






ORIGINAL RESEARCH

High Prevalence of Acquired Thrombophilia Without Prognosis Value in Patients With Coronavirus Disease 2019

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BACKGROUND: Recent literature reports a strong thrombotic tendency in patients hospitalized for a coronavirus disease 2019 (COVID-19) infection. This characteristic is unusual and seems specific to COVID-19 infections, especially in their severe form. Viral infections can trigger acquired thrombophilia, which can then lead to thrombotic complications. We investigate for the presence of acquired thrombophilia, which could participate in this phenomenon, and report its prevalence. We also wonder if these thrombophilias participate in the bad prognosis of severe COVID-19 infections.

METHODS AND RESULTS: In 89 consecutive patients hospitalized for COVID-19 infection, we found a 20% prevalence of PS (protein S) deficiency and a high (ie, 72%) prevalence of antiphospholipid antibodies: mainly lupus anticoagulant. The presence of PS deficiency or antiphospholipid antibodies was not linked with a prolonged activated partial thromboplastin time nor with D-dimer, fibrinogen, or CRP (C-reactive protein) concentrations. These coagulation abnormalities are also not linked with thrombotic clinical events occurring during hospitalization nor with mortality.

CONCLUSIONS: We assess a high prevalence of positive tests detecting thrombophilia in COVID-19 infections. However, in our series, these acquired thrombophilias are not correlated with the severity of the disease nor with the occurrence of thrombotic events. Albeit the strong thrombotic tendency in COVID-19 infections, the presence of frequent acquired thrombophilia may be part of the inflammation storm of COVID-19 and should not systematically modify our strategy on prophylactic anticoagulant treatment, which is already revised upwards in this pathological condition.

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Key Words: coronavirus disease 2019 ■ thrombophilia ■ thrombosis

Many studies have already reported a strong thrombotic tendency from patients hospitalized for severe coronavirus disease 2019 (COVID-19) infection.¹⁻³ This propensity for thrombosis also occurs in patients with high prophylactic anticoagulant dose.¹ This characteristic is unusual and seems specific to COVID-19 infections, especially in their severe form.

The aim of our study was to search for probable acquired coagulopathies that could participate in this phenomenon and to report their prevalence.

METHODS

In consecutive patients hospitalized for a proven COVID-19 infection in 4 different departments of our

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CLINICAL PERSPECTIVE

What Is New?

- We found a strong prevalence of acquired thrombophilia in patients hospitalized for a coronavirus disease 2019 infection, especially a 72% prevalence of antiphospholipid antibodies and a 20% rate of PS (protein S) deficiency.
- These thrombophilias were not more frequent in patients with severe versus nonsevere coronavirus disease 2019 illness and did not correlate with other biological parameters or with clinical events.

What Are the Clinical Implications?

- Highlighting these acquired thrombophilias should not systematically modify the prophylactic anticoagulant treatment in patients with coronavirus disease 2019.

Nonstandard Abbreviations and Acronyms

aPL	antiphospholipid antibody
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
COVID-19	coronavirus disease 2019
dRVVT	diluted Russell viper venom time
LA	lupus anticoagulant
PC	protein C
PS	protein S

institution, we performed an extended coagulation assessment.

Patients were considered to be carrying a severe form if they required mechanical ventilation, noninvasive ventilation, or intensive monitoring in the intensive care unit. Nonsevere patients were hospitalized in 2 dedicated units.

In addition to activated partial thromboplastin time (aPTT), prothrombin time, D-dimer and fibrinogen concentrations, PC (protein C), and PS (protein S), and antithrombin deficiencies, as well as the presence of antiphospholipid antibodies (aPLs), were looked for. All supporting data are available within the article.

Blood samples were routinely handled according to the current recommendations for preanalytical phase,⁴ and plasma was obtained by centrifugation at 2000g to 2500g and 18°C for 15 minutes, within 2 hours after sampling. Routine coagulation tests were immediately performed, and the remaining

plasma was stored frozen in aliquots at -80°C until evaluated after having undergone a second cycle of centrifugation.

Prothrombin time and aPTT were measured using HemosIL RecombiPlasTin 2G and HemosIL SynthASil aPTT, respectively (Werfen, Bedford, MA). Results were expressed as the ratio of the patient's clotting time/the clotting time of a normal pooled plasma. Fibrinogen (in g/L) was measured using the HemosIL QFA reagent. D-dimer (in ng/mL fibrinogen equivalent unit) was measured using a latex-based immunoturbidimetric assay (HemosIL D-dimer HS500). Antithrombin, PC, and PS activities (in IU/dL) were measured using HemosIL Liquid Antithrombin, HemosIL Protein C, and HemosIL Protein S Activity, respectively. A deficit was considered when levels of antithrombin, PC, and PS were $<70\%$, $<70\%$, and $<64\%$, respectively.

Lupus anticoagulant (LA) assays were performed according to the recommendations of the International Society on Thrombosis and Haemostasis, using screening, mixing, and confirmation tests and applying the updated guidelines^{5,6} by the mean of the silica clotting time (HemosIL Silica Clotting Time) and the diluted Russell viper venom time (dRVVT) (HemosIL dRVVT Screen and dRVVT Confirm). Test results were expressed as the screen/confirm ratios, and normal ranges were <1.16 and <1.20 , respectively. Anticardiolipin and anti- $\beta 2$ -glycoprotein1 IgG and IgM antibodies were measured using chemiluminescent assays: AcuStar analyzer (Werfen). The cutoff values to define positivity were previously calculated by the reagents' manufacturer, according to the Sydney revised Sapporo criteria,⁶ using the 99th percentile of the distribution of results in 250 samples from apparently healthy blood bank donors and harmonized to be 20 U/mL for all antibodies tested.⁷ Single lots of these reagents were used throughout the study. These assays were done before any anticoagulation. Patients presenting a severe form of COVID-19 infection received a high prophylactic dose of low-molecular-weight heparin (enoxaparin, 40 mg subcutaneously twice a day) in accordance to recent guidelines in COVID-19 management,⁸ whereas those hospitalized for a nonsevere form received enoxaparin, 40 mg once a day.

Statistical Analysis

Continuous data are represented as median and interquartile range. The normality of the distribution of the variables was assessed using the Kolmogorov-Smirnov test. Comparisons between 2 groups were made with Student *t* test in case of normally distributed variables or with the Mann-Whitney *U* test in case of not normally distributed variables. Nominal values

are expressed as number (percentage) and compared with χ^2 tests. A probability of ≤ 0.05 was considered statistically significant throughout. Stata v9 software was used for statistical analysis.

This trial is part of the Cardiovascular Complications and COVID-19 study (ClinicalTrials.gov number NCT04335162; Agence Nationale de Sécurité du Médicament et des Produits de Santé Registration number of the study 2020-A01197-32). All patients signed an informed consent. Institutional review board approval was obtained.

RESULTS

Eighty-nine consecutive patients were included. The characteristics of our population are reported in Table 1. None of these patients had a history of thrombotic event.

In 31 cases, the COVID-19 infection was severe and required intensive care and/or ventilation. CRP (C-reactive protein) peak value was 105 mg/L. Median fibrinogen value was 6.45 (interquartile range, 5.96–6.75) g/L. Median D-dimer concentration was 1799 (interquartile range, 1441–2352) ng/mL. Nine symptomatic deep venous thrombosis without pulmonary embolism and 7 symptomatic pulmonary embolisms occurred during hospitalization. Altogether, 11% died. In this series, we had no arterial thrombosis.

Coagulation test results are reported for the whole population and in severe and nonsevere patients in Table 2.

As already described in the literature, although prothrombin time and aPTT were not different, D-dimer concentrations were higher in severe versus nonsevere patients ($P < 0.001$). Fibrinogen concentration was not significantly higher in severe group ($P = 0.1$).

Table 1. Characteristics of Patients Hospitalized for COVID-19 Infection

Characteristics of Patients With COVID-19 (n=89)	
Age, y	68 (63–71)
Male sex, %	68.5
CRP, mg/L	105 (85–103)
D-dimer, ng/mL	1799 (1441–2352)
Fibrinogen, g/L	6.45 (5.96–6.75)
PT, %	83 (81–85)
aPTT, s	29.7 (29.3–30.1)
Severe form, n (%)	31 (35)
DVT or PE, n (%)	14 (15.7)
Death, n (%)	10 (11)

Data are given as median (interquartile range), unless otherwise indicated. aPTT indicates activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DVT, deep vein thrombosis; PE, pulmonary embolism; and PT, prothrombin time.

We found a low prevalence of PC or antithrombin deficiency. The median values of which were 58% (interquartile range, 54%–62%) and 64% (interquartile range, 61%–69%), respectively. Considering the whole population, 20% of our patients presented a significant PS deficiency with a median PS value of 31% (interquartile range, 24%–45%). The prevalence of PS deficiency was not different between severe and nonsevere patients (22% versus 19%). The median values of PS deficit were also not different in severe versus nonsevere patients (32% [interquartile range, 24%–42%] versus 31% [interquartile range, 25%–45%]).

We found a high prevalence of aPLs. Indeed, 71.9% of patients presented at least one positive test for aPLs. There was no difference in the prevalence between both groups. For 59 patients (66.3%), the aPL positive test was an LA with a median titer of positivity of 1.36 (interquartile range, 1.33–1.41); for 6 cases (6.7%), it was a $\beta 2$ -glycoprotein1, IgG alone in 4 cases, IgM alone in 1 case, both IgG and IgM in 1 case, with a median titer of positivity of 44.7 (interquartile range, 23–1404). In 7 cases (7.9%), it was an anticardiolipin, IgG in 5 cases, IgM in 2 cases, with a median titer of positivity of 36.3 (interquartile range, 23–260).

Two patients (2.2%) were double positive (LA+ $\beta 2$ -glycoprotein1 for both), and 3 (3.4%) were triple positive. All of these results have been confirmed in a second assay.

None of these patients knew that they had an antiphospholipid syndrome (APS) or had presented any manifestation that could be related to an unknown APS. The presence of aPLs was not correlated with the initial aPTT values ($P = 0.55$).

By defining the severity of COVID-19 infection by the need for intensive care hospitalization and/or mechanical ventilation, the presence of aPLs was found in 71% of severe patients (22/31) versus 72.4% (42/58) in less severe patients ($P =$ not significant).

A correlation between the presence of PS deficiency or aPL positivity and other proposed severity markers of COVID-19 infection was investigated (Table 3). Neither D-dimer nor fibrinogen nor CRP concentrations were higher in patients with a PS deficiency or aPL positivity. For our patients whose anticoagulant treatment had not been modified according to the presence of thrombophilia, we found no correlation between the positivity of these thrombophilia tests and the occurrence of deep vein thrombosis or pulmonary embolism, nor with mortality during hospitalization.

The same was true if we take into account only the double or triple aPL positive patients.

Finally, none of these coagulation abnormalities was linked to mortality.

Table 2. Prevalence of Coagulation Abnormalities in the Population With COVID-19 and Comparison Between Severe and Nonsevere Forms

Variable	All Patients (n=89)	Severe (n=31)	Nonsevere (n=58)	P Value
PT, %	83 (81–85)	82 (76–87)	83 (81–87)	0.93
aPTT, s	29.7 (29.3–30.1)	30.1 (28.7–31.4)	29.7 (29.3–30.1)	0.6
D-dimer, ng/mL	1799 (1441–2352)	4303 (2176–5993)	1435 (1010–1796)	0.001
Fibrinogen, g/L	6.45 (5.96–6.75)	7.05 (5.9–8.0)	6.2 (5.8–6.6)	0.1
PC deficiency prevalence, % (n)	2.2 (2)	0	3.4 (2)	0.54
PC activity, %	58 (54–62)		58 (54–62)	/
PS deficiency prevalence, % (n)	20.2 (18)	22.6 (7)	19 (11)	0.78
PS activity, %	31 (24–45)	32 (24–42)	31 (25–45)	0.91
Antithrombin deficiency prevalence, % (n)	6.7 (6)	12.9 (4)	3.4 (2)	0.21
Antithrombin activity, %	64 (61–69)	63 (61–66)	64 (62–66)	0.95
aPL, % (n)	71.9 (64)	71.0 (22)	72.4 (42)	0.90
LA, % (n)	66.3 (59)	61.3 (19)	69 (40)	0.85
β ₂ -Glycoprotein1, % (n)	6.7 (6)	3.2 (1)	8.6 (5)	0.20
Anticardiolipin, % (n)	7.9 (7)	6.5 (2)	8.6 (5)	0.35
Double positif, % (n)	2.2 (2)	0	3.4 (2)	0.45
Triple positif, % (n)	3.4 (3)	0	5.2 (3)	0.40

Data are given as median (interquartile range), unless otherwise indicated. Double positive were LA+anticardiolipin. aPL indicates antiphospholipid antibody; aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; LA, lupus anticoagulant; PC, protein C; PS, protein S; and PT, prothrombin time.

DISCUSSION

Mounting evidence supports the strong propensity for thrombosis in patients with COVID-19, especially in their severe clinical presentation.¹

Previous series quickly warned against the risk of unusual thrombosis as well as the possibility of occurrence of thrombosis despite a well-conducted preventive or even curative treatment.¹ The high levels of D-dimers in

severe forms, the level of which has been reported to be a severity factor, are a stigma of a significant activation of coagulation resembling the disseminated intravascular coagulation of other infectious pathological condition.^{9,10}

To counteract this, recommendations for higher preventive anticoagulation doses were quickly issued in many countries.⁸

The explanation for this unusual thrombotic risk is certainly not single factored. In this context, it seemed

Table 3. Severity Markers of COVID-19 Infection and Clinical Events According to the Presence of aPL

Variable	No aPL (n=25)	aPL (n=64)	P Value
Severe form, %	36	34	0.89
CRP, mg/L	184 (122–258)	181 (146–218)	0.85
D-dimer, ng/mL	1834 (989–4375)	1782 (1411–2743)	0.94
Fibrinogen, g/L	6.45 (4.56–7.25)	6.45 (5.87–6.76)	0.61
aPTT, s	29.8 (29.2–30.2)	30.2 (28.6–32)	0.55
PT, %	82 (81–86)	83 (76–87)	0.92
PC deficiency prevalence, % (n)	4 (1)	1.5 (1)	0.49
PC activity, %	61	63	0.83
PS deficiency prevalence, % (n)	20 (5)	20 (13)	0.97
PS activity, %	32 (25–44)	34 (28–54)	0.83
Antithrombin deficiency prevalence, % (n)	8 (2)	6.2 (4)	0.99
Antithrombin activity, %	64 (61–66)	63 (61–67)	0.90
DVT, %	12	9	0.71
PE, %	4	9	0.40
Death, %	12	11	0.89

Data are given as median (interquartile range), unless otherwise indicated. The same results are true considering lupus anticoagulant instead of aPL. aPL indicates antiphospholipid antibody; aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DVT, deep vein thrombosis; PC, protein C; PE, pulmonary embolism; PS, protein S; and PT, prothrombin time.

necessary to look for the possibility of acquiescent coagulopathies.

In our series, we found a 20% rate of PS deficiency with a median value of 31% (interquartile range, 24%–45%). Several mechanisms responsible for these PS deficiencies could be ruled out, such as liver failure (normal prothrombin time), vitamin K deficiency (normal PC and vitamin K clotting factor levels), and coagulation activation (PS usually within the normal ranges as it is not consumed).

Of note, PS deficiency had already been described in acute viral infection.¹¹ In particular, it has been reported in patients infected with HIV for whom anti-thrombin and PC levels were within the normal range of concentration, whereas PS was significantly decreasing. We found the same pattern. The presence of specific antibodies has been hypothesized as a mechanism potentially responsible for such acquired deficiency in people infected with HIV.¹¹ Recently, a moderate decrease in PS activity has been described in a series of patients with COVID-19 without any correlation with the severity of COVID-19 infection.¹²

The prevalence of aPLs we found is high. In our series of COVID-19 infections, 7 patients of 10 had an aPL.

The positivity of aPLs in healthy controls is about 1.5% to 2%.¹³ During a viral infection, the increase in aPL prevalence is a well-known phenomenon.^{14,15} It has been reported with widely varying figures, particularly in HIV and hepatitis C virus. For example, the prevalence of aPLs in patients with hepatitis C virus compared with healthy controls has been reported up to 18.6% versus 1.78%.¹³ Most often in the literature, infection-driven anticardiolipin antibodies are the most common type of aPL, whereas in our series, LA were largely predominant.

Zhang et al reported 3 cases of COVID-19 infection with APS complicated by multiple cerebral infarctions.¹⁶ Bowles et al reported a high prevalence of aPL positivity in 34 patients, tested because of a prolonged aPTT.¹⁷ In a series of 56 patients, Harzallah et al reported a 45% prevalence of LA, independently of aPTT values. In these studies, correlation with thrombotic clinical events or with the severity of COVID-19 infection^{18,19} was not investigated. We believe the search for such correlation is an important feature of our study.

Although the presence of β 2-glycoprotein1, anticardiolipin, and LA is accepted as independent risk factor for the episodes of vascular thrombosis in APS, the thrombotic complications of the same infection-induced antibodies are not as well demonstrated.²⁰ However, they have been described, in particular, for certain viruses, like parvovirus B19 or cytomegalovirus²¹ or in animal models.^{22,23}

In our series, we did not find any correlation between the presence of any aPL or LA alone and the

proposed markers of severity of COVID-19 infection: D-dimer, CRP, or the occurrence of symptomatic venous thromboembolic events or death (Table 3). This suggests that the presence of aPLs in COVID-19 disease, at least LA in our series, may only be a phenomenon concomitant with the inflammation storm but does not represent a prognosis risk factor per se. It also could signify that we do not need to change our antithrombotic strategy for patients with COVID-19 in whom an aPL would be detected.

However, considering that even transient appearance of aPL may, in genetically predisposed individuals, lead to the development of APS,^{20,24} a 12-week check is advisable.

One could also argue that these thrombophilias were preexisting while quiescent, but the absence of history of thrombosis and the context are more suggestive of acquired anomalies. A biological confirmation should anyway be necessary after recovery.

CONCLUSIONS

The thrombotic propensity for severe COVID-19 infections is unusual and has rarely been reported in other viral infections. The inflammatory phase may be responsible, but it does not explain everything. The search for acquired thrombophilia appeared to be relevant. In our series, we found a 20% prevalence of PS deficiency and a 71% prevalence of aPLs, mainly LA. In our series, both do not seem to explain the occurrence of thrombosis and are not correlated to COVID-19 severity or prognosis. Until proved otherwise, the identification of these anomalies should not change our behavior in COVID-19 disease management. As aPLs may be transient but can also persist and trigger an authentic APS, a control at 12 weeks in all patients with COVID-19 having presented aPL seems necessary.

ARTICLE INFORMATION

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