Scientific letter

Arterial thrombotic complications in hospitalized patients with COVID-19

Complicaciones arteriales trombóticas en pacientes hospitalizados con COVID-19

To the Editor,

The focus of the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has shifted from Asia to Europe and the United States. Spain is currently the second country per number of cases, with the first case reported on January 31, 2020. Madrid is the most affected Spanish area and our hospital has attended the largest number of coronavirus disease 2019 (COVID-19) patients within the region.

Although respiratory failure remains the landmark and the main cause of death of moderate or severe COVID-19 disease, several cardiovascular complications and numerous cases of thromboembolic disease have been reported.[1–3] Despite the suggestion of an underlying prothrombotic state, data regarding the risk of acute arterial thrombotic events are scarce. The aim of this study was to describe the characteristics and outcomes of all patients attended due to an acute arterial thrombosis in the coronary, cerebral and peripheral circulation during a 1-month period at the peak of the present COVID-19 pandemic.

Categorical variables are presented as counts and percentages and the comparisons were made using the chi-square test or the Fisher exact test. Continuous variables are presented as mean ± standard deviation (or median and interquartile range as appropriate) and were compared using the Student *t*-test or the Wilcoxon rank-sum test. All data were analyzed using the Stata version 14.2 statistics package, (StataCorp, United States). A P value $< .05$ was considered statistically significant for all analyses.

During March 2020, 87 patients received a diagnosis of acute arterial thrombosis at the Hospital Universitario La Paz: 17 patients with acute coronary syndrome, 18 patients with acute peripheral arterial thrombosis, and 52 patients with ischemic stroke. Among them, 38 (43.7%) tested positive for SARS-CoV-2. This represents 1.8% of the total of 2.021 patients with confirmed COVID-19 disease attended in our center during the same period. Baseline characteristics are summarized in table 1. The mean age was

Table 1
Patients' baseline characteristics

Variable	All patients (n = 87)	COVID-19 (n = 38)	Non-COVID-19 (n = 49)	*P*
Baseline characteristics				
Age, y	69.6 ± 14.0	72.1 ± 14.3	67.6 ± 13.5	.14
Male sex	58 (66.7)	23 (60.5)	35 (71.4)	.29
Hypertension	54 (62.1)	25 (65.8)	29 (50.2)	.53
Diabetes	32 (36.8)	12 (31.6)	20 (40.8)	.38
Dyslipidemia	46 (52.9)	19 (50.0)	27 (55.1)	.64
Smoking	16 (18.4)	5 (13.2)	11 (22.5)	.50
Number of major CV risk factors				.28
0	15 (17.2)	9 (23.7)	6 (12.2)	
1-2	51 (58.6)	22 (57.9)	29 (59.2)	
3-4	21 (24.2)	7 (18.4)	14 (28.6)	
Peripheral artery disease	15 (17.2)	6 (15.8)	9 (18.4)	.75
Ischemic stroke	7 (8.1)	2 (5.3)	5 (10.2)	.46
Coronary artery disease	14 (16.1)	4 (10.5)	10 (20.4)	.25
Atrial fibrillation/flutter	10 (11.5)	6 (15.8)	4 (8.2)	.32
Therapeutic anticoagulation prior to admission	11 (12.6)	6 (15.8)	5 (10.2)	.52
COPD	14 (16.1)	10 (26.0)	4 (8.2)	.04
Chronic kidney disease[a]	6 (6.9)	2 (5.3)	4 (8.2)	.69
On admission data, laboratory data, and in-hospital management				
Signs/symptoms of COVID prior to thrombotic event	N/A	32 (84.2)	N/A	N/A
Atrial fibrillation/flutter during admission	18 (20.7)	12 (31.6)	6 (12.2)	.04
Therapeutic anticoagulation during admission	18 (20.7)	12 (31.6)	6 (12.2)	.04
Affected arterial territory				.14
Coronary	17 (19.5)	4 (10.5)	13 (26.5)	
Cerebral	52 (59.8)	24 (63.2)	28 (57.1)	
Peripheral	18 (20.7)	10 (26.3)	8 (16.3)	
Simultaneous thrombus at different locations	13 (14.9)	11 (28.9)	2 (4.1)	.01
Pneumonia	31 (35.6)	31 (81.6)	0 (0.0)	< .01

Table 1 *(Continued)*
Patients' baseline characteristics

Variable	All patients (n = 87)	COVID-19 (n = 38)	Non-COVID-19 (n = 49)	*P*
Hemoglobin, g/dL	12.3 ± 2.3	12.1 ± 2.0	12.5 ± 2.5	.55
Lymphocyte, x 10^6/L	992.0 ± 491.3	791.8 ± 440.7	1147.2 ± 475.8	< .01
Platelets, x 10^9/L	306 ± 157	328 ± 159	290 ± 156	.27
Ferritin, ng/dL	1078.3 ± 1045.4	1334.4 ± 1084.4	423.8 ± 575.4	.02
D-dimer, ng/mL	7929 ± 12 133	9032 ± 11 867	6206 ± 12 729	.47
APTT, seg	26.8 ± 4.3	26.8 ± 4.6	26.8 ± 4.1	.99
Fibrinogen, mg/dL	671 ± 309	780 ± 304	589 ± 289	< .01
C-reactive protein, mg/L	80.2 ± 100.1	124.7 ± 99.5	44.7 ± 86.6	< .01
LDH, UI/L	467.5 ± 337.6	524.8 ± 357.6	403.4 ± 308.3	.19
IL-6, pg/mL	N/A	359.5 ± 434.5	N/A	N/A
LVEF, %	55.2 ± 12.1	54.5 ± 15.8	55.5 ± 10.8	0.71
DIC ISTH score	1 (1-3)	3 (1-4)	1 (1-1)	< .01
Coronary angiography	16 (94.1)	4 (100.0%)	12 (92.3%)	1.00
Percutaneous coronary intervention[b]	14 (82.4%)	4 (100)	10 (76.9)	1.00
Vascular surgery[c]	13 (72.2)	5 (50.0)	8 (100)	.04
Stroke reperfusion treatment[d]	21 (40.4)	9 (37.5)	12 (42.9)	.70
Clinical outcomes				
DVT/PE	5 (5.8)	4 (10.5)	1 (2.0)	.16
Critical care admission	5 (5.8)	5 (13.2)	0 (0.0)	.01
Bleeding[e]	9 (10.3)	9 (23.7)	0 (0.0)	< .01
Death	19 (21.8)	17 (44.7)	2 (4.1)	< .01

CV, cardiovascular; COPD, chronic obstructive pulmonary disease; COVID, coronavirus disease; LVEF, left ventricular ejection fraction; DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis; DVT, deep vein thrombosis; PE, pulmonary embolism.
Data are expressed as No. (%) for categorical data or mean ± standard deviation for continuous data.
[a] Chronic kidney disease was defined as kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause.
[b] Refers to the proportion of patients undergoing percutaneous coronary interventions among those with thrombotic events in the coronary territory (n = 17).
[c] Refers to the proportion of patients undergoing bypass surgery, surgical embolectomy or amputation among those with thrombotic events in the peripheral territory (n = 18).
[d] Refers to the proportion of patients undergoing fibrinolysis or percutaneous intervention among those with thrombotic events in the cerebral territory (n = 52).
[e] Refers to ISTH major or clinically relevant nonmajor bleeding.

69.6 ± 14.0 years and the patients were predominantly male (66.7%). Interestingly, 13 patients showed simultaneous thrombosis of different vessels within the same arterial territory. A total of 19 (21.8%) died during the index hospital admission.

When comparing COVID-19 with non-COVID-19 patients, significant differences were observed only in the proportion of patients with chronic obstructive pulmonary disease. Nevertheless, COVID-19 patients tended to have a lower cardiovascular risk profile. On the other hand, this group showed significantly higher inflammatory markers than the non-COVID-19 cohort and higher mortality during hospital admission.

Notably, simultaneous thrombosis of different arteries was significantly more frequent among COVID-19 patients. Of 38 COVID-19 patients, 11 showed simultaneous thrombosis of different locations (7 had multiterritory ischemic stroke, 3 acute lower limb arterial ischemia due to occlusion of the terminal aorta, and 1 patient had an infarction with thrombus in 2 different coronary arteries). Interestingly, only 1 of them had a history of atherosclerosis (coronary artery disease) and 3 of these patients also had venous thromboembolic disease (2 of them pulmonary embolism and 1 deep vein thrombosis).

The mean time to death was 10.3 ± 6.5 days. The main cause among COVID-19 patients was respiratory failure due to acute respiratory distress syndrome (8 patients, 47.1%) followed by neurological (7 patients, 41.1%) and cardiac causes (2 patients, 11.8%). Both deaths in the non-COVID-19 group were neurological.

We observed a significant proportion of hospitalized COVID-19 patients with clinically relevant arterial thrombotic complications. We did not include patients with elevation of cardiac biomarkers[4] that did not require a change in clinical management or prompted the need for coronary angiography. Moreover, angina and neurological symptoms may have been neglected in patients with severe respiratory failure (who may be at higher risk of thrombotic events[5]). Therefore, the real proportion of patients with arterial thrombosis may be even higher.

Regarding multiterritory thrombosis, we did not perform dedicated work-up to rule out a preexisting prothrombotic state. Nevertheless, the COVID-19 infection may have triggered these episodes, given that this feature is significantly more frequent among COVID-19 patients.[2,6]

The fact that the COVID-19 cohort did not have a highly significant cardiovascular risk profile compared with the non-COVID-19 cohort, and the notable finding of significantly more frequent simultaneous thrombosis support the hypothesis of a systemic prothrombotic state associated with SARS-CoV-2.[6] A higher risk of arterial thrombosis has been previously described in association with bacteremia and other respiratory viruses,[4] but the specific pathophysiology of COVID-19 disease remains an open field for basic and clinical research.

In conclusion, hospitalized patients with COVID-19 have a significant risk of acute arterial thrombosis. Significantly higher mortality and more frequent simultaneous thrombosis of different arteries were observed in these patients than in non-COVID patients. Clinicians managing these patients should maintain a high level of suspicion and lower thresholds for appropriate testing when clinically indicated.

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Electrocardiographic/QT interval monitoring with a portable device in hospitalized patients with COVID-19: a protocol proposal

Control electrocardiográfico del intervalo QT mediante dispositivo portátil en pacientes ingresados por COVID-19. Propuesta de protocolo

To the Editor,

The pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is posing a major challenge to the international scientific community and to health care worldwide. The lack of effective treatments has obligated the experimental or compassionate use of drug combinations, so that most protocols include combinations of protease inhibitors (lopinavir/ritonavir), antimalarials (chloroquine/hydroxychloroquine), and antibiotics and immunomodulators such as azithromycin,[1] among others. Many societies have already issued warnings about the use of these drugs and QT interval prolongation and the increased risk of sudden cardiac death from ventricular arrhythmias,[2] further aggravated by the use of antiemetics and antidiarrheals for the relief of gastrointestinal symptoms. While effective therapeutic tools against the virus remain unavailable, efforts should be made to optimize the prescription and safety of currently used drugs. Given that these patients are in respiratory isolation, it is difficult to perform serial electrocardiograms (ECGs). Thus, the Food and Drug Administration has included among its recommendations the use of remote connection devices such as the KardiaMobile 6L (AliveCor, United States). This device has previously been approved for the detection of atrial fibrillation and QT monitoring in this setting[3] and has already been mentioned in protocols such as that proposed by the Mayo Clinic.[4] Although other devices with similar benefits are currently available, such as EKGraph (Sonohealth, United States), WIWE (myWIWE Diagnostics, Hungary), and Wecardio (BORSAM Biomedical Instruments, China), our hospital has chosen the AliveCor device for its use in the electrocardiographic monitoring protocol. The large volume of patients and the lack of experience with the aforementioned drugs have led to the acquisition of this device for monitoring the corrected QT interval (QTc). This approach has advantages over conventional ECG: ease of use, affordability, small size, remote data transmission (which minimizes the risk of contaminating the receiving device), and simplicity of disinfection in 70° alcohol. This device can obtain brief ECG recordings (30 s), allowing many patients to be monitored in little time. A receiver (mobile phone or tablet) is needed that connects via bluetooth with a range of at least 10 linear meters. Although the device provides 6 leads for the frontal plane of the ECG, for simplicity we decided to use the 1-lead option. There is another version of the device that only provides 1-lead ECG, but it is not equipped with a bluetooth connection and so it would need to be close to the receiver. Before starting the protocol, and as an internal validation process, QTc was measured in lead V_5 on conventional 12-lead ECG and in the

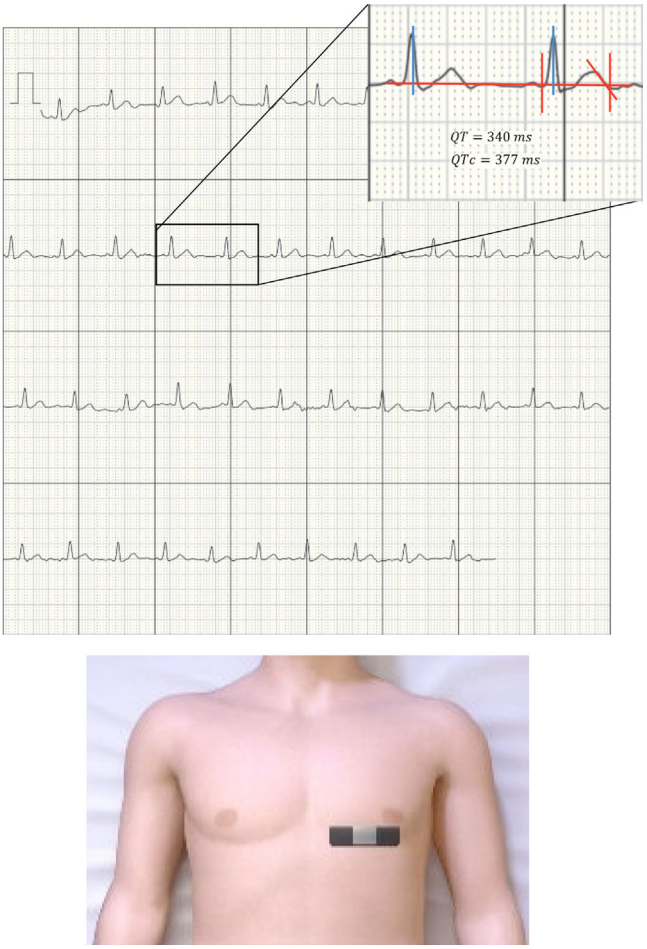

Figure 1. Recording obtained with the AliveCor Kardiamobile 6L device. Image used with the permission of AliveCor.