COVID-19 merit further investigation into the use of these agents to restore the redox balance.

HCQ

HCQ inhibits the disruption of annexin A5 by anti-β_2-glycoprotein I antibodies and reduces Toll-like receptor 7 activation *in vitro*, reducing thrombosis in APS mouse models. HCQ has shown efficacy in preventing recurrent venous thromboembolism in a small, non-randomized prospective study in patients with APS [143]. An *in vitro* study demonstrated the antiviral properties of chloroquine to SARS-CoV-2 [144]. However, observational studies of the use of chloroquine and HCQ in COVID-19 patients reported contradictory results, with one study showing antiviral properties [145], whereas other studies reported the absence of such effects [146]. Additionally, two large retrospective studies found no clinical benefit of HCQ with or without azithromycin in COVID-19 patients [147, 148]. Perhaps, future randomized controlled trials evaluating the role of HCQ in COVID-19 patients with aPLs could shed light on the discrepancy in clinical efficacy and outcomes.

Defibrotide

Defibrotide exerts haemostatic properties by increasing the release of prostacyclin and prostaglandin E_2, reduces the levels of leukotriene B4 and modulates platelet activity. It has been used off label in two patients with CAPS [20, 149], with a satisfactory outcome in one patient. There are at least two clinical trials investigating the use of this agent in COVID-19 patients.

Conclusions

We present a hypothetical model to elucidate the pathophysiology of APS in COVID-19. We also describe the clinicopathological similarities between CAPS and severe COVID-19 disease. In light of this, antithrombotic therapy would be the mainstay of treatment to minimize the progression of COVID-19. Effective screening strategies for aPLs in the early phase of COVID-19 are highly desirable in order to stratify patients into low- and high-risk groups. Preventive measures can be initiated in high-risk groups to reduce thromboembolic complications and mortality in COVID-19 patients. We acknowledge that the similarity of COVID-19 to APS is less striking when compared with CAPS. Given that CAPS is a multisystem disorder and is a relatively rare phenomenon in APS, we would like to highlight the possibility that these similarities could have occurred by chance. Thus, further research is needed to help us gain a better understanding COVID-19 pathophysiology and to develop effective strategies in the management of this disease.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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