Antiphospholipid Antibodies in Critically Ill Patients With COVID-19

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Objective. Coagulopathy is one of the characteristics observed in critically ill patients with coronavirus disease 2019 (COVID-19). Antiphospholipid antibodies (aPLs) contribute to coagulopathy, though their role in COVID-19 remains unclear. This study was undertaken to determine the prevalence and characteristics of aPLs in patients with COVID-19.

Methods. Sera collected from 66 COVID-19 patients who were critically ill and 13 COVID-19 patients who were not critically ill were tested by chemiluminescence immunoassay for anticardiolipin antibodies (aCLs), anti-β2-glycoprotein I (anti-β2GPI) (IgG, IgM, and IgA), and IgG anti-β2GPI-domain 1 (anti-β2GPI-D1). IgM and IgG anti-phosphatidylserine/prothrombin (anti-PS/PT) antibodies were detected in the serum by enzyme-linked immunosorbent assay.

Results. Of the 66 COVID-19 patients in critical condition, aPLs were detected in 31 (47%). Antiphospholipid antibodies were not present among COVID-19 patients who were not in critical condition. The IgA anti-β2GPI antibody was the most commonly observed aPL in patients with COVID-19 and was present in 28.8% (19 of 66) of the critically ill patients, followed by IgA aCLs (17 of 66, or 25.8%) and IgG anti-β2GPI (12 of 66, or 18.2%). For multiple aPLs, IgA anti-β2GPI + IgA aCLs was the most common antibody profile observed (15 of 66, or 22.7%), followed by IgA anti-β2GPI + IgA aCL + IgG anti-β2GPI (10 of 66, or 15.2%). Antiphospholipid antibodies emerged ~35–39 days after disease onset. A dynamic analysis of aPLs revealed 4 patterns based on the persistence or transient appearance of the aPLs. Patients with multiple aPLs had a significantly higher incidence of cerebral infarction compared to patients who were negative for aPLs (P = 0.023).

Conclusion. Antiphospholipid antibodies were common in critically ill patients with COVID-19. Repeated testing demonstrating medium to high titers of aPLs and the number of aPL types a patient is positive for may help in identifying patients who are at risk of developing cerebral infarction. Antiphospholipid antibodies may be transient and disappear within a few weeks, but in genetically predisposed patients, COVID-19 may trigger the development of an autoimmune condition similar to the antiphospholipid syndrome (APS), referred to as “COVID-19–induced APS-like syndrome.” Long-term follow-up of COVID-19 patients who are positive for aPLs is of great importance in understanding the pathogenesis of this novel coronavirus.
INTRODUCTION

In patients affected with coronavirus disease 2019 (COVID-19) who are critically ill, we and other investigators have observed that the disease is associated with a proinflammatory and hypercoagulable state and an increased risk of thrombotic events (i.e., pulmonary embolism and cerebral infarction), which are characterized by marked elevations in the levels of d-dimers (1–6). Currently, the etiology leading to hypercoagulability in COVID-19 remains unclear.

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPLs) and a wide series of clinical manifestations, from recurrent arterial and/or venous thrombotic events to recurrent fetal loss. Antiphospholipid antibodies have long been considered as one of the contributors to a hypercoagulable state and to the development of the subsequent thrombotic events. In addition to their pathogenic role in APS, aPLs are crucial to the diagnosis of APS. The 2006 criteria for APS recommend that routine tests for the presence of lupus anticoagulant (LAC), IgM and/or IgG anticardiolipin (aCL), and IgM and/or IgG anti-β₂-glycoprotein I (anti-β₂GPI) antibodies be conducted (7). In addition, the 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report highlighted non-criteria aPLs, including IgA anti-β₂GPI, IgM/IgG anti-phosphatidylerine/prothrombin (anti-PS/PT), and anti-β₂GPI-domain I (anti-β₂GPI-DI) antibodies, as being associated with APS, especially seronegative APS (8).

We have previously reported the presence of aPLs in 3 critically ill patients with COVID-19 (9). However, it remains unclear whether these aPLs are pathogenic or whether they are persistent. In this study, we summarize the prevalence and characteristics of aPLs in 66 critically ill patients with COVID-19 and identify clinical features based on the presence of aPLs.

PATIENTS AND METHODS

Clinical settings and patients. Consecutive critically ill patients with suspected COVID-19 who were admitted to an intensive care unit (ICU) designated for patients with COVID-19 were included in this cross-sectional study. This unit, which was managed by a multidisciplinary team from Peking Union Medical College Hospital (PUMCH) in the Sino-French New City Branch of Tongji Hospital (Wuhan, China), was set up on an emergency basis in order to treat the most critically ill patients during the outbreak of COVID-19. The criterion for inclusion was any patient identified as being treated in our ICU from January to April 2020. The criterion for exclusion were as follows: 1) any patient who was not diagnosed as having COVID-19 and 2) any patient with COVID-19 who was not assessed for aPLs. A total of 66 COVID-19 patients in critical condition were included in the final results of this study.

COVID-19 patients who visited the fever clinic at PUMCH in Beijing, China were also included in the present study. The criterion for inclusion was any consecutive patient who visited the fever clinic at PUMCH in Beijing. The criterion for exclusion was any patient who was not diagnosed as having COVID-19. A total of 13 patients with COVID-19 from the Beijing clinic were included in the present study, none of whom were critically ill. Diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was confirmed in all patients by reverse transcription–polymerase chain reaction (RT-PCR) or serologic testing according to the Chinese Recommendations for Diagnosis and Treatment of Novel Coronavirus Infection (Pilot 7th version). Clinical characteristics and laboratory findings at the time of admission, which were collected from electronic medical records, are listed in Table 1. The study was approved by the Research Ethics Commission of PUMCH, and the requirement for informed consent was waived by the Ethics Commission (ZS-2303).

Detection of aPLs in serum samples. Serum aCL and anti-β₂GPI (IgG, IgM, and IgA) and IgG anti-β₂GPI-DI were determined by a chemiluminescence immunoassay (Inova) (10), with cutoff values for positivity set at >20 chemiluminescent units according to the manufacturer’s recommendations. IgG/IgM anti-PS/PT were determined by enzyme-linked immunosorbent assay (Inova) (11), and cutoff values for positivity were set at >30 chemiluminescent units according to the manufacturer’s recommendations.

Lupus anticoagulant. Detection of LAC in human citrated plasma was performed by HemosIL dilute Russell’s viper venom time (dRVVT) screening and HemosIL dRVVT confirmation assays, as recommended by the International Society on Thrombosis and Haemostasis.

Statistical analysis. Where appropriate, Mann-Whitney U test, chi-square test, or Fisher’s exact test were used to compare differences between patients who were positive for aPLs and those who were negative for aPLs. The Kruskal-Wallis test followed by Dunnett’s multiple comparison test was used to compare differences between patients who were negative for all aPLs, patients who were positive for a single aPL or a low number of multiple aPLs, and patients who had medium to high titers of multiple aPLs. P values less than 0.05 (2-sided) were considered statistically significant. All statistical analyses were performed using SPSS software version 20 (SPSS Inc).

RESULTS

We first determined the prevalence and characteristics of aPLs in patients with COVID-19. Using the manufacturer’s recommended cutoff value of >20 chemiluminescent units, aPLs were
| Characteristic | Patients who were critically ill (n = 66) | Patients positive for aPLs (n = 31) | Patients who were not critically ill (n = 13) |
|---------------|------------------------------------------|-------------------------------------|---------------------------------------------|
| Age, mean ± SD years | 64.5 ± 12.3 | 66.5 ± 13.3 | 65.2 ± 7.5 | 35.2 ± 19.3 |
| Sex, no. female/male | 17/18 | 5/11 | 5/10 | 7/6 |
| Comorbidity | | | | |
| Hypertension | 17 (48.6) | 8 (50.0) | 8 (53.3) | 0 |
| Diabetes | 6 (17.1) | 3 (18.8) | 4 (26.7) | 0 |
| Coronary heart disease | 8 (22.9) | 0 | 2 (13.3) | 0 |
| Lung disease | 5 (14.3) | 1 (6.2) | 1 (6.7) | 0 |
| Carcinoma | 1 (2.9) | 1 (6.2) | 2 (13.3) | 0 |
| Chronic kidney disease | 0 | 0 | 1 (6.7) | 0 |
| Chronic liver disease | 4 (11.4) | 0 | 1 (6.7) | 1 (9.1) |
| Autoimmune diseases | 2 (5.7) | 0 | 0 | 0 |
| Thrombotic history | | | | |
| Cerebral infarction | 4 (11.4) | 3 (18.8) | 2 (13.3) | 0 |
| Myocardial infarction | 1 (2.9) | 1 (6.2) | 0 | 0 |
| Other thoracic events | 0 | 0 | 0 | 0 |
| Symptoms on admission | | | | |
| Fever (temperature ≥37.3°C) | 31 (88.6) | 14 (87.5) | 13 (86.7) | 8 (61.5) |
| Cough | 32 (91.4) | 12 (75.0) | 10 (66.7) | 9 (69.2) |
| Sputum | 12 (34.3) | 6 (37.5) | 4 (26.7) | 0 |
| Dyspnea | 28 (80.0) | 15 (93.8) | 11 (73.3) | 0 |
| Myalgia | 9 (25.7) | 4 (25.0) | 3 (20.0) | 0 |
| Fatigue | 15 (42.9) | 3 (18.8) | 8 (53.3) | 0 |
| Diarrhea | 12 (34.3) | 3 (18.8) | 2 (13.3) | 0 |
| Headache | 6 (17.1) | 2 (12.5) | 3 (20.0) | 0 |
| Nausea or vomiting | 9 (25.7) | 1 (6.2) | 3 (20.0) | 0 |
| Disease severity status | | | | |
| General | 0 | 0 | 0 | 12 (92.3) |
| Severe | 0 | 0 | 0 | 1 (7.7) |
| Critical | 35 (100) | 16 (100) | 15 (100) | 0 |
| ARDS | 12 (34.3) | 7 (43.8) | 6 (40.0) | 0 |
| Respiratory failure | 23 (65.7) | 13 (81.2) | 11 (73.3) | 0 |
| Laboratory findings on admission, mean ± SD | | | | |
| White blood cell count, 10⁹/liter | 13.5 ± 6.3 | 14.3 ± 7.1 | 13.5 ± 7.2 | 7.3 ± 2.4 |
| Total neutrophil count, 10⁹/liter | 12.1 ± 5.9 | 12.1 ± 6.8 | 12.1 ± 6.7 | 3.3 ± 1.6 |
| Total lymphocyte count, 10⁹/liter | 0.6 ± 0.6 | 0.8 ± 0.6 | 0.7 ± 0.4 | 1.7 ± 0.7 |
| Red blood cell count, 10¹²/liter | 3.5 ± 0.9 | 4.1 ± 1.2 | 3.5 ± 0.6 | 4.5 ± 0.6 |
| Platelets, 10⁹/liter | 150.6 ± 102.9 | 177.9 ± 83.9 | 185.0 ± 83.2 | 223.0 ± 62.8 |
| Hemoglobin, gm/liter | 108.5 ± 23.7 | 120.8 ± 28.3 | 107.3 ± 22.2 | 134.1 ± 14.8 |
| ALT, units/liter | 38.1 ± 64.2 | 68.4 ± 165.7 | 28.9 ± 19.5 | 14.2 ± 7.5 |
| AST, units/liter | 37.8 ± 30.7 | 180.4 ± 583.7 | 34.0 ± 18.7 | – |
| LDH, units/liter | 510.1 ± 292.9 | 533.6 ± 458.8 | 447.9 ± 219.5 | – |
| Creatinine, μmoles/liter | 106.6 ± 125.9 | 74.6 ± 40.5 | 76.3 ± 37.2 | 52.3 ± 23.5 |
| eGFR, ml/minute/1.73 m² | 83.0 ± 35.0 | 89.8 ± 31.7 | 86.9 ± 24.8 | – |
| High-sensitivity cardiac troponin I, pg/ml | 594.9 ± 2,410.0 | 607.0 ± 1,921.2 | 215.7 ± 497.6 | – |
| NT-proBNP, pg/ml | 3,029.6 ± 5,306.6 | 1,756.2 ± 2,189.2 | 2,016.9 ± 2,217.6 | – |
| Prothrombin time, seconds | 17.6 ± 3.5 | 17.6 ± 7.5 | 16.1 ± 1.0 | – |
| APTT, seconds | 45.4 ± 21.0 | 45.8 ± 7.6 | 41.36 ± 6.44 | – |
| Fibrinogen, gm/liter | 3.6 ± 2.1 | 4.8 ± 1.6 | 4.5 ± 1.2 | – |
| D-dimer, μg/liter | 10.9 ± 8.8 | 10.2 ± 9.0 | 8.9 ± 7.6 | – |
| Procalcitonin, ng/ml | 0.8 ± 1.9 | 0.3 ± 0.4 | 1.2 ± 2.0 | 0.2 ± 0.1 |
| High-sensitivity CRP, mg/liter | 88.7 ± 84.3 | 98.1 ± 57.6 | 99.5 ± 51.8 | – |
| Interleukin-6, pg/ml | 289.5 ± 877.5 | 277.3 ± 539.1 | 103.1 ± 125.3 | – |

(Continued)
aPLs IN CRITICALLY ILL PATIENTS WITH COVID-19

Subsequently, we determined when aPLs emerged in those patients who were positive for these antibodies. Among the 31 patients positive for aPLs, serum was obtained from 10 patients who showed aPL negativity at an early time point after disease onset and aPL positivity at a later time point. Analysis of these patients’ sera revealed that aPLs emerged a median of ~39 days after disease onset (Supplementary Table 1, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41425/abstract). Taken together, these findings demonstrate that aPLs emerge later in the disease course, suggesting that critically ill patients who have a longer disease duration are likely to have aPLs.

Dynamic changes in both the numbers and titers of aPLs during the course of COVID-19 in critically ill patients were investigated further. Due to the retrospective nature of this analysis, data from multiple time points during which serum was tested for aPLs were only available for 6 patients (Figure 1). Generally, types and titers of aPLs increased from a single type of aPL with low titers to multiple types of aPLs with high titers. For the later time points, those 6 patients exhibited different antibody patterns. In patient 1, medium levels of IgG anti-β2GPI (present in 4 [6.1%] of 66 critically ill patients). All 66 critically ill patients were screened for the presence of LAC, with 2 patients testing positive for LAC. These findings suggest that COVID-19 preferentially induced aPLs of the IgA isotype and, to a lesser extent, aPLs of the IgG isotype.
time points (Figure 1C). In patient 6, high levels of IgA aCL+ IgA anti-β2GPI + IgG anti-β2GPI were maintained for ~2 weeks (Figure 1D). These results suggest that levels of aPLs fluctuate and exhibit different dynamic patterns among different patients with COVID-19.

Last, we assessed the clinical relevance of aPLs in critically ill patients with COVID-19 (Table 1). Mounting evidence suggests that positivity for multiple aPLs or having moderate to high titers of aPLs is more useful in predicting the possibility of cerebral infarction in COVID-19 patients compared to positivity for a single aPL or low titers of multiple aPLs. We divided the group of patients who were positive for aPLs into the following subcohorts: 1) a single/multiple low group (patients who were positive for a single aPL or positive for at least 1 aPL with low titers of all aPLs ≤40 chemiluminescent units, as previously described [12]) and 2) a multiple medium/high group (patients who were positive for at least 1 aPL and had moderate levels ≤40 chemiluminescent units) of the detected aPLs. The 3 groups consisting of critically ill patients had similar clinical and laboratory features, but the multiple medium/high group had a significantly higher incidence of cerebral infarction compared to the group of patients who were negative for aPLs (0% versus 33.3%) (P = 0.023), suggesting that aPLs (both numbers and titers) may be helpful in predicting the occurrence of cerebral infarction in COVID-19.

### DISCUSSION

The full spectrum of COVID-19 is still under intense investigation, but increasing evidence suggests that most critically ill patients experience coagulopathy (1–3). Antiphospholipid antibodies have been considered to be one of the mechanisms leading to a proinflammatory and hypercoagulable state. In the present study, we found that aPLs were present in a substantial number of critically ill patients with COVID-19. Although it remains unclear whether aPLs contribute to the hypercoagulable state in COVID-19, our findings suggest the possibility that aPLs may be implicated in this process.

Infection-induced aPL production has been widely acknowledged (13,14). Of particular interest is the fact that we found IgA, an isotype found to be specific to mucosal immunity, as the most common isotype of the aPLs assessed. As COVID-19 mainly affects pulmonary and intestinal mucosa, the preferential production of the IgA isotype may be associated with the breakage of mucosal immune tolerance. IgA anti-β2GPI

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**Table 2.** Prevalence and characteristics of aPLs in patients with COVID-19*

| Any aPL | Critically ill patients (n = 66) | Patients who were not critically ill (n = 13) |
|---------|-------------------------------|---------------------------------|
| Single aPL |                               |                                 |
| aCL     |                               |                                 |
| IgA     | 17 (25.8)                     | 0                               |
| IgG     | 4 (6.0)                       | 0                               |
| IgM     | 2 (3.0)                       | 0                               |
| LAC     | 2 (3.0)                       | 0                               |
| Anti-β2GPI |                               |                                 |
| IgA     | 19 (28.8)                     | 0                               |
| IgG     | 12 (18.2)                     | 0                               |
| IgM     | 1 (1.5)                       | 0                               |
| IgG D1  | 2 (3.0)                       | 0                               |
| Anti-PS/PT |                               |                                 |
| IgM     | 7 (10.6)                      | 0                               |
| IgG     | 0                             | 0                               |

| Multiple aPLs | | |
| IgA aCL + IgA anti-β2GPI | 15 (22.7) | 0 |
| IgM aCL + IgM anti-β2GPI | 1 (1.5) | 0 |
| IgA anti-β2GPI + IgG anti-β2GPI | 1 (1.5) | 0 |
| LAC + IgA aCL + IgA anti-β2GPI | 1 (1.5) | 0 |
| IgA aCL + IgA anti-β2GPI + IgG anti-β2GPI | 10 (15.2) | 0 |
| IgA aCL + IgG anti-β2GPI + IgM aCL | 1 (1.5) | 0 |
| IgA aCL + IgA anti-β2GPI + IgM anti-PS/PT | 1 (1.5) | 0 |
| IgA aCL + IgG aCL + IgA anti-β2GPI + IgG anti-β2GPI | 4 (6.1) | 0 |
| LAC + IgA aCL + IgG aCL + IgA anti-β2GPI + IgG anti-β2GPI | 1 (1.5) | 0 |

*Values are the number (%). Cutoff values for positivity for all antiphospholipid antibodies (aPLs) except IgM/IgG anti-phosphatidylserine/prothrombin (anti-PS/PT) antibodies were set at >20 chemiluminescent units based on the recommendations of the manufacturer. Cutoff values for positivity for IgM/IgG anti-PS/PT antibodies were set at >30 chemiluminescent units according to the manufacturer's recommendations. COVID-19 = coronavirus disease 2019; aCL = anticardiolipin antibody; LAC = lupus anticoagulant; anti-β2GPI = anti-β2-glycoprotein; IgG D1 = IgG anti-β2GPI-D1.
antibodies preferentially target the C-terminal portion of β2GPI (domains 4 and 5) (15). Thus, the presence of IgA aPLs may suggest a novel subgroup of clinically relevant APS in critically ill COVID-19 patients. Interestingly, we found that although IgA aCLs and IgA anti-β2GPI antibodies transiently appeared in a subgroup of patients, they also persisted in other subgroups of patients. Unfortunately, we could not perform long-term follow-up of the patients evaluated in the present study. A prospective evaluation of the aPLs observed in COVID-19 patients in the present study is needed in order to investigate whether these antibodies are persistently present and/or pathogenic in patients with COVID-19, and whether long-term anticoagulant therapy may be required.

While it remains unclear whether IgA aPLs are pathogenetic in APS, in vivo mouse studies have demonstrated that IgA anti-β2GPI induced significantly larger thrombi and higher tissue factor levels compared to controls (16). IgA anti-β2GPI antibodies are significantly and independently associated with arterial thrombosis and with all thromboses in patients with systemic lupus erythematosus and APS (16). In addition, the presence of IgA anti-β2GPI has been described as an independent risk factor for acute myocardial infarction (15,17) and acute cerebral ischemia (18). In the present study, we found that patients with multiple aPLs, including IgA and IgG anti-β2GPI and IgA and IgG aCLs, displayed significantly higher incidence of cerebral infarction. Unfortunately, due to the critical condition of those patients as well as the limitation of the isolation ward, a large number of patients could not be screened by ultrasound, and therefore many thrombotic events may be underrepresented. It is also worth mentioning that the patients who developed cerebral infarction may have already had atherosclerosis and aPLs. It would be of great interest to assess whether the detection of medium to high levels of multiple aPLs may help in identifying critically ill patients with COVID-19 at risk of developing cerebral infarction in future studies.

This study has several limitations. Due to the retrospective nature of this study, in the analysis of aPLs at each time point, we only had data for 1 time point for some of the patients, whereas for other patients, although we had data for more than 1 time point, there was already positivity for aPLs at the early time point. Thus, data from only 10 patients were assessed in the analyses. The small sample size may make the present study subject to potential analytical bias. Further prospective studies on the time point at which aPLs emerge after disease onset are needed.

In conclusion, the clinical significance of aPLs in critically ill patients with COVID-19 remains to be determined. In some patients, transient increases in aPLs may be accompanied by thrombotic complications (14). It is important to note that, although in some patients, these antibodies may be transient and disappear within a few weeks, in other genetically predisposed patients, COVID-19 may trigger the development of “COVID-19–induced APS-like–syndrome.” Long-term follow-up of COVID-19 patients who are positive for aPLs would be beneficial to the overall body of research investigating the

Figure 1. Dynamic changes in the levels of antiphospholipid antibodies (aPLs) during coronavirus disease 2019 (COVID-19) infection in 6 critically ill patients. A, Medium levels of IgG anti-β2-glycoprotein I (aβ2GP1) persisted after a transient appearance of IgA anti-β2GP1 + IgA anticardiolipin antibodies (aCLs) in patient 1. B, Medium levels of IgA anti-β2GP1 + IgA aCLs persisted after a transient appearance of IgG anti-β2GP1 in patient 2 (left) and patient 3 (right). C, Transient appearance of aPLs in patient 4 (left) and patient 5 (right) was observed. D, High levels of IgA aCL + IgA anti-β2GP1 + IgG anti-β2GP1 persisted in patient 6. CU = chemiluminescent units.
effects of COVID-19 during active disease as well as the possible long-term outcomes of this novel coronavirus.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Y. Li had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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