JIM Letter to the Editor

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High frequency of antiphospholipid antibodies in critically ill COVID-19 patients: a link with hypercoagulability?

Dear Editor,

Coronavirus disease 2019 (COVID-19) is associated with both severe systemic inflammation and a prothrombotic state, as reflected by significant increases in fibrinogen and D-dimers levels that have been associated with poor prognosis [1] and high rates of severe pulmonary embolism [2]. A recent report suggested a role for antiphospholipid antibodies (aPLA) in the thrombotic manifestations associated with severe COVID-19 [3]. As we also recently noticed unexplained lengthening of activated partial thromboplastin time (aPTT) in some critically ill COVID-19 patients, we explored our patients for aPLA positivity. We retrospectively reviewed the profile of aPLA in 25 patients with confirmed SARS-CoV-2 infection admitted to our tertiary ICU at La Pitié-Salpêtrière Hospital, Paris, France, from 14 March to 8 April 2020. aPLA detection included lupus anticoagulant (LA, diluted Russell viper venom time (dRVVT)), anti-cardiolipin antibodies (IgG/M/A), anti-β2GP1 antibodies (IgG/M/A) and antiphospholipid antibodies (IgG/M). In accordance with the ethical standards of French legislation, only nonopposition of patient's surrogate for utilization of the deidentified data was obtained. The ICU database was registered with the national data protection authority (CNIL 1950673). Twenty-five patients with confirmed SARS-CoV-2 infection with complete clinical and biological data were included in the study. Mean age at admission was 47.7 (range 35–64), and male-to-female ratio was 2.1 (see Table 1). All patients had refractory COVID-19-related ARDS requiring extracorporeal membrane oxygenation and were receiving nonfractioned heparin with an aimed aPPT ratio of 1.5-2. LA, anti-cardiolipin, anti-β2GP1 and antiphospholipid were positive in 23 (92%), 13 (52%), 3 (12%) and 18 (72%) patients, respectively. Considering LA, any anti-cardiolipin and any anti-β2GP1 antibodies, 8 (32%) patients had single APLa positivity, 13 (52%) had double positivity, 3 (12%) had triple positivity, and only one (4%) was triple negative. Serum fibrinogen level was elevated in 18 (72%) patients at the time of LA detection, and D-dimers were highly elevated in all patients. Massive pulmonary embolism was diagnosed in six patients, all aPLA positive. We herein describe the profile of aPLA positivity in a series of 25 critically ill patients with severe COVID-19 infection. The frequency of aPLA in our COVID-19 patients is strikingly high. Most patients had positive LA and double aPLA positivity which are associated with a high risk of venous and arterial thrombosis in antiphospholipid syndrome patients [4]. Six patients had proven pulmonary embolism, an infrequent finding in severe ARDS under ECMO [5]. No patient had significant medical history and especially no systemic lupus erythematosus of antiphospholipid syndrome (APS). The APS is a autoimmune disease defined by thrombotic events occurring in patients with persistent aPLA positivity [4]. Several viral diseases have been shown to induce aPLA, mostly chronic infections such as the human immunodeficiency, hepatitis C and B viruses, but also acute infections due to Herpesviridae, adenoviruses and influenza viruses. Both positive association and negative association with thrombotic event have been reported [6]. Indeed, aPLA are not necessarily associated with thrombosis, especially if they are not persistent over time. Our observation raises several issues. First, does COVID-19 specifically induces aPLA? Second, are these antibodies persistent over time? Third, are they responsible for the prothrombotic state observed in SARS-CoV-2 patients and what are the respective roles of severe systemic inflammation, or d-dimers/fibrinogen elevation? Lastly, should every COVID-19 patient benefit from early and full anticoagulation? Further research is required to investigate the pathophysiology of aPLA and to determine the level of anticoagulation required in COVID-19 patients.

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None.

Conflict of interest statement

None.

Contributor Ship

All authors significantly contributed to the study design, data collection, manuscript drafting and final approval.

Table 1. *Clinical findings and antiphospholipid antibodies' profile in 25 critically ill patients with severe COVID-19 infection*

Patient						Anti-cardiolipin antibodies[c]			Anti-β2GP1 antibodies[d]				Antiphospholipid antibodies[e]			
Unit		Age	Thrombotic	n APLa tests	LA dRVVT[b] Ratio	IgG UGPL	IgM UMPL	IgA UAPL		IgG	IgM	IgA	IgG U mL^{-1}	IgM μ mL^{-1}	Fibrinogen g L^{-1}	d-Dimer μg mL^{-1}
ULN	Gender	Years	event	positivity[a]	< 1.2	< 15	< 15	< 15	Screening	<15	<15	<15	< 15	< 0.5	< 4.0	< 0.5
1	M	35		Single	**1.4**	7	6	5	Negative				14	10	7.5	3.9
2	M	48		Double	**1.4**	**26**	8	**18**	Negative				**17**	**18**	9.2	3.7
3	W	44		None	1.0	<4	<4	7	Negative				9	6	3.8	17.9
4	W	49	MPE	Single	**1.5**	<4	6	5	Negative				9	**17**	5.9	>20
5	M	43		Single	**1.7**	<4	<4	4	Negative				9	7	3.7	2.0
6	M	58		Single	**1.6**	4	4	2	**Positive**	4	<1	2.9	**19**	10	8.6	6.6
7	W	59	MPE	Single	**1.3**	<4	<4	9	Negative				10	10	6.2	>20
8	M	45		Triple	**1.6**	**29**	**15**	**29**	**Positive**	3	<1	**56**	**20**	**26**	6.6	>20
9	M	56	MPE	Double	**1.7**	**55**	**17**	**77**	Negative				**44**	**17**	5.3	5.8
10	M	41		Double	**1.5**	**40**	9	14	Negative				**49**	**27**	2.9	>20
11	M	39		Double	0.9	4	**16**	8	Negative				6	**19**	3	>20
12	M	53		Double	**1.4**	**51**	8	8	Negative				**21**	14	6	>20
13	M	48		Single	**1.8**	10	7	13	Negative				14	9	7.6	>20
14	W	43		Single	**1.6**	5	6	10	Negative				9	13	7.3	13.2
15	W	49		Double	**2.1**	**21**	14	**38**	Negative				**18**	**21**	2.7	>20
16	W	55	MPE	Double	**1.3**	10	**20**	8	Negative				**17**	**47**	7.7	15.6
17	M	40		Double	**2.6**	**19**	<4	**19**	Negative				**19**	8	7	>20
18	M	41	MPE	Double	**1.4**	**26**	10	8	Negative				**44**	**17**	7.1	>20
19	W	43		Triple	**1.3**	**24**	13	12	**Positive**	3	4	**26**	**18**	**19**	5.1	>20
20	M	55		Double	**1.4**	**29**	13	14	Negative				**24**	**31**	2.2	11.7
21	M	64		Triple	**1.7**	8	11	**24**	**Positive**	**17**	<1	**79**	12	**18**	4.4	>20
22	M	35		Double	**1.5**	**18**	8	4	Negative				13	10	7.2	7.6
23	M	39		Double	**1.7**	**21**	**23**	7	Negative				**33**	**32**	4.8	>20
24	W	62	MPE	Double	**1.3**	**26**	6	**25**	Negative				**34**	12	5.9	>20
25	M	50		Single	**1.3**	<4	9	*15*	Negative				**24**	**15**	3.3	>20

Bold values are above the upper limit of the normal of the test.
APL, antiphospholipid antibodies; COVID-19, coronavirus disease 2019; dRVVT, diluted Russell viper venom time; LA, lupus anticoagulant; M, man; MPE, massive pulmonary embolism; n, number; ULN, upper limit of normal value; W, women.
[a]Includes lupus anticoagulant, anti-cardiolipin antibodies and anti-β2GP1 antibodies.
[b]DRRVT screen and confirm were performed on a CS5100 analyzer using LA1 and LA2 reagent, SIEMENS (Saint-Denis, France). Results presented herein are the confirmed dRVVT ratio.
[c]QUANTA Lite® ACA IgG III, INOVA (San Diego, CA, USA).
[d]Thermoscientific EliA beta-2 Glycoprotein-1 IgG/M/A-well (Phadia, Uppsala, Sweden).
[e]PHOSPO-LISA IgG/IgM, THERADIAG (Marne-la-Vallée, France); includes anti-phosphatidyl serine, anti-phosphatidyl ethanolamine, anti-cardiolipin s and anti-β2GP1 antibodies.

Ethical approval informations

In accordance with the ethical standards of French legislation, only nonopposition of patient's surrogate for utilization of the deidentified data was obtained. The ICU database was registered with the national data protection authority (CNIL 1950673).

Data sharing statement

All data are presented in the manuscript.

Author Contribution

Corinne Frere: Conceptualization (equal); Investigation (equal); Methodology (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Makoto Miyara:** Conceptualization (equal); Investigation (equal); Methodology (equal); Validation (equal); Writing-review & editing (equal). **Zahir Amoura:** Conceptualization (supporting); Validation (equal); Writing-review & editing (equal). **Isabelle Martin-Toutain:** Formal analysis (equal); Investigation (supporting); Writing-review & editing (equal). **Guillaume Hekimian:** Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Alain Combes:** Conceptualization (equal); Methodology (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

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