JIM Letter to the Editor

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Response to Letter: 'Reply to "High frequency of antiphospholipid antibodies in critically ill COVID-19 patients: a link with hypercoagulability?"'

To the Editor,

We read with great interest the comment by Suarez-Perez et al. on our article [1]. We share their concerns regarding the need for a cautious interpretation of antiphospholipid antibodies (aPLA) positivity in patients with coronary virus disease 2019 (COVID-19). Herein, we would like to add further insights in the discussion.

First, many studies from all around the world have reported heterogeneous frequencies of aPLA in various population of COVID-19 patients since our publication (Table 1). It is uneasy yet to draw a clear conclusion on such contradictory findings. Whilst several cohorts found comparable results [2–9], others reported very low percentage of positive patients [4,10–13]. A study linked the sickness of the COVID-19 to anti-cardiolipin (aCL) IgG frequency, suggesting that COVID-19 disease severity could explain the discrepancy between reports [5]. Second, although we agree that only medium and high levels of IgG or IgM aCL or anti-β2GP1 are considered in the antiphospholipid syndrome (APS) classification, most of our patients were positive for lupus anticoagulant (LA), which is the aPLA most strongly associated with the onset of thrombotic events. Third, we do think that the persistence of aPLA away from acute infection would be a crucial element for the diagnosis of COVID-19-induced APS. Yet, maybe transient aPLA can participate to the severity and to the thrombotic manifestations of SARS-CoV-2 pneumonia. Indeed, many viral infections have been previously shown to be associated with aPLA positivity, without further evidence of their pathogenic role, except in a few isolated cases [14]. Fourth, we acknowledge that the diagnosis of LA in COVID-19 is challenging since several factors, including pre-analytical, analytical and postanalytical factors, might be responsible for false-positive results. LA is detected by prolongation of phospholipid-dependent coagulation tests *in vitro*, in the absence of coagulation factor deficiency. The *in vitro* prolongation of coagulation tests is due to an interference with accumulation of coagulation factors on negatively charged phospholipids. Since C-reactive protein also interacts with phospholipids, a marked elevation in C-reactive protein, which is frequently observed in COVID-19 patients, might result in false-positive aPLA results, further limiting interpretation of this testing in COVID-19 patients [15]. Fifth, other COVID-19-induced autoantibodies or autoimmune diseases have been reported [2,16–18]. Of note, a recent study revealed a cumulative incidence of detectable anti-PF4-heparin antibodies higher than expected (12% at 25 days) in 88 severe COVID-19 patients who received at least 5 days of unfractionated heparin [19]. Some reports disclosed cross-reactivity between SARS-CoV-2 and human proteins, suggesting that a molecular mimicry mechanism could explain these autoimmune manifestations [17,20,21].

Larger sample size studies are therefore urgently needed to determine the true frequencies of aPLA in COVID-19 patients, to evaluate their relation to disease severity and thrombotic events and to assess their persistence away from the acute infection.

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Conflict of interest statement

No conflict of interest to declare.

Author contribution

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

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Table 1. *Frequencies of antiphospholipid antibodies and thrombotic events in various cohort of COVID-19 patients*

References	Setting	n[a]	Lupus anticoagulant positivity (%)	Anti-cardiolipin antibodies positivity (%)			Anti-β2GP1 antibodies positivity (%)			Thrombotic events (%)
				IgG	IgM	IgA	IgG	IgM	IgA	
[1]	ICU	25	92	52	20	28	4	0	12	24
[22]	ICU	3	0	100	0	0	100	0	100	100
[6]	ICU	74	85	12						36.4
[2]	ICU	29	–	24.1	10.3	–	17.2	27.5	–	–
[3]	ICU	19	5.2	10.5	5.2	31.6	31.6	0	36.8	63.1
[13]	ICU	122	–	5.7	6.6	0	15.6	9	6.6	–
[8]	ICU	31	67.7	19.3	3.2	9.7	9.7	3.2	9.7	29.0
[7]	ICU	57	87.7	–	–	–	–	–	–	18
[4]	Mixed	79	2.5	5.1	2.5	21.5	15.2	1.3	24.0	31.6
[5]	Mixed	56	–	28.5	5.3	–	17.8	7.1	–	–
[11]	Mixed	172	–	4.7	23	3.5	2.9	5.2	4.1	–
[12]	MW	24	–	0	2	–	0	2	–	100
[10]	MW	45	11.1	2.2	2.2	–	4.4	4.4	–	–
[9]	–	34	91	–	–	–	–	–	–	5.7
[23]	–	56	45	10						–
Range		3–172	0–92	0–100	0–20	0–31.6	0–100	0–9	4.1–100	5.7–100

ICU, intensive care unit; IgA, A immunoglobulin; IgG, G immunoglobulin; IgM, M immunoglobulin; MW, medical ward; Ref, reference.
[a]Number of patients.

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