RESEARCH LETTER

Thromboinflammatory state and venous thromboembolic events in patients with coronavirus disease 2019 admitted to a nonintensive care unit: a prospective study

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Introduction Most patients with coronavirus disease 2019 (COVID-19) experience mild symptoms, but about 19% of them develop a severe illness.[1,2] A striking feature of COVID-19 is the rapid progression of respiratory failure which often requires that the patient be transferred to an intensive care unit (ICU).[2] Recent reports highlight the role of systemic thromboembolic disease and pulmonary microvascular thrombosis in rapid clinical worsening.[3]

Numerous studies conducted in ICUs have demonstrated the existence of a COVID-19–associated coagulopathy (CAC).[1,2] However, few studies have evaluated whether clotting abnormalities occur even in patients hospitalized outside the ICU.

The main objectives of the present study were: a) to assess the values of inflammatory and selected coagulation parameters as well as the rate of venous thromboembolism (VTE) in patients with COVID-19 hospitalized in a medical ward other than ICU; b) to compare the characteristics of patients with mild disease with those with moderate and severe disease.

Patients and methods We conducted a prospective, observational, single-center study evaluating 85 patients with a laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, consecutively admitted to the COVID-19 ward of the San Giovanni di Dio Hospital in Florence, Italy, from April 1 to April 30, 2020. This 60-bed ward was managed by staff specializing in internal medicine and was dedicated to patients not requiring intensive care. The diagnosis of SARS-CoV-2 infection was confirmed using a single reverse transcriptase–polymerase chain reaction assay on nasopharyngeal swab specimens.

Patients were divided into 3 groups, according to the level of peripheral capillary oxygen saturation (SpO_2): 1) mild disease group: patients not requiring oxygen (SpO_2 ≥94% on room air); 2) moderate disease group: patients requiring oxygen (SpO_2 <94% on room air); 3) severe disease group: patients requiring noninvasive ventilation (SpO_2 <94% on 60% oxygen).

All patients underwent laboratory tests and ultrasound of the whole leg within the first 3 days of hospitalization and every 3 to 10 days thereafter. Computed tomography pulmonary angiography (CTPA) was performed in case of clinical suspicion of pulmonary embolism (PE), worsening of respiratory conditions, or proximal lower limb deep vein thrombosis.

Each patient provided a written consent to participate in the study. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Institutional Review Board of the Department of Medicine of the local health unit Azienda USL Toscana Centro.

Statistical analysis Data were presented as number (percentage) for categorical variables and mean (SD) or median (interquartile range) when appropriate for continuous variables. Normality of data distribution was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were compared with the *t* test, while the Mann–Whitney test was used to compare variables with nonnormal distribution. Categorical variables were compared with the χ^2 test or the Fisher exact test. The 3 groups were compared using the analysis of variance or the Kruskal–Wallis test. *P* values for

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2-group post-hoc comparisons were adjusted with the Bonferroni correction. Multivariable logistic regression model was performed to identify the predictors of VTE. GNU PSPP Statistical Analysis Software (https://www.gnu.org/software/pspp/; Free Software Foundation, Inc, Boston, Massachusetts, United States) was used for statistical analysis. A *P* value of less than 0.05 was considered significant.

Results Among the 85 patients (42 men; mean age, 75.9 years) evaluated, 81 (95.3%) were on low-molecular-weight heparin prophylaxis (76 with 4000 or 6000 IU per day and 5 with 4000 IU twice a day), 2 were on direct oral anticoagulant therapy for atrial fibrillation and 2 were receiving pneumatic intermittent compression of the legs due to recent major bleedings.

We detected 20 cases of deep vein thrombosis (8 proximal and 12 distal) in 18 patients. CTPA was performed in 12 patients and PE was diagnosed in 6 patients (2 cases of massive PE, 4 cases of segmental and / or subsegmental PE). Overall, 21 patients (24.7%) had at least 1 episode of VTE. Age, sex, or number of comorbidities did not significantly differ between patients with and without VTE (TABLE 1).

The median values of all the inflammatory parameters were above the reference ranges. C-reactive protein (CRP) and serum amyloid A protein levels were significantly higher in patients with VTE than in those without VTE. The median level of D-dimer was above the upper reference limits and it was significantly higher in patients with VTE than in those without VTE, but also in the latter group it was above the reference range (TABLE 1). None of the patients showed severe thrombocytopenia (platelet count, <50 000/μl), severe prolongation of prothrombin time and activated partial thromboplastin time, or reduction of fibrinogen concentration (<100 mg/dl).

D-dimer (odds ratio [OR], 1.001; 95% CI, 1.0001–1.002; *P* = 0.01) and CRP (OR, 1.06; 95% CI, 1–1.12; *P* = 0.03) levels on admission were predictive of VTE in the multivariable logistic regression analysis.

Length of stay, in-hospital mortality, and the necessity for a transfer to ICU were similar in patients with and without VTE (TABLE 1).

Patients with mild, moderate, and severe disease A total of 21 patients had mild disease, 24 had moderate disease, and 40 had severe disease.

The median values of the inflammatory parameters, except interleukin 6, in patients with mild disease were above the reference ranges (TABLE 1). In particular, CRP was above the upper limit of the reference range in 18 patients (86%), ferritin in 14 (67%), serum amyloid A protein in 16 (76%), and interleukin 6 in 14 (67%). The median values of the inflammatory parameters were significantly lower in patients with mild disease than in those with severe disease.

In patients with mild disease, the median level of D-dimer was well above the reference limits. Fibrinogen and D-dimer concentrations were above the upper limit of the reference range in 21 (100%) and 18 (86%) patients with mild disease, respectively.

A single patient (5%) with mild disease had VTE, in comparison with 7 patients (29%) with moderate disease and 13 patients (33%) with severe disease (*P* = 0.05 and *P* = 0.02, respectively). Length of stay did not significantly differ among the 3 groups. Among patients with mild, moderate, and severe disease, we observed 0, 2, and 14 deaths, respectively (TABLE 1).

Discussion The main results of this study are the following: 1) the rate of VTE was remarkably high in patients with COVID-19 admitted to a nonintensive care unit; 2) the great majority of these patients, even those with mild disease, showed significant alterations in the inflammatory indices and in some of the coagulation markers.

Venous thromboembolism complications Systematic venous ultrasound of the legs, together with CTPA, allowed to detect VTE in 24.7% of patients. A rate of VTE varying from 20% to 79% has been reported in ICU patients.[4,5] Few data are available for non-ICU patients: 2 studies reported a prevalence of VTE ranging from 0% to 6%,[6,7] while a French study described a VTE prevalence of 22%.[8] The latter percentage as well as the one observed in the present study (24.7%) is much higher than that described in non–COVID-19 patients, which varies from 0.5% to 8%.[9] This finding is even more remarkable if we consider that the vast majority of patients included in our study were receiving thromboprophylaxis with low-molecular-weight heparin.

The incidence of VTE was particularly high in patients with moderate (29%) and severe disease (33%), while it was only 5% in those with mild disease.

Hyperinflammation and hypercoagulability: thromboinflammation The inflammation indices and some parameters of the coagulation system, such as D-dimer and fibrinogen concentrations, were on average very high in our patients, particularly in those with VTE. Furthermore, elevated D-dimer and CRP levels were independent risk factors for VTE. Extremely high concentrations of D-dimer and CRP were recently reported in a woman with PE associated with COVID-19 pneumonia,[10] and the authors suggested that such high levels of these parameters should prompt physicians to rule out PE.

On the other hand, none of the patients showed severe thrombocytopenia, severe prolongation of prothrombin time and activated partial thromboplastin time, or reduction of fibrinogen concentration. These results support the existence of a new condition of severe hypercoagulability called CAC, characterized by hyperfibrinogenemia

TABLE 1 Demographic and clinical characteristics of the study population

Variable		All patients (n = 85)	Presence of VTE			COVID-19 severity			
			VTE patients (n = 21)	Non-VTE patients (n = 64)	*P* value	Mild disease (n = 21)	Moderate disease (n = 24)	Severe disease (n = 40)	*P* value
Sex, n (%)	Male	42 (49)	14 (67)	28 (44)	0.08	6 (29)	12 (50)	24 (60)	0.07
	Female	43 (51)	7 (33)	36 (56)		15 (71)	12 (50)	16 (40)	
Age, y, mean (SD)		75.9 (12.7)	77.5 (8.6)	75.4 (13.8)	0.38	75.5 (16)	81.3 (10.9)	72.9 (10.9)	0.03[a]
Comorbidities, n, median (IQR)		2 (1–3)	2 (1–3)	2 (1–3)	0.79	2 (1–3)	2 (1–3)	2 (1–4)	0.55
Obesity, n (%)		6 (7.1)	1 (4.8)	5 (7.8)	>0.99	0	1 (4.2)	5 (12.5)	–
CRP, mg/dl, median (IQR); reference range, <0.5 mg/dl		7.5 (2.9–15.1)	13.3 (6.7–19.6)	7.2 (2.6–14)	0.04	2.5 (1.4–4.2)	8.5 (5.8–18)	13.7 (6.1–17.4)	<0.001[b,c]
Ferritin, ng/ml, median (IQR); reference range, 20–200 ng/ml		611 (275–970)	737 (474–1236)	596 (271–847)	0.19	218 (138–584)	474 (279–718)	1038 (590–1299)	<0.001[a,c]
SAA, mg/l, median (IQR); reference range, <10 mg/l		271 (101–827)	529 (204–1130)	197 (87–752)	0.03	138 (69–267)	252 (106–822)	493 (144–1420)	0.04[c]
IL-6, pg/ml, median (IQR); reference range, <16 pg/ml		22.8 (11–43.9)	33 (13.9–61.7)	21.8 (10.4–38.2)	0.13	10.5 (3–21.7)	19.1 (7.9–30.1)	38 (21.9–56)	<0.001[a,c]
Platelet count, $\times 10^3$/µl, mean (SD); reference range, 150–400 $\times 10^3$/µl		222 (93)	245 (98)	198 (94)	0.21	203 (79)	236 (125)	225 (78)	0.5
Fibrinogen, mg/dl, mean (SD); reference range, 150–400 mg/dl		712 (141)	735 (154)	704 (136)	0.41	639 (121)	720 (138)	743 (142)	0.03[c]
D-dimer, ng/ml, median (IQR); reference range, <500 ng/ml		1443 (576–5716)	7014 (1200–29 236)	1203 (665–4061)	0.002	990 (565–4780)	1443 (799–5348)	1742 (886–6810)	0.28
Length of hospital stay, d, median (IQR)		19 (12–26)	20 (14–31)	18 (12–24)	0.19	15 (7–22)	18 (14–24)	19 (13–30)	0.33
In-hospital death, n (%)		16 (19)	4 (19)	12 (19)	>0.99	0	2 (8)	14 (35)	–
Transfer to ICU, n (%)		3 (3)	2 (10)	1 (1)	0.15	0	0	3 (7.5)	
Death and/or transfer to ICU, n (%)		19 (22)	6 (29)	13 (20)	0.43	0	2 (8)	17 (43)	

a Post-hoc analysis for comparisons of the stages of disease severity: $P < 0.05$ for moderate vs severe disease

b Post-hoc analysis for comparisons of the stages of disease severity: $P < 0.05$ for mild vs moderate disease

c Post-hoc analysis for comparisons of the stages of disease severity: $P < 0.05$ for mild vs severe disease

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IL-6, interleukin 6; IQR, interquartile range; SAA, serum amyloid A protein; VTE, venous thromboembolism

and elevated D-dimer levels,[11] and distinguished from disseminated intravascular coagulation by the absence of thrombocytopenia and consumption of coagulation factors. However, disseminated intravascular coagulation has sometimes been reported in the more advanced stages of COVID-19.[11] Varga et al[12] have demonstrated viral infection of the endothelial cells across vascular beds of different organs in a series of patients with COVID-19, with induction of endothelialitis. It is likely that endothelial damage triggers a prothrombotic cascade that leads to in situ thrombosis. Therefore, it is conceivable that at least some cases of the distal PE that we have detected are actually manifestations of thrombotic phenomena which occurred at the level of the small pulmonary arteries, rather than consequences of an embolism. The association of hyperinflammation with CAC is summarized by the term "thromboinflammation,"[11] a condition documented so far in ICU patients, but which seems to be already present in patients with mild disease, in whom VTE is rare.

Strengths and limitations of the study The strength of this study lies in its prospective design and the systematic search of VTE in all patients. The study population included patients with different stages of COVID-19 severity, which allowed us to evaluate even patients with mild disease, so far excluded in most studies. However, the study also has some limitations: first, it was only performed in a single center; second, it included a relatively small number of patients.

Conclusions A remarkably high rate of VTE has been detected in patients with COVID-19 hospitalized in a nonintensive care unit. These results, together with the evidence of systemic thromboinflammation found even in patients with mild disease, suggest to evaluate the usefulness of early initiation of antinflammatory and anticoagulant therapy in patients treated for COVID-19.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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