

## Presence of antiphospholipid antibodies in COVID-19: a case series study

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated coagulopathy are particularly worrisome in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), as these diseases carry an increased risk of thrombotic complications. Mathian *et al* recently reported the clinical course of COVID-19 in a series of 17 patients with SLE under chronic hydroxychloroquine therapy.<sup>1</sup> Of note, only one patient (6%) presented thrombosis despite the fact that four patients (24%) had a history of secondary APS, and five patients (29%) were receiving oral anticoagulants. Antiphospholipid (aPL) antibodies were not measured in these patients during active SARS-CoV-2 infection.<sup>1</sup>

The American Society of Hematology recently stated that 'at the current time, 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'.<sup>2</sup> Furthermore, almost all the available information refers to the lupus anticoagulant, with frequencies ranging from 45% to 87%.<sup>3,4</sup> This paucity of data led us to test a panel of aPL antibodies in blood specimens from 21 patients hospitalised in the intensive care unit between 12 and 19 April, due to severe or critical COVID-19, and received at our laboratory on 20 April to measure interleukin-6 levels. Anticardiolipin, anti- $\beta_2$  glycoprotein I, antiprothrombin, antiphosphatidylserine, antiphosphatidylinositol and antiannexin V antibodies were measured, each in IgM and IgG isotypes. Subsequently, demographic and clinical data were obtained from electronic medical records. Sera collected before the SARS-CoV-2 pandemic from 12 healthy individuals, matched for age and sex, were tested as controls.

Pertinent results are summarised in table 1. The median age of patients was 62 years; 43% were men; and a high number of comorbidities were observed (median Charlson Comorbidity Index of 3). A total of 19 patients (90%) had shortness of breath on admission, and 12 (57%) eventually required invasive mechanical ventilation during hospitalisation. Elevated levels of D-dimer, ferritin and C reactive protein were found at presentation.

Of the 21 patients with COVID-19 studied, 12 had at least one circulating aPL antibody, whereas only 1 of the 12 controls yielded a positive result (57% vs 8%; Fisher's exact test,  $p=0.009$ ). The most frequently detected aPL antibodies were antiannexin V IgM (19%), anticardiolipin IgM (14%), antiphosphatidylserine IgM (14%), anticardiolipin IgG (10%) and antiphosphatidylserine IgG (10%) antibodies. One patient had triple positivity (8%); three patients had double positivity (25%); and the remaining eight had a single positivity (67%). Age and number of comorbidities tended to be lower in patients with aPL antibodies. In contrast, levels of D-dimer, ferritin and C reactive protein were higher both on admission and throughout the hospital stay in these patients. Elevated levels of interleukin-6 ( $>40$  pg/mL) were found only in patients with aPL antibodies. The type of therapies administered in both groups was similar, except for a greater number of patients with aPL antibodies who received glucocorticoids (50% vs 0; Fisher's exact test,  $p=0.018$ ).

The occurrence of hospital outcomes was followed up to 30 days after aPL antibody measurement. Two patients presented pulmonary thromboembolism despite being on heparin: a 28-year-old man with a previous diagnosis of

**Table 1** Main clinical and laboratory data of 21 patients with severe or critical COVID-19


	Total (N=21)	Positive aPL antibodies (n=12)	Negative aPL antibodies (n=9)
Age (years)	62 (54–67)	55 (49–63)	67 (62–68)
Male sex, n (%)	9 (43)	6 (50)	3 (33)
Days of symptom onset	7 (5–9)	7 (4–8)	7 (5–9)
Charlson Comorbidity Index	3.0 (1.0–4.0)	1.5 (1.0–3.0)	4.0 (2.0–5.0)
Coexisting conditions, n (%)			
Hypertension	12 (57)	5 (42)	7 (78)
Diabetes mellitus	8 (38)	3 (25)	5 (56)
Dyslipidaemia	7 (33)	3 (25)	4 (44)
Obesity	7 (33)	5 (42)	2 (22)
Coronary artery disease	3 (14)	2 (17)	1 (11)
Stroke	1 (5)	0	1 (11)
Current smoker	2 (10)	2 (17)	0
Pulmonary disease	2 (10)	2 (17)	0
Chronic kidney disease	3 (14)	1 (8)	2 (22)
Chronic heart failure	2 (10)	0	2 (22)
Cancer	1 (5)	0	1 (11)
Main findings at hospital admission			
Fever, n (%)	13 (62)	7 (58)	6 (67)
Shortness of breath/respiratory distress, n (%)	19 (90)	12 (100)	7 (78)
White cell count ( $\times 10^3$ per $\text{mm}^3$ )	6.5 (4.9–10.4)	7.0 (5.4–12.1)	6.2 (4.9–9.6)
Platelet count ( $\times 10^3$ per $\text{mm}^3$ )	179 (146–198)	179 (156–193)	171 (143–240)
D-dimer (ng/mL)	339 (177–484)	387 (207–484)	303 (132–446)
Ferritin ( $\mu\text{g/L}$ )	557 (156–882)	677 (490–1249)	199 (112–326)
C reactive protein (mg/L)	139 (57–210)	200 (95–256)	86 (57–144)
Intubation, n (%)	12 (57)	7 (58)	5 (56)
Laboratory values at the time of aPL measurements			
White cell count ( $\times 10^3$ per $\text{mm}^3$ )	7.8 (6.9–10.6)	8.6 (6.7–13.2)	6.4 (5.7–9.8)
Platelet count ( $\times 10^3$ per $\text{mm}^3$ )	260 (212–349)	262 (201–332)	259 (229–349)
D-dimer (ng/mL)	417 (216–613)	437 (206–601)	403 (278–621)
Ferritin ( $\mu\text{g/L}$ )	604 (365–1353)	1038 (580–1392)	443 (237–547)
C reactive protein (mg/L)	90 (17–219)	140 (60–270)	39 (17–129)
Serum interleukin-6 levels $>40$ pg/mL, n (%)	2 (10)	2 (17)	0
Treatment, n (%)			
Heparin	18 (86)	9 (75)	9 (100)
Glucocorticoids	6 (29)	6 (50)	0
Hydroxychloroquine	15 (71)	9 (75)	6 (67)
Azithromycin	18 (86)	10 (83)	8 (89)
Lopinavir plus ritonavir	11 (52)	6 (50)	5 (56)
Positive aPL antibodies, n (%)			
Anticardiolipin IgM	3 (14)	3 (25)	0
Anticardiolipin IgG	2 (10)	2 (17)	0
Anti- $\beta_2$ glycoprotein I IgM	0	0	0
Anti- $\beta_2$ glycoprotein I IgG	1 (5)	1 (8)	0
Antiprothrombin IgM	1 (5)	1 (8)	0
Antiprothrombin IgG	0	0	0
Antiphosphatidylserine IgM	3 (14)	3 (25)	0
Antiphosphatidylserine IgG	2 (10)	2 (17)	0
Antiphosphatidylinositol IgM	0	0	0
Antiphosphatidylinositol IgG	0	0	0
Antiannexin V IgM	4 (19)	4 (33)	0
Antiannexin V IgG	1 (5)	1 (8)	0
Pulmonary thromboembolism	2 (10)	2 (17)	0
Major bleeding, n (%)	1 (5)	1 (8)	0
Ventilator-associated pneumonia, n (%)	3 (14)	1 (8)	2 (22)
In-hospital deaths, n (%)	4 (19)	2 (17)	2 (22)
Discharged, n (%)	13 (62)	9 (75)	4 (44)

Data are presented as median (IQR) unless otherwise specified. aPL, antiphospholipid.

idiopathic pulmonary hypertension who had anticardiolipin IgG antibodies and a 63-year-old woman with a history of Fahr syndrome and hypoparathyroidism who had antiannexin V IgM antibodies. Both patients had extremely high levels of D-dimer and C reactive protein throughout the follow-up and eventually died of haemodynamic complications. Necropsy studies were not performed. Despite the fact that most patients received heparin, the only clinically significant bleeding was spontaneous retroperitoneal haematoma in a 44-year-old man with antiphosphatidylserine IgM and antiannexin V IgM antibodies who recovered with conservative management. Two patients in whom no aPL antibodies were observed eventually died of multisystem organ failure. As of 18 May, 13 patients (62%) had been discharged from the hospital; 4 (19%) remained hospitalised; and 4 (19%) died.

In this case series study, a high frequency (57%) of both 'criteria and non-criteria' aPL antibodies was found in patients with severe and critical COVID-19. These aPL antibodies appear to be associated with a hyperinflammatory state characterised by extremely high levels of ferritin, C reactive protein and interleukin-6; meanwhile, an association with pulmonary thromboembolism may be suggested. During acute infection, thrombosis or inflammation, different aPL antibodies may transiently arise, and it should not be assumed that a patient with COVID-19-associated coagulopathy and aPL antibodies has catastrophic APS.<sup>5</sup> Indeed, although COVID-19-associated coagulopathy and catastrophic APS may share clinical and laboratory features, both diseases are likely to have a different underlying pathophysiology. However, the high frequency and wide variety of aPL antibodies observed in patients with COVID-19 cannot be ignored.

Currently, there are limited data on the occurrence of aPL antibodies during SARS-CoV-2 infection, and further studies are required to determine whether these represent a simple epiphenomenon or are actually involved in COVID-19-associated coagulopathy.

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