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ANTIPHOSPHOLIPID SYNDROME (S ZUILY, SECTION EDITOR)

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-β_2-glycoprotein I (aβ_2-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 aβ_2-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•, 7, 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-β_2-

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glycoprotein I (aβ_2-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 antibod* 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 21studies. 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 aβ_2-GPI was also variable in most studies: between 0% and 39% of patients had aβ_2-GPI IgG and between 0% and 34% of patients had aβ_2-GPI IgM. The proportion of triple positivity (combined positivity for LA, aCL and aβ_2-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 aβ_2-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 aβ_2-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

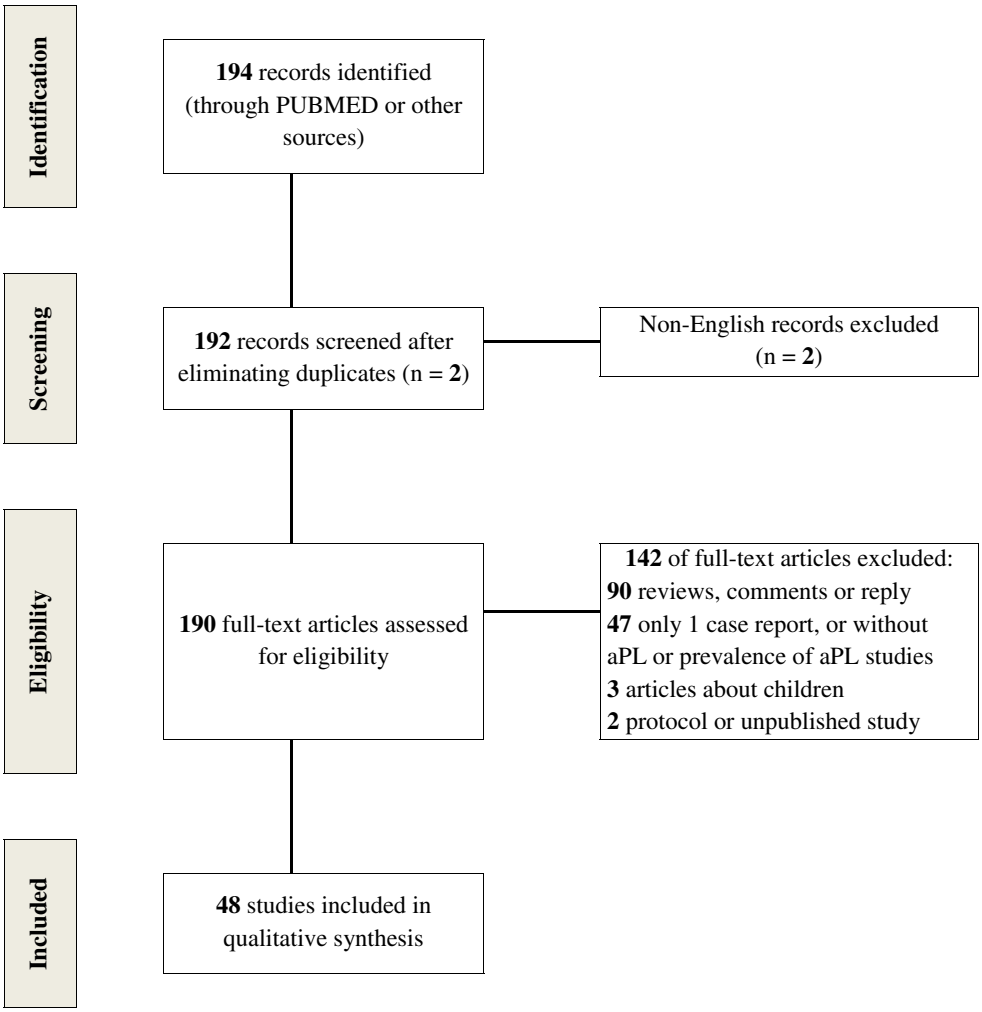

Fig. 1: Flowchart

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 aβ_2-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 aβ_2-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, aβ_2-GPI and aCL in severe and non-severe COVID-19 patients [43], and other authors did not find more aPL (aCL or aβ_2-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

Table 1 Characteristics of studies describing ICU patients.

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 aβ$_2$-GPI IgG, IgA	0 3 3;3	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 aβ$_2$-GPI IgA aβ$_2$-GPI IgG, IgM (aPS or aPE or aCL or aβ$_2$-GPI) IgG, IgM	23 7 13;5 3 1;0 15;14	NA	6 PE
Fan et al. [11]	07/2020	China	ICU	86	aPL: LA or aCL or aβ$_2$-GPI	12	NA	6 strokes
Amezcua-Guerra et al. [12]	08/2020	Mexico	ICU	21	aCL IgG, IgM aβ$_2$-GPI IgG, IgM aPS/PT IgG, IgM aPI IgG, IgM aAV IgG, IgM	2;3 1;0 2;4 0;0 1;4	NA	2 PE
Devreese et al. [13••]	09/2020	Belgium	ICU	31	LA aCL IgA aCL IgG, IgM aβ$_2$-GPI IgA aβ$_2$-GPI IgG, IgM aPS/PT IgG, IgM	21 3 6;1 3 3;1 3;4	*At 1 month:* 1/10 LA 0/4 aCL 1/2 aβ$_2$-GPI tested again	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 aβ$_2$-GPI IgG, IgM aβ$_2$-GPI IgA	7;8 19;11 8	NA	NA
Zhang et al. [15]	10/2020	China	ICU	19	LA aCL IgA aCL IgG, IgM aβ$_2$-GPI IgA aβ$_2$-GPI IgG, IgM	1 6 2;1 7 6;0	NA	4 ATE 1 VTE 7 micro-thrombi
Fan et al. [16]	10/2020	Singapore	ICU	12 for LA, 4 for others aPL among 12 patients	LA aCL IgG, IgM aβ$_2$-GPI	6 1;2 2	NA	NA
Alharthy et al. [17]	10/2020	Saudi Arabia	ICU	3	aCL aβ$_2$-GPI IgG, IgM	3 3;3	NA	1 DVT
Siguret et al. [18]	11/2020	France	ICU	74	LA aCL or aβ$_2$-GPI	63 9	NA	26 DVT, 4 PE, 1 stroke, 1 CVC thrombosis
Frapard et al. [19]	12/2020	France	ICU	37	aβ$_2$-GPI or aCL IgA aβ$_2$-GPI or aCL, IgG or IgM	7 6	NA	21 VTE 11 circuit thrombosis
Van der Linden et al. [20]	12/2020	Sweden	ICU	23	aCL IgA aCL IgG, IgM aβ$_2$-GPI IgA aβ$_2$-GPI IgG, IgM	19 7;9 20 7;8	NA	9 PE 3 DVT
Vlachoyiannopoulos et al. [21]	12/2020	Greece	ICU	29	aCL IgG, IgM aβ$_2$-GPI IgG, IgM	7;3 5;7	NA	NA
Karahan et al. [48]	03/2021	Turkey	ICU	26 for LA, 31 for other aPL, among 31 patients	LA aCL IgG, IgM aβ$_2$-GPI IgA aβ$_2$-GPI IgG, IgM	6 0;2 2 0;0	NA	1 stroke 1 MI 2 others thrombotic events
Mullaguri et al. [51]	04/2021	USA	ICU	2	aCL IgM, IgA	2,1	NA	2 strokes, 2 PE

Table 1 (continued)

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
Trahtemberg et al. [53]	04/2021	Canada	ICU	22	aCL IgG, IgM $a\beta_2$-GPI IgG, IgM $a\beta_2$-GPI-DI IgG aPS/PT IgG, IgM	13;7 0;0 0 0;1	NA	NA
Najim et al. [54]	04/2021	Qatar	ICU	60	LA aCL IgG, IgM $a\beta_2$-GPI IgG, IgM	21 0;0 1;1	NA	1 VTE 2 ATE

Abbreviations. *aPL*: antiphospholipid antibodies. *aCL*: anti-cardiolipin antibody. *$a\beta_2$-GPI*: anti-beta2glycoprotein I. *aPS/PT*: anti-phosphatidylserine/prothrombin. *aPI*: anti-phosphatidylinositol. *aAV*: anti-annexin V. *aPE*: anti-phosphatidyl ethanolamine. *Ig*: immunoglobulin. *$a\beta_2$-GPI-DI IgG*: anti-domain 1 β_2-GPI. *NA*: information not available. *ICU*: intensive care unit. *LA*: lupus anticoagulant. *ATE*: arterial thrombosis event. *VTE*: venous thrombosis event. *PE*: pulmonary embolism. *CVC*: central venous catheter. *DVT*: deep vein thrombosis. *ECMO*: extracorporal membrane oxygenation. *MI*: myocardial infarction. *LI*: acute lower limb ischemia. *SI*: splenic infarction. *USA*: United States of America

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 $a\beta_2$-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 $a\beta_2$-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

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 aβ_2-GPI	25 5	NA	NA
Bowles et al. [23]	07/2020	UK	NA	34	LA	31	NA	1 VTE
Gazzaruso et al. [24]	07/2020	Italy	MW	45	LA aCL IgG, IgM aβ_2-GPI IgG, IgM	21 1;1 2;3	NA	NA
Popovic et al. [25]	07/2020	France	NA	11	aCL aβ_2-GPI	3 1	NA	11 MI
Galeano-Valle et al. [26]	08/2020	Spain	MW	24	aCL IgG, IgM aβ_2-GPI IgG, IgM	0;2 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 aCL IgG, IgM aβ_2-GPI IgA aβ_2-GPI IgG, IgM	16 2 15;3 4 7;8	NA	17 VTE 1 stroke
Reyes et al. [28]	08/2020	USA	NA	68	LA aCL IgG, IgM aβ_2-GPI IgG, IgM	38 0;1 0;1	NA	17 DVT, 7 PE 6 ATE 2 strokes
Rothstein et al. [29]	09/2020	USA	NA	9	aPL	9	NA	strokes
Hossri et al. [30]	10/2020	USA	NA	2	LA aCL IgG, IgM aβ_2-GPI	0 2 0	NA	Stroke, LI, SI
Previtali et al. [31]	10/2020	Italy	NA	35	aCL IgA aCL IgG, IgM aβ_2-GPI aPS/PT IgG, IgM	0 1;2 0 1;2	Autopsy series	10 thromboembolic events 4 PE 2 strokes
Gazzaruso et al. [32]	11/2020	Italy	NA	192	LA	95	NA	
Kanso et al. [33]	11/2020	France	MW	2	LA	1	NA	1 PE
Guillet et al. [34]	12/2020	France	NA	4	LA aCL IgG, IgM	1 0;1	NA	4 ATE (MI, LI, aortic thrombosis)
Cristiano et al. [35•]	01/2021	Italy	MW	92	aCL IgG, IgM aβ_2-GPI IgG, IgM aPS/PT IgG, IgM aAV IgG, IgM	3;1 0;2 2;3 4;3	NA	NA
Balanchivadze et al. [36]	01/2021	USA	NA	2	aCL IgG, IgM aβ_2-GPI IgA	2;2 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	LA aCL IgA aCL IgG, IgM aβ_2-GPI IgA aβ_2-GPI IgG, IgM	21 31 8;8 6 5;3	NA	9 PE 1 DVT 1 aortic thrombus
Anaya et al. [49]	04/2021	Colombia	NA	120	aCL IgG, IgM aβ_2-GPI IgG, IgM	2;22 0;17	NA	NA

Abbreviations. *aPL*: antiphospholipid antibodies. *aCL*: anti-cardiolipin antibody. *aβ_2-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

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 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 aβ$_2$-GPI IgG, IgM	5 0;1 1;1	NA	6 strokes
Pascolini et al. [39]	09/2020	Italy	Mixed	33	aCL IgG, IgM aβ$_2$-GPI IgG, IgM	3;5 2;2	NA	NA
Bertin et al. [40]	11/2020	France	Mixed	56	aCL, IgG, IgM aβ$_2$-GPI IgG, IgM	16;3 1;4	NA	Strokes
Zuo et al. [41•]	11/2020	USA	Mixed	172	aCL IgA aCL IgG, IgM aβ$_2$-GPI IgA aβ$_2$-GPI IgG, IgM aPS/PT IgG, IgM	6 8;39 7 5;9 42;31	NA	NA
Lerma et al. [42]	11/2020	USA	Mixed	64	aCL IgG, IgM aβ$_2$-GPI IgG, IgM aPS/PT IgG, IgM	1;1 1;2 1;3	NA	NA
Ferrari et al. [43]	11/2020	France	Mixed	89	LA aCL aβ$_2$-GPI	59 7 6	NA	14 VTE
Gutiérrez et al. [44]	12/2020	Spain	Mixed	27	LA aCL (IgG or IgM) aβ$_2$-GPI IgA aβ$_2$-GPI (IgG or IgM)	6 0 1 1	NA	2 LI 6 DVT 10 PE 2 strokes
Xiao et al. [45]	12/2020	China	Mixed	79	LA IgA aCL, aβ$_2$-GPI aCL IgG, IgM aβ$_2$-GPI IgG, IgM aβ$_2$-GPI-DI IgG aPS/PT IgG, IgM	2 17;19 4;2 12;1 2 0;7	NA	19 DVT 5 strokes 1 MI
Tvito et al. [46]	02/2021	Israel	Mixed	43	LA aCL or aβ$_2$-GPI	16 0	NA	3 thrombotic events
Bauer et al. [47]	02/2021	Germany	Mixed	17	LA	3	NA	NA
Serrano et al. [50]	04/2021	Spanish	Mixed	474	aCL and/or aβ$_2$-GPI IgG, IgM aβ$_2$-GPI IgA aPS/PT IgG or IgM	28 71 22	NA	9 thrombotic events
Vollmer et al. [52]	04/2021	France	Mixed	79 patients with LA positivity 56 for aCL and aβ$_2$-GPI, 53 for other aPL among	LA aCL IgG, IgM aβ$_2$-GPI IgG, IgM aPE aPS aPT aAV	79 1;13 0;3 1 1 10 1	*At 3 months:* 0/42 LA tested again	30 VTE, 27 PE 5 DTP or superficial VT 10 ATE, 9 strokes, 0 MI, 1 mesenteric infarction 5 CT, 5 ECMO or RRT circuit Clotting
Gendron et al. [55]	04/2021	France	Mixed	115 for LA, 97 for aCL IgA, 98 for aβ$_2$-GPI IgA, 109 for aPT 148 for other aPL among 154 patients	LA aCL IgA aCL IgG, IgM aβ$_2$-GPI IgG, IgM aβ$_2$-GPI IgA aPS/PT IgG, IgM aPT IgG, IgM	70 3 9;2 5;3 2 0;7 11;10	NA	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-phosphatidylserine, *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 epiphenomenon 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 aβ_2-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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- •• Of major importance

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