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LETTER TO THE EDITOR

Thrombosis and antiphospholipid antibodies in patients with SARS-COV-2 infection (COVID-19)

Dear Editors,

In March 2020, the infection caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was declared a pandemic by the World Health Organization. This global health emergency had in Spain one of its epicenters.

As the scientific community gained clinical experience about COVID-19 (coronavirus disease 2019) and more and more clinical reports were published, an increased thrombotic risk was observed in patients infected with this novel virus. Subsequently, this hypothesis was confirmed with the performance of the first autopsies, being deep vein thrombosis and massive pulmonary embolisms common findings.

Several references exist in the literature to the possible relation between the presence of a lupus anticoagulant (LA) and the prothrombotic state experienced by these patients.[1,2]

In our center, we retrospectively analyzed 27 patients who had been tested for antiphospholipid antibodies between March 13th and April 26th of 2020, during their hospital admission due to COVID-19 (confirmed by a positive RT-PCR for SARS-CoV-2 in a nasopharyngeal swab). Informed consent was obtained, and no change in clinical practice was made according to the results. All of them were on prophylactic heparin, and the determinations were made 24 hours after the last dose. Their clinical and laboratory characteristics are described in Table 1. Patients receiving warfarin or direct oral anticoagulants were excluded.

For the detection of lupus anticoagulant (LA), the dilute Russel viper venom test (dRVVT, HemosIL™, reagent: HemosIL dRVVT Screen/Confirm, Instrumentation Laboratory, Werfen) and the silica clotting time (SCT, HemosIL™, reagent: HemosIL Silica Clotting Time, Instrumentation Laboratory, Werfen) were used with screen/confirm reagents, while for the determination of anticardiolipin (aCL) antibodies (IgM and IgG) and anti-beta-2 glycoprotein I antibodies (IgA, IgM and IgG) a serological enzyme-linked immunosorbent assay (ELISA) was performed (reagent: QUANTA aB2GPI Lite, INOVA Diagnostics).

A total of 6 patients (22,2%) were positive for LA and 1 (3.7%) for IgA anti-beta-2 glycoprotein I antibodies. No double antibody positivity was found.

A total of 15 patients (55,5%) had a thrombotic event from which only 3 had a positive antiphospholipid antibody determination (2 for LA, 1 for IgA anti-beta-2 glycoprotein I antibodies). From them, 13 patients had thrombotic risk factors such as hypertension, dyslipidemia, diabetes, obesity, smoking habit, or cancer.

A total of 6 patients (22,2%) required admission to an intensive care unit due to respiratory failure following an acute respiratory distress syndrome (ARDS), 5 of them experienced a thrombotic event, being pulmonary embolism the most frequent among them (56%). In 3/6 (50%), LA was positive. This last finding entails a higher percentage of patients with LA positivity among critical patients compared to the total number of patients (22,2% of LA positivity), as described by Helms J et al.[1]

A total of three patients died of respiratory failure, they all suffered at least 1 thrombotic event (1 of them endured simultaneously a deep vein thrombosis, a pulmonary embolism, and an ischemic stroke), and only 1 had a confirmed LA.

Antiphospholipid antibodies can be temporarily detected during infectious episodes, and in this specific setting, they are not clearly related to an increased thrombotic risk. Moreover, given the possibility of LA false positives due to an elevated C-reactive protein and its high affinity for phospholipids, this determination is not recommended in such episodes.[2]

In accordance with Zhang et al,[3] we do not consider the testing of LA cost-effective when performed to every COVID-19 patient, because of its high variability among them. In addition, LA positivity does not seem to predict thrombotic risk or have a clinical utility in deciding when to modify antithrombotic therapy, as mentioned by Harzallah et al,[4] even though our LA positivity rate was lower (45% vs 22.2%), as it was for the remaining antiphospholipid antibodies (10% vs 3.7%).

Regarding the possible usefulness of a prolonged activated partial thromboplastin time (aPTT) (reagent used: SynthASil, Instrumentation Laboratory, Werfen) as a guide to test for the presence of antiphospholipid antibodies, just like Bowles et al[5] and Connell et al[6] describe, we did not find it useful, only 1 of our 27 patients had a prolonged aPTT and presence of LA, while the remaining patients with positive LA had no coagulation abnormalities.

We agree with Beyrouti R et al,[7] considering a prolonged aPTT not a very sensitive test to predict the possible positivity of LA, because of the potential interference of other factors that can shorten (such as factor VIII) or prolong it (such as factor XII or C-reactive protein).

In conclusion, according to our experience, LA determination may be unnecessary for COVID-19 patients due to its high variability in acute infections and its lack of predictive capability of thrombotic

TABLE 1 Characteristics of the patients

Characteristics	Patients (n=27)	Reference range
Age (years)	58 (20-90)	
Gender		
Female	55,6%	
Male	44,4%	
Cardiovascular risk factors		
Hypertension	37%	
Dyslipidemia	33%	
Diabetes	11%	
Smoker	14,8%	
Obesidad (BMI > 30 Kg/m2)	18,5%	
Medical history		
Autoimmune disease	11.1% (3/27)	
Cancer	7% (2/27)	
Laboratory findings		
Hemoglobin	13,6 (9,2-16,2)	g/dL [13.0-16.8]
Platelets	222.000 (108.000-599.000)	×1000/μL [140-450]
Lymphocytes	1100 (100-3100)	×1000/μL [1.2-4.0]
LDH	329 (190-811)	U/L [135-225]
CRP	7,32 (0,04-36,6)	mg/dL [0.10-0.50]
Ferritin	1070 (137-7459)	ng/mL [30-400]
Fibrinogen	648 (373-1412)	mg/dL [200-560]
IL-6	252 (0-782)	pg/mL [<40]
D-dimer	2367 (223-8138)	ng/mL [<500]
Prothrombin activity	83 (60-115)	% [75-140]
Prothrombin time	12,8 (10,7-16,5)	s [9.7-13.9]
aPTT	TTPa: 32 (21-48)	s [26-39]
Lupus anticoagulant	22,2% (6/27)	
Anticardiolipin antibodies	0% (0/27)	
Anti-B2 glycoprotein I antibodies	3,7% (1/27)	
ICU		
Admission	22,2% (6/27)	
Median stay (days)	25 (6-30)	
Thrombotic event		
Arterial	Lower extremities arterial ischemia 7,4% (2/27)	
Venous	Deep vein thrombosis 22,2% (6/27)	
	Pulmonary embolism 37% (10/27)	
	Stroke 7,4% (2/27)	
Death	11,1% (3/27)	

risk, except in critical patients whose clinical situation is already an additional risk factor.

All SARS-CoV-2-infected patients should receive antithrombotic prophylaxis regardless of the presence of LA due to their increased thrombotic risk as a consequence of multiple factors (hyperinflammation, platelet activation, and endothelial dysfunction) and its positivity should not change this practice.

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CONFLICTS OF INTEREST

None of the authors have any conflict of interest in relation to the information reported here.

AUTHOR CONTRIBUTIONS

Gutiérrez López de Ocáriz X., Castro Quismondo N., and Vera Guerrero E. collected the date processed statistics and wrote the manuscript. Rodríguez Rodríguez M., Ayala Díaz R., and Martínez López J. revised the manuscript.

INFORMED CONSENT

All patients gave verbal consent for studies with their biological samples.

The authors declare that data supporting the findings of this study are available within the article.

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