Systematic Review of Antiphospholipid Antibodies in COVID-19 Patients: Culprits or Bystanders?

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Abstract
Purpose of Review COVID-19 patients have a procoagulant state with a high prevalence of thrombotic events. The hypothesis of an involvement of antiphospholipid antibodies (aPL) has been suggested by several reports. Here, we reviewed 48 studies investigating aPL in COVID-19 patients.

Recent Findings Prevalence of Lupus Anticoagulant (LA) ranged from 35% to 92% in ICU patients. Anti-cardiolipin (aCL) IgG and IgM were found in up to 52% and up to 40% of patients respectively. Anti-β2-glycoprotein I (aβ2-GPI) IgG and IgM were found in up to 39% and up to 34% of patients respectively. Between 1% and 12% of patients had a triple positive aPL profile. There was a high prevalence of aβ2-GPI and aCL IgA isotype. Two cohort studies found few persistent LA but more persistent solid phase assay aPL over time.

Summary aPL determination and their potential role is a real challenge for the treatment of this disease.

Keywords Antiphospholipid antibodies · Lupus anticoagulant · Thrombosis · COVID-19

Introduction
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is at the origin of coronavirus disease 2019 (COVID-19), which has immersed the world in a new global pandemic since early 2020. In the first descriptions in China, COVID-19 clinical manifestations are dominated by respiratory symptoms with pneumonia and inflammatory state [1, 2]. With the progress of the pandemic, a significant number of thrombotic events were identified. Indeed, the incidence of both arterial and venous thromboembolism is high in COVID-19 patients [3], sometimes in spite of preventive anticoagulant treatment [4, 5]. In some cases, this viral infection may be associated with modifications in coagulation parameters revealing a procoagulant state in COVID-19 patients associated with poor clinical outcome [6–8]. Zhang et al. first suggested a possible correlation between antiphospholipid antibodies (aPL) and thrombosis by reporting three cases of COVID-19 patients with multiple thrombosis and anti-cardiolipin (aCL), immunoglobulin (Ig) A, and anti-β2-
glycoprotein I (aβ₂-GPI) IgA and IgG positivity [9]. Many case series and cross-sectional studies have been published in order to further investigate the role of these aPL during COVID-19 infection. Thus, the aim of this systematic review was firstly to analyze the frequency of aPL in COVID-19 patients in different settings and to evaluate their persistence over time and secondly, to analyze the role of aPL during the infection in particular their participation in thrombotic events.

Methods

We conducted a systematic review of all articles about aPL in COVID-19 patients. We performed this search for international English articles in Medline database with the following keywords: “(antibody, antiphospholipid[MeSH Terms] OR antibody syndrome, antiphospholipid[MeSH Terms] OR lupus anticoagulant[MeSH Terms] OR lupus anticoagulant OR anticardiolipin OR anti-beta2 glycoprotein I OR antiphospholipid antibody* OR antiphospholipid antibody syndrome) AND (coronavirus, sars[MeSH Terms] OR COVID OR coronavirus disease 2019)”. Each article published was analyzed and only studies evaluating the prevalence of aPL in case series of at least two COVID-19 patients over 18 years old were included. Percentages were calculated from studies of more than 10 patients. Single patient case reports and studies of children were excluded.

Results

Study Selection

We identified a total of 190 publications (last search on May 4, 2021) after excluding duplicates and non-English papers. Of the 190 references selected, 142 were excluded as indicated in the Flowchart (Fig. 1). Overall, 48 studies were eligible for a complete analysis of their results [6••, 9, 10, 11, 12, 13••, 14–55]. Only two reports were cohort studies with repeated assays for aPL after one month for the first [13••] and between 3 and 6 months for the second [52]. Eight publications were case reports from two to six patients [9, 17, 30, 33, 34, 36, 38, 51]. Other publications were cross-sectional studies.

Prevalence of Lupus Anticoagulant

Tables 1, 2, and 3 display the main results for studies evaluating aPL in intensive care units (ICU, Table 1), medical ward (MW) or without specific information (Table 2), and both ICU and MW patients (Table 3). According to the type of antibodies, there was a high prevalence of lupus anticoagulant (LA), from about 35% up to 90% in ICU patients with one exception: a study found LA in 5% of patients [15]. In studies combining ICU and MW patients, the prevalence of LA was between 20% and 66% except for one study who found LA in 2% of patients [45]. In MW patients, two studies have performed LA assays and found a prevalence of 39% and 46% [32, 37]. In studies without information on patients setting, prevalence was between 22% and 91%. Of note, Bauer et al. did not find more LA in COVID-19 patients on admission to their emergency department compared to patients without COVID-19 [47]. A total of 91% of these COVID-19 patients were subsequently hospitalized.

The strict application of the three-step LA testing recommended by the International Society on Thrombosis and Haemostasis (ISTH) [56] was explicitly described by 18 among 23 studies performing LA assays. Inflammation parameters were reported in 17 among 21 studies. Mean fibrinogen and C-reactive protein (CRP) were higher than normal values in all these studies. CRP and fibrinogen values varied between 36 and 286 mg/L and 4.2 and 7.6 g/L respectively. Several studies found a statistical association between the presence of LA and the levels of CRP or fibrinogen [28, 32, 55]. The two studies with the lowest prevalence of LA (2% and 5%) had the lowest level of fibrinogen (4.5 and 4.4 g/L respectively).

Prevalence of other aPL

The prevalence of aCL IgM varied between 0% and 40% and the prevalence of aCL IgG varied between 0% and 59%. The prevalence of aβ₂-GPI was also variable in most studies: between 0% and 39% of patients had aβ₂-GPI IgG and between 0% and 34% of patients had aβ₂-GPI IgM. The proportion of triple positivity (combined positivity for LA, aCL and aβ₂-GPI antibodies) was from 1% to 12% across studies. Assays for aPL and the cut-off used were explicitly described in 21 among 32 studies.

Many studies have also investigated less conventional antibodies (i.e., that are not classification criteria nor assayed in routine clinical practice as opposed to LA, IgG and IgM aCL and aβ₂-GPI). Thus anti-phosphatidylserine/prothrombin (aPS/PT) were found in 0% to 24% of patients, and anti-annexin V (aAV) in 3% to 19% of patients. One study performed anti-phosphatidylinositol (aPI) IgG and IgM only in ICU patients. No aPI were found. IgA aCL were found more frequently, from 20% to more than 90%, except for four studies that described a low prevalence between 0 and 4% [27, 31, 41•, 55]. IgA aβ₂-GPI was present from 0% to 86% of patients.

aPL in COVID-19 Outpatients

Almost all publications studied hospitalized patients only, while Gatto et al. studied both hospitalized and COVID-19
outpatients [27]. They did not show any association between the presence of aPL and thrombotic events or with the necessity to hospitalize patients [27]. The prevalence of LA was 30% and 1% to 8% for the other aPL in COVID-19 outpatients.

**Persistence Over Time**

Two studies followed-up aPL persistence over time. The first study was conducted in ICU patients [13••] and investigated the persistence of aPL at 1 month. Initially 23 out 31 patients had at least one aPL (mostly LA, in 67% of patients). At 1 month, 10 patients were tested again and only one had persistent aPL. Thus, aPL were confirmed at 1 month for only 1 among 10 positive LA, 0 among 4 aCL and 1 among 2 aβ2-GPI IgG. Persistent LA and aβ2-GPI were present in the same patient.

A second study performed aPL assays between 3 and 6 months after a first positive LA test [52]. A total of 42 patients among 79 patients initially tested positive for LA were tested again. LA was found negative in all these patients. In these 42 patients, 7 were positive for aCL, 1 for aβ2-GPI and 5 for unconventional antibodies. Authors did not indicate if these antibodies were similar to the initial samples.

**Association of aPL, COVID-19 Severity and Thromboses**

Some studies have found a high prevalence of aPL [6•, 18, 23, 37, 43, 57] while others found a low prevalence and this could be linked to disease severity [19, 24, 26, 35•, 42, 45, 55]. Xiao et al. found aPL in 31 out of 66 patients requiring ICU admission but not in patients with noncritical conditions [45]. Several studies suggested that aCL IgG or IgM were highly and independently associated with COVID-19 severity [40, 52, 58]. However, others studies did not confirm these results. Ferrari et al. found a similar prevalence for LA, aβ2-GPI and aCL in severe and non-severe COVID-19 patients [43], and other authors did not find more aPL (aCL or aβ2-GPI) between patients with COVID-19 related acute respiratory disease syndrome and patients with pneumonia-associated acute respiratory disease syndrome in ICU [19, 53]. One study did...
| Study (reference)        | Date     | Study location | Setting | Patients included in analysis, n | Tests performed (Exposure to aPL) | Positive aPL, n | Outcome: aPL persistent, type (ratio) | Thrombotic Events, n |
|-------------------------|----------|----------------|---------|---------------------------------|----------------------------------|----------------|--------------------------------------|----------------------|
| Zhang et al. [9]        | 04/2020  | China          | ICU     | 3                               | LA, aCL IgA, αβ₂-GPI IgG, IgA    | 0              | NA                                   | Strokes, MI, LI      |
| Helms et al. [6•]       | 06/2020  | France         | ICU     | 57                              | LA                               | 50             | NA                                   | NA                   |
| Pineton de Chambrum et al. [10] | 06/2020  | France         | ICU     | 25                              | LA, aCL IgA, aCL IgG, IgM, αβ₂-GPI IgA | 23             | NA                                   | 6 PE                 |
| Fan et al. [11]         | 07/2020  | China          | ICU     | 86                              | aCL IgG, IgM, αβ₂-GPI IgG, IgM, αPS or aPE or aCL or αβ₂-GPI IgG, IgM | 4                 | NA                                   | 6 strokes            |
| Amezcu-Guerra et al. [12] | 08/2020  | Mexico         | ICU     | 21                              | aCL IgG, IgM, αβ₂-GPI IgG, IgM, aPS/PT IgG, IgM, aPI IgG, IgM, aAV IgG, IgM | 23              | 7                                    | NA                   |
| Devreese et al. [13••]  | 09/2020  | Belgium        | ICU     | 31                              | LA, aCL IgA, aCL IgG, IgM, αβ₂-GPI IgG, IgM | 21              | At 1 month: 1/10 LA                  | 4 CVC thrombosis, 2 Clotting of dialysis circuit, 3 Clotting of ECMO circuit, 2 DVT 1 Stroke |
| Borghi et al. [14]      | 10/2020  | France         | ICU     | 122                             | aCL IgG, IgM, αβ₂-GPI IgG, IgM, aPS/PT IgG, IgM | 72              | 19;11                                | NA                   |
| Zhang et al. [15]       | 10/2020  | China          | ICU     | 19                              | LA, aCL IgA, aCL IgG, IgM, αβ₂-GPI IgG, IgM | 4               | NA                                   | 4 ATE 7 micro-thrombi |
| Fan et al. [16]         | 10/2020  | Singapore      | ICU     | 12 for LA, 4 for others aPL among 12 patients | aCL, aCL IgG, IgM, aβ₂-GPI IgG, IgM | 6               | 0;2                                  | 2 strokes            |
| Alharthy et al. [17]    | 10/2020  | Saudi Arabia   | ICU     | 3                               | aCL, aβ₂-GPI IgG, IgM, aPS/PT IgG, IgM | 6               | NA                                   | 1 DVT                |
| Siguret et al. [18]     | 11/2020  | France         | ICU     | 74                              | LA, aCL or aβ₂-GPI                | 3               | NA                                   | 26 DVT, 4 PE, 1 stroke, 1 CVC thrombosis |
| Frapard et al. [19]     | 12/2020  | France         | ICU     | 37                              | aβ₂-GPI or aCL IgA, aβ₂-GPI or aCL, IgG or IgM | 7               | NA                                   | 21 VTE 11 circuit thrombosis |
| Van der Linden et al. [20] | 12/2020  | Sweden         | ICU     | 23                              | aCL IgA, aCL IgG, IgM, aβ₂-GPI IgG, IgM | 19              | NA                                   | 9 PE 3 DVT           |
| Vlachoyiannopoulos et al. [21] | 12/2020  | Greece         | ICU     | 29                              | aCL IgG, IgM, aβ₂-GPI IgG, IgM, aPS/PT IgG, IgM | 6               | NA                                   | NA                   |
| Karahan et al. [48]     | 03/2021  | Turkey         | ICU     | 26 for LA, 31 for other aPL, among 31 patients | aCL IgG, IgM, aβ₂-GPI IgG, IgM, aPS/PT IgG, IgM | 6               | NA                                   | 1 stroke 1 MI 2 others thrombotic events |
| Mullaguri et al. [51]   | 04/2021  | USA            | ICU     | 2                               | aCL IgM, IgA                      | 2               | NA                                   | 2 strokes, 2 PE      |
not find more LA in COVID-19 non-survivors than in survivors [32], likewise other studies did not find any association between overall aPL positivity and in-hospital mortality [50, 55].

Regarding the risk of thrombosis several studies have found a statistical association between the presence of aPL and thrombotic events [6*, 28, 37], or between their presence and the inflammatory state of the patients [12, 55]. Indeed, Le Joncour et al. found more aPL (aCL IgG and IgM and aβ2-GPI IgA) in patients with thrombotic events in MW. These patients had also higher neutrophils counts and higher D-Dimers and CRP levels. However, this was not in line with other authors who did not find an association between the presence of aPL and the thrombotic complications [18, 55].

Specific studies analyzed the prevalence of aPL in COVID-19 patients with stroke or myocardial infarction. In these retrospective studies, between 78% and 83% of stroke had aPL [11, 29], and 36% of myocardial infarction [25]. They highlighted that the presence of multiple aPL with moderate serum titers of at least one type of aPL was found to be statistically associated with a higher incidence of cerebral infarction [11, 45].

It was not possible to extract data from the primary studies to determine an overall association between aPL positivity and thromboses. A meta-analysis of individual patients’ data would be timely to draw definitive conclusions.

**aPL and Coagulation Parameters**

Overall results reported are conflicting. Two studies have studied coagulation in COVID-19 patients with or without LA. Patients with LA had a higher level of inflammation markers (CRP and fibrinogen) but the same level of D-Dimers [32, 55]. Zuo et al. showed a positive association with the presence of Neutrophil Extracellular Traps (NETs), platelet count and neutrophil activation (by calprotectin assay) [41*]. They did not find a statistical association with levels of D-Dimers. Likewise, one study showed that levels of D-Dimers, ferritin and CRP were higher in COVID-19 patients with aPL [12] while another comparison between patients with or without autoantibodies (including aPL and antinuclear antibodies) [39] and did not find any significant difference in blood parameters. Several studies did not show any differences between COVID-19 patients with aPL or not [28, 43, 45, 46]. Finally, Bauer et al. did not find any difference on activated protein-C resistance between patients with or without COVID-19 [47].

**Discussion**

There was a great discrepancy in aPL prevalence in studies, from 0% to 90% according to aPL type and isotype. A high proportion of LA were identified in ICU patients. There was a high prevalence of IgA isotypes during COVID-19 infection. Several studies suggested an association between aPL and a high incidence of thrombotic events. However other studies question this association between aPL and thrombotic events and some questions remain unsolved.

**Pathogenic Role of aPL?**

Zhang et al. were the first to suggest a pathogenic role of aPL. They found aCL and aβ2-GPI IgA positivity in stroke patients. Although IgA is one of the unconventional aPL, it has been described as a potential source of thrombosis and pregnancy morbidity [59]. Furthermore Hasan Ali et al. confirmed in their study that IgA were highly and independently associated with COVID-19 [60]. Similar data were later reported by other studies linking thrombosis to other isotypes of aPL, and suggested a pathogenic role, partly because they are more prevalent in severe patients in ICU. Pathological mechanisms...
could be associated with NETs release and endothelial cells activation, studied in vitro with IgG isotype [41*, 61]. In these in vitro studies aPL during COVID-19 infection seem to contribute to a prothrombotic state like aPL responsible for

### Table 2 Characteristics of studies describing MW patients (or without information)

| Study (reference)          | Date   | Study location | Setting   | Patients included in analysis, n | Tests performed (Exposure to aPL) | Positive aPL, n | Outcome: aPL persistent, type (ratio) | Thrombotic Events, n |
|----------------------------|--------|----------------|-----------|----------------------------------|-----------------------------------|----------------|--------------------------------------|----------------------|
| Harzallah et al. [22]      | 04/2020| France         | NA        | 56                               | LA aCL or aβ2-GPI                 | 25             | NA                                   | NA                   |
| Bowles et al. [23]         | 07/2020| UK             | NA        | 34                               | LA aβ2-GPI                        | 31             | 1 VTE                                |                      |
| Gazzaruso et al. [24]      | 07/2020| Italy          | MW        | 45                               | LA aCL, IgG, IgM                  | 21             | NA                                   | NA                   |
| Popovic et al. [25]        | 07/2020| France         | NA        | 11                               | aCL aβ2-GPI                       | 3              | 11 MI                                |                      |
| Galeano-Valle et al. [26]  | 08/2020| Spain          | MW        | 24                               | aCL IgG, IgM                       | 0:2            | NA                                   | 24 VTE               |
| Gatto et al. [27]          | 08/2020| Italy          | NA        | 72 for LA 121 for IgA, 112 for other isotype, among 122 patients | LA aCL IgA                   | 2              | NA                                   | 17 VTE               |
| Reyes et al. [28]          | 08/2020| USA            | NA        | 68                               | LA aCL IgG, IgM                   | 38             | 17 DVT, 7 PE                         |                      |
| Rothstein et al. [29]      | 09/2020| USA            | NA        | 9                                | aCL IgG, IgM                       | 0              | Stroke, LI, SI                        |                      |
| Hossri et al. [30]         | 10/2020| USA            | NA        | 2                                | aCL IgG, IgM                       | 0              | NA                                   |                      |
| Previtali et al. [31]      | 10/2020| Italy          | NA        | 35                               | aCL IgA                           | 0              | Autopsy series 10 thromboembolic events | 4 PE, 2 strokes      |
| Gazzaruso et al. [32]      | 11/2020| Italy          | NA        | 192                              | aCL IgG, IgM                       | 95             | NA                                   |                      |
| Kanso et al. [33]          | 11/2020| France         | MW        | 2                                | aCL IgG, IgM                       | 1              | NA                                   | 1 PE                 |
| Guillet et al. [34]        | 12/2020| France         | NA        | 4                                | aCL IgG, IgM                       | 1              | 4 ATE (MI, LI, aortic thrombosis)     |                      |
| Cristiano et al. [35*]     | 01/2021| Italy          | MW        | 92                               | aCL IgG, IgM                       | 3:1            | NA                                   |                      |
| Balanchivadze et al. [36]  | 01/2021| USA            | NA        | 2                                | aCL IgG, IgM                       | 0:2            | At 3 months: 0/2 tested again         | 2 PE                 |
| Le Joncour et al. [37]     | 02/2021| France         | MW        | 53 for LA 104 for other aPL, among 104 patients | aCL IgA                    | 21             | NA                                   | 9 PE                 |
| Anaya et al. [49]          | 04/2021| Colombia       | NA        | 120                              | aCL IgA                           | 2:2:2          | 1 aortic thrombus                     |                      |

Abbreviations. aPL: antiphospholipid antibodies. aCL: anti-cardiolipin antibody. aβ2-GPI: anti-beta2glycoprotein I. aPS/PT: anti-phosphatidylserine/prothrombin. aAV: anti-annexin V. Ig: immunoglobulin. NA: information not available. MW: medicine ward. LA: lupus anticoagulant. ATE: arterial thrombosis event. VTE: venous thrombosis event. PE: pulmonary embolism. DVT: deep vein thrombosis. MI: myocardial infarction. LI: acute lower limb ischemia. SI: splenic infarction. UK: United Kingdom. USA: United States of America
Table 3  Characteristics of studies describing patients from various settings (MW + ICU)

| Study (reference)        | Date   | Study location | Setting | Patients included in analysis, n | Tests performed (Exposure to aPL) | Positive aPL, n | Outcome: aPL persistent, type (ratio) | Thrombotic Events, n |
|--------------------------|--------|----------------|---------|----------------------------------|-----------------------------------|----------------|--------------------------------------|----------------------|
| Beyrouti et al. [38]     | 08/2020| UK             | Mixed   | 6                                | LA aCL IgG, IgM, aβ2-GPI IgG, IgM | 5              | 0:1                                  | 6 strokes             |
| Pascolini et al. [39]    | 09/2020| Italy          | Mixed   | 33                               | aCL IgG, IgM, aβ2-GPI IgG, IgM    | 3              | 3:5                                  | NA                   |
| Bertin et al. [40]       | 11/2020| France         | Mixed   | 56                               | aβ2-GPI IgG, IgM, aβ2-GPI IgG, IgM| 1              | 1:4                                  | NA                   |
| Zuo et al. [41]          | 11/2020| USA            | Mixed   | 172                              | aCL IgA, aCL IgG, IgM, aβ2-GPI IgG, IgM | 6              | 8:39                                 | NA                   |
| Lerma et al. [42]        | 11/2020| USA            | Mixed   | 64                               | aCL IgA, aβ2-GPI IgG, IgM         | 1              | 1:1                                  | NA                   |
| Ferrari et al. [43]      | 11/2020| France         | Mixed   | 89                               | aCL, aβ2-GPI IgG, IgM, aPS/PT IgG, IgM | 59             | 7                                    | 14 VTE                |
| Gutiérrez et al. [44]    | 12/2020| Spain          | Mixed   | 27                               | aCL (IgG or IgM) aβ2-GPI IgA, aβ2-GPI-IgG (IgG or IgM) | 6              | NA                                   | 2 LI, 6 DVT, 10 PE, 2 strokes |
| Xiao et al. [45]         | 12/2020| China          | Mixed   | 79                               | aCL IgA, aCL IgG, aβ2-GPI IgG, IgM | 2              | 17:19                                | 19 DVT, 5 strokes, 1 MI |
| Tviito et al. [46]       | 02/2021| Israel         | Mixed   | 43                               | aCL or aβ2-GPI IgG, IgM, aPS/PT IgG, IgM | 16             | 1                                    | 3 thrombotic events   |
| Bauer et al. [47]        | 02/2021| Germany        | Mixed   | 17                               | aCL or aβ2-GPI IgG, IgM, aPS/PT IgG, IgM | 3              | NA                                   | NA                   |
| Serrano et al. [50]      | 04/2021| Spanish        | Mixed   | 474                              | aCL and/or aβ2-GPI IgG, IgM aβ2-GPI IgA, aPS/PT IgG or IgM | 28             | 71                                   | 9 thrombotic events   |
| Vollmer et al. [52]      | 04/2021| France         | Mixed   | 79 patients with LA positivity 56 for aCL and aβ2-GPI, 53 for other aPL among 154 patients | LA aCL IgA, aCL IgG, IgM aβ2-GPI IgA, aPS/PT IgG or IgM | 79             | 170:13                                | At 3 months: 30 VTE, 27 PE |
| Gendron et al. [55]      | 04/2021| France         | Mixed   | 115 for LA, 97 for aCL IgA, 98 for aβ2-GPI IgA, 109 for aPT 148 for other aPL among 154 patients | LA aCL IgA, aCL IgG, IgM aβ2-GPI IgG, IgM aβ2-GPI IgA, aPS/PT IgG, IgM | 70             | 3                                    | Only for LA positivity: 19 VTE, 15 symptomatic PE, 6 symptomatic DVT |

Abbreviations. aPL: antiphospholipid antibodies, aCL: anti-cardiolipin antibody, aβ2-GPI: anti-beta2glycoprotein I, aPS/PT: anti-phosphatidylserine/prothrombin, aPS: anti-phosphatidylycerin, aPT: anti-thrombin, aAV: anti-annexin V, aPE: anti-phosphatidyl ethanolamine, Ig: immunoglobulin, aβ2-GPI-DI IgG: anti-domain 1 β2-GPI, NA: information not available, ICU: intensive care unit, MW: medicine ward, LA: lupus anticoagulant, VTE: venous thrombosis event, PE: pulmonary embolism, LI: acute lower limb ischemia, CT: catheter thrombosis, ECMO: Extra Corporeal Membrane Oxygenation, RRT: Renal Replacement Therapy, UK: United Kingdom, USA: United States of America
antiphospholipid Syndrome (APS) or catastrophic APS (CAPS) [62, 63].

**Against such a Pathogenic Role?**

It is widely known that aPL can appear during a viral infection. During other viral infections, aPL prevalence varies from 2% to 63% depending on the aPL studied, they are classical known to be transient and non-pathogenic [64, 65]. Yet during COVID-19, some authors have suggested a pathological role to aPL to explain high number of thrombotic events. However some authors did not show any relationship of aPL and thromboses [18, 54, 55]. Differences of aPL prevalence could be observed in all types of aPL studied. The main reason is probably linked to aPL tests and the interpretation of the results. Assays may be affected by several analytical factors, including methodological issues due to the heterogeneity of aPL, different tests from one laboratory to another, and pre-analytical factors due to the clinical condition of the patient in whom the assay is performed [57]. In particular inflammation may cause false positive determination of LA [66–68]. The latest recommendations of the ISTH suggest not to test for LA in the acute phase of inflammation when possible [69••]. The presence of anticoagulant treatments may also interfere with LA tests [56, 70], and finally a higher prevalence of aPL is usually found in elderly people with chronic diseases (up to 18%), who are at high risk for severe COVID-19 [71–73], and in severe patients in ICU without COVID-19 [74, 75].

Presence or absence of aPL is not sufficient to determine the patient's thrombotic profile: high aPL titers and the simultaneous presence of several aPL increase thrombotic risk [76, 77]. Isolated LA is an independent risk factor for myocardial infarction and ischemic stroke [78, 79], but interpretation of positivity may be difficult in critical care patients.

Many studies do not clearly report titers, associations of several aPL and their isotypes. Finally, the severity of the clinical condition could explain in part the presence of aPL.

**Persistence of aPL Over Time**

The persistence over time has been studied only twice [13, 52]. Results with the low persistence of aPL at one month must be contrasted by the large number (more than 50%) of those lost for follow-up in the first study. Indeed, the follow-up in this situation is difficult, especially in ICU patients, with many deaths. The second cohort study did not find any LA in patients tested again. The other aPL seem to be more persistent, suggesting that positive LA can be frequent in COVID-19 patients at their admission in relation to the acute inflammatory phase.

It has been reported that the majority of aPL tested in ICU patients were identified within 10 days of admission [53]. A study of conventional and unconventional aPL at different time points of COVID-19 infection [35•]. Suggested that during the course of the infection, prevalence of different aPL varied over time, possibly linked to the inflammatory phase of the disease. The types of aPL may also vary over time [45]. Unfortunately, their long term persistence overtime has not been studied in most instances.

**And in Clinical Practice?**

Based on these data, routine screening of aPL in COVID-19 patients may be questioned. There are no specific recommendations about aPL and their determination in COVID-19 patients, but the American Society of Hematology (ASH) stated that “there are only very limited data on aPL antibodies in COVID-19 and it is unclear if they represent an epiphennomenon or are actually involved in any haemostatic abnormalities seen in COVID-19 disease” [80].

However, their pathogenic role remains possible. While a systematic screening does not seem indicated, we suggest that aPL testing should be performed in COVID-19 patients with thrombotic events. In addition as indicated in the general recommendations, [69, 80] patients with, thrombotic storms, venous thrombosis at unusual sites or despite preventive anticoagulation or arterial thrombosis in younger patients (<50 years) as well as suggestive obstetrical history or underlying systemic autoimmune diseases should lead to an aPL assessment.

In the same recommendations, patients with systemic lupus erythematosus and COVID-19 should be tested for LA and other aPL in order to assess their thrombotic risk. Indeed, the presence of this antibodies, and even more so their association, would change their management.

When aPL assay is indicated, only LA, IgG/IgM aCL, and IgG/IgM aβ2-GPI should be performed routinely. Indeed, the impact and the role in clinical practice of unconventional aPL (IgA isotype especially), are still debated [59, 81, 82]. Thus, their determination is recommended in well-designed research protocols [76, 83].

In all cases the interpretation of the presence of LA in ICU patients must be done with care due to the inflammatory state of the patients. Titers and combination of aPL should be taken into account for anticoagulant treatment decisions in case of thrombosis. Finally, all identified aPL should be systematically confirmed at 3 months whenever possible.

**Research Agenda**

Simple descriptive data are not sufficient to clearly determine aPL involvement in COVID-19 infection. Further follow-up studies to research the persistence of these antibodies over time are needed. More studies directly investigating the pathogenic role of aPL are important. The issue will be to determine if they participate directly in thrombosis, or if their
presence is only an additional feature of the major infectious pro-inflammatory state of the disease. Future multicenter studies must also standardize with aPL assessment to harmonize the timing of tests, preanalytical and analytical variables and results and their interpretations in this specific context and use a core laboratory if necessary. The determination of the role of unconventional aPL should also be explored in future studies.

**Conclusion**

COVID-19 is a new viral disease causing frequent thrombotic events. The designation of the “perfect culprits”, aPL, has been discussed since the initial findings. However, aPL are frequently found in infected patients. COVID-19 patients experience many thrombotic complications, particularly in ICU, for which aPL could be responsible and that may require specific anticoagulant strategies. aPL screening should currently be reserved for COVID-19 patients with thrombosis or in specific situations such as underlying auto-immune diseases. Finally, more studies investigating the pathogenic role of aPL are important, as well as further follow-up studies to research the persistence of these antibodies over time are needed.

**Declarations**

**Conflict of Interest** The authors declare that they have no competing interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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