Dear Sir,

We have read with great interest the article recently published in your journal under the title 'High frequency of Antiphospholipid Antibodies in Critically ill COVID-19 patients: a Link with Hypercoagulability?' by Pinetron de Cambrun et al. [1]. This article retrospectively describes a series of 25 patients with acute respiratory distress syndrome (ARDS) associated with COVID-19 admitted to the ICU of a tertiary hospital. They found a high prevalence of antiphospholipid antibodies (aPL), which led them to suspect a specific induction of these aPL by SARS-CoV-2 and an association with the prothrombotic state triggered by this disease. Potential need for early anticoagulation therapy for all patients with COVID-19 is suggested on the basis of these findings.

The frequent finding of elevated D-dimer values, which have been found to be an independent factor of poor prognosis, and the high frequency of thrombotic events reported [2] suggest the possibility of a prothrombotic coagulopathy characteristic of SARS-CoV-2. In this regard, following the publication by Zhang et al. [3] of 3 cases with COVID-19 and aPL in the early months of the pandemic there has been increasing interest in researching the possible autoimmune origin of this coagulopathy. After reading the paper by Pinetron de Cambrun et al, we would like to make some considerations on this subject.

According to the revised Sapporo criteria for classification of the antiphospholipid syndrome (APS) [4], the disease is characterized by thrombosis, pregnancy complications or both in patients with persistant aPL: lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or anti-ß2-GPI antibodies. In these criteria, the presence of one or more of the aPL on two or more blood tests at least 12 weeks apart is mandatory.

The persistence of the antibodies is very important because the presence of transient aPL, as mentioned by the authors, has been described in the context of other viral infections, and is rarely associated with thrombosis. Therefore, we believe that the results should be interpreted with caution.

Furthermore, in the current APS guidelines only medium and high levels of antibodies are included as diagnostic criteria to improve the specificity of the tests. In the article, of the 25 patients studied only 3 had IgG and/or IgM aCL with moderate or high titres (>40 GPL or MPL units), and most of them had low titres between 20 and 39 units. Likewise, isotype IgA aCL and anti-ß2-GPI are not included as APS classification criteria because their role in APS-associated clinical events remains controversial [4]. We have observed that all of the 3 patients who were considered anti-ß2-GPI positive were so because of the IgA isotype. Other antiphospholipid antibodies are also not included in the revised Sapporo Criteria.

Vlachoyiannopoulos et al. [5] tested the serum of 29 unselected severely ill patients with COVID-19 admitted to an intensive care unit in Greece. They found that 7 patients had positive aCL antibodies (24.1%, 4 IgG, 3 IgG + IgM) and 10 had positive anti-ß2-GPI antibodies (34.5%, 2 IgG, 5 IgM, 3 IgG + IgM) without associated thromboembolic complications.

In another cohort of COVID-19 patients admitted to an internal medicine ward, Galeano-Valle et al. [6] found only 2 out of 24 patients (8.3%) with aCL IgM and anti-ß2-GPI IgM weakly positive, which suggests that the presence of aPL is not frequent amongst patients with COVID-19 pneumonia who suffer venous thromboembolism. They did not assess LA since testing is not recommended in acutely ill patients because results may be influenced by several factors, including the administration of heparin and a severe inflammatory state, both of which are present in patients with COVID-19. These factors could explain why in the cohort of Pinetron de Cambrun et al. LA is found in 23/25 patients (92%).
We consider the role of aPL in COVID-19 of great interest, but we believe that for the moment data are limited, and therefore, their interpretation must be made with caution. Further studies are needed to clarify these issues and to draw conclusions on their prevalence, their influence on the prothrombotic state present in SARS-CoV-2 infection and, therefore, on the indication for anticoagulant therapy in all patients systematically.

Conflict of Interest Statement
The authors declare that there are no financial, labour or other relationships that may constitute a conflict of interest with respect to this work.

Author Contribution
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