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COVID-19 and the antiphospholipid syndrome

Manuel Serrano [a], Gerard Espinosa [b], Antonio Serrano [a], Ricard Cervera [b,*]

[a] Department of Immunology, Healthcare Research Institute I+12, Hospital 12 de Octubre, Madrid, Spain
[b] Department of Autoimmune Diseases, Hospital Clínic, Insititut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Catalonia, Spain

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has resulted in a global pandemic. Most COVID-19 patients are asymptomatic or have flu-like symptoms. However, around 15% of the patients may have severe disease, including unilateral or bilateral pneumonia with acute respiratory distress syndrome and progressive hypoxemia that may require mechanical ventilation assistance. A systemic inflammatory response syndrome occurs in the most severe forms of COVID-19, with multiorgan involvement which can be life threatening caused by a cytokine storm. Although what best characterizes COVID-19 are the manifestations of the respiratory system, it has been shown that it also acts at the cardiovascular level, producing coagulation abnormalities, which causes thrombotic events mainly in the arteries/arterioles, microcirculation and venous system, and potentially increased mortality risk. This multiorgan vascular disease overlaps with other known microangiopathies, such as thrombotic microangiopathy or paroxysmal nocturnal hemoglobinuria, where complement overactivation plays an important role in the pathophysiology of thrombosis. Furthermore, coagulopathy secondary to COVID-19 occurs in the context of an uncontrolled inflammatory response, reminiscent of APS, especially in its catastrophic form. This review summarizes the current knowledge regarding the relationship between COVID-19 and the APS.

1. Introduction

Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic. Most COVID-19 patients are asymptomatic or have flu-like symptoms [1]. However, around 15% of the patients may have severe disease, including unilateral or bilateral pneumonia with acute respiratory distress syndrome (ARDS) and progressive hypoxemia that may require mechanical ventilation assistance. A systemic inflammatory response syndrome (SIRS) occurs in the most severe forms of COVID-19, with multiorgan involvement which can be life threatening caused by a cytokine storm. Analytically, lymphopenia and marked elevation of C-reactive protein, ferritin, D-dimers, cytokines and chemokines stand out [2,3].

SIRS secondary to COVID-19 occurs in a pattern similar to, but still distinct from, the autoinflammatory macrophage activation syndrome that complicates several autoimmune diseases, such as systemic juvenile idiopathic arthritis and systemic lupus erythematosus (SLE) [4–6].

In some reports, >50% of hospitalized patients with moderate to severe COVID-19 have circulating autoantibodies, which opens the question whether SARS-CoV2 can produce a loss of host tolerance, triggering an autoimmune disease [7]. The deregulation of the immune response has been shown to be a key element in the unefficient responses against viruses. It is well known that cytomegalovirus, parvovirus B19, and Epstein-Barr virus (EBV) are environmental triggers of autoimmunity in genetically predisposed individuals [8]. These viruses can trigger autoimmunity through various mechanisms, such as the tendency to cause persistent infection, modulate the host's immune response by causing loss of self-tolerance producing autoreactive lymphocytes, or generating abnormal responses by molecular mimicry, superantigen activity and the stimulation of inflammatory signaling, including type I IFN production [9–11]. The type of organized immune response against SARS-CoV2 infection is decisive in the prognosis of the disease and, in fact, high Th2 responses are associated with a fatal outcome [12,13]. Conversely, immunomodulatory drugs, especially glucocorticoids [14], inhibitors of cytokines (or their receptors) [15], and blockers of cytokine-mediated signaling as Janus kinase (JAK) inhibitors [16,17] seem to improve survival in severe cases of COVID-19. Some clinical features of moderate to severe COVID-19 are reminiscent of those seen in autoimmune diseases such as inflammatory arthritis, SLE,

* Corresponding author at: Servei de Malalties Autoimmunes, Hospital Clínic, Villarroel, 170, 08036 Barcelona, Catalonia, Spain.
E-mail address: rcervera@clinic.cat (R. Cervera).

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antiphospholipid syndrome (APS), and anti-MDA5 syndrome [18–20]. In addition, there are numerous case reports of patients developing classifiable autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, and type 1 diabetes, concomitantly with or immediately after SARS-CoV-2 infection [21–26]. Furthermore, severe cases of COVID-19 can be explained by the existence of preformed autoantibodies [7]. However, work remains to be done to determine whether these antibodies are important contributors to severe disease or an epiphenomenon of marked inflammation.

2. COVID coagulopathy and imunothrombosis

What best characterizes COVID-19 are the manifestations of the respiratory system, although it has been shown that it also acts at the cardiovascular level, producing coagulation abnormalities, which causes thrombotic events mainly in the arteries/arterioles, microcirculation and venous system [27,28] and potentially increased mortality risk as a consequence [1]. These findings have also been confirmed at necropsies [29,30]. These events appear more frequently in an acute infection, but they can also occur during the convalescence [29].

The reported thromboembolic (TE) event rate in COVID-19 patients with severe disease is quite heterogeneous. The state of hypercoagulability and thromboembolic complications correlates with a more severe course of the disease, the need for admission to intensive care units (ICU), and higher risk of mortality [31]. These can be present in approximately 50% of ICU patients whose stay is two weeks or longer and were independent of whether the patients had received standard-dose thromboprophylaxis [32].

Laboratory findings confirm the existence of prothrombotic state. D-dimer, fibrin, C-reactive protein levels, lactate dehydrogenase (LDH), and moderate thrombocytopenia are usually elevated in patients affected by COVID-19 coagulopathy. Therefore, the infection constitutes an additional contributing factor that predisposes to a prothrombotic state [33].

Pulmonary microangiopathy with evidence of activated platelets, thrombi, and neutrophil extracellular traps (NETs) within vessels has been detected. In addition, infiltration of neutrophils, monocytes, and macrophages have been described in additional organs beyond the lungs, including the heart, central nervous system, and liver [27,34]. In addition to cell activation and local infiltration, there are other several mechanisms that could contribute to develop coagulopathy in SARS-CoV2 infection. Endothelial activation that stimulates Toll-like receptors, thus producing systemic inflammation, and prothrombotic state increasing levels of von Willebrand factor, and activating the tissue factor pathway [35]. In addition, there are indirect mechanisms such as decreased diffusion of gases producing ARDS and tissue hypoxia [36]. Low oxygen levels at tissues activates cellular transcriptional changes elaborating hypoxia-inducible transcription factors (HIF-1 and HIF-2) which, in turn, increases thrombin levels [37]. The infection generates a large number of apoptotic cells [38] creating a proinflammatory environment that can cause ARDS and thrombosis [39]. Therefore, the strong immune response secondary to COVID-19 infection induces expression of procoagulant factors that implies activation of complement, platelets and neutrophils, triggering coagulopathy and thrombi formation (immunothrombosis) through the pathway [40].

NETs are three-dimensional extracellular networks of decondensed chromatin, histones and antimicrobial proteins. Their function is to trap and kill microorganisms, preventing their expansion at the site of infection [41]. NETs have cytotoxic activity causing NETosis, and endothelial dysfunction [42]. In this way, NETs are amplifiers of inflammation, increasing self-antigen exposure and autoantibody production. Thus promoting the generation of aberrant immune response like autoimmune procceses [43], and long-term COVID-19 [44]. It has been demonstrated that NETs can contribute to formation of thrombi in COVID-19 patients with respiratory distress [45].

Moreover, the complement system usually plays an important role in the context of inflammation, thrombosis and activation of the innate response. Complement deposits have been reported in the lung and skin tissue that suggests systemic activation of three known complement activation pathways, classical, alternative and lectin-based complement pathways in severe disease [46–48]. This multiorgan vascular disease overlaps with other known microangiopathies, such as thrombotic microangiopathy (TMA) or paroxysmal nocturnal hemoglobinuria (PNH), where complement overactivation plays an important role in the pathophysiology of thrombosis [49,50]. Furthermore, coagulopathy secondary to COVID-19 occurs in the context of an uncontrolled inflammatory response, reminiscent of APS, especially in its catastrophic form [51,52].

3. APS and thrombosis [51]

APS is a systemic autoimmune disease characterized by the appearance of thrombosis and obstetric morbidity (clinical criteria) in a patient with persistently high levels of antiphospholipid antibodies (aPL).

The APS classification criteria require the coexistence of at least one clinical (thrombosis or obstetric morbidity) and one laboratory criterion (positivity of at least one aPL) [30]. The aPL included in these criteria are lupus anticoagulant (LA), anticardiolipin (aCL), and anti-β-2-glycoprotein I (aβ2GPI) antibodies of the IgG or IgM isotypes. Currently there are no defined diagnostic criteria for APS, however, the classification criteria are often used in some situations for diagnosis despite their low sensitivity. In addition, a second determination of aPL at least 12 weeks apart for confirmation to avoid false positives is required [53].

APS can be divided into 3 forms: primary APS, associated with another autoimmune disease (such as SLE), and catastrophic APS (CAPS), characterized by the generation of thrombosis in different locations in a short period of time, developing a systemic coagulopathy with a high mortality rate, a situation very similar to coagulopathy due to COVID-19 [54].

3.1. APS beyond classification criteria

APS diagnosis goes beyond classification criteria. In addition to the clinical characteristics included in the classification criteria, there are other characteristics associated to APS, even more frecuent than clinical classification criteria, such as livedo reticularis or thrombocytopenia [55]. There are also aPL not included in the classification criteria. The most known are a) anti-phosphatidylserine/prothrombin antibodies (aPS/PT), associated to with unexplained recurrent pregnancy loss [56], and thrombosis possibly due to its possible correlation with the presence of LA [57]; b) aPL directed to domain I of β2GPI (IgG) have high specificity (97.12%) for thrombosis, but their sensitivity is still moderate (64.32%) [58,59]; and c) IgA isotype aPL have also been associated with thrombotic events. Current evidence does not recommend their testing because it does not increase the diagnostic accuracy of the APS [60]. This is because IgA aCL positivity is poorly correlated to clinical manifestations. However, IgA aβ2GPI presence has been associated to thrombotic events [61] and stroke [62]. They are the most prevalent aPL (30%) in patients with end-stage organ failure (kidney or heart) where β2GPI is produced. Thrombotic events can appear even after the replacement of these organs by either cardiac or renal transplantation [63,64].

The origin of aPL remains unknown. Molecular mimicry theory suggests the influence of microbial and viral agents that goes in favour of an infectious etiology [65]. Similarities of β2GPI with some molecular structures of several microorganisms have been described [66]. This phenomenon could occur in predisposed individuals when self-tolerance mechanisms fail and produce an abnormal response because their immune system responds to their own molecular structures due to their similarity to microbial peptides [67]. Therefore, the steady state would not be restored after the resolution of the infection and the presence of autoantibodies remains.

The mechanism of thrombosis-induction by aPL is also not fully understood. Meroni et al. [68] proposed the "two hits" theory: the presence of aPL (first hit) induces a thrombophilic state, but clotting takes place only in the presence of another thrombophilic condition (second hit) that implies an activation of innate immunity, such as inflammation, infection, or surgery, is required to trigger the thrombotic event.

4. Prevalence of aPL in COVID-19 patients

Zhang et al. [69] were the first to report the presence of aPL associated to thrombotic events in three patients with COVID-19. Interestingly, IgA aPL was the most prevalent isotype.

After this finding, numerous studies were published reporting high prevalence of aPL in COVID-19 patients, and positivity for any aPL ranged between 5 and 71% (Table 1). This prevalence can be highly variable, depending on the type of patient cohort (severe vs non-severe patients) [70] and the aPL studied (consensus vs. extra criteria).

Regarding criteria aPL, the most prevalent was LA, present approximately in 50% of patients [71–73], specially among ICU patients reaching 90% [74–76]. Elevation of aPTT can be present in 91% of these patients [77]. When LA is not analyzed, aCL [78–80], or aβ2GPI [51] are the most prevalent aPL. Positivity of IgG and IgM aCL and aβ2GPI is around 15%. Double positivity can be present in 25–50% of these patients [81], most frequently associated to LA positivity [82].

Despite not being as well studied as consensus aPL, 54% of studies

Table 1
Set of studies on aPL presence in COVID-19 patients.

Author and reference		Setting	Study design	Control group	Center	Patients included	aPL with LA	Extra criteria aPL	aPL confirmation >12w	aPL prevalence	Clinical Association
		NO									
Borghi et al.	51	ICU	P	N	M	122	N	Y	N	N/A	N
Zhang Y et al.	69	ICU	R	N	U	3	Y	Y	N	N/A	Y
Gazzaruso et al.	71	N/A	R	N	U	192	Only LA	N	N	50%	N
Constans et al.	72	Both	P	N	U	211	Only LA	N	N	60%	Y
Najim et al.	73	ICU	P	N	U	60	Y	N	N	37%	N
Helms et al.	74	ICU	P	N	M	150	Only LA	N	N	N/A	Y
Pineton et al.	75	ICU	R	N	U	25	Y	N	N	72%	N
Siguret et al.	76	ICU	P	N	U	74	Y	N	N	88%	N
		NO									
Bowles et al.	77	ICU	P	N	U	35	Only LA	N	N	91%	N
Trahtemberg et al.	78	ICU	R	Y	U	22	N	Y	N	N/A	N
		NO									
Galeano-Valle et al.	79	ICU	P	N	U	24	N	N	N	N/A	N
Pascolini et al.	80	Both	P	N	U	33	N	N	N	25%	Y
Amezcua-Guerra et al.	81	ICU	R	N	U	21	N	Y	N	57%	N
Vollmer et al.	82	Both	P	N	U	79	Y	Y	y	N/A	Y
Espinosa et al.	83	Both	P	N	U	158	Y	Y	Y	37%	N
Gil-Etayo et al.	84	Both	P	Y	U	362	N	Y	Y	17%	Y
		NO									
Gasparini et al.	85	ICU	R	N	U	173	N	Y	N	35%	N
		NO									
Le joncour et al.	86	ICU	P	N	U	104	Y	Y	N	47%	Y
Frapard et al.	87	ICU	R	Y	U	68	Y	Y	N	30%	N
Xiao et al.	88	Both	R	N	U	66	Y	Y	N	47%	Y
		NO									
Cristiano et al.	90	ICU	R	Y	U	92	N	Y	N	N/A	N
Lerma et al.	91	Both	R	Y	U	64	N	Y	N	5%	N
Gatto et al.	93	NA	R	Y	M	122	Y	Y	N	N/A	N
Gendron et al.	94	Both	P	Y	M	154	Y	Y	N	N/A	N
Bertin et al.	96	Both	R	N	U	56	N	N	N	N/A	Y
		NO									
Gazzaruso et al.	97	ICU	R	N	U	45	Y	N	N	N/A	Y
		NO									
Anaya et al.	98	ICU	R	N	U	120	N	N	N	N/A	Y
Zuo et al.	99	Both	R	N	U	172	N	Y	N	52%	Y
Fan et al.	100	ICU	R	N	U	86	Y	Y	N	N/A	Y
		NO									
Reyes et al.	101	ICU	R	N	U	68	Only LA	N	N	N/A	Y
Vlachoyiannopoulos et al.	102	ICU	R	N	U	29	Y	N	N	N/A	N
		NO									
Rosales-Castillo et al.	103	ICU	P	N	U	189	Y	N	Y	N/A	N
Devreese et al.	104	ICU	P	N	U	31	Y	Y	N	74%	N
		NO									
Atalar et al.	105	ICU	R	N	U	73	Y	N	N	20%	N
Gutierrez et al.	106	Both	P	N	U	27	Y	Y	N	26%	N
		NO									
Previtali et al.	107	ICU	R	N	U	35	N	Y	N	N/A	N
Ferrari et al.	108	Both	P	N	U	89	Y	N	N	72%	N
		NO									
Sciascia et al.	109	ICU	P	Y	U	87	Y	Y	Y	53%	N
Tvito et al.	110	Both	R	N	U	43	Y	N	N	37%	N
Karahan et al.	112	ICU	R	Y	U	31	Y	Y	N	26%	N
Serrano et al.	122	Both	P	Y	M	474	Y	Y	N	24%	Y

Abbreviations: aPL: antiphopholipid antibodies, ICU: intensive care unit, LA: lupus anticoagulant; M: multicenter, N: no, N/A: not available, P: prospective, R: retrospective, U: unicenter, Y: Yes.

included in this review have determined extra-criteria aPL. Interestingly, extra-criteria aPL have been as frequently detected as consensus aPL [83], and even more prevalent in many studies [81,84–88]. However, there is great variability in the prevalence of these aPL. Prevalence of different extra-criteria aPL has been shown up to 24% for aPS/PT, [81] 19% for anti annexin A5 IgM patients [81], 33% IgA aCL [86] and 28.8% for IgA aβ2GPI [88], and their presence has been associated with more severity [89]. On the other hand, other studies reported low prevalence (<5%) of extra-criteria aPL [51,90,91].

Overall, the high aPL prevalence was confirmed in five multicenter studies [51,74,92–94]. Three of them included control populations (without COVID-19) to make a prevalence comparison.

Gatto et al. [93] made an aPL screening in a cohort of 122 patients, including hospitalized and home-quarantined. Despite finding high prevalence rates of 22% and 13.4% for LA and IgG aCL respectively, they found no significant differences when compared with cohorts of patients with primary APS or with other systemic autoimmune diseases.

Another study with the largest studied cohort included 474 patients, 35 of them suffered thrombotic events during follow-up. The prevalence for any aPL was 23.6% and the most prevalent aPL were IgA aβ2GPI with 15% positivity. Interestingly, no significant differences in aPL prevalence when compared with a reference population of similar age [92].

Gendron et al. [94] found a high prevalence for LA (70%); however, the prevalence of the rest of aPL is around 5%, except for IgG aPS/PT antibodies with 11% positivity, without significant differences in prevalence compared to patients without COVID-19.

The differences in prevalence of aPL observed in the numerous published studies vary depending on whether they analyze the aPL included in the classification criteria, or those not included. Diagnostic kits for criteria aPL are very well standardized, there are hardly any differences between the number of positives comparing the systems based on beads, with respect to those of solid phase. However, different detection systems for aPL not included in consensus, are very heterogeneous. Depending on the kit used, the number of positives is highly variable, especially in IgA aβ2GPI antibodies [51,95]. Studies which show low prevalence (<5%) for these aPL used this beads-based methods [51,94]. On the other hand, those studies which determined IgA aβ2GPI by solid phase-based assays, show higher prevalence levels [83,84,86,92].

5. Clinical association of aPL in COVID-19

There is not consensus about the pathogenicity of aPL during the SARS-CoV2 infection. The aPL have been observed only in critically ill patients [88], however there are many studies that report similar prevalences in patients with noncritical conditions [84–86,96]. Some studies have described a higher prevalence of aPL in patients with higher disease severity, ICU requirement, high mortality, ARDS, and renal or ventilation failure [80,83,87,88,92,96–98]. Combined aPL positivity is associated with a higher incidence of ischemic stroke in a cohort in which the most prevalent aPL are IgA isotype. Furthermore, the pathogenicity of IgG aPL has been demonstrated in an animal model [99].

Fewer studies found an association between aPL and thrombotic events and stroke [82,84,86,88,100,101]. A prospective study with 361 patients showed asscociation between aPL and incidence of thrombosis in the first six months after COVID-19 (OR: 3.7, 95% CI (1.7–8.1) [84]. Other multicenter study showed association of IgG aβ2GPI to thrombotic events; however, statistical significance was not found in multivariant analysis [92].

On the other hand, most studies, despite having shown the high prevalence of aPL, did not find clinical association with severe COVID-19, thrombosis, or other manifestations related to APS [51,71,76–79,81,83,85,87,90,91,93,94,102–110].

Some authors suggest that the aPL found in COVID-19 are different from those presented by patients with APS, so these would be an epiphenomenon without pathogenicity [51]. The aPL profile was different when comparing patients with known APS and patients with aPL detected in the context of infections [109]. Domain I of β2GPI is the main immunogenic epitope targeted by aβ2GPI antibodies in APS patients because it is strongly associated with thrombosis [111]. It has been described that only 5% recognize the β2GPI domain I in COVID-19 patients with aPL positivity [51]. A multicenter study that analyzed aPL in COVID-19 patients showed that the prevalence and titers of aPL or LA were not consistently increased nor associated with thrombosis when measured at a single timepoint [93]. The aPL profile in COVID-19 patients differed from that of APS patients but was similar to those suffering from other infections [109]. In their first measurement, they found that, although 52.9% of COVID-19 patients were positive for at least one aPL (29% LA positive, 10.3% positive for 2 or more aPL), no thrombotic events were observed in these patients.

The absence of association with the clinical manifestations of APS despite the high prevalence of aPL in patients with COVID-19 could be explained by the methodology of the different studies. Most of the studies did not include control cohorts, so there was no population to compare to be able to affirm the presence of high prevalence of aPL in COVID-19. The studies which include control group (other infections, or autoimmune diseases) did not show significant differences in aPL prevalence [84,87,93,94,109], except IgG and IgM aCL (59% vs 35% and 32% vs. 10% respectively) [78], LA [112] and IgA aβ2GPI [92]. It is known that elderly patients have higher prevalence of aPL [113] and other autoantibodies such as antinuclear antibodies [114]. However, studies typically use blood donor controls, this population only comprises ages 18–65 years [92].

The aPL cut-off is very important to estimate a prevalence figure as well as a clinical association. Most of the studies carried out have used the cut-off recommended by the manufacturer. However, given the great heterogeneity of geographical areas, as indicated by the classification criteria [53], the most appropriate way to set the aPL cut-off is to perform the 99th percentile on the population studied.

Another critical factor that influences the statistical association is the number of patients included in the studies. Most studies included fewer than 50 patients; therefore, for this review studies with fewer than 25 patients were excluded. This problem makes it very difficult to establish a statistical association between aPL and APS clinical events. Strikingly, the study with the largest cohorts did show an association between the presence of aPL and thrombosis [84,92].

The aCL have been reported in the context of infectious diseases as false positives [115,116]. In addition, aPL in COVID-19 very rarely recognize domain I of β2GPI [51]. The clinical association of IgM aPL with thrombosis is quite controversial [117]. However, aPL of IgG and IgA isotypes could already be performed before infection because it involves a class switch from IgM to IgG or IgA. This process requires a latency time that can last up to 2 weeks, so it is unlikely that these antibodies are generated during acute infection [118].

Methodology used to determine aPL is also very important. As occurs in prevalence, there is controversy about clinical clinical implications of IgA aβ2GPI antibodies. Because of the lack of standardization of the different assays, depending on the system chosen to detect these antibodies, results can be very heterogeneus [119]. To have reliability is mandatory to use accredited based on solid phase assays (ELISA). Thus, semi-solid phase systems have lower sensitivity (based on antigens-coated beads) [51,95]. This variability does not occur in the case of aPS/PT, because practically all the published studies used the same ELISA kit [51,74,78,83,84,87,88,91,93,99,104,107,109].

Plasma levels of β2GPI (main antigen of aPL) could indirectly play an important role beyond aPL. Although no relationship was found between the presence of aPL and clinical events, low serum β2GPI levels has been associated with a higher risk of ventilatory failure [56]. They have also been associated with greater predisposition for sepsis and mortality in ICU patients [120] and recover during convalescence [99]. Low levels of β2GPI are associated with recurrent thrombosis in patients with partial β2GPI deficiency (missense mutation), although the

mechanisms involved are unknown [121]. This suggests that both a decreased production or a high consumption of the protein could occur in situations of organic stress. Therefore, patients in the early stages of COVID-19 would react in a way similar to an acquired partial deficiency of β2GPI triggered by the infection. During recovery, this deficiency corrects itself, the patients recovering their β2GPI levels in blood. This hypothesis has been supported by the results of some studies [122].

6. aPL persistence

To meet APS classification criteria, aPL positivity must be confirmed in 2 determinations 12 weaks apart because they can appear temporarily and nonspecifically during acute infectious episodes [123]. However, most of the studies reviewed only made one determination, and those that did make a second, made it <12 weeks apart. Only 2 studies systematically confirmation to all aPL positive patients according to the classification criteria [82,83].

The aPL can become negative in the second determination. This phenomenon is more common for LA [82,83,88,104,109], but it has been observed also for the rest of aPL [109]. On the contrary, one study reported that LA can remain positive [103]. Levels of aCL and aβ2GPI antibodies do not present significant variations in a second measurement [82,104] a strong agreement between both determinations for criteria aPL (Weighted kappa: 0.85) and for IgA aβ2GPI antibodies (Weighted kappa: 0.91). However, concordance in measurements of anti-PS/PT antibodies was weak (Weighted kappa 0.43–0.52) [84]. The low agreement between aPS/PT samples could be due to already described correlation LA and aPS/PT antibodies [57]. In antibodies against SARS-CoV2, the opposite phenomenon occurs, where logically a large increase is observed in a second determination. This suggests that the presence of aPL is independent of infection in most patients with aPL [84]. However, Espinosa et al. [83] described that only 25% of retested patients presented with the same aPL profile in both samples.

7. Final remarks

COVID-19 leaves us with several lessons about aPL:

1. To carry out a prevalence study, control groups with demographic characteristics similar to the study population must be included, since otherwise it cannot be ensured that there is a high prevalence of aPL, without being able to compare with the free population of illness.
2. An adequate cut off must be used, avoiding using the one recommended by the manufacturer, and 99th percentile must be calculated according to the population to be studied.
3. Extra-criteria aPL can be associated with clinical events, and have been shown to be as prevalent or more so than consensus ones, so it is important to carry out a complete aPL screening, including both criteria and extra-criteria antibodies.
4. To determine IgA aβ2GPI antibodies, it is important to use standardized methods based on solid phase, avoiding those based on beads.
5. The heterogeneity of the results on the clinical association of aPL could be due to the fact that most of the studies are single-center and have been carried out in very small cohorts of patients, and in many cases with a low incidence of thrombotic events, which could lead to statistical hypothesis testing errors, both type I error (rejection of a true null hypothesis) and type II error (the mistaken acceptance of a false null hypothesis).
6. A second determination of aPL must be performed with a minimum separation of 12 weeks, since it has been seen that LA can become negative, although the rest of aPL do not usually become negative but can change the positivity profile of the antibodies.
7. Despite the lack of consensus on the role of aPL in COVID-19, studies with a larger number of patients have shown a clinical association.
8. Low serum levels of the protein β2GPI, the main target of aPL, could be associated to morbidity in the context of acute infection.

It is commonly accepted that aPL in the context of COVID-19 could be an epiphenomenon secondary to the infection. The aPL carriers could have 2 different behaviors. On the one hand, during the first days of infection, there is an aPL-independent mechanism secondary to SARS-CoV2 infection. And in the other hand, aPL carriers would have an additional later risk of thrombosis. The presence of aPL (first hit) is not sufficient to provoke a thrombotic event, it is necessary an intense inflammatory activity (second hit), like COVID-19, that triggers a thrombotic event [69, 127]. Thus, aPL would have an additive effect on the risk of thrombosis generated by the infection itself.

However, it has been demonstrated the pathogenesis in animal models [124] of aPL that recognize epitopes located in domains 3 and 4 of β2GPI [66,125]. Interestingly, these epitopes of domains 3 and 4 are found in hidden areas in the closed (circular) form of β2GPI (most common conformation in circulation), only exposed after the activation of the molecule and its transformation in open conformation [126].

In conclusion, this pandemic may be a unique opportunity to understand the relationship between infections and APS; however, in order to make a solid evaluation, multicenter studies with large cohorts of patients must be carried out, to avoid results as heterogeneous as those obtained to date, which may give a false idea that aPLs are of no importance in the context of COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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