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COVID-19 and antiphospholipid antibodies

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ABSTRACT

Antiphospholipid syndrome and the coagulopathy of COVID-19 share many pathophysiologic features, including endotheliopathy, hypercoagulability, and activation of platelets, complement pathways, and neutrophil extracellular traps, all acting in concert via a model of immunothrombosis. Antiphospholipid antibody production in COVID-19 is common, with 50% of COVID-19 patients being positive for lupus anticoagulant in some studies, and with non-Sapporo criteria antiphospholipid antibodies being prevalent as well. The biological significance of antiphospholipid antibodies in COVID-19 is uncertain, as such antibodies are usually transient, and studies examining clinical outcomes in COVID-19 patients with and without antiphospholipid antibodies have yielded conflicting results. In this review, we explore the biology of antiphospholipid antibodies in COVID-19 and other infections and discuss mechanisms of thrombogenesis in antiphospholipid syndrome and parallels with COVID-19 coagulopathy. In addition, we review the existing literature on safety of COVID-19 vaccination in patients with antiphospholipid antibodies and antiphospholipid syndrome.

1. Introduction

One of the major mediators of morbidity and mortality in coronavirus disease 2019 (COVID-19) is a coagulopathy characterized by increased risks of arterial, venous, and microvascular thrombosis [1,2]. A multitude of pathophysiologic processes drive this hypercoagulable state, including endotheliopathy, cellular activation and inflammation, complement activation, autoantibody generation, cytokine dysregulation, and fibrinolytic derangements, all supporting a model of immunothrombosis as observed in other microvascular inflammatory diseases [3–15].

Antiphospholipid syndrome (APS) is an autoimmune, thromboinflammatory disease characterized by thrombosis and/or pregnancy loss in the presence of one or more antiphospholipid antibodies (aPL) [16]. APS can occur as a primary disorder or concomitantly with another underlying autoimmune disease such as systemic lupus erythematosus [17]. A diagnosis of APS may be established on the basis of the revised Sapporo criteria, which require thrombotic or obstetrical complications and persistent positivity for lupus anticoagulant (LA) or high-titre anti-cardiolipin (aCL) or anti-beta-2 glycoprotein I (aβ2GPI) IgG or IgM antibodies [18]. The primary pathogenic antibodies in APS are aβ2GPI, which activate endothelial cells, leading to a hypercoagulable state. Other “non-Sapporo” criteria aPL such as antiphosphatidylerine and prothrombin antibodies (aPS/PT) have also been described in APS, but their clinical significance is uncertain [19].

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LA testing is a complex, multi-step process [20]. The first test, a screening test, measures clotting times in the presence of a reagent exquisitely sensitive to the presence of phospholipids (e.g., Russell’s viper venom) [20]. If the clotting time as measured in the screening test is prolonged, a mixing study is done utilizing an equal volume of the patient’s plasma with normal pooled plasma; failure of the mixing study to correct the prolonged clotting time is suggestive of the presence of an inhibitor. The final confirmatory test involves the addition of excess phospholipid to shorten or correct the prolonged coagulation test; correction of a prolonged clotting time with added phospholipid and not with control plasma is characteristic of LA. A number of factors may lead to false positive LA testing, most commonly anticoagulant medications that prolong clotting time measurements.

The presence of aPL in COVID-19 was first reported early in the pandemic by investigators in Beijing, who identified three patients with COVID-19, multiple cerebral infarctions, and, in one case, limb ischemia, who tested positive for aCL IgA and a2GPI IgA and IgG antibodies [21]. Several subsequent studies followed exploring potential links between APS and COVID-19 based on similar immunothrombotic features of both diseases [22]. In this review, we explore the prevalence and significance of aPL in COVID-19, the shared mechanisms of thrombosis in APS and COVID-19 coagulopathy, and the implications of COVID vaccination in APS patients.

2. Mechanisms of thrombogenesis in APS

aPL are not thrombogenic on their own, and a multiple-hit model is believed to explain the progression from aPL to thrombotic or obstetrical sequelae. Binding of aPL to endothelial cells and monocytes induces expression of cellular adhesion molecules and tissue factor, triggering activation of endothelial cells and of the coagulation cascade [23–25]. aPL also cause production of inflammatory cytokines such as interleukin-6, interleukin-8, and vascular endothelial growth factor [26]. aPL binding to β2GPI activates apolipoprotein E receptor 2, leading to upregulation of protein phosphatase 2A and down regulation of Akt and endothelial nitrous oxide synthase, reducing levels of nitric oxide, an anti-inflammatory and vasodilatory substance [27]. Together, these factors all lead to increased oxidative injury, activating the endothelium for thrombus generation [28,29]. Binding and endosomal uptake of aPL by monocytes and dendritic cells activates NADPH oxidase, producing superoxide and upregulating expression of Toll-like receptors 7 and 8, amplifying oxidative stress and inflammation and further driving thrombosis in APS [30]. a2GPI disrupt annexin A5, an anticoagulant protein found in placental and vascular endothelium, augmenting the risks of thrombosis and miscarriage in APS [31,32].

Platelets are also a major mediator thrombosis in APS [33]. a2GPI bind to multiple receptors on platelet surfaces, including platelet glycoprotein (GP) Ibα, GP Ibβ/IIIa (integrin αIIbβ3), and apolipoprotein E receptor 2, with p38MAPK phosphorylation and release of multiple procoagulant molecules including thromboxane A2 and platelet factor 4, all leading to platelet activation [34]. In murine models, infusion of a2GPI leads to activation of endothelial cells, platelets, and monocytes [35]; a2GPI-β2GPI complexes selectively bind the platelet thrombus rather than the endothelium, amplifying platelet activation, leading to enhanced endothelial activation and fibrin generation [36]. P-selectin on platelets and endothelial cells as well as endothelial cell surface markers such as intercellular cell adhesion molecule-1 and vascular endothelial cell adhesion molecule-1 recruit leukocytes to platelet thrombi and endothelial cells in the presence of aPL [34,37].

In addition, aPL may activate the complement system, particularly the alternative complement pathway [38]. In murine models, complement deficient-mice are resistant to aPL-induced thrombosis or fetal loss [39–41]. APS patients near the time of a thrombotic event demonstrate increased complement activation as measured via a modified Ham assay and cell surface deposition of terminal complement C5b-9, while germline mutations can be identified in patients with catastrophic APS [42]. a2GPI complexes trigger the classical complement pathway by binding to C1q, activating C3b and engaging the alternative pathway [43]. A role for complement activation is further underscored by the successful use of eculizumab, a terminal complement inhibitor, in treating some patients with obstetrical or catastrophic APS [38].

The production of extracellular webs of chromatin by neutrophils, a.k.a. neutrophil extracellular traps (NETs), is an emerging hallmark of APS. NETs are complexes of decondensed chromatin with histones and neutrophil granule proteins released by neutrophils in response to various infectious and non-infectious stimuli. This process of NET production and release, known as NETosis, leads to activation of platelets, endothelial cells, and complement proteins [44]. Under normal conditions, NETs physically immobilize microbes and release antimicrobial substances such as antimicrobial peptides, histones and proteases [44]. When dysregulated, NETs may precipitate endothelial damage and thrombosis, contributing to the microvascular complications seen in numerous autoimmune diseases. Mice treated with IgG fractions from APS patients have higher circulating levels of cell-free DNA compared to controls, while thrombi from APS mice are enriched for citrullinated histone H3, a NET marker [45]; moreover, selective agonism of the adenosine A2A receptor in a mouse APS model suppresses aPL-mediated NETosis and reduces thrombosis [46]. These studies highlight a potential role for NETosis in the pathogenesis of thrombosis in APS.

3. aPL and infections

aPL are known to develop transiently in the setting of numerous types of infections. Syphilis was the first infection to be linked with aPL [47,48]; historically, a falsely positive Rapid Plasma Reagin test was a hallmark of the presence of LA and aCL antibodies due to the presence of cardiolipin in the reagent. In one systematic review and meta-analysis, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) were the two most frequent viruses reported to be involved in aPL generation, with HIV, hepatitis B virus (HBV), HCV, and Epstein-Barr virus (EBV) associated with the development of aCL antibodies and HCV and EBV additionally associated with a2GPI antibody formation [47]. The prevalence of aCL in HIV, EBV, and HCV appears to be much higher than LA [49–51].

Among bacterial infections, Hansen’s disease, Staphylococci, Streptococci, tuberculosis, Coxiella, Mycoplasma, Salmonella, Lyme disease, leptospirosis, and various forms of bacterial endocarditis have also been implicated in aPL production [47]. Parasitic
infections like malaria, kala azar, and toxoplasmosis also lead to aPL production [47].

One mechanism for production of aPL in infections may be molecular mimicry due to antigenic similarity and cross-reacting antibodies between the infectious agent and β2GPI in host tissue [48]. Haemophilus influenzae, Neisseria gonorrhoea, and Clostridium tetani share epitope homology with the β2GPI molecule, which may explain production of aβ2GPI antibodies in these and other bacterial infections [47]. However, the breadth of microbial agents associated with aPL generation is striking, and additional processes may account for aPL production across a range of different infections.

In most instances, aPL that arise in the setting of infection are transient phenomena restricted to active infection, while chronic infections such as HIV and HCV may demonstrate persistence of aPL whose clinical significance is unknown [48]. Some studies of aPL report increased rates of thromboembolic events with HBV or HCV and increased pregnancy-related events with parvovirus [48], while most other studies suggest that aPL in the setting of infection are clinically quiescent [47].

4. aPL in COVID-19

Numerous studies in the literature have described high rates of aPL in hospitalized patients with COVID-19 [52–60]. The rates of aPL in these studies are higher than those reported in other viral infections, but the analyses are all potentially confounded by reporting bias and the use of anticoagulation at the time that LA testing was performed, leading to the potential for falsely positive LA results [61]. In addition, acute phase reactants such as C-reactive protein may increase the risk of a false-positive LA result [60].

In the largest meta-analysis of aPL in COVID-19, which analyzed 1159 hospitalized patients with COVID-19 and at least one aPL across 21 different studies, the pooled prevalence rate of one or more aPL (aCL IgM or IgG, aβ2GPI, LA, or aPS/PT) was 46.8% [49]. The pooled prevalences for each of LA, aCL IgM or IgG, and aβ2GPI IgM or IgG were 50.7%, 13.9%, and 6.7% respectively. Of the total study population, 14.3% of patients were double positive for two Sapporo criteria aPL tests while 6.1% were triple positive for all three. The prevalence of aCL (28.8 versus 7.1%) and aβ2GPI (12.0 versus 5.8%) was significantly higher in critically ill versus non-critically ill patients, mirroring other analyses of aPL in critical illness outside of COVID-19 [62]. Another systematic review observed a wide range of prevalence of aPL in COVID-19 patients across different studies in the literature, with LA positivity reported in 35–90% of COVID-19 patients in the intensive care unit (ICU) and 20–66% for ICU and medical ward patients combined, and with 1–12% of patients being triple positive [22]. In this study, a high prevalence of non-Sapporo criteria antibodies was also observed (aCL IgA, 20% to more than 90% of patients; aβ2GPI IgA, 0–86%; aPS/PT, 0–24%; anti-annexin V antibodies, 3–19%) [21].

While most studies of aPL in COVID-19 have focused on hospitalized patients, one retrospective multicenter study examining both hospitalized and ambulatory COVID-19 patients found no significant difference in prevalence of aPL between these two populations (50% versus 43.3%, respectively) [49,51,63–65].

A few mechanisms have been proposed to explain the development of aPL in COVID-19: molecular mimicry, neoepitope formation, and phosphatidylserine exposure [31,66]. Coronavirus are structurally comprised of four proteins: spike (S), membrane, envelope, and nucleocapsid [67]. The S glycoprotein, containing two subunits (S1 and S2), determines antigenic diversity of the virus and host tropism [68]. The S1 subunit allows the virus to attach to the host cell receptor while S2 mediates fusion of the viral capsid with the host cell membrane [31]. In molecular mimicry, the S1 and S2 glycoprotein subunits of the SARS-CoV-2 viral S protein form a phospholipid-like epitope that induces formation of aPL, which can trigger an autoimmune response if the antigenic determinants are similar to host human tissue [69]. The neoepitope model postulates that oxidative stress in COVID-19 causes a change in confirmation of β2GPI, a plasma protein involved in hemostasis and immunity, creating a neoepitope for the generation of aβ2GPI [70]. During pathogenesis of APS, oxidative stress leads to a thiol exchange reaction and formation of disulfide bonds in domains I and V of the β2GPI protein, leading to a conformational change that renders β2GPI immunogenic [71,72]. It is possible that oxidative stress from COVID-19 may induce similar conformational changes in β2GPI and consequent generation of aPL. Phosphatidylserine, located on the inner surface of the lipid bilayer, may become exposed during infection with COVID-19 or other viruses through the action of phospholipid scramblase, which may trigger aPL production as well as inflammatory and thrombogenic responses [66].

In the above studies, the ~50% reported prevalence of LA in COVID-19 is much higher than in other viral infections [49–51]. At first glance, this difference appears intriguing based on the increased association of LA with thrombosis compared to aCL or aβ2GPI in APS, but reporting bias confounds any direct comparisons [63].

aPL generated during COVID-19 infection tend to demonstrate only transient elevation. One study of 31 ICU patients with COVID-19 found 23 (74.2%) with at least one aPL, but on repeat testing 1 month later, only one of the 10 patients retested had persistent aPL [73]. Another study of 79 hospitalized COVID-19 patients (mostly in the ICU) with an initially positive LA found that none of 42 who were retested between 3 and 6 months later had a positive LA, while 10 patients (23.8%) remained positive for other aPL [74]. Another study of critically ill COVID-19 patients examined aPL at multiple time points in six patients and observed distinct patterns of aPL positivity over time [75]: in some patients, aPL peaked around 30–50 days after disease onset, then declined over subsequent days, while other patients demonstrated more transient aPL positivity [75].

Compared to APS, aPL titres generated in COVID-19 are generally lower, with a preponderance of weakly reactive antibodies against domains 1 and domains 4–5 of β2-GPI, in contrast to strong reactivity against β2GPI domain 1 as seen in APS [76]. In studies of APS, aβ2GPI with strong reactivity against domain 1 are believed to be thrombogenic, while aβ2GPI with reactivity to domains 4–5 are generally not thrombogenic [76–78]. In light of this and the transient nature of aPL in COVID-19, the thrombogenicity of these antibodies is uncertain.
Table 1
Summary of studies of antiphospholipid antibodies in patients with COVID-19. Abbreviations: aPL, antiphospholipid antibodies; CVC, central venous catheter; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MI, myocardial infarction; PE, pulmonary embolism.

| Study [reference] | Study location | Setting | Number of patients | aPL tests performed | Number of patients with positive aPL, n | aPL persistent, type (ratio) | Thrombotic Events, n |
|-------------------|----------------|---------|-------------------|---------------------|------------------------------------------|----------------------------|---------------------|
| Zhang et al. [21] | China          | ICU     | 3                 | • LA                | 0 N/a                                    | Strokes MI, LI              |                     |
|                   |                |         |                   | • aCL IgA           | 3                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgG, IgA | 3; 3                                     |                            |                     |
| Helms et al. [52] | France         | ICU     | 57                | • LA                | 50 N/a                                   | N/a                        | N/a                 |
| Pineton de Chambrum et al. [115] | France | ICU | 25                | • LA                | 23 n/a                                   | 6 PE                       |                     |
| Fan et al. [93]   | China          | ICU     | 86                | • LA, aCL or aβ2-GPI IgG, IgM | 12 n/a                                   | 6 strokes                   |                     |
| Amezcu-Guerra et al [116] | Mexico | ICU | 21                | • aCL IgG, IgM      | 2; 3 n/a                                  | 2 PE                       |                     |
| Devreese et al. [117] | Belgium | ICU | 31                | • LA                | 21 At 1 month: 1/10 LA 0/4 aCL 1/2 aβ2-GPI IgA IgG, IgM tested again | 4 CVC thrombosis, 2 Clotting of dialysis circuit, 3 Clotting of ECMO circuit, 2 DVT 1 Stroke |                     |
| Borghi et al. [118] | France | ICU | 122               | • aCL IgG, IgM      | 7; 8 n/a                                  | N/a                        |                     |
| Zhang et al. [119] | China          | ICU     | 19                | • LA                | 16 n/a                                    | 4 ATE 1 VTE 7 micro-thrombi |                     |
| Fan et al. [120]  | Singapore      | ICU     | 12 for LA, 4 for others aPL among 12 patients | • LA                | 6 n/a                                    | n/a                        |                     |
| Alharthy et al. [121] | Saudi Arabia | ICU | 3                 | • LA                | 6 n/a                                    | 1; 2                       |                     |
| Siguret et al. [122] | France | ICU | 74                | • LA, aCL or aβ2-GPI IgG, IgM | 63 n/a                                   | 26 DVT, 4 PE, 1 stroke, 1 CV thrombosis |                     |
| Frapard et al. [123] | France | ICU | 37                | • aβ2-GPI or aCL IgA | 7 n/a                                    | 21 VTE 11 circuit thrombosis |                     |

(continued on next page)
| Study [reference] | Study location | Setting | Number of patients | aPL tests performed | Number of patients with positive aPLs, n | aPL persistent, type (ratio) | Thrombotic Events, n |
|------------------|----------------|---------|--------------------|---------------------|------------------------------------------|-----------------------------|---------------------|
| Van der Linden et al. [124] | Sweden | ICU | 23 | • aβ2-GPI or aCL, IgG or IgM | 19; 7 | n/a | 9 PE, 3 DVT |
| | | | | • aCL IgA, IgM | 7; 9 | | |
| | | | | • aβ2-GPI IgA | 20 | | |
| | | | | • aβ2-GPI IgG, IgM | 7; 8 | | |
| Vlachoyiannopoulos et al. [125] | Greece | ICU | 29 | • aCL IgG, IgM | 7; 3 | n/a | n/a |
| Karahan et al. [126] | Turkey | ICU | 26 for LA, 31 for other aPLs, among 31 patients | • aCL IgG, IgM | 6 | n/a | 1 stroke, 1 MI, 2 others thrombotic events |
| | | | | • aβ2-GPI IgA | 2 | | |
| Mullaguri et al. [127] | USA | ICU | 2 | • aCL IgM, IgA | 2, 1 | n/a | 2 strokes, 2 PE |
| Trahtemberg et al. [128] | Canada | ICU | 22 | • aCL IgG, IgM | 13; 7 | n/a | n/a |
| | | | | • aβ2-GPI IgA, IgM | 0; 0 | | |
| | | | | • aβ2-GPI-DI IgG | 0 | | |
| | | | | • aPS/PT IgG, IgM | 0; 1 | | |
| Najim et al. [129] | Qatar | ICU | 60 | • LA | 21 | NA | 1 VTE, 2 ATE |
| | | | | • aCL IgG, IgM | 0; 0 | | |
| | | | | • aβ2-GPI IgA, IgM | 1; 1 | | |
| Harzallah et al. [130] | France | NA | 56 | • LA | 25 | n/a | n/a |
| | | | | • aCL or aβ2-GPI IgA, IgM | 5 | | |
| Bowles et al. [131] | UK | NA | 34 | • LA | 31 | n/a | 1 VTE |
| | | | | • aCL IgG, IgM | 31 | | |
| | | | | • LA | 21 | n/a | n/a |
| Gazzaruso et al. [82] | Italy | MW | 45 | • aCL IgG, IgM | 15; 3 | | |
| | | | | • aβ2-GPI IgA, IgM | 4 | | |
| | | | | • aβ2-GPI IgG, IgM | 7; 8 | | |
| Popovic et al. [132] | France | NA | 11 | • aCL IgG, IgM | 16 | n/a | 17 VTE, 1 stroke |
| | | | | • aβ2-GPI IgA, IgM | 2 | | |
| Galeano-Valle et al. [133] | Spain | MW | 24 | • aCL IgG, IgM | 16 | n/a | 17 VTE, 1 stroke |
| | | | | • aβ2-GPI IgA, IgM | 2 | | |
| | | | | • aβ2-GPI IgG, IgM | 7; 8 | | |
| Gatto et al. [65] | Italy | NA | 72 for LA, 121 for IgA, 112 for other isotype, among 122 patients | • LA | 16 | n/a | 17 VTE |
| | | | | • aCL IgA, IgM | 16 | | |
| | | | | • aCL IgG, IgM | 15; 3 | | |
| | | | | • aβ2-GPI IgA, IgM | 4 | | |
| | | | | • aβ2-GPI IgG, IgM | 7; 8 | | |
| Reyes et al. [91] | USA | NA | 68 | • LA | 38 | n/a | 17 DVT, 7 PE, 6 ATE, 2 strokes |
| | | | | • aCL IgG, IgM | 38 | | |
| | | | | • aβ2-GPI IgA, IgM | 0; 1 | | |
| | | | | • aβ2-GPI IgG, IgM | 0; 1 | | |
| Rothstein et al. [94] | USA | NA | 9 | • aPL | 9 | NA | strokes |
| Hosri et al. [134] | USA | NA | 2 | • LA | 0 | NA | Stroke, LI, SI |

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Table 1 (continued)

| Study [reference] | Study location | Setting | Number of patients | aPL tests performed | Number of patients with positive aPLs, n | aPL persistent, type (ratio) | Thrombotic Events, n |
|-------------------|----------------|---------|--------------------|---------------------|----------------------------------------|----------------------------|----------------------|
| Previtali et al. [135] | Italy | NA | 35 | aCL IgG, IgM | 0 | Autopsy series | 10 thromboembolic events |
|                   |                   |         |                    | a2GPI IgG, IgM | 0 | 1; 2 | 4 PE |
|                   |                   |         |                    | aPS/PT IgG, IgM | 0 | 1; 2 | 2 strokes |
| Gazzaruso et al. [58] | Italy | NA | 192 | LA | 95 | NA |
| Kanou et al. [136] | France | MW | 2 | LA | 1 | NA | 1 PE |
| Guillet et al. [137] | France | NA | 4 | LA | 1 | NA | 4 ATE (MI, LI,aortic thrombosis) |
| Cristiano et al. [138] | Italy | MW | 92 | aCL IgG, IgM | 3; 1 | NA | NA |
|                   |                   |         |                    | a2GPI IgG, IgM | 0; 2 | 2 | At 3 months: 0/2 tested again |
|                   |                   |         |                    | aPS/PT IgG, IgM | 2; 3 | 2 PE |
|                   |                   |         |                    | aAV IgG, IgM | 4; 3 | |
| Balanchivadze et al. [139] | USA | NA | 2 | LA | 21 | NA | 9 PE |
|                   |                   |         |                    | aCL IgG, IgM | 31 | 8; 8 | 1 DVT |
|                   |                   |         |                    | a2GPI IgG, IgM | 6 | 5; 3 | 1 aortic thrombus |
|                   |                   |         |                    | aPS/PT IgG, IgM | 2; 3 | 2 PE |
|                   |                   |         |                    | aAV IgG, IgM | 4; 3 | |
| Anaya et al. [140] | Colombia | NA | 120 | aCL IgG, IgM | 2; 22 | NA | NA |
|                   |                   |         |                    | a2GPI IgG, IgM | 0; 17 | |
|                   |                   |         |                    | aPS/PT IgG, IgM | 5; 3 | |
| Beyrouti et al. [141] | UK | Mixed | 6 | LA | 5 | NA | 6 strokes |
|                   |                   |         |                    | aCL IgG, IgM | 0; 1 | 1 | 1 |
|                   |                   |         |                    | a2GPI IgG, IgM | 1; 1 | 2 | 2 |
| Pascolini et al. [142] | Italy | Mixed | 33 | aCL IgG, IgM | 3; 5 | NA | NA |
|                   |                   |         |                    | a2GPI IgG, IgM | 2; 2 | |
| Bertin et al. [80] | France | Mixed | 56 | aCL IgG, IgM | 16; 3 | 1; 4 | NA | Strokes |
| Zuo et al. [98] | USA | Mixed | 172 | aCL IgA | 6 | NA | NA |
|                   |                   |         |                    | aCL IgG, IgM | 8; 39 | 7 | |
|                   |                   |         |                    | a2GPI IgG, IgM | 5; 9 | 42; 31 | |
| Lerma et al. [143] | USA | Mixed | 64 | aCL IgG, IgM | 1; 1 | NA | NA |
|                   |                   |         |                    | a2GPI IgG, IgM | 1; 2 | 1; 3 | |
| Ferrari et al. [83] | France | Mixed | 89 | LA | 59 | NA | 14 VTE |

(continued on next page)
| Study [reference] | Study location | Setting | Number of patients | aPL tests performed | Number of patients with positive aPLs, n | aPL persistent, type (ratio) | Thrombotic Events, n |
|------------------|----------------|---------|-------------------|---------------------|----------------------------------------|----------------------------|---------------------|
|                  |                |         |                   |                     |                                        |                            |                     |
| Gutiérrez et al. [144] | Spain | Mixed | 27 | • aCL 7 | NA 2 LI | 6 DVT 10 PE 2 strokes |  |
|                   |                |         |                   | • aβ2-GPI 6        |                                        |                            |                     |
|                   |                |         |                   | • eCL (IgG or IgM) 6 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgA 0 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI (IgG or IgM) 1 |                                        |                            |                     |
| Xiao et al. [57]  | China         | Mixed   | 79 | • LA 2 | NA 19 DVT | 5 strokes 1 MI |  |
|                   |                |         |                   | • IgA aCL, aβ2-GPI 17; 19 |                                        |                            |                     |
|                   |                |         |                   | • eCL IgG, IgM 4; 2 |                                        |                            |                     |
| Tvito et al. [145] | Israel        | Mixed   | 43 | • LA 16 | NA 3 thrombotic events |  |
|                   |                |         |                   | • aCL or aβ2-GPI 0 |                                        |                            |                     |
| Bauer et al. [146] | Germany       | Mixed   | 17 | • LA 3 | NA NA | NA |  |
| Serrano et al. [59] | Spanish       | Mixed   | 474 | • aCL and/or aβ2-GPI IgG, IgM 28 | NA 9 thrombotic events |  |
| Vollmer et al. [74] | France | Mixed | 79 patients with LA positivity 56 for aCL and aβ2-GPI, 53 for other aPL | • LA 79 | 19 VTE, 27 PE 5 DVT or superficial VT 10 ATE, 9 strokes, 0 MI, 1 mesenteric infarction 5 CT, 5 ECMO or RRT circuit Clotting |  |
|                   |                |         |                   | • aCL IgG, IgM 1; 13 | 0/42 LA tested again 0/42 LA |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgG, IgM 0; 3 |                                        |                            |                     |
|                   |                |         |                   | • aPE 1 |                                        |                            |                     |
|                   |                |         |                   | • aPS 1 |                                        |                            |                     |
| Gendron et al. [87] | France | Mixed | 115 for LA, 97 for aCL IgA, 98 for aβ2-GPI IgA, 109 for aPT 148 for other aPL among 154 patients | • LA 70 | At 3 months 30 VTE, 27 PE 5 DVT or superficial VT 10 ATE, 9 strokes, 0 MI, 1 mesenteric infarction 5 CT, 5 ECMO or RRT circuit Clotting Only for LA positivity: 19 VTE 15 symptomatic PE 6 symptomatic DVT |  |
|                   |                |         |                   | • IgA 3 | 19 VTE, 27 PE 5 DVT or superficial VT 10 ATE, 9 strokes, 0 MI, 1 mesenteric infarction 5 CT, 5 ECMO or RRT circuit Clotting Only for LA positivity: 19 VTE 15 symptomatic PE 6 symptomatic DVT |  |
|                   |                |         |                   | • aβ2-GPI IgG, IgM 9; 2 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgG, IgM 5; 3 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgA 2 |                                        |                            |                     |
|                   |                |         |                   | • aPS/PT IgG, IgM 0; 7 |                                        |                            |                     |
|                   |                |         |                   | • aPT IgG, IgM 11; 10 |                                        |                            |                     |
|                   |                |         |                   | • aCL IgG, IgM 11; 41 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgG, IgM 6; 10 |                                        |                            |                     |
|                   |                |         |                   | • aPS/PT IgG, IgM 3; 8 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI-DI IgG 10 |                                        |                            |                     |
|                   |                |         |                   | • aCL IgG, IgM 11; 0 |                                        |                            |                     |
|                   |                |         |                   | • aβ2-GPI IgG, IgM 1; 0 |                                        |                            |                     |
|                   |                |         |                   | • aPS/PT IgG, IgM 0; 4 |                                        |                            |                     |

(continued on next page)
5. aPL and clinical outcomes in COVID-19

Individual studies have drawn a diverse range of conclusions about correlations between aPL in COVID-19 and clinical outcomes such as disease severity, laboratory markers, thromboembolic complications, and mortality (Table 1). Some studies have described either a strong and statistically significant association between aPL and disease severity or mortality, or an enrichment of aPL positivity among hospitalized COVID-19 patients as a function of disease severity, while others have not [74,79–86]. Elevated levels of acute phase reactants such as C-reactive protein and fibrinogen have been observed in COVID-19 patients with a positive LA test in a couple prospective studies [82,87]. Other studies, however, have not observed differences in these parameters [42,71,83,88,89].

In the largest meta-analysis of aPL in COVID-19, no association between aPL positivity and mortality was found [49]. A number of

| Study [reference] | Study location | Setting | Number of patients | Number of aPL tests performed | Number of patients with positive aPL, n | aPL persistent, type (ratio) | Thrombotic Events, n |
|------------------|----------------|---------|--------------------|----------------------|------------------------------------|------------------------|----------------------|
| Lee et al. [149] | Korea          | Mixed   | 105                | • aCL IgG, IgM      | 2; 29                              | 2 in hospital thrombosis  |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 4; 4                                |                        |                      |
|                  |                |         |                    | • aPS/PT IgG, IgM  | 0; 3                                |                        |                      |
| Gil-Etayo et al. [96] | Spain        | Mixed   | 390                | • aCL IgG, IgM      | 8; 10                              | 24 PE, 8 thrombotic stroke, 4 DVT and 1 arterial thrombosis |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 4; 10                              | 12; 16                  |                      |
|                  |                |         |                    | • aPS/PT IgG, IgM  | 7; 9                                | 8; 9                    |                      |
| Constans et al. [85] | Spain        | Mixed   | 211                | • LA                  | 128                                | 2 PE, 2 MI, 2 ischemic stroke |                      |
| Emmenegger et al. [150] | Germany   | Mixed   | 95                 | • aCL IgG, IgM      | 0,12%                              | NA                     | NA                   |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 2,04,42,67%                        |                        |                      |
|                  |                |         |                    | • aPS/PT IgG, IgM  | 0,28%                              |                        |                      |
|                  |                |         |                    | • aAV IgG, IgM      | 2,04,29,33%                        |                        |                      |
| Shi et al. [151] | USA            | Mixed   | 118                | • aCL IgG, IgM      | 4,29                               | NA                     | NA                   |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 2,5                                |                        |                      |
|                  |                |         |                    | • aPS/PT IgG, IgM  | 28,18                              |                        |                      |
| Atalar et al. [152] | Turkey         | Mixed   | 73                 | • aCL IgG, IgM      | 0,3                                | 3 thrombosis           |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 0,7                                |                        |                      |
|                  |                |         |                    | • LA                  | 12                                 | NA                     |                      |
| Shah et al. [153] | USA            | Mixed   | 20 (Hospitalized COVID-19 patients with a thromboembolic event) | • aCL IgG, IgM | 12                                 | NA                     |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 1,10                               |                        |                      |
| Bertin et al. [154] | France       | Mixed   | 157                | • aCL IgG, IgM      | 41,13                              | 8 Thromboembolic events |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 6,10                               |                        |                      |
|                  |                |         |                    | • aPE IgG, IgM      | 25,6                               |                        |                      |
| Espinosa et al. [155] | Spain        | Mixed   | 158 for first sample, 58 for second sample | • aCL IgG, IgM | 11,5                               | 27 PE, 1 CVA           |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 6,2                                |                        |                      |
|                  |                |         |                    | • LA                  | 24                                 | 17                     |                      |
|                  |                |         |                    | • aPS/PT IgG, IgM  | 3,9                                | 1,7                    |                      |
| Rosales-Castillo et al. [156] | Granada | Mixed   | 189 for first sample, 69 for second sample | • aCL IgG, IgM | 3,7                                | No thromboembolic event |                      |
|                  |                |         |                    | • aβ2-GPI IgG, IgM | 6,9                                |                        |                      |
|                  |                |         |                    | • LA                  | 24                                 | 26                     |                      |
studies have described either an association between aPL and thrombosis in COVID-19, or an increased representation of aPL in COVID-19 patients with thrombotic complications including deep venous thrombosis, pulmonary embolism, stroke, or myocardial infarction [54,90-96]. By contrast, other studies, including the largest meta-analysis of aPL in COVID-19, have found no association with thrombosis [49,97]. Differences in aPL titres, persistence, and structural biology in COVID-19 compared to APS as described earlier may contribute to some of this variation.

One study found elevated markers of neutrophil function and NET formation in sera from 172 hospitalized patients with COVID-19 and high aPL titres [98]. In this study, IgG antibodies purified from COVID-1 patients with high aPL titres triggered NETosis in vitro, suggesting that aPL in some patients with COVID-19 may display biological activity, although their clinical relevance remains uncertain [86].

6. Pathophysiologic similarities between APS and COVID-19

APS and the coagulopathy of COVID-19 share many similar mechanisms that are believed to drive microvascular injury and thrombosis [99] (Fig. 1). In both APS and COVID-19, the production of nitric oxide is reduced due to inhibition of endothelial nitric oxide synthase, predisposing the endothelium to injury [99]. Markers of endothelial activation and damage including von Willebrand factor, tissue-type plasminogen activator, and soluble thrombomodulin correlate with disease severity in COVID-19, with upregulated expression of angiogenesis genes in lung tissue, underscoring the importance of the endothelium in COVID-19, similar to APS [88,99,100]. Complement activation has a significant role in both APS and COVID-19. SARS-CoV-2 activates all three complement pathways; viral antigens form immune complexes that activate the classical pathway while the spike protein of SARS-CoV-2 binds mannose-binding lectin, activating the lectin pathway [99]. The alternative complement pathway on cell surfaces is triggered by F-spike proteins (subunit 1 and 2), a mechanism that can be blocked using a Factor D inhibitor [43]. C3 convertase production by binding of the pathogen to a component of the alternative pathway can also activate the alternative pathway [43]. Skin and lung samples as well as elevated membrane attack complex levels in sera of patients, delineate the activation of these pathways in COVID-19, similar to thrombotic APS [43,89,101].

NETosis may be a central part of the pathogenesis of both APS and COVID-19 coagulopathy. In COVID-19, hyperstimulation of the immune system leads to NET production and microvascular occlusion as evidenced by myeloperoxidase-DNA and citrullinated histone H3 complexes, similar to APS [102]. NETosis may also function in mediating acute lung injury in COVID-19 [103].

Platelet activation is a hallmark of both APS and COVID-19 thrombosis. COVID-19 infection alters platelet transcriptomes and leads to aggregate complexes of platelets with neutrophils, monocytes, and lymphocytes and platelet-monocyte aggregates in severe COVID-19 express tissue factor [5,104]. Moreover, sera from COVID-19 patients has been shown to lead to increased platelet apoptosis via IgG-mediated mechanisms [105]. Activated platelets in COVID-19 also express S100A8/S100A9 (MRP8/MRP14, calprotectin), correlating with markers of endothelial cell activation [106]. Hence, through various mechanisms platelet activation leads to increased thrombosis in COVID-19, similar to APS.

Fig. 1. Common mechanisms of thrombosis shared by antiphospholipid syndrome and COVID-19. Abbreviations: ACE2, angiotensin converting enzyme-2; aPL, antiphospholipid antibody; β2GPI, beta-2 glycoprotein-I; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; NETosis, neutrophil extracellular trap formation and release. (Figure created using BioRender.com.)
7. COVID-19 vaccination in APS

Questions regarding the safety and efficacy of COVID vaccines in patients with aPL or APS have been frequently been raised, with a few studies reporting overall favorable tolerance and minimal complications [107]. One multicenter Italian survey study evaluated 161 patients with triple positive APS who received either the Moderna or the Pfizer-BioNTech COVID-19 vaccine [107]. Following the first vaccine dose, 83% experienced either no adverse reaction or minimal local signs/symptoms at the site of injection, while 12% had flu-like symptoms for less than 1 day and 4% for more than 1 day; 1% sought medical care, and no patients required hospitalization. Following the second dose, 68% had a minimal local reaction at the injection site; 22% had flu-like symptoms for less than 1 day and 8% for more than 1 day, while 2% sought medical care. One patient developed deep venous thrombosis 39 days after receiving the second dose. No patients required hospitalization or developed a severe allergic reaction after either dose [107].

A separate single-institution Italian survey study evaluated 102 patients who received either the Moderna or Pfizer-BioNTech COVID-19 vaccine, included 52 patients with APS and 50 with aPL and no clinical APS features [108]. Of the total study patients, 76% experienced injection-site pain, fatigue, or headache; all reported symptoms were transient and resolved within 10 days. Overall, 71% of patients classified their symptoms as mild and 29% as moderate. One patient with thrombotic APS and chronic thrombocytopenia on long-term vitamin K antagonist therapy experienced self-limiting purpuric lesions on her calves 10 days after the second vaccine dose. Together, these two studies suggest that adverse events following COVID-19 vaccination with either the Moderna or Pfizer-BioNTech vaccine in patients with aPL or APS are mostly mild and self-limited [108].

A rare complication of COVID-19 vaccination is vaccine-induced thrombotic thrombocytopenia (VITT), which may arise within several weeks following vaccination with adenovirus vector-based formulations such as ChAdOx1 nCoV-19 (AstraZeneca) or Ad26.COV2.S (Johnson & Johnson/Janssen) [109]. VITT arises as a result of antibodies against platelet factor 4 (PF4), similar to heparin-induced thrombocytopenia (HIT). Parallels among VITT, HIT, and APS have often been described, as all three are antibody-mediated processes associated with thromboembolic manifestations. Patients with VITT or HIT may be positive for aPL, although the clinical significance of aPL in these conditions is uncertain [110–113]. One study of 126 aPL-positive patients (89 with APS, 37 with asymptomatic aPL) who mostly received the Pfizer-BioNTech COVID-19 vaccine found anti-PF4 antibodies in 9 patients, with no significant change in anti-PF4 antibody titres before or after vaccination in either APS or asymptomatic aPL-positive patients [114]. Sera from patients with high-titre anti-PF4 antibodies did not alter in vitro platelet aggregation, and no cases of VITT were observed, even in the few study patients who received an adenovirus vector-based COVID-19 vaccine [114].

8. Conclusions and summary

APS and COVID-19 share many pathophysiologic features common in microvascular and immunothrombotic diseases, including endotheliopathy, platelet activation, complement activation, and NETosis, among others. Despite these shared features, a role for aPL in pathogenesis of COVID-19 remains uncertain. aPL occur at high prevalence in patients with COVID-19, with LA reported in ~50% of patients with COVID-19 and non-Sapporo criteria aPL being common; however, studies suggest that aPL titres in COVID-19 are usually only transiently elevated, and overall aPL titres in COVID-19 appear to be lower than those reported in APS. Biological differences in αβ2GPI antibody epitopes in APS compared to COVID-19 may underlie some of the differences in pathogenicity of aPL in these two conditions. A correlation between aPL positivity and disease outcomes in COVID-19 such as thrombosis or mortality remains unclear with different studies reporting varying results. Further investigation is required to delineate the significance of aPLs in mediating disease severity, thrombosis, and other outcomes in COVID-19. COVID-19 vaccination has been established to be generally safe in APS patients.

Practice points

- Antiphospholipid syndrome and COVID-19 share many pathophysiologic features common in immunothrombotic diseases
- Antiphospholipid antibodies are common in COVID-19, yet their clinical relevance is uncertain
- COVID-19 vaccination is generally safe in patients with antiphospholipid syndrome or antiphospholipid antibodies.

Research agenda

- Further studies are needed to explore the biological similarities and differences of antiphospholipid antibodies in COVID-19 and antiphospholipid syndrome and to understand the clinical implications of antiphospholipid antibodies in COVID-19

Declaration of competing interest

None of the authors report any conflicts of interest.

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