

# COVID-19 and Antiphospholipid Antibodies: Time for a Reality Check?

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## Abstract

Antiphospholipid antibodies (aPL) comprise a panel of autoantibodies that reflect a potential prothrombotic risk in several autoimmune conditions, most notably antiphospholipid (antibody) syndrome (APS). aPL can be divided into those that form part of the laboratory criteria for APS, namely, lupus anticoagulant (LA), as well as anticardiolipin antibodies (aCL) and anti- $\beta$ 2-glycoprotein I antibodies (a $\beta$ 2GPI) of the immunoglobulin G and M classes, and those that form a group considered as “non-criteria antibodies.” The noncriteria antibodies include, for example, antiphosphatidylserine antibodies (aPS), antiprothrombin antibodies (aPT), and antiphosphatidylserine/prothrombin complex antibodies (aPS/PT). COVID-19 (coronavirus disease 2019) represents a prothrombotic disorder, and there have been several reports of various aPL being present in COVID-19 patients. There have also been similarities drawn between some of the pathophysiological features of COVID-19 and APS, in particular, the most severe form, catastrophic APS (CAPS). In this review, we critically appraise the literature on aPL and COVID-19. This is a companion piece to a separate review focused on LA. In the current review, we primarily concentrate on the so-called solid phase identifiable aPL, such as aCL and a $\beta$ 2GPI, but also reflect on noncriteria aPL. We conclude that aPL positivity may be a feature of COVID-19, at least in some patients, but in general, identified “solid-phase” aPL are of low titer and not able to be well-linked to the thrombotic aspects of COVID-19. Also, most publications did not assess for aPL persistence, and where persistence was checked, the findings appeared to represent transient aPL. Importantly, high-titer aPL or multiple aPL positivity (including double, triple) were in the minority of COVID-19 presentations, and thus discount any widespread presence of APS, including the most severe form CAPS, in COVID-19 patients.

## Keywords

- ▶ antiphospholipid antibodies
- ▶ anticardiolipin antibodies
- ▶ anti- $\beta$ 2-glycoprotein I antibodies
- ▶ lupus anticoagulant
- ▶ COVID-19
- ▶ microthrombosis
- ▶ thrombosis

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Antiphospholipid antibodies (aPL) comprise a broad panel of autoantibodies that reflect a potential prothrombotic risk in several autoimmune conditions, most notably antiphospholipid (antibody) syndrome (APS).<sup>1,2</sup> aPL can be divided into those that form part of the laboratory criteria for APS and those that do not, being the so-called non-criteria antibodies.<sup>1,2</sup> The aPL forming the laboratory criteria for APS comprise lupus anticoagulant (LA), as well as anticardiolipin antibodies (aCL) and anti- $\beta$ 2-glycoprotein I antibodies (a $\beta$ 2GPI) of the immunoglobulin (Ig) G and M classes.<sup>1,2</sup> The remaining aPL can thus be considered to form another group of aPL and alternatively defined as “noncriteria” antibodies. This latter class of antibodies comprises higher numbers of aPL types, and include, for example, any Ig class of antiphosphatidylserine antibodies (aPS), antiprothrombin antibodies (aPT), antiphosphatidylserine/prothrombin complex antibodies (aPS/PT), antiphosphatidylinositol antibodies, antiannexin V antibodies, and anti- $\beta$ 2GPI-domain 1 antibodies, and also aCL and a $\beta$ 2GPI of IgA class.

To be identified as having APS, there is a requirement to show evidence of at least one of the laboratory criteria (LA, IgG or IgM aCL, or a $\beta$ 2GPI), in medium or high titer, as well as their persistence by retesting on a second occasion some 12 weeks later, plus at least one of the clinical criteria—thrombosis or pregnancy morbidity.<sup>1,2</sup>

While several authors propose added value of noncriteria aPL,<sup>3–6</sup> current guidelines suggest insufficient evidence for their current inclusion as “criteria” aPL for APS.<sup>2</sup> On the other hand, there is also some debate about the value of some of the established criteria aPL, such as aCL IgM and a $\beta$ 2GPI IgM, for identification of APS.<sup>7–9</sup> In any case, LA appears to represent the entity with greatest relevance to thrombosis risk in APS among all the aPL,<sup>10</sup> perhaps followed by a $\beta$ 2GPI of IgG class.

COVID-19 (coronavirus disease 2019) is a prothrombotic disorder and there have been several reports of various aPL being present in COVID-19 patients. There have also been similarities drawn between some of the pathophysiological features of COVID-19 and APS, in particular, the most severe form, catastrophic APS (CAPS). In this review, we critically appraise the literature on aPL and COVID-19. This is a companion piece to a separate review focused on LA.<sup>11</sup> In the current review, we primarily focus on the so-called solid phase identified aPL, such as aCL and a $\beta$ 2GPI, but also reflect on the noncriteria aPL.

## COVID-19

COVID-19 has been declared a pandemic by the World Health Organization (WHO), and is caused by infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). COVID-19 is thought to have originated in Wuhan, China, in late 2019, and at the time of writing has infected over 120 million people and caused nearly 2.7 million deaths.<sup>12</sup> Severe COVID-19 is first and foremost a prothrombotic disorder,<sup>13</sup> with thrombosis appearing in various forms. For example, a recent meta-analysis has indicated a venous thrombosis rate,

including deep vein thrombosis and pulmonary thrombosis, of close to 30% in severe COVID-19.<sup>14</sup> Acute myocardial ischemia (infarction) and cerebrovascular accidents may also develop in as many as 8 and 3% of COVID-19 patients needing intensive care,<sup>15</sup> while systemic coagulopathy and disseminated intravascular coagulation may occur in as many as 7% of such patients.<sup>16</sup> Evidence of microthrombosis in multiple organs including lungs, kidneys, and liver also occurs, although it is only identifiable on autopsy in patients who have died due to COVID-19.<sup>17–20</sup>

As part of a search to investigate the mechanisms that promote thrombosis in COVID-19, many tests of hemostasis have been investigated in patients suffering from this disease. Indeed, many hemostasis tests are abnormal in patients with COVID-19.<sup>21,22</sup> Moreover, COVID-19 appears to affect all aspects of hemostasis, including primary hemostasis (endothelium, platelets, von Willebrand factor), secondary hemostasis/coagulation, and fibrinolysis.<sup>23–28</sup>

## COVID-19 and APS?

Relevant to this review is that there have been several reports of similarities between some of the pathophysiological features of COVID-19 and APS, in particular, the most severe form, CAPS.<sup>29–31</sup> For example, patients with COVID-19 appear to fulfil the main clinical diagnostic criteria for CAPS, with the criteria being evidence of involvement in three or more organs, development of manifestations simultaneously or in less than a week, and confirmation by histopathology of small vessel occlusion in at least one organ.<sup>29</sup> There have also now been many reports identifying various aPL in COVID-19 patients. The search for aPL in COVID-19 may have been sparked by an early publication by Zhang et al<sup>32</sup> in the *New England Journal of Medicine*.

Given that (1) aPL are associated with thrombosis, (2) patients with COVID-19 suffer thrombosis, (3) some aspects of COVID-19 pathology strongly resemble (catastrophic) APS (CAPS), and (4) aPL have been identified in COVID-19 in several studies, several questions arise, including that of the significance of the aPL in COVID-19, as well as any potential involvement in COVID-19 pathology. Is APS, or indeed CAPS, really a feature of COVID-19? We critically appraise the literature to help address these questions. We, however, note that the current review is a companion piece to a previous related review on LA.<sup>11</sup> Here, we focus on the so-called solid phase detected aPL.

## Thrombosis-Associated aPL versus Laboratory-Detected aPL

Similar to the previous review on LA,<sup>11</sup> despite an association of aPL with thrombosis risk in APS and in other potential autoimmune diseases, the presence of a laboratory-detected aPL per se does not, in itself, reflect prothrombotic risk factors, even if persistent, and does not warrant pharmacological intervention in asymptomatic patients,<sup>33,34</sup> except perhaps for those with high-titer aPL and multiple positivity.<sup>35,36</sup> Indeed, laboratory-detected aPL may be found in asymptomatic patients, and otherwise reflect chance

findings. Many of the patients in whom aPL are detected will not develop thrombosis.

### aPL Testing Guidelines and Assay Cut-offs

There are several groups who have provided guidelines on aPL testing.<sup>1,2,7-9,37-39</sup> These identify not only the various types of aPL tests, but also, in some cases, how they should be performed. For example, the LA guidelines provide advice on performance of clot-based (“liquid phase”) tests, and include which tests to perform and also procedural processes on how they should be performed and interpreted.<sup>37-39</sup> Likewise, guidance for the “solid phase” aPL is also available, including which tests to perform and also procedural processes on how they should be performed and interpreted.<sup>1,2,7-9</sup> It needs also to be recognized here, however, that manufacturers of aPL assays cannot be mandated to produce assay kits according to these guidelines and that, in reality, a wide range of methodologies and assays may be employed to identify aPL. Thus, although different workers may report on the same apparent aPL (e.g., aCL of IgG class), differences in methods of detection (e.g., enzyme-linked immunosorbent assay [ELISA] vs. chemiluminescence immunoassay [CLIA]) mean that different findings may be reported using different methods for that same aPL. Therefore, variation in literature reporting for any given aPL will reflect a variety of factors, including both a difference in the COVID-19 cohort evaluated and the method employed to detect a particular aPL.

Furthermore, there are differences in how laboratories and manufacturers may assign a cut-off value for defining a positive aPL result. In general, the recommendations indicate the 99th percentile of at least 120 normal individuals, or >40 GPL or MPL units. However, some methods and laboratories will assign positivity with lower cut-off values, and thus potentially identify a greater proportion of aPL-positive cases. According to current guidelines, APS is not assigned unless medium to high titers are identified (generally meaning >40 GPL or MPL units).<sup>1,2</sup> Furthermore, many automated methods for solid-phase aPL are now available, including chemiluminescence-based immunoassays (e.g., CLIA on AcuStar/BioFlash). These methods may use alternate units such as arbitrary chemiluminescence units (CU). Interestingly, the manufacturers may have tried to at least partially harmonize cut-off values, which in most cases are around 20 GPL, MPL, or CU. However, other cut-off values may be used, depending on the assay and methodology, such as 8, 15, or 40 GPL, MPL, or CU.

### Literature Search

To give some additional background to this narrative review, we searched the PubMed database (<https://pubmed.ncbi.nlm.nih.gov>) using various iterations of COVID-19 together with various iterations of LA and (anti)phospholipid antibodies. An initial search performed on February, 22, 2021, was later updated to be current as of March 6, 2021. Of over 200 separate articles identified by this search, we then excluded general reviews, commentaries, and papers otherwise found to be irrelevant to the topic. We also

excluded single-case reports, but small case series were included.

### Results of the Literature Review: Is aPL Present in COVID-19?

We have already described the literature on LA in COVID-19.<sup>11</sup> A summary of the literature arising from our search and related to other (i.e., solid phase identified) aPL is given in ►Table 1. Note, however, that some studies reported on both solid-phase aPL and LA, and in some cases did not separately identify findings. Irrespective, as for the case with LA,<sup>11</sup> there was also a large body of publications related to solid-phase aPL.<sup>31,32,40-76</sup> Although additional relevant papers are likely available in the literature, the captured articles are sufficient for us to critically review the main literature to date. As for LA,<sup>11</sup> there was a wide variety of methods employed to identify solid-phase aPL (►Table 1), but sometimes the methodology was not reported. There was a wide variety also in COVID-19 case numbers and type, including in some reports “severe” COVID-19, using a variety of definitions (i.e., needing mechanical ventilation or intensive care; mortality).

Of interest, solid-phase aPL was not always detected in patients with COVID-19, as some studies clearly reported “no aPL” or very few cases of aPL in their patient cohort (►Table 1). However, most publications instead reported a small or notable proportion of their COVID-19 cohorts as expressing solid-phase aPL, although the incidence rarely approached that identified for LA, in which >80% of COVID-19 cases were sometimes identified to have LA.<sup>11</sup> Nevertheless, like the case for LA, there does also seem to be a dichotomy of opinions around the presence or not of solid-phase aPL in COVID-19. To put a graphical perspective to the data, ►Fig. 1 plots the findings from the literature identified in ►Table 1 according to percentage positive for aPL versus number of investigated cases. A statistically relevant pattern cannot be seen. Note, however, that in some publications aPL were described as a composite and thus would also have included LA.

One of the earliest reports on the presence of aPL in COVID-19 was by Zhang et al.<sup>32</sup> This was a case series report of three patients with COVID-19 in intensive care unit who suffered serious sequelae including multiple infarcts in which aPL were detected. This study no doubt prompted a wider search for aPL in subsequent COVID-19 cohorts, but can be criticized in many ways. First, the methodology used for aPL detection was not identified, nor were the titers of identified aPL (high or low?). Persistence of aPL was also not evaluated. As the study focused on a particular small group of COVID-19 patients, there was also clear patient selection bias. In other words, the study focused on three patients with serious clinical sequelae who also happened to have aPL. There was no evidence of cause or effect. To take a dichotomous perspective, the first paper we identified to report on COVID-19 in this arena was from Yasri and Wiwanitkit, in 2020.<sup>40</sup> These investigators used data collected “according to public official report of CDC of Thailand, the second country

**Table 1** Summary of literature related to antiphospholipid antibody (aPL) testing in COVID-19

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Yasri and Wiwanitkit 2020 <sup>40</sup>	From accumulated 2,369 COVID-19 patients (as of August 4, 2020) with 30 deaths, 1 patient (0.04%) had APS	2,369	NR	71 (0.04%)	NR	NR	NR	NR	
Lerma et al 2020 <sup>41</sup>	64 COVID-19	64	BioPlex 2200 APLS multiplex platform (Bio-Rad) for IgG and IgM aCL and aPL; aPL: IgG aPL and aPL = prior history aPL/SLE; 1 × IgM aPL and aPL; 1 × IgM aPL/PT; 3 patients had aPL/PT IgM and 1 × IgG	Total 6/64 (9.4%) had positive aPL; 3 patients had aPL by aPL and aPL (1 × strong IgG aPL and aPL = prior history aPL/SLE; 1 × IgM aPL and aPL; 1 × IgM aPL/PT); 3 patients had aPL/PT IgM and 1 × IgG	NR	No evidence of COVID-19-related VTE in any aPL-positive patient	NR	No	
Zhang et al 2020 <sup>32</sup>	3 cases with COVID-19 ICU	3	NR	3 cases positive for aCL IgA, aPL IgA, and IgG	NR	NR	NR	Yes (Neg)	Selection bias
Galeano-Valle et al 2020 <sup>42</sup>	24 COVID-19 pneumonia and diagnosed DVT or PE (from 785 COVID-19 patients admitted to internal medicine ward); incidence of VTE in this population was 6.5%; none had known thrombophilia; 45.8% patients presented PE alone, 9 (37.5%) patients presented DVT alone, and 4 (16.6%) patients presented PE and DVT	24	aCL and aPL ELISA (Orgentec) aCL NRR was IgM 0–7 U/mL, IgG 0–10 U/mL; aPL NRR was IgM 0–8 U/mL, IgG 0–8 U/mL	2 patients (8.3%) weakly positive for: aCL IgM (19.3 U/mL, 15.8 U/mL); aPL IgM (14.1 U/mL, 16.2 U/mL); aCL IgG and aPL IgG negative in all patients	Yes	"Prevalence of aPL among COVID-19 patients with VTE in our cohort was low, suggesting that these might not be involved in the pathogenesis of VTE in patients with severe COVID-19 pneumonia"	NR	"LA not assessed since testing not recommended in acutely ill patients and under anticoagulant therapy"	
Previtali et al 2020 <sup>31</sup>	75 patients deceased due to COVID-19. Serum samples, collected 24 hours before death and frozen at –20°C, were available only for 35 patients out of 75 autopsies	35	IgA, IgG, and IgM aCL and aPL by Bio-FLASH CIA (Inova Diagnostics); manufacturer's cut-off 20 CU used; IgG and IgM aPL/PT by commercial ELISA (QUANTA Lite, Inova Diagnostics), using manufacturer's cut-off (30 units).	3/35 (8.6%) were aPL-positive: 1 × aCL IgG and 2 × aCL IgM but all values were low (<3 × the cut-off). No patients were positive for aCL IgA or for any aPL isotype. 3/35 (8.6%) patients were positive for aPL/PT, 1 × IgG and 2 × IgM, but values were <2 × cut-off. No patient showed simultaneous positivity for aCL and aPL/PT	Yes	"Our patients fulfilled the main clinical diagnostic criteria for CAPS: evidence of involvement in three or more organs; development of manifestations simultaneously or in less than a week, confirmation by histopathology of small vessel occlusion in at least one organ. However, almost all the patients were negative for aPL. Only 6/35 (17.1%) patients showed very low and not relevant antibodies levels. Slightly and transient increase of aPL may be a common finding during any kind of infection, whereas CAPS is always characterized by very high levels of aPL"	NR	No	"On the basis of our results, CAPS is probably not involved into the pathogenesis of COVID-19"
Gatto et al 2020 <sup>43</sup>	122 COVID-19; 53 hospitalized, 69 nonhospitalized	122	IgG/IgM aPL and aCL assayed using homemade ELISA methods following European Forum on aPL antibody recommendations. Cutoff values for medium-high levels calculated as greater than 99th percentile of sera from 120 healthy blood donors matched for age and sex with study	Overall ~18%: IgG aCL: 15/112 (13.4%); IgM aCL: 3/112 (2.7%); IgA aCL: 2/121 (1.7%); IgG aPL: 7/112 (6.3%); IgM aPL: 8/112 (7.1%); IgA aPL: 4/121 (3.3%). No substantial differences in rates in hospitalized vs. nonhospitalized	Yes	No. "We could not demonstrate a significant association between positive aPL and thrombosis in this relatively large cohort of COVID-19 patients. ...thereby questioning the true pathogenic value of such findings during acute SARS-CoV-2 infection"	NR	Yes	Provided useful comparative data on other autoimmune rheumatic diseases (oARD) and APS

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Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Signoret et al 2020 <sup>44</sup>	74 consecutive mechanically ventilated patients with COVID-19. Received prophylactic (73%) or therapeutic (27%) LMWH or UFH on admission. Thrombotic events reported in 28 patients (38%), including 26 DVT, 4 PE, 1 stroke, and 1 extensive venous catheter thrombosis	74	$\beta$ 2GPI-dependent aCL IgG/IgM and $\beta$ 2GPI IgG quantified using CLIA (Acustar, Werfen)	Elevated aCL IgG/IgM and/or $\beta$ 2GPI IgG antibodies, in 5/74 (18%) and 4/74 (9%), respectively	Partly, 9 patients (12%) had elevated aCL IgG/IgM and/or $\beta$ 2GPI IgG (titer ranges, 23–100 CU [N=7], 24–237 [N=2], and 21–64 [N=3]), including 7 with positive LA and two with negative LA	No	NR	Yes (more prevalent than other aPL)	
Fan et al 2020 <sup>45</sup>	86 patients with confirmed COVID-19. 7/86 exhibited new stroke and 6 (7%) cases were ischemic (i.e., patients with acute ischemic stroke [AIS])	86	"APS panel," including aPL (unspecified methods)	NR (12/86 [37.5%] were positive with APS panel; 7/80 [26.9%] patients without AIS; 5/6 [83.3%] patients with AIS)	No	Yes. A significantly higher prevalence of aPL observed in patients with AIS than in those without stroke (83.3 vs. 26.9%, $p < 0.05$ )	NR	Yes (part of "APS panel")	
Pineton de Chambrun et al 2021 <sup>46</sup>	Assessed aPL profile in 25 patients with prolonged aPTT and confirmed SARS-CoV-2 admitted to ICU	25	aCL (IgG/IgM) (QUANTA Lite, Inova) and $\beta$ 2GPI (-IgG/IgM/A; Thromboscintific), and "aPL panel" (IgG/IgM; PHOSPO-USA, THERADIAG; includes aPS, antiphosphatidyl ethanolamine, aCL, and $\beta$ 2GPI antibodies)	LA, aCL, $\beta$ 2GPI, and "aPL panel" were positive in 23/25 (92%), 13/25 (52%), 3/25 (12%), and 18/25 (72%) patients, respectively	Yes	NR	NR, but mentioned important for future studies to confirm APS	Yes (dRVVT)	Selection bias; assessed patients with COVID-19 and aPL identified by prolonged aPTT
Popovic et al 2021 <sup>47</sup>	83 patients who underwent primary percutaneous coronary intervention for STEMI comprising 11 COVID-19 and 72 non-COVID	11	NR	"APS" in 4/11 COVID-19 (36.4%) (3/7 aCL; 1/7 $\beta$ 2GPI); cf. 7/72 (9.7%) non-COVID-19 (7/72 aCL; 7/72 $\beta$ 2GPI)	No	No	ND	No	aPL positivity does not in itself identify APS
Rothstein et al 2020 <sup>48</sup>	844 hospitalized patients with COVID-19; 20 (2.4%) had confirmed ischemic stroke, and 8 (0.9%) had ICH	844	NR	aPL present in 7/9 (78%) tested patients with ischemic stroke; exclusively aCL, with no patient having	No	No	NR	Yes	

Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Devreese et al 2020 <sup>19</sup>	31 consecutive confirmed COVID-19 patients admitted to ICU	31	aCL and aβ2GPI IgG, IgM, and IgA measured by AcuStar CLIA (Werfen). A cut-off value of 20 U/mL applied. aPS/PT IgG and IgM measured by QUANTA Lite ELISA (Inova Diagnostics) with cut-off value 30 U/mL	newly positive aβ2GPI antibodies or LA 23/31 (74.2%) patients had at least one aPL positive. 8/31 (25.8%) patients were negative for all criteria aPL (LA, aCL, and aβ2GPI IgG and IgM). Positive aPL as follows: IgG aCL: 6/31 (19.4%); IgM aCL: 1/31 (3.2%); IgA aCL: 3/31 (9.7%); IgG aβ2GPI: 2/31 (6.5%); IgM aβ2GPI: 1/31 (3.2%)	Yes. Most aPL positive were low titers (e.g., titers of aCL IgG ranged from 22.4 to 36.2 U/mL). Triple-positive patients were rare, and titers of aCL and aβ2GPI were high only in minority of patients	No. 7/19 thrombotic patients had at least one aPL. 16/22 patients without thrombosis were aPL positive, among them two triple positives.	4/5 retested aPL-positive patients were negative on a second occasion; 5th had reduced titer; cf. original result	Yes	"The aPL antibody profiles demonstrated in COVID-19 patients have a low-risk profile for thrombosis"
Reyes et al 2020 <sup>50</sup>	187 aPL tests requested in 2-month period of 2020; 119 non-COVID vs. 68 with COVID	68	NR	Positive/tested (%): • No thrombotic vs. thrombotic event: n = 36 vs. 32; aCL IgG antibody 0/32 vs. 0/30. ACL IgM antibody 0/32 vs. 1/30 (3.3%). aβ2GPI IgG 0/32 vs. 0/32. aβ2GPI IgM 0/30 vs. 1/30 (3.3%) • LA negative vs. LA positive: n = 36 vs. 32. aCL IgG 0/34 vs. 0/28. aCL IgM antibody 0/34 vs. 1/28 (3.6%). aβ2GPI IgG 0/35 vs. 0/27. aβ2GPI IgM 0/33 vs. 1/27 (3.7%). Prior APS 0 vs. 1 (3.3%) (p = NS for all)	No	No (except LA).	Not mentioned, except in introduction as important for APS diagnosis	Yes	Selection bias; assessed COVID-19 patients in whom aPL were requested
Amezcu-Guerra et al 2020 <sup>51</sup>	21 patients hospitalized in ICU over a 1-week period, due to severe or critical COVID-19 vs. 12 controls	21	aCL, aβ2GI, aPT, aPS, antiphosphatidylinositol and antiannexin V antibodies were measured, each in IgM and IgG isotypes	12/21 (57.1%) overall: Positive aPL antibodies, n (%) Total group (n = 21) vs. positive aPL group (n = 12): aCL IgM 3 (14%) vs. 3 (25%) aCL IgG 2 (10%) vs. 2 (17%) aβ2GPI IgM 0 vs. 0 aβ2GPI IgG 1 (5%) vs. 1 (8%) aPT IgM 1 (5%) vs. 1 (8%) aPT IgG 0 vs. 0 aPS IgM 3 (14%) vs. 3 (25%) aPS IgG 2 (10%) vs. 2 (17%) Antiphosphatidylinositol IgM 0 vs. 0 Antiphosphatidylinositol IgG 0 vs. 0 Antiannexin V IgM 4 (19%) vs. 4 (33%)	No	"The occurrence of hospital outcomes was followed up to 30 days after aPL antibody measurement. Two patients presented PE despite being on heparin"	NR	No	"12/21 (57.1%) had at least one circulating aPL, vs. only 1/12 controls (p = 0.009). The most frequently detected aPL antibodies were antiannexin V IgM (19%), aCL IgM (14%), aPS IgM (14%), aCL IgG (10%), and aPS IgG (10%). One patient had triple positivity (8%); three patients had double positivity (25%); and the

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Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
de Ocaiz et al 2020 <sup>52</sup>	27 COVID-19 cases that had been tested for aPL during their hospital stay	27	aCL (IgM and IgG) and aβ2GPI (IgA, IgM, IgG) by commercial ELISA (QUANTA Lite, Inova Diagnostics)	Antianxin V IgG1 (5%) vs. 1 (8%) aCL in 0% (0/27) aβ2GPI in 3.7% (1/27)	No	No	NR	Yes (positivity in 6/27 [22.2%]). No double antibody positivity was found	remaining eight had single positivity (6.7%) Selection bias; COVID-19 that had been tested for aPL during their hospital stay
Cuenca Saez and Gomez-Biezna, 2020 <sup>53</sup>	11 patients with chilblain-like lesions, some of whom had had clinical manifestations associated with SARS-CoV-2 infection up to 2 weeks prior to onset of the skin lesions. 5 later identified with COVID-19	5	NR	"All 5 COVID-19 patients had increased IgA aCL; while this increase was slightly high, it was not considered positive according to the reference parameters of the external laboratory"	No	NR	NR	Yes, but NR	
Tvito et al 2021 <sup>54</sup>	43 consecutive COVID-19	43	aCL IgM/IgG and aβ2GPI IgM/IgG performed by commercial ELISA (ORGENTEC)	aCL and aβ2GPI negative in all patients	No	No	NR	Yes, 16/43 (37%) LA positive	
Bertin et al 2020 <sup>55</sup>	56 COVID-19 patients. Cohort divided into moderate (n = 27) vs. severe group (n = 29) according to clinical presentation at sampling	56	aCL and aβ2GPI (IgG, IgM) performed by ELISA (method not otherwise reported)	Moderate vs. severe: aCL IgG 3/27 (11.1%) vs. 13/29 (44.8%) aCL IgM 3/27 (11.1%) vs. 0/29 (0%) aβ2GPI IgG 1/27 (3.4%) vs. 0/29 (0%) aβ2GPI IgM 2/27 (6.8%) vs. 2/29 (6.9%)	No	Yes. "Differences in the aPL profile between the two groups were observed only for IgG aCL. Univariate and multivariate analyses showed that the levels of IgG aCL were significantly associated with severe COVID-19 manifestations (odds ratio [OR] = 6.50; p = 0.009) and (OR = 8.71; p = 0.017), respectively"	NR	No	
Ferrari et al 2020 <sup>56</sup>	89 consecutive patients hospitalized for COVID-19. Also, separated into severe (n = 31) vs. nonsevere (n = 58)	89	aCL and aβ2GPI (IgG, IgM) measured using CLIA (AcuStar, Werfen). Cut-off values to define positivity as previously calculated by reagent manufacturer, according to Sydney revised Sapporo criteria, using 99th percentile of the distribution of results in 250 apparently healthy blood bank donors harmonized to 20 U/ml for all antibodies	"71.9% patients presented at least one positive aPL test. There was no difference in prevalence between groups. For 59 patients (66.3%), the aPL positive test was an LA (median titer of 1.36 [IQR, 1.33–1.41]); for 6 cases (6.7%), it was aβ2GPI, IgG alone in 4 cases, IgM alone in 1 case, both IgG and IgM in 1 case, with a median titer of positivity of 44.7 (IQR, 23–1.404). In 7 cases (7.9%), it was an aCL. IgG in 5 cases, IgM in 2 cases, with median titer of positivity of 36.3 (IQR, 23–260). 2 patients (2.2%) were double positive (LA + aβ2GPI for both), and 3 (3.4%) were triple positive.	Yes (but combined ranges for IgG and IgM)	No difference in aPL (or LA) positivity between severe and nonsevere COVID-19. No correlation between aPL positivity and occurrence of DVT or PE, nor with mortality during hospitalization	NR	Yes	

Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments		
Pascolini et al 2021 <sup>57</sup>	33 consecutive patients with COVID-19; 31 (94%) with interstitial pneumonia, vs. 25 age- and sex-matched patients with fever and/or pneumonia with etiologies other than COVID-19 as the pathological control group	33	aCL and aβ2GPI (IgG, IgM) assessed using FEIA (Thermo Fisher).	All results were confirmed in a second assay. 15/33 (45%) tested positive for at least one autoantibody, including 11 who tested positive for ANAs (33%), 8 positive for aCL (IgG and/or IgM; 24%), and 3 positive for aβ2GPI (IgG and/or IgM; 9%).	Yes	Yes. "Patients who tested positive for autoantibodies had a significantly more severe prognosis than other patients: 6/15 patients (40%) with autoantibodies died due to COVID-19 complications during hospitalization, whereas only 1/18 patients (5.5%) who did not have autoantibodies died (p = 0.03). Patients with poor prognosis (death due to COVID-19 complications) had a significantly higher respiratory rate at admission (23 breaths per minute vs. 17 breaths per minute; p = 0.03) and a higher frequency of autoantibodies (86 vs. 27%; p = 0.008)."*	NR	No			
Hasan Ali et al 2020 <sup>58</sup>	64 patients with COVID-19; divided into cohort with mild illness (nCOVID; 41%), discovery cohort with severe illness (sdCOVID; 22%), and confirmation cohort with severe illness (sccCOVID; 38%)	64	aCL and aβ2GPI (IgG, IgM) by FEIA on a Phadia 250 analyzer (Thermo Fisher Diagnostics AG, Switzerland).	NR	Yes, partly.	Yes. "Severely ill COVID-19 patients had significantly higher aCL IgA (sdCOVID mean, 6.38 U/ml [SD, ±0.96; p < 0.001]; sccCOVID mean, 4.86 U/ml [SD, ±0.84; p < 0.001]), aβ2GPI IgA (sdCOVID mean, 8.50 U/ml [SD, ±3.86; p < 0.001]), sccCOVID mean, 4.71 U/ml [SD, ±2.17; p < 0.001], and aCL IgM (sdCOVID mean, 4.01 U/ml [SD, ±0.88; p = 0.003]; sccCOVID mean, 10.35 U/ml [SD, ±5.48; p < 0.001]). We found significant differences only in the sdCOVID but not the sccCOVID cohort with 2 other aPL antibodies: aCL IgG (sdCOVID mean, 8.23 U/ml [SD, ±4.02; p = 0.02]; sccCOVID mean, 2.42 [SD, ±0.54; p = 0.09]) and aβ2GPI IgG (sdCOVID mean, 1.57 U/ml [SD, ±0.23; p = 0.002]; sccCOVID mean, 1.58 U/ml [SD, ±0.85; p = 0.15]). No significant difference was found among aβ2GPI IgM among the cohorts (sdCOVID mean, 1.07 U/ml [SD, ±0.25; p = 0.16]; sccCOVID mean, 2.00 U/ml [SD, ±0.72; p = 0.16])"		No	ND, but mentioned important for future studies to confirm APS	Only 1 patient in terminal-stage group had positive LA accompanied with high level of multiple aPLs (IgA aCL > 352.0 CU; IgA aβ2GPI, 396.7 CU; IgG aCL, 20.2 CU; IgG, aβ2GPI 45.5 CU)	
Zhang et al 2020 <sup>59</sup>	20 COVID-19 patients admitted to ICU	20	aCL and aβ2GPI (IgG, IgM, IgA) determined by CLIA (QUANTA Flash assays, Inova Diagnostics) according to manufacturer instructions. Cut-off values for positivity were set > 20 CU based on manufacturer recommendations.	10/19 patients (52.6%) had positive aCL and/or aβ2GPI, and 7/10 patients had multiple isotypes of aPLs. (n positive for separate aPL: aCL IgG 6, IgG 2, IgM 1; aβ2GPI IgA 7, IgG 6, IgM 0; LA 1)	No	"All 4 patients who developed cerebral infarction during the hospitalization had aPLs with multiple isotypes. No thrombotic events occurred in 9 aPL negative patients. Patients positive for aPLs had lower 28-day mortality compared to those with negative for aPL (40.0 vs 88.9%, odd ratio 0.074, 95% CI 0.139–0.871, p 0.057)"*			Yes (LA reported present in 5/12 reported patients)		
Tan et al 2020 <sup>60</sup>	Review of all studies reporting acute ischemic stroke (AIS) occurrence in	135	Varied/ unspecified (review)	For aCL, 20% (2/10) tested positive for IgM and 42.9% (3/7) tested positive for IgA.	No	"A notable number of (AIS) cases tested positive for aPL and a high mortality rate (38%) was reported (in COVID-19 AIS)"	NR				

(Continued)



Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Lee et al 2020 <sup>61</sup>	COVID-19 patients. 39 studies comprising 135 patients; pooled incidence of AIS in COVID-19 patients was 1.2%			No patient (0/9) tested positive for IgG aCL. For aβ2GPI: 10% (1/10) of those tested were positive for IgM. 38.5% (5/13) tested positive for IgG, and 42.9% (3/7) tested positive for IgA	No	No	NR	Yes, mentioned	
	28 studies included in a systematic review; 7 studies for the meta-analysis. The pooled frequency of stroke in COVID-19 patients was 1.1% (95% CI: 0.8–1.3). A total sample of 8,771 participants included in the systematic review	8,771	Varied/unspecified (review)	"The majority of studies did not capture information on presence of aPL. Of 9 studies reporting information, 7 reported positive findings for presence of aPL and 2 reported the absence of aPL"	No	No	NR	NR	
Tu et al 2020 <sup>62</sup>	9 studies and 14 COVID-19 patients with cerebral venous thrombosis	14	Varied/unspecified (review)	2/14 (14.3%) patients positive for aPL	No	No	NR	NR	
Xiao et al 2020 <sup>63</sup>	66 COVID-19 patients who were critically ill and 13 COVID-19 patients who were not critically ill	79	aCLs and aβ2GPI (IgG, IgM, IgA) by CLIA, and IgG anti-β2GPI–domain 1 (anti-β2GPI–D1), IgM and IgG anti-β2GPI by ELISA	"aPLs detected in 31/66 (47%) critical COVID-19, aPL not present among COVID-19 patients not in critical condition. IgA aβ2GPI antibody was the most commonly observed aPL in patients with COVID-19 and was present in 28.8% (19/66) of the critically ill patients, followed by IgA aCL (17/66, 25.8%) and IgG aβ2GPI (12/66, 18.2%). For multiple aPLs, IgA aβ2GPI + IgA aCLs was the most common antibody profile observed (15/66, 22.7%), followed by IgA aβ2GPI + IgA aCL + IgG aβ2GPI (10/66, 15.2%). aPL emerged ~35–39 days after disease onset"	Selected patients shown graphically	Yes. "Patients with multiple aPLs had a significantly higher incidence of cerebral infarction compared to patients who were negative for aPLs ( $p=0.023$ )"	NR	Yes (2/66 [3.0%] critically ill patients were LA positive)	
Borghesi et al 2020 <sup>64</sup>	ELISA and chemiluminescence assays were used to test 122 sera of patients suffering from severe COVID-19. Of them, 16 displayed major thrombotic events	122	aCL and aβ2GPI detected by CLIA QUANTA Flash (- IgG/IgA/IgM; Inova Diagnostics, San Diego, CA) according to manufacturer instructions. Cut-off values were 20 CU. In-house ELISAs were also used for detection of aCL IgG/IgM and aβ2GPI IgG/IgA/IgM. aPS/PT IgG/IgM detected by	"aβ2GPI IgG/IgA/IgM was the most frequent in 15.6/6/9.0% of patients, while aCL IgG/IgM was detected in 5.7/6.6% by ELISA. Comparable values were found by CLIA, aPS/PT IgG/IgM detectable in 2.5 and 9.8% by ELISA. Reactivity against domain 1 and 4–5 of β2GPI was limited to 3/58 (5.2%) tested sera for	Provided graphically; comparison clearly showed lower aPL titers in COVID-19 patients than found in classical APS	No association between thrombosis and aPL was found	NR	No	"aPL show a low prevalence in COVID-19 patients and are not associated with major thrombotic events. aPL in COVID-19 patients are mainly directed against β2GPI but display an epitope specificity

**Table 1** (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Woodruff et al 2020 <sup>65</sup>	31 critically ill patients with COVID-19 and no known history of autoimmunity (later magically morphed to 52)	31 or 52?	commercial ELISA (otherwise unspecified)	each domain and did not correlate with aCL/ab2GPI or with thrombosis*	No	"The presence of autoreactivity could be clearly correlated with increasing serum levels of CRP"	NR	NR	different from antibodies in APS"
Fan et al 2020 <sup>66</sup>	12 ICU patients with severe COVID-19 (either mechanical ventilation or on high-flow oxygen)	12	aCL (IgM, IgG) quantified using Inova ELISA; ab2GPI using Euroimmun ELISA, both performed on Inova Quanta-Lyser 3000	2/4 (50%) patients tested positive for aPL (aCL IgG ×1; aCL IgM ×2; ab2GPI ×2).	No	NR (all patients were severe)	NR	Yes (LA detected in 6/12 (50% patients)	"These findings suggest that half of patients hospitalized with COVID-19 become positive for aPL and that these autoantibodies are potentially pathogenic"
Zuo et al 2020 <sup>67</sup>	Measured 8 types of aPL in serum samples from 172 patients hospitalized with COVID-19	172	aPL quantified in sera using: Quanta Lite kits (Inova Diagnostics Inc.) according to manufacturer instructions. aCL: IgG, IgM, IgA ab2GPI: IgG, IgM, IgA aPS/PT: IgG, IgM	Any positive aPL 89/172 (52%), comprising: aCL: IgG 8/172 (4.7%), IgM 39/172 (23%), IgA 6/172 (3.5%) ab2GPI: IgG 5/172 (2.9%); IgM 9/172 (5.2%), IgA 7/172 (4.1%); aPS/PT: IgG 42/172 (24%), IgM 31/172 (18%)	No	"Higher titers of aPL associated with neutrophil hyperactivity, including release of neutrophil extracellular traps (NETs), higher platelet counts, more severe respiratory disease, and lower clinical estimated glomerular filtration rate. Similar to IgG from patients with APS, IgG COVID-19 promoted NET release from neutrophils isolated from healthy individuals. Furthermore, injection of IgG purified from COVID-19 patient serum into mice accelerated venous thrombosis in two mouse models"	Mentioned as criteria for APS, but not mentioned for this study	No	"Relevant clinical information (whether patients were receiving anticoagulation therapy at the time of LAC testing or had a history of aPL positivity/APS) was rarely provided
Gazzaruso et al 2020 <sup>68</sup>	250 COVID-19 patients from 23 studies	250	Various/unspecified (mini-review)	"As of 1 June, 2020, we identified 23 studies, in which 250 COVID-19 patients were tested for aPL; 145/250 (58%) were aPL positive. LA present in 64% tested COVID-19 patients, aCL in 9%, and ab2GPI in 13%. When aCL isotypes reported, IgM was most frequent. In studies with aPL test details, 65% of patients (135/209) had a clinically meaningful aPL profile (LA and/or moderate-to-high titers of aCL/ab2GPI)"	No	Generally, no (except: IgM aCL IgA ab2GPI, and triple positivity—statistically higher titers in patients with thrombotic event [n = 11], cf. patients without thrombotic event [n = 93])	No reports of studies included information on confirmatory aPL testing at 12 weeks.	Yes	"A subgroup of 53 assessed for LA; 21/53 (39.6%) patients positive for LA"
Le Joncour et al 2021 <sup>69</sup>	104 COVID-19 patients hospitalized in a medicine ward: patients with thrombotic event (n = 11) vs. patients without thrombotic event (n = 93)	104	Patients tested for presence of aCL, ab2GPI, using ELISA QUANTA Lite (IgG/IgM/IgA aCL; Inova Diagnostics, San Diego, CA) and FEIA (-IgG/IgM/IgA ab2GPI; Phadia, Uppsala, Sweden), with	Overall, 49/104 (47.1%) patients had at least one aPL. aCL was noted in 35/104 (33.7%) patients, mostly IgA aCL. ab2GPI were found in 9/104 (8.7%) patients. IgG, IgM, and IgA	No (reported as "fold UIN," otherwise undefined)	ND but recognized as study limitation	NR	"aPL, even weak and/or transient, are common in COVID-19 patients hospitalized in a medicine ward. In this prospective	

(Continued)

Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Novelli et al 2021 <sup>70</sup>	264 Medline records COVID and aPL – 230 excluded (reviews, not related) = 34 studies assessed	Total 3,288 COVID-19 patients	Various/not specified (review)	a $\beta$ 2GPI were positive in 8.7, 2.9, and 5.8%, respectively. Double or triple aPL seropositivity was found in 11.1 and 1.9%, respectively	No	No. "The association with aPL is not clear in the analysis of patients with thrombosis"	NR	Included	cohort, 64% of patients with a thrombotic event were found to have aPL. Only the presence of aCL and a $\beta$ 2GPI anti-bodies were significantly associated with occurrence of thrombotic events. Although our results suggest that aPL are common in non-severe COVID-19, their relationship with thrombosis and COVID-19-associated coagulopathy will necessitate more dedicated studies"
Frapard et al 2020 <sup>71</sup>	37 COVID-19-related acute respiratory disease syndrome (CARDS) vs. non-COVID pneumonia-associated ARDS (n = 31)	37	NR	CARDS vs. non-CARDS: Any aPL: 11/37 (30%) vs. 9/31 (29%). aCL or a $\beta$ 2GPI IgA: 7/37 (19%) vs. 6/31 (19%) aCL or a $\beta$ 2GPI IgM or IgG: 6/37 (16%) vs. 4/31 (13%)	No	No. "prevalence of aPL was nonsignificantly different between CARDS and non-CARDS overall (11 [30%] vs. 9 [29%], p = 0.950), and whatever type of antibody considered. The rate of thrombotic events was in the same range in patients with vs. without aPL (23 [48%] vs. 9 [45%], p = 0.83), and these findings were similar when considering separately the type of aPL antibodies (IgA vs. IgG/IgM) or the type of thrombotic event"	NR	No	"aPL titers are not consistently defined in these studies, making the clinical course difficult to evaluate"
Cristiano et al 2021 <sup>72</sup>	92 COVID-19 patients (48 late infection [L]), 44 early infection [E]), vs. 44 control subjects (CS)	92	IgG/IgM aCL and IgG/IgM a $\beta$ 2GPI using the fully automated BIO-FLASH instrument (Inova Diagnostics, San Diego, CA) with QUANTA Flash APS aCL family and a $\beta$ 2GPI family reagents (Inova Diagnostics, San Diego, CA). aPT ELISA IgG/IgM ELISA (Demeditec Diagnostics GmbH, Kiel,	EI group: 2/44 (4.54%) positive to IgG/IgM aCL or IgG/IgM a $\beta$ 2GPI: 1 with IgG aCL = 27.9 CU; 1 with IgM aCL = 34.3 CU, and IgM a $\beta$ 2GPI = 31.5 CU. LI group: 3/48 (6.25%) positive to IgG/IgM aCL or IgG/IgM a $\beta$ 2GPI. In particular, 1 had IgG aCL = 39.9 CU, 1 had IgM a $\beta$ 2GPI	Yes	Probably not	No	No	"Low aPL prevalence, likely excluding an involvement in the pathogenesis of CAC. Interestingly, IgG/IgM aPT and antiannexin-V positive cases, detected in late infection group,

Table 1 (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Shi et al 2021 <sup>73</sup>	Cultured endothelial cells were exposed to sera from 118 unique patients hospitalized with COVID-19	(118)	"We focused on IgG and IgM isotypes of two types of aPL that accounted for the majority of positive tests in a recent study: aCL and aPS/PT"	"We detected strong and consistent correlations between all four antibodies and the three markers of endothelial cell activation (E-selectin, VCAM-1, and ICAM-1). The only correlation that was not statistically significant was between anti-PS/PT IgM and VCAM-1"	NA	"Depletion of total IgG from aCL-high and aPS/PT-high samples markedly restrained upregulation of E-selectin, VCAM-1, and ICAM-1; supplementation of control serum with patient IgG was sufficient to trigger endothelial cell activation"	NA	NA	"These data are the first to reveal that patient antibodies are a driver of endothelial cell activation in COVID-19 and add important context regarding thrombo-inflammatory effects of autoantibodies in severe COVID-19"
Hamadé et al <sup>74</sup>	41 COVID-19 patients	41	aCL and aB2GPI IgG/IgM determined by BioPlex 2200 (Bio-Rad)	9/41 (22%) developed VTE and 7/41 (17%) were positive for aPL of which 5 had isolated LA. The 6th patient was double aPL positive	Yes	"Among the 7 patients with aPL antibodies 2 (28.60%) had VTE. However, the incidence of VTE in patients negative for aPL was also significant as 20.6% (7/34).	ND, but mentioned important for future studies to confirm APS	Yes	"Not only the incidence of aPL was quite significant within our cohort, but also we

(Continued)

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**Table 1 (Continued)**

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Karahan et al 2021 <sup>75</sup>	31 COVID-19 patients in ICU (COVID group) and 28 non-COVID-19 critically ill patients (non-COVID group)	31	aCL commercial ELISA (Orgentec Diagnostika) in a fully automatic ELISA Analyzer. aβ2GPI ELISA determined with TriturusVR Analyzer (Diagnostics Grifols, S.A., Barcelona, Spain)	(IgM aCL (147.8U/ml) and aβ2GPI (97.3U/ml). The 7th was triple positive, IgM aCL 85.6U/ml, IgM aβ2GPI 63.0U/ml, and LA	Yes (COVID group aCL IgM 14.0, 12.6; aβ2GPI IgA 12.8, >300; non-COVID group: aCL IgG 16.8, 17.4; aβ2GPI IgA 22.3, 25.7, 71.1, 116)	aPL were significantly associated with the transfer to ICUs, $p = 0.018^*$		Yes (LA was the most common aPL present in 6/26 [23.1%] of the COVID-19 group, while 3.6% of the non-COVID group was LA positive [1/28] [ $p = 0.047$ ])	observed 28.6% of VTE in aPL-positive patients*
				*aPL were positive in 25.8% of the COVID group (8/31) and 25% of the non-COVID group (7/28). In the COVID group, aCL IgM, and IgG were positive in 6.45 and 0%, respectively (2/31 vs. 0/31). In the non-COVID group, ACA IgM was not positive in any patient, while ACA IgG was positive in 7.14% (2/28). aβ2GPI IgG and IgM tests were not positive in any patient in either the COVID or the non-COVID group. aβ2GPI IgA were positive in 6.45 and 14.29%, respectively (2/31 vs. 4/28)**		No. *aPLs were equally positive in critically ill patients among COVID-19 or non-COVID-19 patients. Only LA was more observed in COVID-19 patients. Thrombosis: 2/4 COVID were aPL positive vs. 0/2 non-COVID. Thrombosis negative: 7/27 COVID aPL positive vs. 7/26 non-COVID"	"After recovery of COVID-19 and other diseases requiring ICU follow-up, aPL tests were repeated. However, 1/9 aPL positive patients in the COVID-19 group and 2/7 aPL positive patients in the non-COVID group died within 28 days ( $p = 0.38$ ). After 28 days one of the aPL positive patients in the COVID-19 group and one of the aPL positive patients in the non-COVID group also died. Among the retests taken from the remaining 11 aPL-positive patients, only one patient in the non-COVID group had a positive aβ2GPI IgA test. One patient in the non-COVID group with tested aβ2GPI IgA titer of 24.2 U/ml		

**Table 1** (Continued)

Study	Case descriptions and main findings	Number of COVID-19 cases	Methods for aPL	Number of aPL positive (%)	Reported aPL levels?	Link to COVID-19 severity?	Assessed aPL persistence?	Assessed LA?	Comments
Beyouiti et al 2020 <sup>16</sup>	6 consecutive patients assessed over 2-week period in 2020 with acute ischemic stroke and COVID-19	6	Not specified	1/6 (16.7%). 5/6 IgG and IgM aCL and aβ2GPI negative; 1 × low titer IgG and IgM aβ2GPI	No	NR	after 12 weeks and was found to be significantly lower than baseline <sup>16</sup> NR		

Abbreviations: aβ2GPI, anti-β2-glycoprotein I antibodies; aCL, anticardiolipin antibodies; AIS, acute ischemic stroke; aPL, antiphospholipid antibodies; aPS, antiphosphatidylserine antibodies; aPT, antiprothrombin complex antibodies; aP5/PT, antiphosphatidylserine/prothrombin complex antibodies; APS, antiphospholipid (antibody) syndrome; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; CAPS, catastrophic antiphospholipid (antibody) syndrome; CLIA, chemiluminescence immunoassay; CRP, C-reactive protein; CU, chemiluminescent units; dRVVT, dilute Russell's viper venom time; DVT, deep vein thrombosis; ED, emergency department; ELISA, enzyme-linked immunosorbent assay; FEIA, fluorescence enzyme immunoassay; ICU, intensive care unit; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; LA, lupus anticoagulant; LMWH, low-molecular-weight heparin; NA, not applicable; ND, not done; NNP, pool normal plasma; NRR, normal reference range; NR, not reported; PE, pulmonary embolism; SCT, silica clotting time; SD, standard deviation; SLE, systemic lupus erythematosus; UFH, unfractionated heparin; ULN, upper limit of normal; VTE, venous thromboembolism.

Note: Data in the table exclude single-case studies, and are listed in order of PubMed listing. Note that wide variety of methods (not always documented) may be used to assess antiphospholipid antibodies (aPL). This will have an influence on findings, but this is not always understood by authors who report on findings. Data also show findings from occasional reviews.

in the timeline of this novel coronavirus outbreak” and identified that that APS was rare in COVID-19. From the accumulated 2,369 COVID-19 patients (as of April 8, 2020) with 30 deaths, only 1 patient (0.04%) had been identified with APS.

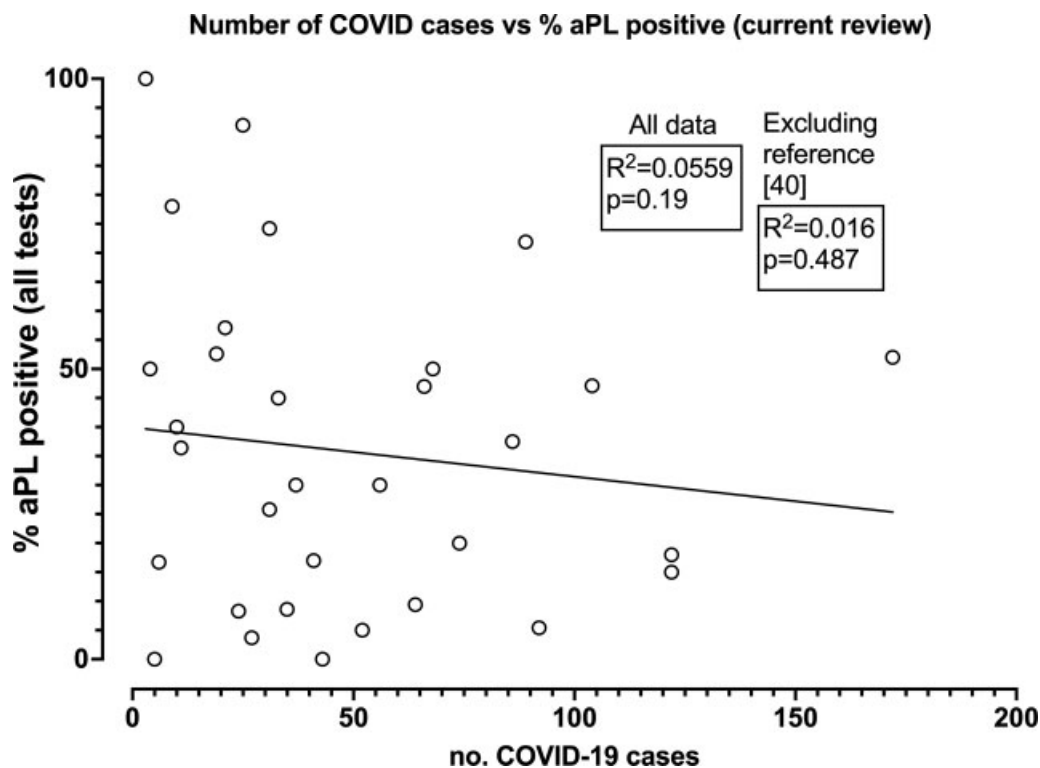
**Selection Bias in the Literature**

One could hypothesize that the reported incidence of COVID-19-associated aPL would be higher in small cases series due to potential selection bias, as identified previously for the Zhang et al report for aPL,<sup>32</sup> and as proposed also for the previous LA review.<sup>11</sup> Thus, selection bias in the literature is likely where authors investigate aPL. First, researchers are more likely to publish positive rather than negative findings; this is particularly likely for small case series or single-case studies. Second, researchers may actively look for aPL in select COVID-19 patient cohorts, such as those with raised activated partial thromboplastin time, prompting a search for LA, or with clinical suspicion of aPL. In such studies, a relatively high incidence of aPL may be identified. One can propose that this might be anticipated, irrespective of the presence of COVID-19.

Of note, we excluded single-case studies from our literature review since these amalgamate several avenues for selection bias, and hence are more likely to publish positive case findings, and also patient selection bias. The literature on aPL also includes studies with and without investigation of LA, so aPL percentage data would fluctuate, being generally higher when LA is included.<sup>11</sup> Our literature search also uncovered several previous reviews on the topic of aPL in COVID-19. One review, by Novelli et al,<sup>70</sup> identified 264 Medline records on COVID and aPL. After excluding 230 references (reviews, not related), they included 34 studies totaling 3,288 COVID-19 patients, and identified 547/3,288 (16.6%) cases reported to be aPL positive (including LA). This review included single-case studies. For interest, we have plotted the proportion of cases positive for aPL, as reported in this review, against the number of cases included in each study in ►Fig. 2. Unlike our review findings (►Fig. 1), where no relationship was found, the data from Novelli et al<sup>70</sup> instead show a clear statistically significant relationship, driven mostly by inclusion of many case reports of aPL positivity in COVID-19 (i.e., obviously, 100% of cases).

**Incidence of aPL in COVID-19**

Excluding single-case studies, the incidence of reported cases positive for aPL, in some studies also including LA, as derived from our own review, and as summarized in ►Table 1 and ►Fig. 1, is 33% (median), with an interquartile range (IQR) of 11 to 52%. As noted, most of the higher incidence group seem to be driven by the presence of LA, which we previously reported,<sup>11</sup> and which was sometimes reported in >80% of tested cases. The reported incidence of “solid phase” identified aPL (i.e., aCL, aβ2GPI, etc.) was generally lower (►Table 1 and ►Fig. 3). Also, of interest, a curvilinear relationship appears to exist between the



**Fig. 1** The relationship (or lack thereof) between COVID-19 case numbers reported in the literature and the proportional identification of antiphospholipid antibody (aPL) positive cases, as summarized from **Table 1**. The associated  $R^2$  and  $p$ -value have been provided using all data from publications in **Table 1** as well as excluding the data from Yasri and Wiwanitkit.<sup>40</sup> Where specific information on overall % aPL positive is not given, an approximate value calculated from the presented data is included.

number of included COVID-19 cases and the incidence of some specific classes of aPL (**Fig. 3A, B**), again potentially suggestive of selection bias.

### Titer of aPL in COVID-19

In general, most aPL, where identified, were of fairly low titer, and thus high-titer aPL were rarely identified (**Table 1**).

#### Criteria aPL (Excluding LA)

**Fig. 4** provides a summary of aPL titers reported in the literature for APS “criteria” aPL (but excluding LA, as reported elsewhere<sup>11</sup>). In some cases, the range of aPL data was provided for the entire COVID-19 cohort, and in some other cases, it was only reported for patients positive for aPL. The perception of titer for COVID-19 obviously increases when only positive cases are considered. Two studies provided numerical data for a series of reported cases, allowing this differential to be highlighted. Thus, individual values for a reasonable number of COVID-19 cases were provided by Devreese et al<sup>49</sup> and Pineton de Chambrun et al,<sup>46</sup> permitting calculation of median and IQR values both for their entire aPL cohorts and for only positive cases (**Fig. 4**).

Excluding LA, which was the subject of the prior review,<sup>11</sup> aCL titers for COVID-19 cohorts were often in the same range as the expected “normal reference range,” which generally used a cut-off of 20 units for both IgG and IgM classes, noting here that different methods may use different measurement

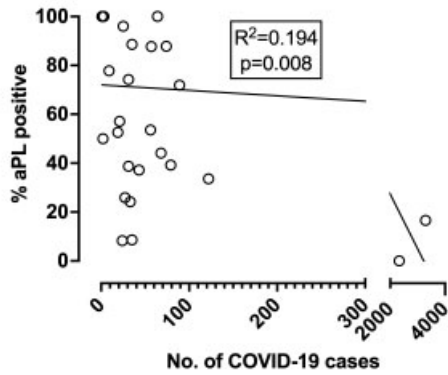
units (e.g., GPL units for some ELISA-based assays, in line with the original “Harris” standards, vs. CU for the CLIA method on AcuStar/BioFlash). Naturally, considering only positive aPL cases, the aPL titer by definition will exceed the cut-off value, but even here could only be considered as a low titer in most studies (e.g., <40 units). Although ranges on occasion did include high titers in some studies, these were in the minority and for only a few patients overall. In two studies, a comparison was made with COVID-19 and “classical” APS cohorts.<sup>43,64</sup> Data from one of these studies, from Gatto et al,<sup>43</sup> are included in **Fig. 4**. These authors studied a relatively large number of cases ( $n=122$ ), divided into hospitalized and nonhospitalized COVID-19 cases, as well as a separate control group of “other autoimmune rheumatic diseases.” Borghi et al<sup>64</sup> also studied 122 COVID-19 patients and provided comparative data with an APS cohort, represented graphically in their report. In both studies,<sup>43,64</sup> the titers identified in data from their APS cohorts greatly exceeded those identified in the COVID-19 cohorts.

As per general studies on aPL, the most common criteria aPL identified in COVID-19 studies, and those tending to include higher titer aPL cases, were for aCL IgG and IgM and  $\beta$ 2GPIb IgG.  $\beta$ 2GPIb IgM positivity or high titer was less often identified (**Table 1**, **Fig. 3A**, and **Fig. 4**).

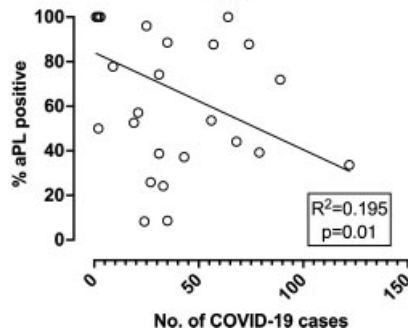
#### Noncriteria aPL

A large number of noncriteria aPL have also been investigated in COVID-19 (**Table 1**). Among these studies, most data are available for aCL IgA and  $\beta$ 2GPIb IgA, and then for aPS/aPT.

**A. Number of COVID cases vs % aPL positive from ref [70]; all data**



**B. Number of COVID cases vs % aPL positive from ref [70]; excluding ref [40]**



**Fig. 2** The relationship between COVID-19 case numbers reported in the literature and the proportional identification of antiphospholipid antibody (aPL) positive cases, using data from Novelli et al.<sup>70</sup> (A) Data including those from Yasri and Wiwanitkit<sup>40</sup> who reported a single case of APS, presumably having positive aPL, from 2,369 COVID-19 patients. (B) Data excluding that from Yasri and Wiwanitkit.<sup>40</sup>

Some data on titer are also provided (→Table 1, →Fig. 5). In general, fewer cases of COVID-19 were found with noncriteria aPL than criteria aPL (→Table 1 and →Fig. 3B, C), and where reported, titers tended to be similar to those of criteria aPL (→Table 1 and →Fig. 5), except for occasional patients.

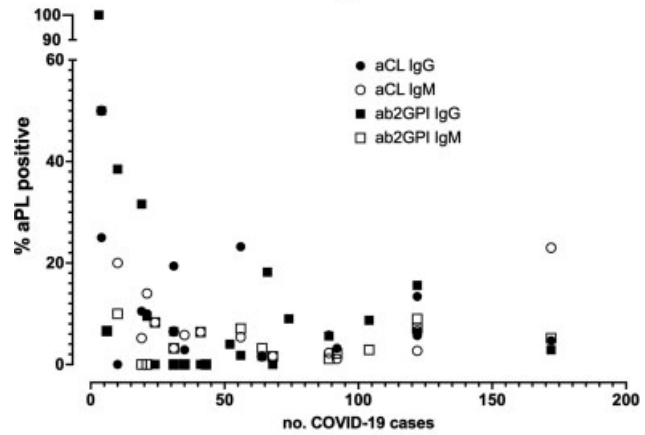
**Multiple Positivity for aPL**

Multiple positivity for aPL was rarely reported. Thus, double and triple positivity was only reported for a few isolated individuals (→Table 1).<sup>49,51,56,59,63,69,74</sup>

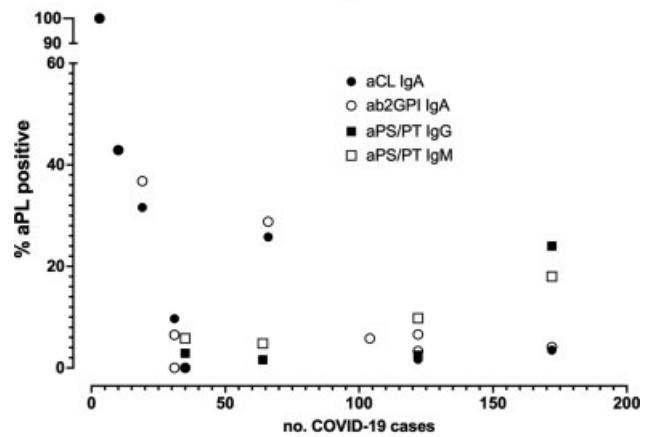
**Persistence of aPL Positivity versus Transient Positivity**

To identify aPL as a specific feature of an autoimmune disorder such as APS, one has to prove the persistence of that positivity, generally by repeating the test(s) on a second sample some 12 weeks after the first positive test result.<sup>1,2,37-39</sup> Again, most researchers reporting on LA positivity in COVID-19 either did not mention this or did not undertake repeated testing. Thus, persistence of aPL positivity was not evaluated in most studies, and hence could not be proven. In the two studies that did attempt to look at

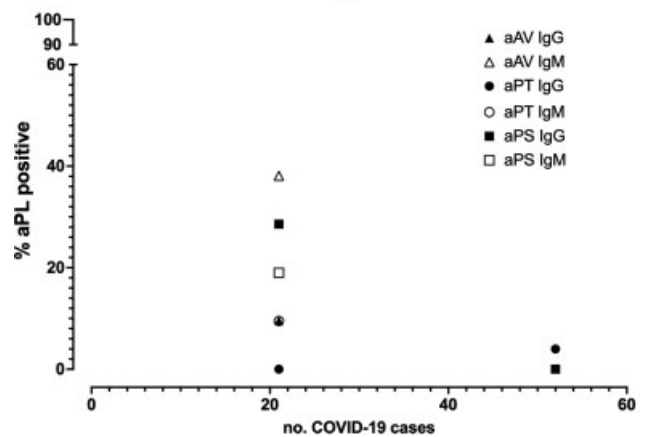
**A.**



**B.**



**C.**

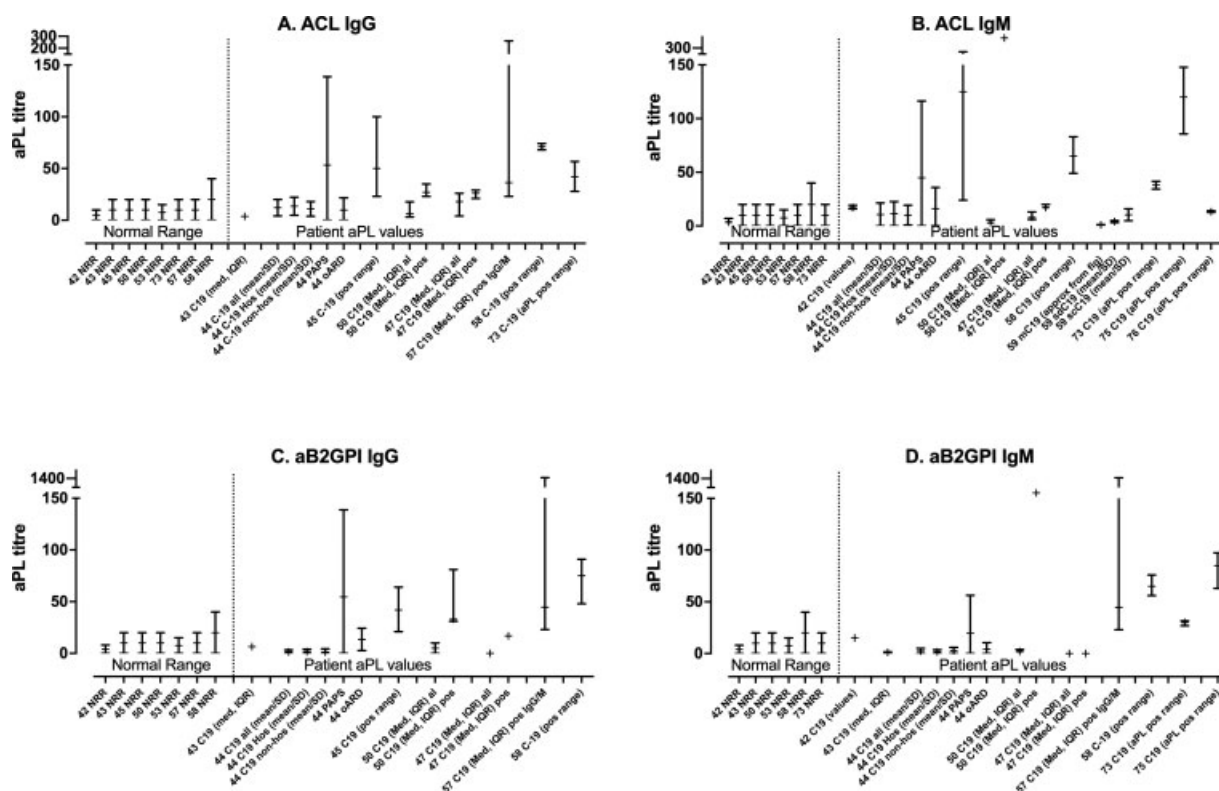


**Fig. 3** The relationship between COVID-19 case numbers reported in the literature and the proportional identification of solid-phase-detected antiphospholipid antibody (aPL) positive cases according to tested aPL. (A) “Criteria” aPL and (B, C) “noncriteria” aPL. aAV, antiannexin V antibodies; aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-glycoprotein I antibodies; aPS, antiphosphatidylserine antibodies; aPT, antiprothrombin antibodies; aPS/PT, antiphosphatidylserine/prothrombin complex antibodies.

persistence, most cases initially positive for aPL then became negative for aPL,<sup>49</sup> or else repeat testing was complicated by the ongoing patient morbidity or their death.<sup>75</sup> Thus, it

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**Fig. 4** (A–D) Summary findings for antiphospholipid (antibody) syndrome (APS) “criteria” antiphospholipid antibodies (aPL) (excluding LA) from ►Table 1 showing the range of normal expected findings (NRR, normal reference range) vs. cases of COVID-19. Note that the study reference number is provided in the text detail along the x-axis. The ranges reported in the literature reflect different data capture methods, including mean  $\pm$  standard deviation (SD), or median/interquartile range (IQR), or individual values. Sometimes ranges are for entire COVID-19 cohorts (i.e., including aPL-negative cases) and sometimes only for aPL-positive cases. Naturally, by definition, where only positive aPL case values are provided, these will inevitably be higher than those of NRRs or entire cohort values. In cases where titer value ranges included high titers, these were invariably small case numbers out of the entire COVID-19 cohort. aCL, anticardiolipin antibodies; a $\beta$ 2GPI, anti- $\beta$ 2-glycoprotein I antibodies.

seems that any aPL positivity that may be identified in COVID-19 patients is mostly transient.

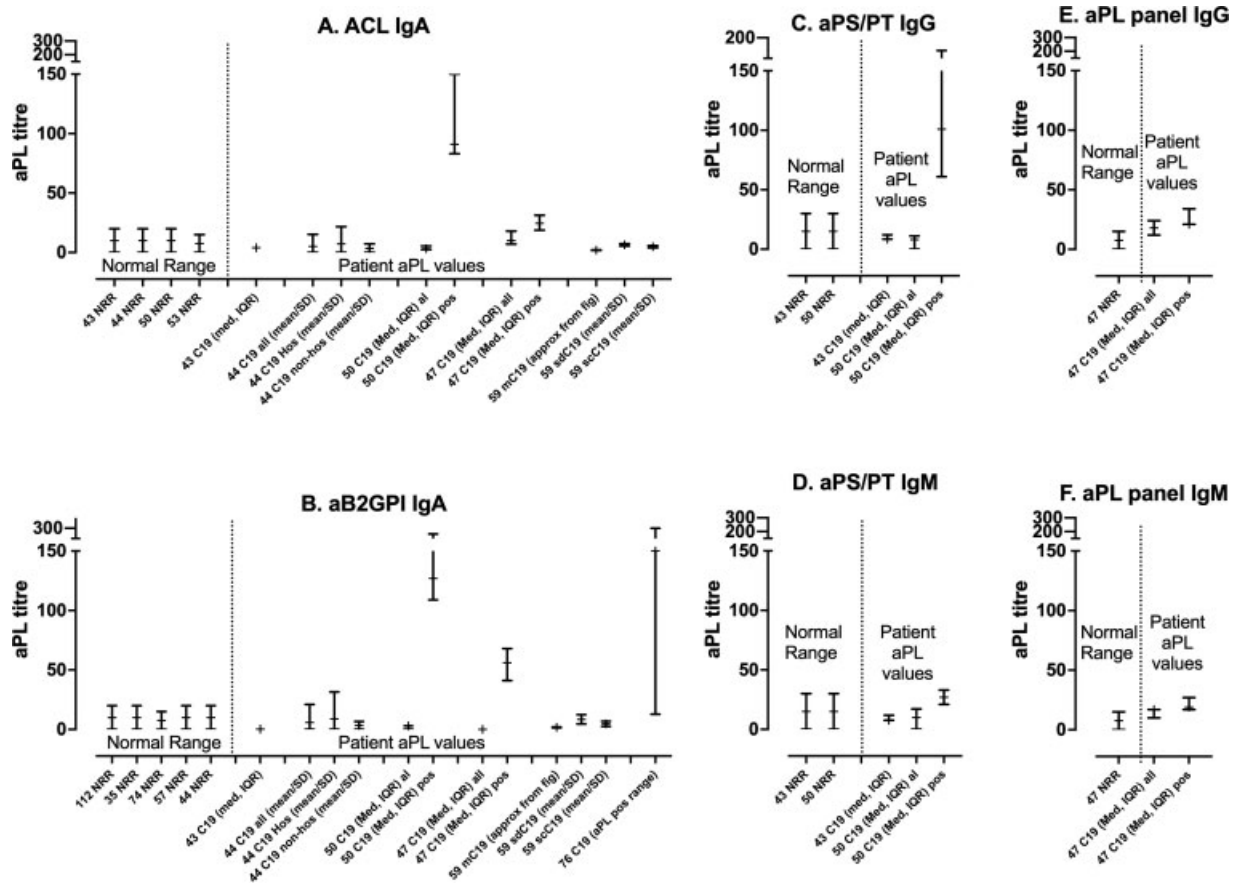
### Transient aPL Are a Common Feature of Severe Viral Infections

As extensively discussed in the companion review on LA,<sup>11</sup> sick patients with various viral infections in a range of conditions may have aPL appear transiently.<sup>77,78</sup> It may also be possible to separate groups of patients and aPL profiles. Abdel-Wahab et al,<sup>77</sup> for example, reported three different groups of patients following viral infection; “group 1 included patients who fulfilled the criteria for definitive APS (24.6%), group 2 included patients who developed transient aPL with thromboembolic phenomena (43.7%), and group 3 included patients who developed transient aPL without thromboembolic events (31.7%).” Thus, secondary cases of APS due to viral infections have been reported.<sup>78</sup> Secondary cases of APS due to infectious agents potentially evolving into CAPS have also been reported and include infections from hepatitis C virus, herpes zoster, bacteria, fungi, and parasites and acute Q fever.<sup>79</sup> The induction of molecular mimicry that leads to production of a $\beta$ 2GPI autoantibodies has been proposed as putative cause of secondary APS and CAPS.<sup>80,81</sup>

Thus, the finding of aPL positivity in COVID-19 is not unique to COVID-19. To our knowledge, there is no evidence available on comparative infections with other viral agents to identify if the situation in COVID-19 with respect to aPL positivity is worse or greater than that of other severe viral infections. In part, it is also likely that other viral diseases have not been as extensively studied as COVID-19, owing to their relatively lower epidemiologic burden.

### Does aPL Positivity in COVID-19 Reflect a Risk Factor for Thrombosis?

Only a few studies investigated whether aPL positivity inferred additional thrombotic risk. Few studies identified a statistical difference in thrombotic risk for aPL-positive versus aPL-negative patients or substantial aPL positivity in their thrombosis cohorts (LA only<sup>45,50</sup>),<sup>55,57–59,63</sup> whereas most did not.<sup>31,41–44,47–49,52,54,56,61,62,64,69–72,74,75</sup> There are many potential confounders to consider, and it is unlikely that such confounders were considered in all published comparisons. Thus, transient aPL positivity may develop in the sickest patients, who will then be most at risk of thrombosis, and therefore aPL may just reflect an association with, rather than be responsible for, the pathophysiological events. Irrespective, whether aPL positivity in COVID-19



**Fig. 5** (A–F) Summary findings for antiphospholipid (antibody) syndrome (APS) “noncriteria” antiphospholipid antibodies (aPL) from ▶Table 1 showing the range of normal expected findings (NRR, normal reference range) vs. cases of COVID-19. Note that the study reference number is provided in the text detail along the x-axis. The ranges reported in the literature reflect different data capture methods, including mean  $\pm$  standard deviation (SD), or median/interquartile range (IQR), or individual values. Sometimes ranges are for entire COVID-19 cohorts (i.e., including aPL-negative cases) and sometimes only for aPL positive cases. Naturally, by definition, where only positive aPL case values are provided, these will inevitably be higher than those of NRRs or entire cohort values. In cases where titer value ranges included high titers, these were invariably small case numbers out of the entire COVID-19 cohort. aCL, anticardiolipin antibodies; a $\beta$ 2GPI, anti- $\beta$ 2-glycoprotein I antibodies; aPS/PT, antiphosphatidylserine/prothrombin complex antibodies.

truly reflects an additional risk factor for thrombosis remains currently unresolved. Consistent with patterns identified in APS,<sup>1,2</sup> those with multiple aPL positivity in COVID-19 are most likely to have an association with thrombosis, and double and triple positivity was only identified in a few patients in a few publications.<sup>49,51,56,59,63,69,74</sup>

## Conclusion

Taking all this information into consideration, we need to recognize that aPL positivity does represent a feature of COVID-19, at least in some patients, and potentially those who are the sickest or have the most severe infection. However, this does not indicate APS or CAPS for most patients. Also, there appears to be a higher proportion of LA identified in patient cohorts<sup>11</sup> than “solid-phase” aPL, as identified in this review, although additional confounders exist in LA identification in COVID-19.<sup>11</sup>

Nevertheless, additional confounders also need to be considered for other aPL. In particular, repeat testing for persistence of aPL was rarely performed or described, and when reported, suggested a transient nature of the identified

aPL. Such transient aPL do not identify an autoimmune disease in the classic sense of APS,<sup>1,2</sup> can be commonly observed in other viral infections,<sup>77,78</sup> and thus do not seem to be unique to COVID-19. There are also questions remaining over the “additional” thrombotic risk imposed by the aPL identified in COVID-19 in these studies, as transient aPL developed from viral infections are often not associated with thrombosis. In regard to incidence and titer, not only was the typical incidence of “solid-phase” aPL often low, but also, where identified, the titer was also generally low. This was true of both criteria “solid-phase” aPL (aCL and a $\beta$ 2GPI of IgG and IgM class; ▶Fig. 4) and noncriteria aPL (▶Fig. 5). Certainly, where comparative data for “classical” APS were given,<sup>49,64</sup> the titers found in COVID-19 patients were considerably lower. In those case where high proportions of “solid-phase” aPL were detected, the cut-off value used to define positivity was not always identified; if a low cut-off is applied, this will then identify a higher number of positive cases. In any case, titers considered medium or high (i.e., generally  $>40$ ) were in the minority, as were those with multiple positivity, both of which increase the likely association with thrombosis.

Thus, better studies are needed to address the residual question regarding the true frequency of aPL in COVID-19, and whether these laboratory-detected aPL truly contribute to enhance the thrombotic risk in COVID-19. Nevertheless, some good-quality studies have already been published, and these should likely guide opinion. These studies are those that reported on aPL cognizant of the potential confounders, including C-reactive protein and anticoagulant therapy for LA, and that also looked at persistence of antibodies, titer of aPL, and multiple positivity, and provide comparative data with classical APS. However, these were in the minority of published studies. All this is not to say that APS cannot develop in patients with COVID-19. As already mentioned, there are certainly similarities between the worst presentation of APS, namely, CAPS, and what occurs in the sickest patients with COVID-19. However, there are also some notable differences, including general lack of high-titer aPL, lack of persistence for aPL, and unclear relationship between the detected aPL and COVID-19-associated coagulopathy, along with many other prothrombotic abnormalities (e.g., endothelial cell injury, platelet hyperactivation, prolonged immobilization) that would justify an enhanced thrombotic risk by themselves. Also, some patients with COVID-19 must by chance have APS, and thus these may reflect a coincident finding.

#### Conflict of Interest

None declared.

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