Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Antiphospholipid antibodies and COVID-19

Dear Editor,

An unusually high prevalence of thromboembolic events has been observed during the course of coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While the mechanisms involved in the hypercoagulable state that can develop into coagulopathy in COVID-19 patients remain to be elucidated, an increased prevalence of anti-phospholipid (aPL) antibodies in COVID-19 patients has been reported by several groups. This is important because the presence of aPL antibodies can result in abnormalities that include prolonged clotting times and/or clinical manifestations that can range from thrombocytopenia to more severe anti-phospholipid syndrome (APS), being the acquired prothrombotic state contributed by aPL antibodies responsible for a significantly increased risk of arterial, venous, and micro-vascular thrombosis [1].

In the case of SARS-CoV-2 infection (Fig. 1), early studies identified an unexpected high incidence of aPL antibodies in COVID-19 patients [2–4] in the intensive care unit (ICU) [5], with a cumulative rate of 27.6% within 24 h from the admission to the hospital [6]. Moreover, autopsies revealed deep venous thrombosis in up to 58% of severe COVID-19 patients in which venous thromboembolism had not been previously suspected [7].

aPL antibodies typically comprise anti-cardiolipin antibodies, anti-β_2-glycoprotein I (β_2GPI) antibodies, and lupus anti-coagulants. Less prevalent aPL antibodies include antibodies to prothrombin, phosphatidylserine, phosphatidylethanolamine, and to the phosphatidylserine/prothrombin complex [8].

In a series of 21 ICU hospitalized patients with severe or critical COVID-19, 67% patients had at least a single aPL positivity, 25% had double positivity, and 8% had triple positivity [9]. Anti-cardiolipin IgM were present in 14% of those patients and anti-cardiolipin IgG in 10%. Importantly, 9.5% aPL-seropositive patients died within 30 days after aPL antibody measurements, while 19% remained hospitalized [9].

In another investigation on 31 ICU COVID-19 patients, 7 of 9 thrombotic patients had at least one aPL antibody and 16 of 22 patients without thrombosis were also aPL antibody-positive [10]. aPL autoantibodies were present in 52% of 172 patients hospitalized with COVID-19 and included anti-cardiolipin IgM in 23%, anti-phosphatidylserine/prothrombin (aPS/PT) IgG in 24%, and aPS/PT IgM in 18% [11]. The finding that another study found about 12% prevalence of anti-cardiolipin IgG/M/anti-β_2GPI IgG [12] indicates variability among patients' cohorts and sites of measurements.

In non-critically-ill (i.e., non-ICU) COVID-19 patients, aPL antibodies were also common [13], having 47.1% patients at last one positive aPL and double or triple aPL seropositivity being present in 11.1% and 1.9% patients, respectively. Anti-cardiolipin antibodies (mostly of the IgA subtype) were present in 33.7% patients, while anti-β_2GPI IgG, IgM and IgA were positive, respectively, in 8.7%, 2.9% and 5.8% of patients. Thrombotic events occurred more frequently in patients with anti-cardiolipin antibodies (45.5% for IgM and IgA; 27.3% for IgG) but high frequency was also observed for anti-β_2GPI IgA (27.3%). Although a limitation of that study was the lack of monitoring over time for the persistence of aPL antibodies, the investigation showed nonetheless that aPL antibodies were frequent in non-severely ill hospitalized COVID-19 patients and associated with thrombotic events in 64% cases [13].

aPL antibodies in COVID-19 patients with coagulopathy and infarcts appear mostly represented by anti-cardiolipin IgA antibodies but also IgA and IgG to β_2GPI [14]. A meta-analysis found 58% positivity for aPL antibodies in 250 COVID-19 patients, being lupus anti-coagulant present in 64%, anti-cardiolipin in 9%, and anti-β_2GPI in 13% patients [15]. Although the positivity for lupus anti-coagulant in COVID-19 patients is generally very high (44.6% to 87%, depending on the studies) and superior to that of anti-cardiolipin IgG/IgM and/or anti-β_2GPI antibodies (8.9%), there is no conclusive evidence of a possible correlation between the presence of lupus anti-coagulant and thrombosis in COVID-19 [3,16] although a concomitant presence of lupus-anti-coagulant with anti-cardiolipin IgM or IgG appears strongly associated with thrombosis during acute COVID-19 infection [13].

Of note, studies have suggested that some aPL antibodies may be transient during COVID-19 [10]. In a cohort of COVID-19 patients where 50.6% displayed thrombosis, with 7.5% having at least one recurrence., about half were positive for aPL antibodies, and a strong association was observed between thrombosis and positivity of anti-cardiolipin IgM (41%), also confirmed at follow up of 3–6 months [16].

Interestingly, an elevated frequency of aPL antibodies belonging to the IgA class in severe COVID-19 has led to the suggestion that this finding could underlie the anti-viral response at mucosal (e.g., bronchial) sites [17]. Whether or not this is the case, one cannot neglect that the immune-triggered, complement-mediated thrombotic microangiopathy (TMA) accompanied by cytokine storm, advanced lung inflammation and sepsis that occurs in the disease [18] often associate with widespread thromboses and disseminated intravascular coagulation (DIC), at last in some critically ill COVID-19 patients. In a study on the risk for thrombotic arterial and venous occlusions in COVID-19, the transfer of IgG purified from patients' sera into mice accelerated venous thrombosis in two different mouse models, suggesting a pathogenicity of the circulating antibodies from about half of hospitalized COVID-19 patients [11]. However, other studies did not identify correlations between aPL antibodies and thrombosis [19,20].

At present, the American Society of Hematology suggests caution in interpreting the associations between aPL antibodies and thromboembolic events in COVID-19 and not only because of the different assays used for the detection of aPL antibodies in different centers and the possibility that

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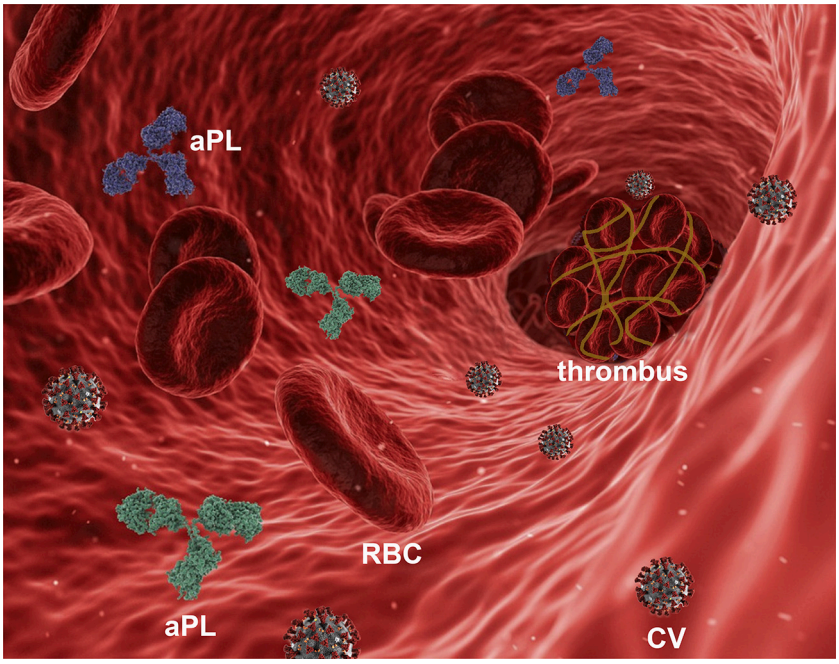

Fig. 1. Schematic representation (not in scale) of a blood vessel with a thrombus and anti-phospholipid antibodies (aPL) in the course of infection with SARS-CoV-2 (CV). RBC, red blood cell.

Table I
Frequency of aPL antibodies in COVID-19 patients from different cohorts.

Type of COVID-19 patients	Total number	% Positivity for aPL	Ref.
Diagnosed as Covid-19	56	45	3
Non-hospitalized	69	43.3	20
Hospitalized	53	50	20
Hospitalized	172	52	11
Severely ill	29	55.2	22
Severely ill/critically ill	21	57.1	9
Critically ill	19	52.6	23

they can be present transiently. Timing of measurements could be a relevant factor because aPL antibodies seem more frequent in critically ill as compared to non-critically ill COVID-19 patients and emerging about 35–39 days after disease onset [21], being anti-β_2GPI IgA the aPL antibodies most common (28.8% of critically ill patients), followed by anti-cardiolipin IgA (25.8%) and anti-β_2GPI IgG (18.2%) [20]. Yet the finding that aPL are frequently present in COVID-19 patients (Table I) poses several questions. For example, are aPL antibodies specifically induced by COVID-19 and, if so, how? How much do aPL antibodies contribute to the prothrombotic state of COVID-19 patients and to the overall clinical picture of the patient? Would all COVID-19 patients with aPL antibodies benefit from early anti-coagulation therapy, even when having different coagulation state characteristics? Addressing these questions will advance the progress in managing COVID-19 and its complications, and possibly lead to an improved therapy of a disease that has rapidly upended routines and working activities for millions of individuals worldwide.

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Declaration of Competing Interest

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Antonio La Cava*
Department of Medicine, University of California Los Angeles, USA

* Corresponding author at: University of California Los Angeles, 1000 Veteran Ave. 32-59, Los Angeles, CA 90095, USA.
E-mail address: alacava@mednet.ucla.edu.