



Lupus Anticoagulant Single Positivity During the Acute Phase of COVID-19 Is Not Associated With Venous Thromboembolism or In-Hospital Mortality

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Objective. The clinical relevance of antiphospholipid antibodies (aPLs) in COVID-19 is controversial. This study was undertaken to investigate the prevalence and prognostic value of conventional and nonconventional aPLs in patients with COVID-19.

Methods. This was a multicenter, prospective observational study in a French cohort of patients hospitalized with suspected COVID-19.

Results. Two hundred forty-nine patients were hospitalized with suspected COVID-19, in whom COVID-19 was confirmed in 154 and not confirmed in 95. We found a significant increase in lupus anticoagulant (LAC) positivity among patients with COVID-19 compared to patients without COVID-19 (60.9% versus 23.7%; $P < 0.001$), while prevalence of conventional aPLs (IgG and IgM anti- β_2 -glycoprotein I and IgG and IgM anticardiolipin isotypes) and nonconventional aPLs (IgA isotype of anticardiolipin, IgA isotype of anti- β_2 -glycoprotein I, IgG and IgM isotypes of anti-phosphatidylserine/prothrombin, and IgG and IgM isotypes of antiprothrombin) was low in both groups. Patients with COVID-19 who were positive for LAC, as compared to patients with COVID-19 who were negative for LAC, had higher levels of fibrinogen (median 6.0 gm/liter [interquartile range 5.0–7.0] versus 5.3 gm/liter [interquartile range 4.3–6.4]; $P = 0.028$) and C-reactive protein (CRP) (median 115.5 mg/liter [interquartile range 66.0–204.8] versus 91.8 mg/liter [interquartile range 27.0–155.1]; $P = 0.019$). Univariate analysis did not show any association between LAC positivity and higher risks of venous thromboembolism (VTE) (odds ratio 1.02 [95% confidence interval 0.44–2.43], $P = 0.95$) or in-hospital mortality (odds ratio 1.80 [95% confidence interval 0.70–5.05], $P = 0.24$). With and without adjustment for CRP level, age, and sex, Kaplan-Meier survival curves according to LAC positivity confirmed the absence of an association with VTE or in-hospital mortality (unadjusted $P = 0.64$ and $P = 0.26$, respectively; adjusted hazard ratio 1.13 [95% confidence interval 0.48–2.60] and 1.80 [95% confidence interval 0.67–5.01], respectively).

Conclusion. Patients with COVID-19 have an increased prevalence of LAC positivity associated with biologic markers of inflammation. However, LAC positivity at the time of hospital admission is not associated with VTE risk and/or in-hospital mortality.

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INTRODUCTION

COVID-19 is caused by SARS-CoV-2 and is associated with nonspecific respiratory syndromes, ranging from mild upper airway symptoms to hypoxemia requiring mechanical ventilation support (1–3). An important feature of COVID-19 is the associated coagulopathy that correlates with disease severity and in-hospital mortality (4,5), without any sign of disseminated intravascular coagulopathy (6), in contrast to previous reports (5). There are increasing reports of venous thromboembolism (VTE) and arterial thrombosis irrespective of the use of pharmacologic thromboprophylaxis (7–14). Both macrothrombosis, in particular pulmonary embolism (PE) (15), and microthrombosis in the lungs have been largely described (16). Microthrombosis could be a consequence of vascular injury and the link between coagulopathy and COVID-19 severity and/or mortality (17).

Antiphospholipid syndrome (APS) is an acquired thrombophilia leading to the use of long-term anticoagulation therapy (18). Classification of APS requires the presence of 1 clinical event (thrombosis or pregnancy morbidity) and persistently positive laboratory test results for at least 1 antiphospholipid antibody (aPL), the latter including lupus anticoagulant (LAC), anticardiolipin antibody (aCL), and IgG and/or IgM anti- β_2 -glycoprotein I (anti- β_2 GPI) antibodies (19,20). Autoantibodies to phospholipids and phospholipid-binding proteins such as antiprothrombin (anti-PT), aCL, or anti- β_2 GPI are involved in leukocyte and endothelial activation and induce both VTE and arterial thrombosis. A combination of positive results of aPL testing, and particularly triple positivity (LAC and aCL, anti- β_2 GPI, same isotype, IgG and/or IgM) identifies patients at high risk for thrombosis and allows a more confident diagnosis of APS. Furthermore, very often, triple-positive patients are also positive for antiphosphatidylserine/prothrombin antibodies (anti-PS/PT) (tetra-positive patients), adding further risk for thromboembolic events to the usual aPL profile (21). Moreover, aPLs are not specific to

APS but can be detected in healthy individuals and in different clinical settings, including autoimmune conditions, some drug treatments, or infectious disease (18). The occurrence of aPLs has been largely described during viral infections (22), and their pathogenicity in these contexts remains controversial.

During the COVID-19 outbreak, several reports described a potential association between aPLs and thrombotic events (23). Previous studies exploring LAC demonstrated between 45% and 88% positivity among different cohorts in the medical ward and/or intensive care unit (ICU) settings (10,23–25). Only 1 study suggested in vitro that aPL positivity in sera of patients with COVID-19 could be prothrombotic, but LAC was not assessed (26). To the best of our knowledge, there is no large cohort study that includes complete screening for LAC and associated aPLs. Moreover, the association of aPLs with VTE or in-hospital mortality in patients with COVID-19 is still a matter of debate. In the present study, we aimed to investigate the prevalence of conventional and nonconventional aPLs and explore their relevance to VTE and mortality outcomes in a large cohort of 249 patients with suspected COVID-19.

PATIENTS AND METHODS

Study design and population. This multicenter, prospective, observational cohort study was conducted at 2 university hospitals in Paris: Hôpital Européen Georges Pompidou and Hôpital Cochin. Patients with suspected SARS-CoV-2 infection were prospectively included from March 14, 2020 to April 20, 2020. Inclusion criteria were age >18 years, and presentation to the emergency department of either hospital with an infectious syndrome and suspected COVID-19 meeting criteria for hospital admission, or direct admission to the hospital. Patients with suspected COVID-19 had ≥ 1 of the following: fever, headache, myalgia, cough, dyspnea, rhinorrhea, or digestive symptoms. All patients with suspected COVID-19 were tested for SARS-CoV-2 infection by nasopharyngeal swab and screened for

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hospitalization criteria based on local guidelines (27) and defined as described in Supplementary Table 1 (available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41777/abstract>). Patients with suspected COVID-19 who met the hospitalization criteria were admitted to dedicated departments (medical ward or ICU) while awaiting laboratory confirmation of SARS-CoV-2 infection. A SARS-CoV-2 infection diagnosis was confirmed by a positive result of a reverse transcriptase–polymerase chain reaction (RT-PCR) assay and/or typical computed tomography (CT) scan findings of pneumonia related to COVID-19.

The study was performed in accordance with the Declaration of Helsinki. All patients provided written informed

consent before they were enrolled (secondary ID: SARCODO 2020-A01048-31; ClinicalTrials.gov identifier: NCT04624997). Baseline characteristics (i.e., demographics, treatment, cardiovascular risk factors, and body mass index [BMI]), clinical data, biologic data, and CT scan evaluations were obtained from the medical records of all included patients, using standardized data collection methods.

Laboratory confirmation of SARS-CoV-2 infection.

Nasopharyngeal swabs were collected at hospital admission in a universal transport medium using an Xpert nasopharyngeal sample collection kit as previously described (28). SARS-CoV-2 was detected using an Allplex 2019-nCoV assay (Seegene), a multiplex

Table 1. Demographic, clinical, and laboratory features of patients at the time of admission, according to COVID-19 viral status*

	Non-COVID-19 patients (n = 95)	Patients with COVID-19 (n = 154)	P
Male, no. (%)	43 (45.3)	111 (72.1)	<0.001
Age, years	76.0 (56.0–87.0)	59.0 (51.0–72.0)	<0.001
BMI, kg/m ²	24.2 (21.4–26.6)	27.1 (24.5–31.5)	<0.001
Days from disease onset to hospital admission	4.0 (1.0–7.0)	7.0 (4.0–8.0)	0.001
CV risk factors, no. (%)			
Hypertension	51 (53.7)	66 (42.9)	0.037
Dyslipidemia	21 (22.1)	29 (18.8)	0.24
Diabetes mellitus	2 (2.1)	36 (23.4)	<0.001
Chronic kidney disease	13 (13.7)	15 (9.7)	0.27
Medical history, no. (%)			
Cancer	26 (27.4)	18 (11.7)	0.03
Coronary heart disease	10 (10.5)	7 (4.5)	0.002
Stroke	10 (10.5)	7 (4.5)	–
Clinical features			
Fever, no. (%)	31 (32.6)	132 (85.7)	<0.001
Headache, no. (%)	9 (9.5)	42 (27.3)	<0.001
Cough, no. (%)	40 (42.1)	122 (79.2)	<0.001
Productive cough, no. (%)	5 (5.3)	15 (9.7)	0.43
Dyspnea, no. (%)	59 (62.1)	106 (68.8)	0.42
Myalgia, no. (%)	12 (12.6)	62 (40.3)	<0.001
Diarrhea, no. (%)	12 (12.6)	38 (24.7)	0.064
Pneumonia on CT scan, no. (%)	26 (27.4)	116 (75.3)	<0.001
ARDS, no. (%)	2 (2.1)	45 (29.2)	<0.001
ICU admission, no. (%)	6 (6.3)	88 (57.1)	<0.001
Temperature, °C	37.1 (36.6–37.5)	38.3 (37.7–39.0)	<0.001
SpO ₂ , %	96.0 (92.0–98.0)	93.0 (89.1–96.0)	<0.001
Respiratory rate, breaths per minute	18.0 (16.0–22.0)	20.5 (18.0–27.8)	0.001
Pulse rate, beats per minute	87.0 (78.0–100.0)	92.0 (80.8–105.3)	0.17
Laboratory features			
White blood cell count, ×10 ⁹ /liter	8.20 (6.45–11.1)	6.40 (4.60–9.00)	<0.001
Hemoglobin, gm/liter	134.0 (115.0–145.0)	128.5 (113.0–143.3)	0.23
Platelet count, ×10 ⁹ /liter	223.5 (181.8–265.3)	196.5 (148.3–281.3)	0.074
Polynuclear neutrophils, ×10 ⁹ /liter	6.44 (4.32–9.41)	4.83 (3.17–7.51)	0.005
Lymphocytes, ×10 ⁹ /liter	1.17 (0.83–1.72)	0.95 (0.66–1.25)	0.001
Monocytes, ×10 ⁹ /liter	0.60 (0.42–0.83)	0.37 (0.25–0.56)	<0.001
CRP, mg/liter	13.6 (2.5–97.6)	104.2 (47.3–173.9)	<0.001
Plasma creatinine, μmoles/liter	78.0 (62.0–110.0)	75.0 (62.0–102.0)	0.78
K-APTT, seconds	29.1 (27.8–32.0)	32.0 (30.0–35.4)	<0.001
PT ratio, %	97.0 (85.8–107.0)	92.0 (81.0–99.0)	0.003
Fibrinogen, gm/liter	4.30 (3.35–5.15)	5.70 (4.85–7.00)	<0.001
D-dimer, ng/ml	894.0 (430.0–2,266.3)	1,170.0 (702.5–2325.5)	0.039
Fibrin monomers, μg/ml	<7.0 (<7.0–<7.0)	<7.0 (<7.0–<7.0)	0.15

* Except where indicated otherwise, values are the median (interquartile range). BMI = body mass index; CV = cardiovascular; CT = computed tomography; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; CRP = C-reactive protein; K-APTT = kaolin activated partial thromboplastin time; PT = thromboplastin time.

RT-PCR assay that detects 3 target genes (E gene, RdRP gene, and N gene) in real time in a single tube. Data were automatically analyzed using Seegene viewer software. Only qualitative data were considered.

Routine blood evaluations. All samples were collected in EDTA, sodium heparin, or 0.129M 9NC trisodium citrate tubes (BD Vacutainer) at the time of admission. Routine laboratory tests were complete blood cell count and creatinine, C-reactive protein (CRP), interleukin-6 (IL-6), and ferritin levels. Global coagulation tests were activated partial thromboplastin time (APTT) (kaolin activated partial thromboplastin [K-APTT] and CK Prest APTT; Diagnostica Stago), prothrombin time (PT) ratio (%), fibrinogen, and soluble fibrin monomer using STA-Liatest FM explored on a STA-R Max coagulometer (both from Diagnostica Stago) as previously described (26). D-dimer levels were determined using a Vidas D-dimer assay (BioMérieux) according to the manufacturer's instructions.

LAC testing. LAC assays were performed at the local center in accordance with the International Society on Thrombosis and Haemostasis Scientific Standardization Committee guidelines (29). Briefly, citrated blood was double centrifuged for 15 minutes at 2,000g at room temperature. The obtained platelet-poor plasma was analyzed for prolonged clotting time using 2 tests (i.e., APTT and dilute Russell's viper venom time [dRVWT]) based on different principles. LAC testing was performed using a 3-step procedure, i.e., for screening, mixing, and confirmation. For the dRVWT test, reagents LA1 and LA2 (Siemens) were used, and for the APTT test, automated APTT (Trinity Biotech) and a reagent with weak sensitivity to LAC (CK Prest) were used. The dRVWT assay contains a heparin-neutralizer that is able to quench unfractionated or low molecular weight heparin (up to 1.0 IU/ml)

that might lead to false-positive detection of LAC. In case of LAC testing in the setting of unfractionated heparin/low molecular weight heparin, anti-factor Xa activity was quantified and verified to be below the heparin-neutralizer cutoff of 1.0 IU/ml (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41777/abstract>).

Solid-phase aPL testing. Using Bio-Flash chemiluminescent immunoassay technology (Quanta Flash β_2 GP1; Inova Diagnostics), IgG, IgM, and IgA aCL and anti- β_2 GPI antibodies were measured in the plasma, with a cutoff value (99th percentile) of 20 arbitrary units (AU), as previously described (30). IgM and IgG anti-PS/PT antibodies were measured in the serum by Quanta Lite enzyme-linked immunosorbent assay (ELISA) (Inova Diagnostics), with a cutoff value (99th percentile) of 30 AU, as previously described (30). IgG and IgM anti-PT antibodies were measured by ELISA (Orgentec Diagnostika), with a cutoff value (99th percentile) of 10 AU.

Statistical analysis. Continuous data are shown as the median (interquartile range [IQR]), and categorical data are shown as percentages. Patients were compared according to COVID-19 viral status and LAC positivity. The Mann-Whitney test was used for assessment of continuous variables, and Fisher's exact test for categorical variables. In the multivariate analysis, we used a logistic regression model to identify risk factors for VTE and in-hospital mortality. The model was adjusted for age, sex, and CRP level (as a binary variable dichotomized according to the median value). In the survival analysis, the start of the study was triggered at the time of diagnosis of SARS-CoV-2 infection and hospitalization. The end of the study was defined either by the death of the patient during hospitalization or by discharge

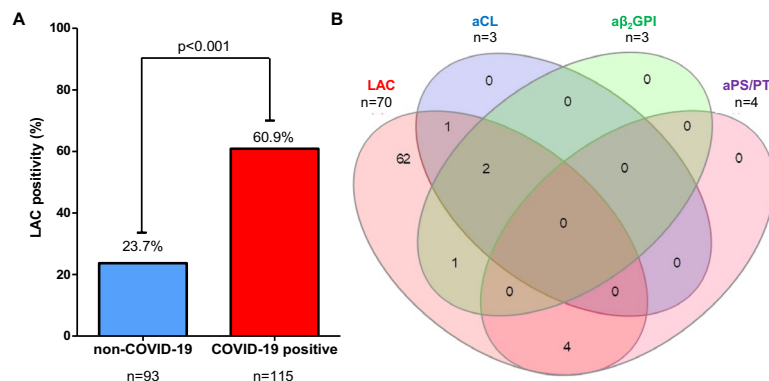


Figure 1. Prevalence of lupus anticoagulant (LAC) positivity in COVID-19 patients admitted to the hospital and its association with other antiphospholipid antibodies (aPLs). **A**, LAC positivity at the time of admission in 115 patients with COVID-19 compared to 93 patients without COVID-19, showing a significant difference between the groups (70 of 115 COVID-19 patients versus 22 of 93 non-COVID-19 patients positive for LAC). **B**, Venn diagram, created using a web-based tool (40), of aPL profiles among patients with COVID-19, showing positivity for each antibody subset either overlapping or not overlapping with positivity for LAC. The findings show that positivity for IgG or IgM anticardiolipin antibody (aCL), IgG or IgM anti- β_2 -glycoprotein I (a β_2 GPI), and IgM anti-phosphatidylserine/prothrombin complex (aPS/PT) (no patients with COVID-19 were positive for IgG anti-PS/PT) was infrequent.

from the hospital. Survival time was calculated as the difference between the date of the diagnosis of SARS-CoV-2 infection and the date of event occurrence (VTE and in-hospital mortality) or the date of hospital discharge. We used the Cox proportional hazards model adjusted for age, sex, and CRP level to investigate the relationship between LAC positivity and patient outcomes (VTE or in-hospital mortality). The Kaplan-Meier method was used to represent the Cox proportional hazards model results according to LAC positivity. In the unadjusted survival analysis, survival curves were compared by log rank test. All analyses were performed using R studio software, including R version 3.6.3. *P* values (2-sided) less than 0.05 were considered significant.

RESULTS

Study population. A total of 249 patients admitted with suspected COVID-19 were included. Among them, 154 (61.8%) had confirmed COVID-19, whereas 95 (38.2%) did not have COVID-19 and were ultimately found to have other diagnoses (Supplementary Table 3, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41777/abstract>). These 2 groups were not strictly comparable in terms of sex, age, BMI, cardiovascular risk factors, medical history, clinical features, and symptoms (Table 1). The group with COVID-19 had a higher proportion of male patients, higher BMI, and a higher frequency of fever and respiratory symptoms described in COVID-19 (1–3). At the time of admission, when compared to non-COVID-19 patients, patients with COVID-19 were more likely to have dyspnea, decreased SpO₂, pneumonia on CT scan, and increased respiratory rate and were more likely to be referred to the ICU, in particular, for acute respiratory distress syndrome. In terms of laboratory features related to coagulation disorders, patients with COVID-19 had higher median D-dimer levels, longer K-APTT, and lower PT ratio. In patients with COVID-19, fibrin monomers were negative and associated with hyperfibrinogenemia without thrombocytopenia.

Higher prevalence of positivity for LAC, but not other aPLs, in patients with COVID-19. LAC was assessed at the time of admission in the majority of patients with confirmed COVID-19 and patients without COVID-19. When compared to non-COVID-19 patients, we observed a higher prevalence of LAC positivity among patients with confirmed COVID-19 (60.9% versus 23.7%; *P* < 0.001) (Figure 1A). Interestingly, among all patients with COVID-19 who were tested for LAC, 9 (7.8%) received hydroxychloroquine at the time of admission, and among them, 6 (67%) were positive for LAC and 3 (33%) were negative for LAC.

The prevalence of positive findings on solid-phase immunoassays for conventional and nonconventional markers of APS in patients with and those without COVID-19 is described in Table 2. IgG, IgM, and IgA aCL positivity was infrequent in both groups (3.2%,

Table 2. Results of solid-phase immunoassays for conventional and nonconventional aPLs*

	Non-COVID-19 patients	Patients with COVID-19	<i>P</i>
IgG aCL			
Titer, median (IQR)	3.0 (2.6–5.5)	3.0 (3.0–9.0)	<0.001
Positive result	3 (3.2)	9 (5.8)	0.088
Missing data	0 (0.0)	6 (3.9)	
IgM aCL			
Titer, median (IQR)	2.8 (1.4–5.5)	2.0 (1.0–3.0)	0.019
Positive result	7 (7.4)	2 (1.3)	0.008
Missing data	0 (0.0)	6 (3.9)	
IgA aCL			
Titer, median (IQR)	2.3 (1.8–4.6)	2.0 (2.0–4.0)	0.22
Positive result	2 (2.1)	3 (1.9)	<0.001
Missing data	2 (2.1)	57 (37.0)	
IgG anti-β₂GPI			
Titer, median (IQR)	6.4 (6.4–6.4)	6.0 (6.0–6.0)	<0.001
Positive result	1 (1.1)	5 (3.2)	0.078
Missing data	0 (0.0)	6 (3.9)	
IgM anti-β₂GPI			
Titer, median (IQR)	1.1 (1.1–2.1)	1.0 (1.0–2.0)	<0.001
Positive result	4 (4.2)	3 (1.9)	0.091
Missing data	0 (0.0)	6 (3.9)	
IgA anti-β₂GPI			
Titer, median (IQR)	4.0 (4.0–4.0)	4.0 (4.0–4.0)	0.55
Positive result	2 (2.1)	2 (1.3)	<0.001
Missing data	2 (2.1)	56 (36.4)	
IgG anti-PS/PT			
Titer, median (IQR)	6.0 (4.0–9.0)	5.0 (4.0–6.0)	0.007
Positive result	0 (0.0)	0 (0.0)	NA
Missing data	0 (0.0)	0 (0.0)	
IgM anti-PS/PT			
Titer, median (IQR)	12.0 (6.0–17.0)	8.0 (5.0–13.0)	0.013
Positive result	10 (10.5)	7 (4.5)	0.12
Missing data	0 (0.0)	0 (0.0)	
IgG anti-PT			
Titer, median (IQR)	4.0 (3.0–6.0)	5.0 (3.0–6.7)	0.12
Positive result	7 (7.4)	11 (7.1)	0.22
Missing data	0 (0.0)	39 (25.3)	
IgM anti-PT			
Titer, median (IQR)	2.0 (1.0–3.0)	3.0 (1.9–4.0)	<0.001
Positive result	5 (5.3)	10 (6.5)	0.003
Missing data	0 (0.0)	39 (25.3)	
LAC assay			
Positive result among tested patients	22/93 (23.7)	70/115 (60.9)	<0.001
Missing data	2 (2.1)	39 (23.2)	

* Except where indicated otherwise, values are the number (%). aPLs = antiphospholipid antibodies; aCL = anticardiolipin antibody; IQR = interquartile range; anti-β₂GPI = anti-β₂-glycoprotein I; anti-PS/PT = anti-phosphatidylserine/prothrombin antibodies; NA = not applicable; anti-PT = antiprothrombin antibody; LAC = lupus anticoagulant.

7.4%, and 2.1%, respectively, in non-COVID-19 patients and 5.8%, 1.3%, and 1.9% in patients with COVID-19). IgM aCLs were significantly more frequent in non-COVID-19 patients (*P* = 0.008). IgG, IgM, and IgA anti-β₂GPI positivity was infrequent in both groups (1.1%, 4.2%, and 2.1%, respectively, in non-COVID-19 patients versus 3.2%, 1.9%, and 1.3% in patients with COVID-19). IgA anti-β₂GPI antibodies were significantly more frequent in non-COVID-19 patients (*P* < 0.001). IgG and IgM anti-PS/PT antibody

Table 3. Demographic, clinical, and laboratory features of patients with COVID-19 at the time of admission according to LAC status*

	LAC negative (n = 45)	LAC positive (n = 70)
Demographic features		
Male	37 (82.2)	48 (68.6)
Age, median (IQR) years	59.0 (45.0–74.0)	59.5 (52.0–72.0)
BMI, median (IQR) kg/m ²	27.3 (24.7–32.1)	27.2 (25.3–30.7)
Time from disease onset to hospital admission, median (IQR) days	5.0 (3.0–9.0)	7.0 (4.0–8.0)
CV risk factors		
Hypertension	18 (40.0)	33 (47.1)
Dyslipidemia	9 (20.0)	16 (22.9)
Diabetes	10 (22.2)	20 (28.6)
Chronic kidney disease	5 (11.1)	9 (12.9)
Medical history		
Cancer	6 (13.3)	7 (10.0)
Coronary heart disease	22 (48.9)	42 (60)
Atrial fibrillation	4 (8.9)	4 (5.7)
Stroke	3 (6.7)	4 (5.7)
Previous DVT	1 (2.2)	1 (1.4)
Previous PE	2 (4.4)	1 (1.4)
Clinical features		
Fever	34 (75.6)	62 (88.6)
Headache	16 (35.6)	24 (34.3)
Cough	33 (73.3)	55 (78.6)
Productive cough	10 (22.2)	5 (7.1)†
Dyspnea	25 (55.6)	48 (68.6)
Myalgia	17 (37.8)	27 (38.6)
Diarrhea	11 (24.4)	13 (18.6)
Pneumonia on CT scan	30 (66.7)	50 (71.4)
ARDS	15 (33.3)	21 (30.0)
Temperature, median (IQR) °C	38.0 (37.4–38.5)	38.4 (37.7–38.8)
SpO ₂ , median (IQR) %	94.0 (89.3–96.0)	92.8 (89.1–95.0)
Laboratory features		
K-APTT, median (IQR) seconds	31.0 (29.2–33.0)	31.9 (30.0–34.0)
PT ratio, median (IQR)	87.0 (80.8–99.0)	93.0 (84.8–102.3)
Fibrinogen, median (IQR) gm/liter	5.3 (4.3–6.4)	6.0 (5.0–7.0)‡
D-dimer, median (IQR) ng/ml	1,503.0 (807.0–2,658.0)	981.0 (634.8–1891.8)
Fibrin monomers, median (IQR) µg/ml	<7.0 (<7.0–<7.0)	<7.0 (<7.0–<7.0)
Plasma creatinine, median (IQR) µmoles/liter	80.5 (58.5–101.8)	79.5 (68.0–117.8)
CRP, median (IQR) mg/liter	91.8 (27.0–155.1)	115.5 (66.0–204.8)§
IL-6, median (IQR) pg/ml	36.0 (16.3–82.5)	28.70 (12.7–97.8)
Ferritin, median (IQR) µg/liter	909.0 (336.0–1,718.0)	731.0 (270.5–1,040.5)
Peak blood test levels during hospitalization		
Plasma creatinine, median (IQR) µmoles/liter	94.5 (74.8–140.5)	101.0 (79.5–278.5)
CRP, median (IQR) mg/liter	148.2 (98.5–237.3)	170.95 (106.8–282.5)
Ferritin, median (IQR) µg/liter	1,005.0 (336.0–2,797.0)	931.50 (377.5–1578.2)
Fibrinogen, median (IQR) gm/liter	7.12 (4.92–8.60)	7.00 (5.60–9.11)
D-dimer, median (IQR) ng/ml	3,767.0 (1,430.0–6,528.5)	3,399.0 (832.8–9,490.5)
Outcomes		
ICU admission	25 (55.6)	43 (61.4)
Length of ICU stay, median (IQR) days	17.0 (5.0–25.0)	18.0 (5.0–30.0)
VTE¶	12 (26.8)	19 (27.1)
Symptomatic PE	10 (22.2)	15 (21.4)
Symptomatic DVT	5 (11.1)	6 (8.6)
Renal replacement therapy	7 (15.6)	16 (22.9)
Discharged	31 (68.9)	39 (55.7)
Deceased	7 (15.6)	17 (24.3)

* Except where indicated otherwise, values are the number (%). LAC = lupus anticoagulant; IQR = interquartile range; BMI = body mass index; CV = cardiovascular; CT = computed tomography; ARDS = acute respiratory distress syndrome; K-APTT = kaolin activated partial thromboplastin time; PT = thromboplastin time; CRP = C-reactive protein; IL-6 = interleukin-6; ICU = intensive care unit; VTE = venous thromboembolism.

† $P = 0.029$ versus LAC-negative patients.

‡ $P = 0.028$ versus LAC-negative patients.

§ $P = 0.019$ versus LAC-negative patients.

¶ Deep vein thrombosis (DVT) alone, pulmonary embolism (PE) alone, or DVT and PE combined.

Table 4. Association between LAC positivity, VTE, and in-hospital mortality outcomes, determined using logistic regression analysis*

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Risk of VTE				
LAC status				
Negative	–	–	–	–
Positive	1.02 (0.44–2.43)	0.95	1.01 (0.42–2.48)	0.98
CRP level†				
<104.2 mg/liter	–	–	–	–
≥104.2 mg/liter	1.70 (0.79–3.75)	0.18	1.67 (0.70–4.15)	0.26
Sex				
Female	–	–	–	–
Male	1.16 (0.50–2.84)	0.74	0.96 (0.35–2.84)	0.93
Age	1.01 (0.98–1.03)	0.67	1.00 (0.97–1.03)	0.94
Risk of in-hospital mortality				
LAC status				
Negative	–	–	–	–
Positive	1.80 (0.70–5.05)	0.24	1.69 (0.58–5.35)	0.35
CRP level†				
<104.2 mg/liter	–	–	–	–
≥104.2 mg/liter	5.72 (2.17–18.03)	0.001	3.30 (1.12–11.32)	0.039
Sex				
Female	–	–	–	–
Male	1.56 (0.62–4.51)	0.37	2.35 (0.61–11.95)	0.25
Age	1.04 (1.01–1.08)	0.004	1.04 (1.01–1.09)	0.030

* LAC = lupus anticoagulant; VTE = venous thromboembolism; OR = odds ratio; 95% CI = 95% confidence interval; CRP = C-reactive protein.

† Dichotomized according to the median value.

positivity was 0.0% and 10.5%, respectively, in non-COVID-19 patients, compared to 0.0% and 4.5% in patients with COVID-19, with no significant difference between the groups. Finally, IgG and IgM anti-PT positivity was 7.4% and 5.3% in non-COVID-19 patients, compared to 7.1% and 6.5% in patients with COVID-19. IgM anti-PT antibodies were significantly more frequent in patients with COVID-19 ($P = 0.003$). Among the 70 patients with COVID-19 with LAC positivity, 62 (88.6%) were negative for other aPLs and 8 (11.4%) were positive for ≥1 other aPL (IgG or IgM aCL and/or anti-β₂GPI, and/or anti-PS/PT) (Figure 1B).

Association of LAC positivity in COVID-19 with markers of inflammation, but not with VTE or in-hospital mortality.

Among patients with COVID-19, those with and those without LAC positivity were comparable in terms of sex, age, BMI, cardiovascular risk factors, medical history, and time from disease onset to hospitalization (Table 3). Furthermore, risk factors for VTE (i.e., age, BMI, cancer, previous deep vein thrombosis/PE) did not differ between groups ($P > 0.05$ for each). However, when compared to patients who were negative for LAC, patients with COVID-19 who were positive for LAC had higher levels of fibrinogen (median 6.0 gm/liter [IQR 5.0–7.0] versus 5.3 gm/liter [IQR 4.3–6.4]; $P = 0.028$) and CRP (median 115.5 mg/liter [IQR 66.0–204.8] versus 91.8 mg/liter [IQR 27.0–155.1]; $P = 0.019$). Strikingly, levels of IL-6 and ferritin were not significantly different between COVID-19 patients who were positive for LAC and those who were negative for LAC.

The percentages of patients who were referred to the ICU who developed VTE and who died in the hospital were not significantly different between LAC-negative and LAC-positive patients with COVID-19 (55.6% versus 61.4%, 26.8% versus 27.1%, and 15.6% versus 24.3%, respectively; $P > 0.05$ for each).

In both univariate and multivariate analyses adjusted for CRP level, age, and sex, LAC positivity was not associated with higher risk of VTE (odds ratio 1.02 [95% confidence interval 0.44–2.43], $P = 0.95$ and odds ratio 1.01 [95% confidence interval 0.42–2.48], $P = 0.98$, respectively) (Table 4). Furthermore, LAC positivity was not associated with higher in-hospital mortality in either the univariate analysis (odds ratio 1.80 [95% confidence interval 0.70–5.05], $P = 0.24$) or the multivariate analysis (odds ratio 1.69 [95% confidence interval 0.58–5.35], $P = 0.35$), in contrast to age (odds ratio 1.04 [95% confidence interval 1.01–1.09], $P = 0.030$) and CRP level (odds ratio 3.30 [95% confidence interval 1.12–11.32], $P = 0.039$ in the multivariate analysis). Finally, Kaplan-Meier survival curves showed that in patients with COVID-19, LAC positivity at the time of admission did not predict the risk of VTE ($P = 0.64$) or in-hospital mortality ($P = 0.26$), even after adjustment for CRP level, age, and sex (Figure 2).

DISCUSSION

COVID-19-associated coagulopathy is associated with microthrombosis, VTE, and arterial thrombotic complications (14,15,31). To the best of our knowledge, the present study is

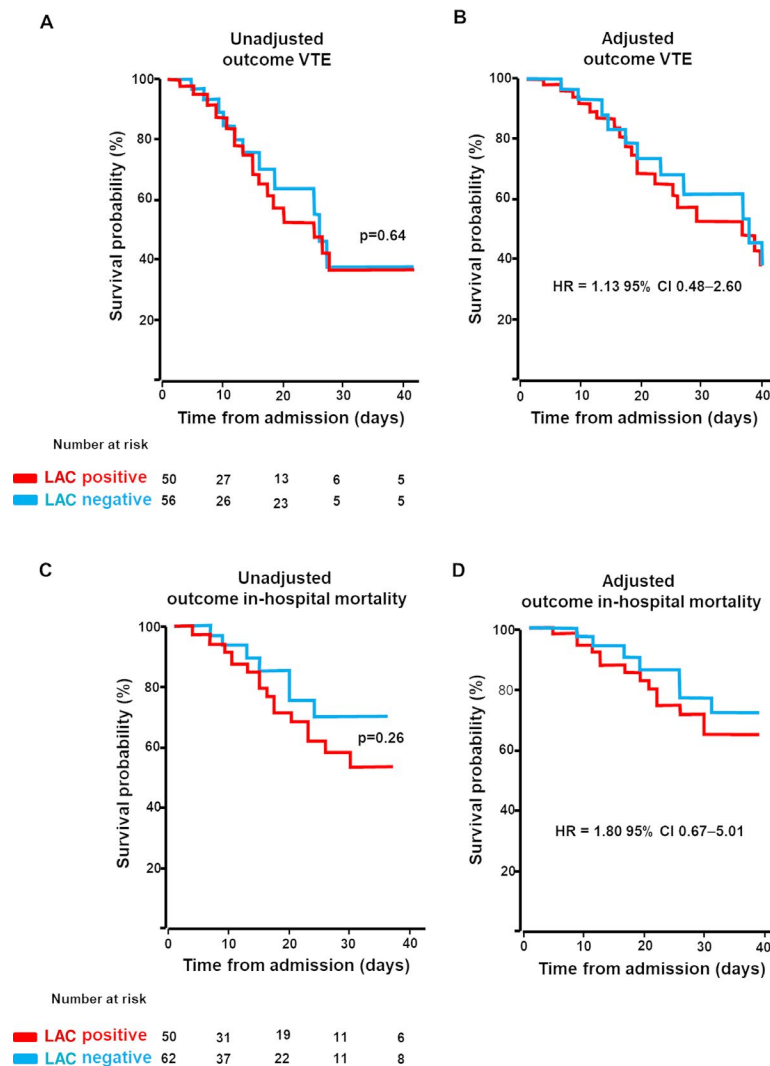


Figure 2. Kaplan-Meier survival curves showing the prognostic value of lupus anticoagulant (LAC) positivity at the time of admission with COVID-19. **A** and **B**, Development of venous thromboembolism (VTE) in patients with COVID-19 according to positivity or negativity for LAC, in an unadjusted analysis (**A**) and after adjustment for C-reactive protein level, age, and sex (**B**). **C** and **D**, In-hospital mortality in patients with COVID-19 according to positivity or negativity for LAC, in an unadjusted analysis (**C**) and after adjustment for C-reactive protein level, age, and sex (**D**). HR = hazard ratio; 95% CI = 95% confidence interval.

the first to test all aPLs in a large cohort of patients with suspected COVID-19, including both confirmed and nonconfirmed COVID-19 cases. We explored the relevance of conventional and nonconventional markers of APS at the time of admission with COVID-19 to assess whether they might play a role in disease prognosis. As described previously (10,23–25), we found a high prevalence of LAC in patients with COVID-19 in contrast with the low prevalence of IgG and IgM aCLs and IgG and IgM anti- β_2 GPI antibodies detected by solid-phase immunoassay. LAC positivity in patients with COVID-19 was significantly associated with markers of inflammation such as fibrinogen and CRP levels, but not IL-6 or ferritin levels. Discrepancies between various markers of inflammation and LAC in terms of their association with COVID-19 suggested that those markers of inflammation do not have the same relevance in COVID-19. Further studies are needed to

decipher the exact involvement of inflammatory proteins in COVID-19 severity and/or COVID-19-associated coagulopathy. LAC testing during the acute phase of inflammatory conditions is not recommended because high CRP and fibrinogen levels may induce false-positive results (29,32,33).

Early during the COVID-19 outbreak, Zhang et al described 3 critical cases of COVID-19, characterized by the absence of LAC and the presence of IgA aCLs, and IgA and IgG anti- β_2 GPI antibodies; more details on titers were not reported (34). The 3 patients experienced ischemic events associated with multifocal thrombosis. In patients with infectious conditions, aPLs can be transiently positive (22), and these antibodies are rarely associated with thrombotic events; therefore, this association is not reliably prognostic in critically ill patients. Whether aPLs in patients with COVID-19 are similar to those in patients with other infectious diseases such

as hepatitis C virus (HCV), HBV, and HIV remain to be determined (18,22). A previous report on 56 patients with COVID-19 described the association of IgG aCL levels with COVID-19 severity (35), but LAC positivity was not tested. Results of one study suggested that aPL positivity could be prothrombotic in vitro and in vivo after accelerated venous thrombosis was observed in mice injected with IgG purified from the serum of aPL-positive patients with COVID-19 (26). However, a major flaw of that study is the absence of aPL specificity in the purified IgG of the patients with COVID-19. LAC was not assessed in the study.

A limitation of our study is the small sample size in both groups and the heterogeneity of the non-COVID-19 control group. In our study, we demonstrated that LAC positivity in patients with COVID-19 was not associated with VTE, in particular PE, or with a poorer prognosis. Our results are in accordance with previous studies of smaller cohorts that suggest the lack of association between aPLs and COVID-19 severity and/or VTE (24,25,36). The high prevalence of stroke (13) or VTE in patients with severe COVID-19 (15,30), in particular PE, is unusual and has rarely been observed in other viral infections such as influenza (8). In the study by Devreese et al, 10 patients with COVID-19 were retested 1 month after the first test, and all but 1 patient who initially tested positive for LAC were negative (37). This reinforces the hypothesis that LAC may be transient and/or artefactual due to the acute phase of infection and increased CRP and fibrinogen levels. Furthermore, Pengo et al showed that among patients with suspected APS, the initial single aPL-positive phenotype was confirmed in only 40% (38).

LACs are heterogeneous antibodies detected under various clinical circumstances in which cellular damage due to infectious, autoimmune, or inflammatory stimuli leads to plasma membrane remodeling, including the release of membrane microparticles and exposure of anionic phospholipids. LAC activity may be induced by anti- β_2 GPI and/or anti-PT antibodies that provoke a dimerization of β_2 GPI and/or prothrombin enhancing their affinity to negatively charge phospholipid (39). Strikingly, this high prevalence of LAC/aPLs in patients with COVID-19 has rarely been observed with other pathologies, which probably reveals significant or massive cellular destruction that is specific to COVID-19.

Medium/low aPL titers were consistently found in patients with COVID-19. We acknowledge that in the present study, aPL testing was performed during the acute phase, which is discouraged according to the guidelines because of potential interference. The guidelines recommend retesting after 3 months to avoid overdiagnosis by classification of transient positivity of aPLs (19,20,33). Of note, heparin therapy was not an issue for LAC testing in our study because our reagents contain heparin neutralizers, and anti-factor Xa activity in patients receiving anticoagulation treatment with heparin was below the cutoff of the neutralizer.

In summary, our study demonstrates that in COVID-19, similar to other acute infectious inflammatory diseases, there is a high prevalence of LAC positivity, but the latter is not associated with

VTE and/or in-hospital mortality. LAC and aPL testing is not recommended and must be discouraged during the acute phase of COVID-19, as is the case in other viral infections. In any case, biologic confirmation after recovery is necessary.

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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. Gendron 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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Analysis and interpretation of data. Gendron, Dragon-Durey, Chocron, Darnige, Fontenay, Terrier, Smadja.

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