Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full Length Article

Systemic thrombosis in a large cohort of COVID-19 patients despite thromboprophylaxis: A retrospective study

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ABSTRACT

Background: Incidence of thrombotic events associated to Coronavirus disease-2019 (COVID-19) is difficult to assess and reported rates differ significantly. Optimal thromboprophylaxis is unclear.
Objectives: We aimed to analyze the characteristics of patients with a confirmed thrombotic complication including inflammatory and hemostatic parameters, compare patients affected by arterial vs venous events and examine differences between survivors and non-survivors. We reviewed compliance with thromboprophylaxis and explored how the implementation of a severity-adjusted protocol could have influenced outcome.
Methods: Single-cohort retrospective study of COVID-19 patients admitted, from March 3 to May 3 2020, to the Infanta Leonor University Hospital in Madrid, epicenter of the Spanish outbreak.
Results: Among 1127 patients, 80 thrombotic events were diagnosed in 69 patients (6.1% of the entire cohort). Forty-three patients (62%) suffered venous thromboembolism, 18 (26%) arterial episodes and 6 (9%) concurrent venous and arterial thrombosis. Most patients (90%) with a confirmed thrombotic complication where under low-molecular-weight heparin treatment. Overt disseminated intravascular coagulation (DIC) was rare. Initial ISTH DIC score and pre-event CRP were significantly higher among non-survivors. In multivariate analysis, arterial localization was an independent predictor of mortality (OR = 18, 95% CI: 2.4–142, $p < .05$).
Conclusions: Despite quasi-universal thromboprophylaxis, COVID-19 lead to a myriad of arterial and venous thrombotic events. Considering the subgroup of patients with thrombotic episodes, arterial events appeared earlier in the course of disease and conferred very poor prognosis, and an ISTH DIC score ≥ 3 at presentation was identified as a potential predictor of mortality. Severity-adjusted thromboprophylaxis seemed to decrease the number of events and could have influenced mortality. Randomized controlled trials are eagerly awaited.

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1. Introduction

On December 31, 2019, Wuhan authorities reported 27 pneumonia cases of unknown etiology [1]. A week later, a virus of the family *Coronaviridae* was identified as the agent causing the cluster [2], and it rapidly spread [3]. On March 11, 2020, the WHO declared the pandemia [4]. Since the beginning of the worldwide outbreak, over 15 million cases have been reported and mortality rate differs substantially among countries, with a global world rate of 5% but as high as 20% in some areas. As of July 16, 2020, Spain has reported 260,000 cases and 28,400 deaths, resulting in a 10% mortality rate [5–7].

Initial reports from China described the clinical picture of the Coronavirus disease of 2019 (COVID-19) [8–11]. It soon came clear that the interaction between the virus and the immune system was key in the pathogenesis, and various authors proposed a hyperinflammatory state, that could explain many of the clinical and laboratory findings. Interestingly, even though prominent abnormalities of hemostatic parameters were promptly described as common and related to poor prognosis [12–17], thrombotic events were not brought to light during the early phase of the pandemic.

By the end of March, the clinical relevance of coagulation impairment potentially reflecting pulmonary micro or macrothrombosis and the association of the disease with a high thrombotic risk began to emerge [18–22]. Some physiopathological hypotheses and autopsy findings supported the likely importance of diffuse pulmonary microthrombosis in the refractory hypoxemia of severe cases [23–26], and the cross-talk between the immune and coagulation systems gained importance [27]. *Poissy* et al reported an increased incidence of pulmonary embolism (PE) [28], and in subsequent weeks, numerous reports reinforced the high risk of venous thromboembolism (VTE), especially in the intensive care unit (ICU) setting [29–35]. Later on, arterial thrombotic episodes such as ischemic strokes (IS) and acute coronary syndromes (ACS) were increasingly described [36–39].

The actual incidence of thrombotic events in COVID-19 patients is difficult to assess accurately, as diagnostic and prophylactic strategies have been very heterogeneous worldwide [40]. Recommendation for universal thromboprophylaxis with low-molecular-weight-heparin (LMWH) has been established by international collaborative groups [41,42], but the ideal dose is under continuous debate [43]. Some groups, including ours, have used protocols based on LMWH-dose escalation according to clinical severity. A similar approach was early suggested by some Chinese authors [44], but it was discarded by most groups around the world due to the inherent risk and lack of evidence.

Herein we report multiple systemic arteriovenous (common and atypical, macro and microvascular) thromboembolic complications diagnosed in the COVID-19 patient cohort admitted to an academic secondary hospital, the first institution designated as COVID-19-only in Madrid, epicenter of the Spanish outbreak.

2. Materials and methods

2.1. Study design

Single-cohort retrospective study of all COVID-19 patients admitted to the Infanta Leonor University Hospital from March 3 to May 3, 2020. Thrombotic events were recorded by reviewing the general authorized Hospital database (COVID-19@Vallecas cohort), clinical notes and radiological tests of patients with a confirmed COVID-19 diagnosis (by means of SARS-CoV-2 positive reverse transcriptase-polymerase chain reaction [RT-PCR] of nasopharyngeal swabs) or diagnosed on clinical grounds according to the European Centre for Disease Prevention and Control (eCDC) criteria [45]. Records were evaluated until hospital discharge or death.

For all patients diagnosed with a thrombotic episode, demographics, clinical, laboratory, radiology and outcome data were collected from the Hospital database. Data regarding thromboprophylaxis and antiplatelet therapy used in the COVID-19 general cohort and in the study subpopulation prior to the diagnosis of thrombosis were extracted from the Hospital protocol and checked by reviewing medical notes and the Pharmacy registry. During the initial phase of the outbreak (March 3 to March 30), COVID-19 patients were considered acutely-ill medical patients with a standard thrombotic risk, so enoxaparin 40 mg subcutaneously (sc) once daily (OD) was recommended, increased to 60 mg sc OD on March 31. Enoxaparin 1 mg/kg sc twice daily (BID) was advised if the patient had a precedent indication for chronic anticoagulation or suffered an acute thrombotic event. On the 9th of April, due to the occurrence of fatal strokes and PE cases and recommendations from the Spanish Society of Thrombosis and Hemostasis [46], a dose-escalating protocol was implemented (Table 1).

2.2. Objectives

The primary aim was to describe the characteristics of hospitalized COVID-19 patients who were diagnosed with thrombotic complications (arterial, venous or microvascular).

Secondary aims included analyzing clinical and laboratory characteristics (mainly hemostatic and inflammatory parameters) of patients diagnosed with a thrombotic episode, comparing differences among patients affected by arterial vs venous events and exploring potential predicting prognostic factors between survivors and non-survivors. Although it was not an initial aim of the study, the obtained data allowed us to estimate the cumulative incidence of thrombotic events among the entire cohort of COVID-19 inpatients.

Table 1
Thromboprophylaxis protocol: escalated dose depending on risk and clinical severity/prognostic factors.

Patient risk stratification	Enoxaparin dose, sc	Enoxaparin dose, sc
Standard risk	MDRD-4 > 30 mL/min	MDRD-4 < 30 mL/min
Body weight		
<60 kg	40 mg (4000 IU) OD	20 mg (2000 IU) OD
60–100 kg	60 mg (6000 IU) OD	20 mg (4000 IU) OD
>100 kg	80 mg (8000 IU) OD	40 mg (4000 IU) OD
Age > 75 years	40 mg (4000 IU) OD	20 mg (2000 IU) OD
High risk: ≥1 thrombotic risk factor OR ≥ 1 poor prognostic factor		
BMI > 30 kg/m^2		
Personal history of VTE or arterial thrombotic events		0.25 mg/kg BID
Underlying thrombophilia	1 mg/kg OD	
COVID-19-associated:		Anti-Xa 0.4–0.6 IU/mL
Lymphocytopenia <700 cells/μL		
D-dimer >3000 μg/L		
Interleukin 6 > 40 pg/mL		
C-reactive protein >150 mg/L		
Age > 75 years	0.75 mg/kg OD	0.25 mg/kg OD
Severely or critically ill patients		
Refractory hypoxemia not responding to anti-inflammatory drugs	0.75–1 mg/kg BID	0.75–1 mg/kg OD
AND		
D-dimer >3000 μg/L *OR* ISTH DIC score ≥ 5		Anti-Xa 0.6–1 IU/mL
Age > 75 years	0.75 mg/kg BID	0.25 mg/kg BID

IU: International Units. OD: once daily. BID: twice daily, once every 12 h. sc: subcutaneous route. MDRD-4: Modification of Diet in Renal Disease. BMI: Body mass index. VTE: Venous thromboembolism. Anti-Xa: Anti-factor Xa activity target. ISTH DIC score: International Society of Thrombosis and Haemostasis overt Disseminated Intravascular Coagulation score.

2.3. Data collection

Data were collected and managed using REDCap (Research Electronic Data Capture) tools, hosted at Ideas for Health Association, a secure web-based software platform designed to support data capture for research studies [47]. Collection ended in June 15.

2.4. Outcomes

The primary outcome was defined by a composite of venous, arterial and microvascular thrombotic events. VTE was defined by PE, deep vein thrombosis (DVT) or atypical venous thrombosis diagnosed by accepted imaging tests. Although screening was not standardized, there was an active search for thrombosis from March 30 onwards. Medical criteria for performing a chest CT pulmonary angiogram (CTPA) were acute respiratory distress syndrome not improving despite treatment, acute deterioration not attributable to other causes or an increasing D-dimer discordant with other inflammatory parameters. Doppler ultrasound (DUS) of the limbs or abdomen were requested based on clinical suspicion, and complete compression ultrasonography (CUS) of the lower limbs was ordered in patients with confirmed PE. Arterial events included IS (defined according to WHO clinical criteria and ascertained by means of brain CT or MRI in every case [48]), ACS (defined by clinical means, ECG changes and cardiac biomarkers as defined by the European Society of Cardiology [49]), aortic thrombi (incidentally identified in CTPA and confirmed by aortic CT angiography), renal and splenic complications detected by contrast-enhanced CT and peripheral artery disease. Acral microvascular ischemic event diagnosis was clinical and confirmed by skin biopsy.

The secondary outcome was the prevalence of disseminated intravascular coagulation (DIC) in patients diagnosed with a thrombotic episode. We retrospectively calculated the International Society on Thrombosis and Haemostasis (ISTH) score for overt DIC [50,51] on admission, at the time of event diagnosis and their difference, in every patient. D-dimer was used to evaluate fibrin related markers: values from 1000–3000 μg/L were interpreted as a moderate increase and $>$ 3000 μg/L as a strong increase, as previously accepted by the Scientific and Standardisation Committee on DIC of the ISTH [51] and used by *Tang* et al. to calculate the grade of DIC in non survivors with COVID-19 [13] (based on a previous report defining cutoff values obtained from more than 1800 samples in intensive care [52]). A score $\geq$ 5 was considered overt DIC.

2.5. Statistical analysis

Characteristics of patients suffering a thrombotic event were analyzed. For categorical variables, Pearson's chi-squared or Fisher's exact test were used. For numerical variables with a normal distribution (checked visually by a histogram and numerically by the Saphiro-Wilk test), mean and standard deviation (SD) are shown; for the other variables, median and interquartile range (IQR) was used. Student's *t*-test or Wilcoxon rank test were performed as appropriate. To identify variables associated with mortality, univariate and multivariate logistic regression models were applied. Reported *p*-values correspond to the 2-tailed analysis; significance threshold set at 0.05. Analysis was performed using the statistical package SAS 9.4 (Copyright©2016 by SAS Institute Inc., Cary, NC, USA).

The cumulative incidence (CIn) of thrombotic events among the entire cohort of COVID-19 patients was calculated using Stata 12 (StataCorp LLC, College Station, TX). For these analyses, six thrombotic complications occurring after the discharge of a first ever hospitalization were excluded, thus avoiding a differential follow-up between those patients diagnosed of thrombotic complications and those who were not. CIn was estimated by the multiple decrement model, with death as a competing risk. The Fine-Gray competing risks regression model was used to estimate the longitudinal risk of thrombosis in the presence of covariates and of a competing event (death). Actuarial survival estimates were used to obtain hazard functions, which represent a conditioned mortality rate for different moments of the follow-up period and provides instant risks for the study event [53].

2.6. IRB approval

The study was carried out in accordance with The Ethics Code of the World Medical Association (declaration of Helsinki). The Institutional Investigation and Ethics Review Board of Infanta Leonor University Hospital (CEI-HUIL) approved the study (Code ILUH R 027-20). Written informed consent was waived due to the retrospective nature of the study.

3. Results

3.1. Thrombotic events

Between March 3 and May 3, 2020, 1127 COVID-19 patients were hospitalized and 80 thrombotic events were diagnosed in 69 patients (6.1% of the entire cohort). Incidence of thrombotic events gradually increased together with the length of admission. The CIn of thrombosis, accounting for the competing risk of death, was 5.8% among those patients who survived and remained admitted for at least ten days; 13.0% by 20 days; and 18.7% by 30 days (Appendix Table 2 and Fig. 1 of the supplementary material). CIn of thrombosis was similar among those patients who required ICU admission ($N = 73$) and those who did not ($N = 1054$). A gender- and age-adjusted Fine-Gray competing risks regression model confirmed that ICU admission was not a predictor for thrombotic events in our cohort (subhazard ratio 1.20, 95% CI 0.57–2.56, $p = .63$).

CIn of PE increased with the time of admission up to 16.1% (95% CI 9.7–23.9) by 30 days of follow-up (Appendix Table 2 supplementary material). The hazard function shows an increase in the risk of presenting PE between the 10th and 19th day of hospital stay. On the contrary, CIn of IS was 1.4% (95% CI 0.7–2.5) by day 10. No strokes occurred later, so the risk depicted by the hazard function rapidly declined from admission.

The median age of the study population was 65 years (range 27–96) and 65% were male. Forty-three patients (62%) suffered VTE, 6 (9%) were diagnosed with both venous and arterial complications, 18 (26%) had only arterial events and 2 patients suffered biopsy-confirmed microvascular ischemic lesions. COVID-19 had been confirmed by a positive RT-PCR in 47 patients (68%) and 22 patients (32%) had a clinical diagnosis of COVID-19, all of them classified as probable cases by eCDC criteria, meeting diagnostic imaging signs (radiological evidence showing lesions compatible with COVID-19) and at least one of the following clinical symptoms (cough, fever, shortness of breath, ageusia or dysgeusia).

The median time from initiation of COVID-19 symptoms to the diagnosis of thrombosis was 16 days (IQR 10–23), and seven patients (10%) were diagnosed at presentation. Four events were incidentally detected (aortic floating thrombi and mural thrombus). Noteworthy, only 7% of the described events were diagnosed in the ICU setting.

Fig. 1 illustrates the anatomical distribution of the events, and patient characteristics and differences among thrombotic subgroups are summarized in Table 2. VTE was the most frequent thrombosis, accounting for 65% of the episodes (52/80; 44 PE, 6 DVT and 2 portal vein thrombosis) and affecting 71% of the patients (49/69).

3.2. Isolated VTE

Out of 43 patients, 38 suffered PE (88%) and 4 DVT (9%); only one had both. Two patients were diagnosed with acute portal vein thrombosis (Fig. 2D), including a 27-year-old healthy man. Median age of this subgroup was 64 years and 67% were men. Obesity was common (28%),

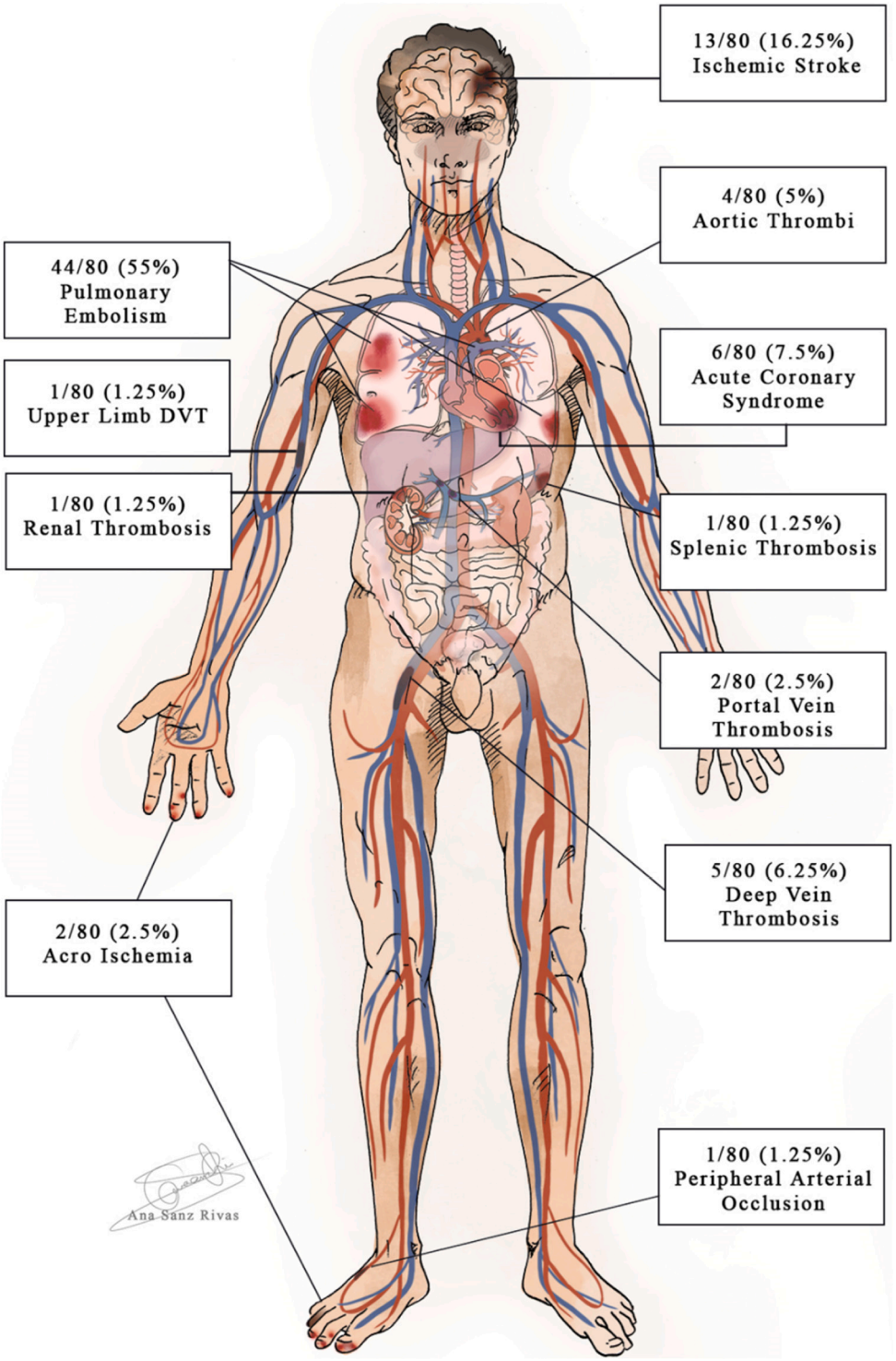

Fig. 1. Human picture depicting thrombotic events in a 1127-patient COVID-19 cohort.

but not other classical VTE risk factors (11%) and a single patient had previous history of VTE. Up to 50% had chronic medical conditions. Median time from COVID-19 symptom onset to VTE diagnosis was 18 days (IQR: 12–24). In this subgroup, pre-event inflammatory markers tended to be lower.

3.3. Co-occurrence of venous and arterial thrombosis

Six patients suffered both venous and arterial events. Four had PE and an IS (two of them also a DVT), one patient had PE and 3 floating thrombi in the descending aorta and the remaining case had PE and a peripheral arterial occlusion.

Regarding all PE cases, the distribution was peripheral in 64% (26/44) and affected the main or lobar arteries in 36% (Fig. 2B); 55% were bilateral. Despite performing CUS or DUS of the lower limbs in 38/44 PE patients (1–3 days after diagnosis), only 3 concomitant underlying DVTs were found.

Table 2
Patient characteristics, classified by thrombotic event subtype.

Patient characteristics	Thrombotic event subtype and number of patients					*p* value
	Arterial ($n = 18$)	Venous ($n = 43$)	Arterial and venous ($n = 6$)	Acro-ischemia ($n = 2$)	Total ($n = 69$)	
Demographics						
Age, years, median (IQR)	71.5 (60–78)	64 (54–72)	67 (55–81)	67.5 (64–71)	65 (56–75)	0.174
Ethnicity, n (%)						
Caucasian	14 (78)	33 (77)	5 (83)	2 (100)	54 (78)	1
Hispanic	4 (22)	10 (23)	1 (17)	0	15 (22)	1
Male gender, n (%)	14 (77)	29 (67)	2 (33)	2 (100)	45 (65)	0.18
Cardiovascular risk factors						
Hypertension, n (%)	13 (72)	20 (46)	2 (33)	1 (50)	36 (52)	0.16
Diabetes, n (%)	6 (33)	6 (14)	0	1 (50)	13 (19)	0.11
Dyslipidemia, n (%)	8 (44)	9 (21)	1 (17)	1 (50)	19 (27)	0.24
Obesity, n (%)	5 (28)	12 (28)	2 (33)	0	19 (27)	0.21
Former smoker, n (%)	6 (33)	5 (12)	1 (17)	0	12 (18)	0.089
Current smoker, n (%)	4 (22)	4 (9)	0	0	8 (12)	
Venous thrombotic risk factors						
Previous VTE, n (%)	0	1 (2)	1 (17)	0	2 (3)	0.28
Active cancer, n (%)	1 (5)	4 (9)	0	0	5 (7)	1
Chronic medical conditions						
Prior stroke, n (%)	1 (5)	3 (7)	1 (17)	0	5 (7)	0.79
Ischemic heart disease, n (%)	0	2 (5)	0	0	2 (3)	1
Chronic obstructive pulmonary disease, n (%)	3 (17)	7 (16)	0	0	20 (29)	0.82
Chronic kidney disease, n (%)	0	1 (2)	0	0	1 (1)	1
Chronic liver disease, n (%)	0	2 (5)	0	0	2 (3)	0.66
Autoimmune disease, n (%)	0	6 (14)	0	0	6 (9)	0.4
Baseline medications						
RAAS inhibitors, n (%)	12 (67)	13 (30)	3 (50)	1 (50)	29 (42)	0.06
Statins, n (%)	8 (44)	10 (23)	2 (33)	1 (50)	21 (30)	0.3
Metformin, n (%)	4 (22)	5 (12)	0	0	9 (13)	0.58
Hospitalization						
Initial COVID-19 symptoms to thrombotic event, days, median (IQR)	9.5 (1–16)	18 (12–24)	18.5 (10−33)	27.5 (24–31)	16 (10−23)	**0.022**
Thrombotic event diagnosis at the time of admission, n (%)	1 (5)	4 (9)	0	0	5 (7)	0.8
Laboratory tests						
Platelet count[a], cells $\times 10^3/mm^3$, median (IQR)	307 (213–390)	266 (190–370)	226 (210–397)	617 (570–664)	288 (203–390)	**0.006**
Peak D-dimer, μg/L, median (IQR)	4,780 (2830–35,000)	14,020 (5,540–35,200)	14,585 (5,540–22,460)	53,140 (21,280–85,000)	13,605 (4,700–35,200)	0.36
Fibrinogen[a], mg/dL, median (IQR)	500 (370–501)	375.8 (242–501)	449.5 (404–501)	398 (295–501)	430.5 (292–501)	0.51
ISTH DIC score[a], mean (SD)	1.83 (1.69)	1.87 (1.28)	1.33 (1.5)	1.5 (2.1)	1.8 (1.38)	0.84
Pre-event ISTH DIC score, mean (SD)	2.6 (1.5)	2.95 (0.73)	2.83 (0.41)	2.5 (0.71)	2.85 (0.94)	0.61
Creatinine[a], mg/dL, median (IQR)	0.98 (0.8–1.3)	0.87 (0.7–1.1)	0.91 (0.9–1)	0.52 (0.4–0.7)	0.9 (0.7–1.1)	0.19
Pre-event IL-6, pg/mL, median (IQR)	109 (30–274)	64 (7–123)	532 (64–1010)	159 (159–159)	67 (12–186)	0.32
Pre-event Ferritin, ng/mL, median (IQR)	536 (340–865)	671 (406–1,087)	1,272 (810–1,807)	846 (687–1,006)	682 (406–1,087)	0.7
Pre-event CRP, mg/L, median (IQR)	44 (11–97.3)	12 (2–58)	33 (14–45.1)	65 (24–105.9)	27 (4–71)	0.91
Treatment						
Pre-event LMWH prophylactic dose, n (%)	14 (77)	38 (88)	6 (100)	1 (50)	59 (86)	0.9
Pre-event LMWH therapeutic dose[b], n (%)	1 (5)	1 (2)	0 (0)	1 (50)	3 (4)	0.06
Hydroxychloroquine, n (%)	18 (100)	40 (93)	6 (100)	2 (100)	66 (96)	0.68
Azithromycin, n (%)	16 (89)	39 (91)	6 (100)	2 (100)	63 (91)	1
Tocilizumab, n (%)	6 (33)	22 (51)	4 (66)	2 (100)	34 (49)	0.21
Corticosteroids, n (%)	11 (61)	30 (70)	5 (83)	2 (100)	48 (70)	0.68
Outcome						
Oxygen therapy during admission, n (%)	18 (100)	42 (98)	6 (100)	2 (100)	68 (99)	0.11
Ventilatory support during admission, n (%)	6 (33)	9 (21)	2 (33)	1 (50)	18 (26)	0.73
ICU admission, n (%)	6 (33)	5 (12)	0	2 (100)	13 (19)	**0.006**
Death, n (%)	8 (44)	1 (2)	1 (17)	1 (50)	11 (13)	**< 0.001**

VTE: Venous thromboembolism. RAAS: Renin–Angiotensin–Aldosterone System. ISTH: International Society of Thrombosis and Haemostasis. DIC score: overt Disseminated Intravascular Coagulation score. IL-6: Interleukin 6. CRP: C reactive protein. LMWH: Low-molecular-weight heparin. ICU: Intensive care unit. IQR: Interquartile range. Bold figures: statistically significant differences.

[a] Initial laboratory investigation, on presentation.

[b] As per described protocol or due to a precedent chronic condition requiring anticoagulation.

3.4. Isolated arterial events

Eighteen patients experienced a total of 24 episodes. Median age was 71 years and 77% were men. Cardiovascular risk factors were prevalent (72% hypertension, 55% former or current smoking, 33% diabetes). Of note, arterial events were diagnosed earlier in the course of the disease (Table 2): median time from COVID-19 symptom onset to IS was 9 days (IQR: 2–17) and to ACS 11.5 days (IQR: 4–16).

Thirteen patients (median age 76 years, range 55–89) suffered an IS. Only one patient had a history of cerebrovascular disease and,

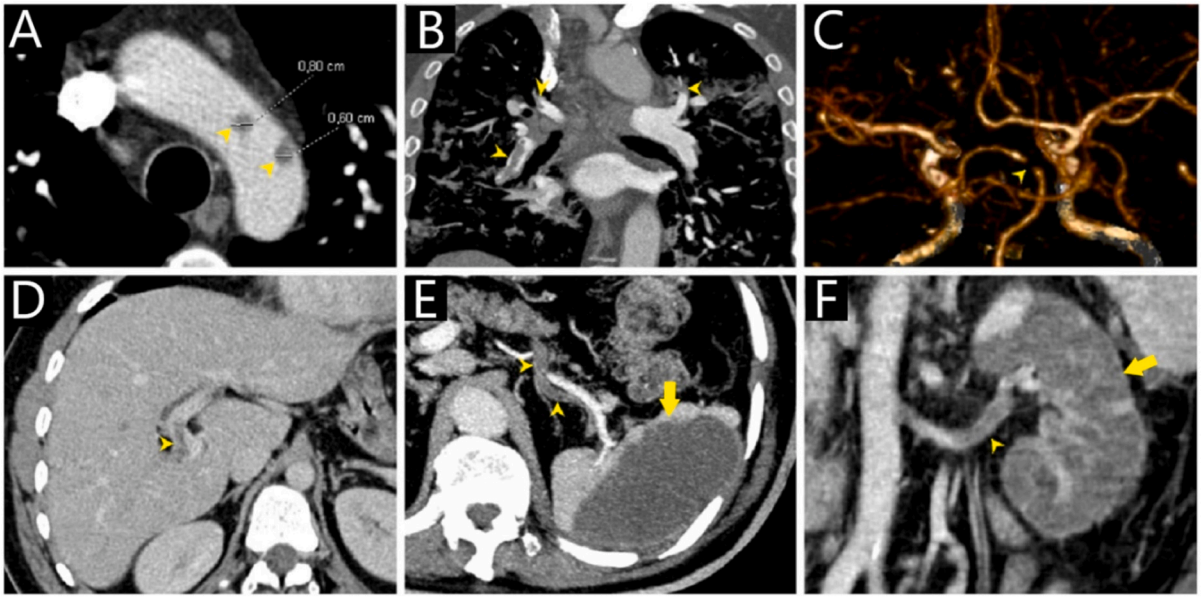

Fig. 2. Representative radiological images of the different thrombotic events.
A. Floating thrombi in the aortic arch. CT pulmonary angiography (CTPA) shows two round filling defects (arrowheads). B. Pulmonary embolism, CTPA, Coronal Multiplanar Reconstruction (MPR). Partial filling defects in the right interlobar/basal trunk, right superior lobar artery and left superior lobar artery (arrowheads). Peripheral bilateral consolidations caused by COVID-19 viral pneumonia. C. Basilar artery thrombosis. Circle of Willis CT angiography, Coronal Volume Rendering Technique (VRT). Non-visualization of the basilar artery (arrowhead) due to basilar artery occlusion. D. Portal vein non-occlusive thrombosis. Single-phase contrast enhanced abdominal CT. Partial filling defect in the posterior branch of the right portal vein (arrowhead). No hepatic infarction was demonstrated. E. Splenic artery thrombosis. Single-phase contrast-enhanced abdominal CT shows a large splenic infarction (arrow) secondary to a large filling defect in the splenic artery (arrowheads). F. Renal artery thrombosis. Single-phase contrast-enhanced abdominal CT, Coronal MPR. Subtotal infarction of the left kidney (arrow) caused by a large thrombus in the left renal artery (arrowhead).

interestingly, all of the events involved large arteries. Seven episodes affected carotid artery depending arteries, 5 vertebrobasilar, and 1 both areas. In 3 patients, 2 or more arterial territories were involved. Intra-arterial thrombus and/or large artery occlusion were observed in 4/6 patients who underwent CT angiography (Fig. 2C). Only one patient had a previously diagnosed atrial fibrillation, one had a symptomatic carotid artery stenosis and another was found to have floating thrombi in the aortic arch, suggesting embolism; in the remaining cases no stroke etiology was found.

Six patients developed an ACS, including 5 ST-elevation myocardial infarctions (MI). Median age was 72 years (range 48–81) and 5 were men. Only one had a prior history of ischemic heart disease. Three patients underwent coronary angiography, all showing multivessel disease.

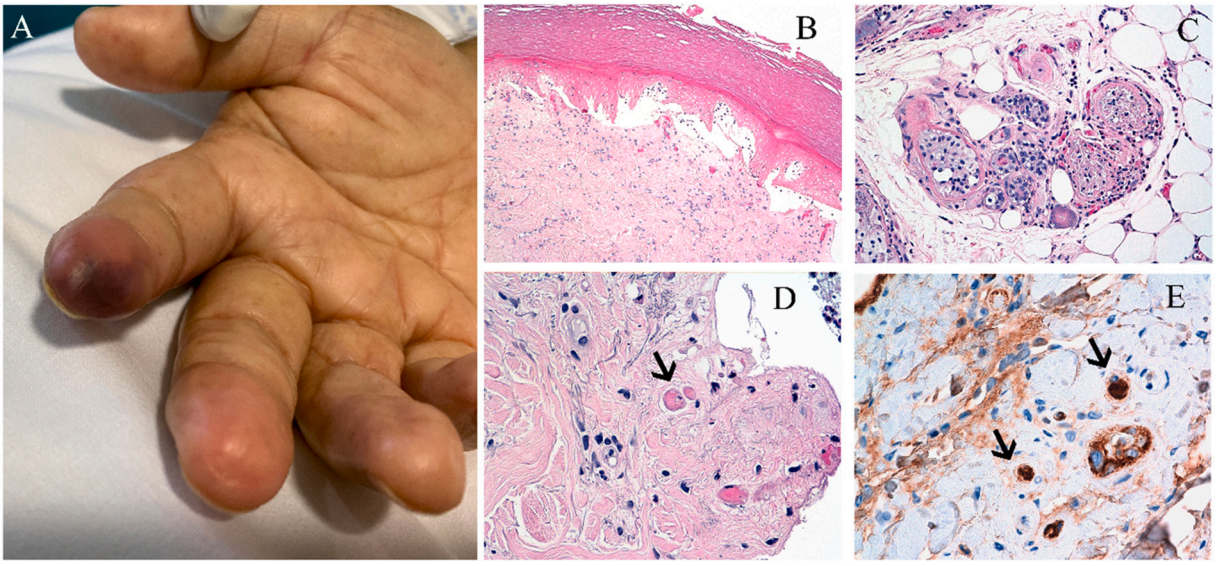

Fig. 3. Acro-ischemic lesions.
A. Acro-ischemic lesions located mainly in the distal side of the right index finger. The first, fourth and fifth fingers were also involved. B. Ischemic changes in acral skin with confluent epidermal necrosis, subepidermal edema, vascular ectasia, and no relevant dermis inflammation (H&E stain, 10×). C. Mild perieccrine inflammatory infiltrate and necrosis of the eccrine glands. (H&E stain, 20×). D. Focal thrombosis (arrow) in papillary dermis capillaries (H&E stain, 40×). E. The small thrombi (arrows) were highlighted by immunostaining to anti-von Willebrand's factor (anti F VIII stain, 40×). H&E: Hematoxylin and eosin.

Among 3 patients diagnosed with free-floating aortic thrombi (Fig. 2A), 2 had thrombi in the aortic arch (one suffering a subsequent IS and another a concurrent ACS) and the other patient had a mural thrombus in the middle segment of the descending thoracic aorta.

Two atypical arterial thrombotic events were diagnosed: a splenic artery thrombosis (Fig. 2E) and a renal artery thrombosis, causing the infarction of the left kidney (Fig. 2F).

One patient developed an acute peripheral artery occlusion in his right distal leg and another 2 acro-ischemia due to microvascular thrombosis in fingers and toes (Fig. 3). One of them suffered from chronic essential thrombocythemia and presented the event in the context of DIC. In both of them, necrotic manifestations appeared 1 month after initial symptoms.

3.5. Hemostatic parameters

Platelet count and fibrinogen levels were both elevated, similarly in all subgroups, on admission. Blood counts and clotting tests (including

Table 3
Comparison of survivors and non-survivors of COVID-19-associated thrombotic events.

Patient characteristics	Survivors ($n = 58$)	Non-survivors ($n = 11$)	Univariate analysis	Multivariate analysis	
			p value	OR (95% CI)	p value
Demographics					
Age, years, median (IQR)	64.5 (55–74.5)	71 (60–78)	0.22		
Ethnicity, n (%)					
Caucasian	45 (78)	9 (82)	0.8		
Hispanic	13 (22)	2 (18)	0.8		
Male gender, n (%)	37 (64)	8 (73)	0.73		
Cardiovascular risk factors					
Hypertension, n (%)	30 (52)	6 (55)	0.86		
Diabetes, n (%)	9 (16)	4 (36)	0.1		
Dyslipidemia, n (%)	14 (24)	4 (36)	0.65		
Obesity, n (%)	3 (5)	1 (9)	0.67		
Smoking, n (%)	9 (15)	2 (18)	0.18		
Venous thrombotic risk factors					
Previous VTE, n (%)	2 (3)	0	1		
Active cancer, n (%)	5 (9)	0	1		
Chronic medical conditions					
Prior stroke/transient ischemic attack, n (%)	4 (7)	1 (9)	0.19		
Ischemic heart disease, n (%)	7 (12)	1 (9)	0.4		
LVEF <40%, n (%)	0	0	–		
Chronic obstructive pulmonary disease, n (%)	10 (17)	0	0.34		
Chronic kidney disease, n (%)	1 (2)	0	1		
Baseline medications					
RAAS inhibitors, n (%)	23 (40)	6 (55)	0.5		
Statins, n (%)	16 (27)	5 (45)	0.12		
Hospitalization					
Initial COVID-19 symptoms to thrombotic event, days, median (IQR)	18.1 (11–24)	10.1 (1–14)	**0.02**		
Thrombotic event diagnosis at the time of admission, n (%)	4 (7)	1 (9)	0.19		
Laboratory tests					
Platelet count[a], cells $\times 10^3/mm^3$, median (IQR)	288 (204–377)	262 (203–407)	0.78		
Peak D-dimer, μg/L, median (IQR)	11,395 (4,640–28,740)	27,350 (7,610–60,190)	0.15		
ISTH DIC score[a], mean (SD)	1.66 (1.33)	2.56 (1.5)	**0.036**	6.96 (0.93–52.2)	0.0589
Pre-event ISTH DIC score, mean (SD)	2.79 (0.97)	3.25 (0.46)	0.06		
ISTH DIC score increment[b], mean (SD)	1.16 (1.26)	1.43 (1.51)	0.6		
Peak Troponin-T, ng/mL, median (IQR)	0.02 (0.016–2.35)	0.52 (0.03–2.39)	0.29		
Creatinine[a], mg/dL, median (IQR)	0.88 (0.7–1.1)	0.98 (0.6–1.3)	0.64		
Pre-event IL-6, pg/mL, median (IQR)	66 (115–172)	151 (64–274)	0.34		
Pre-event Ferritin, ng/mL, median (IQR)	677 (419–1,087)	687 (360–865)	0.84		
Pre-event CRP, mg/L, median (IQR)	29 (4–57)	49 (31–199)	**0.038**	4.78 (0.62–36.8)	0.132
Treatment					
Pre-event LMWH prophylactic dose, n (%)	53 (91)	8 (73)	0.08		
Pre-event LMWH therapeutic dose[c], n (%)	1 (2)	1 (9)	0.24		
Hydroxychloroquine, n (%)	57 (98)	10 (91)	1		
Azithromycin, n (%)	54 (93)	10 (91)	0.6		
Tocilizumab, n (%)	28 (48)	6 (55)	0.73		
Corticosteroids, n (%)	39 (67)	9 (82)	0.25		
Thrombotic event subtype					
Arterial, n (%)	11 (19)	8 (73)	**< 0.001**	**18.79** (2.48–142)	**0.0045**
Venous, n (%)	42 (72)	1 (9)			
Arterial and venous, n (%)	4 (7)	1 (9)			
Microvascular, n (%)	1 (2)	1 (9)			

VTE: Venous thromboembolism. LVEF: Left ventricular ejection fraction. RAAS: Renin–Angiotensin–Aldosterone System. ISTH: International Society of Thrombosis and Haemostasis. DIC score: overt Disseminated Intravascular Coagulation score. IL-6: Interleukin 6. CRP: C reactive protein. LMWH: Low-molecular-weight heparin. Bold figures: statistically significant differences.

[a] Initial laboratory investigation, on presentation.

[b] ISTH DIC score increment: Pre-event score minus initial score.

[c] As per described protocol or due to a precedent chronic condition requiring anticoagulation.

fibrinogen and D-dimer) were performed every 24–72 h in every patient. During hospitalization, thrombocytopenia was rarely seen and hypofibrinogenemia was sporadically detected in a minority of patients (<3%) in a delayed phase of the disease.

VTE patients showed a higher peak D-dimer (highest recorded D-dimer value during admission) than patients with isolated arterial episodes, with a median value around 14,200 μg/L (range 2020–85,000), but the difference did not reach significance. Mean ISTH DIC score at presentation was 1.8 (±1.38) and no patients had DIC. When considering pre-event ISTH score (on the day before or the day of the thrombotic event diagnosis), the mean value was 2.85 (±0.94), 3 patients reached 4 points and only 2 fulfilled DIC criteria (3%). Neither initial nor pre-event score, or the variation between the two, differed significantly among thrombotic subgroups.

3.6. Survivors vs non-survivors

A full description of thrombotic events and outcome is available in supplementary Appendix Table 1. Thirteen patients (19%) were admitted to the ICU during hospitalization. As of June 15, 53 patients had been discharged (77%) and 11 had died (16%). Median follow-up at the time of analysis was 14 days (IQR 4–27). COVID-19 treatments were similar among subgroups. Up to 70% of the patients received corticosteroids, 50% tocilizumab and none hyperimmune plasma.

In the subgroup of patients with isolated VTE, only one patient died (2%). On the contrary, patients who suffered an arterial event or microvascular ischemia had a significantly higher rate of ICU admission and mortality. Six out of 13 stroke patients died (46%), and 3 developed severe neurological sequelae. Regarding ACS cases, 3 patients suffered related complications, including a patient who died of cardiac rupture soon after admission.

Potential differences between survivors and non-survivors are detailed in Table 3.

No dissimilarities were found regarding age, gender, ethnicity, comorbidities or COVID-19 treatments. Interestingly, non-survivors were diagnosed with the thrombotic event earlier in the course of the disease (10.1 vs 18.1 days from symptom onset; $p = .02$). Univariate analysis revealed arterial thrombotic event, initial ISTH DIC score and pre-event CRP as factors potentially associated with mortality. Peak D-dimer was higher among non-survivors, but not reaching significance. Multivariate analysis including initial DIC score, pre-event CRP, peak D-dimer and thrombotic event subtype (arterial vs others), only confirmed arterial thrombosis as a statistically significant prognostic factor: OR for mortality 18 (95% CI: 2.4–142, $p < .005$). DIC score and CRP levels offered interesting results. Patients with an initial ISTH DIC score ≥ 3 showed a 7-fold greater odds for death (95% CI: 0.93–52.2, $p = .058$), and a cut-off point for pre-event CRP of 150 mg/L had an OR for mortality of 4.8 (95% CI: 0.6–36.8, $p = .13$). Area under the curve for the model 0.88.

3.7. Thromboprophylactic protocols

The degree of compliance with the 2 different protocols in the general COVID-19 cohort was 92.5% from March 3 to April 8 and 97.9% from April 9 onwards (when the LMWH-dose escalation protocol was implemented).

Regarding the study group, only 7 patients (10%) were diagnosed with the thrombotic event at the time of admission, so they had received no prophylaxis (4 PE cases and 3 strokes). We confirmed through the Pharmacy registry that the remaining 90% suffered the complication despite being on prophylactic enoxaparin as per protocol (27/69 or 39% were under escalated thromboprophylaxis dosing according to their body weight and renal function) or even on therapeutic LMWH dose (3 patients, 4%). Review of clinical notes ratified that 91.8% and 87.5% of the patients diagnosed with VTE or with an arterial event were under LMWH treatment at the time of diagnosis, respectively (Table 2, supplementary Appendix Table 1). Regarding antiplatelet therapy, 6% of the patients in the VTE group and 20% of those in the arterial event group were on medication at event diagnosis. Therefore we found no differences among thrombotic subgroups.

Although not being the scope of the study, we tried to investigate how the implementation of the escalating-dose protocol could have influenced the rate of thrombotic events or mortality in the entire cohort, using data from the authorized Hospital database and the Pharmacy registry. Out of the 80 different thrombotic episodes described in this manuscript, 69% were diagnosed before April 9. The obvious variation of important factors such as the number of admissions per day, practical constraints, diagnostic awareness, underdiagnosis, accumulated experience, etc. during different phases of the ourbreak, and dynamic changes of prophylactic doses for many patients depending on the clinical situation, discouraged us to compare obtained incidences of thrombosis or death rates as they were surely biased.

During the study period, only 10 significant hemorrhagic events were registered in medical records of the general cohort. Six were considered minor (ecchymosis, epistaxis, peri-tracheostomy bleeding) and 4 mayor (a hemorrhagic stroke, 2 low gastrointestinal bleeding and an episode of hematuria). Only one of the patients who suffered a thrombotic event had a relevant bleeding complication while on treatment (a hemorrhagic transformation of an IS).

4. Discussion

4.1. Thrombotic events

The incidence of thrombotic events in our large COVID-19 cohort, in patients mainly admitted to general wards, was 6.1% despite quasi-universal thromboprophylaxis and 2/3 of the episodes were venous. An Italian single-center study including 388 patients reported a similar incidence of 7.7% [36], mostly VTE.

The incidence of VTE in our study (4.6%; PE 3.9%, DVT 0.5%) was lower than in other series, with reported rates of up to 30% [31,54,55]. A Dutch study involving 200 patients (DVT screening performed in 28%), reported a 20% incidence of VTE (PE 6.6%; DVT 13.2%) despite routine LMWH prophylaxis [32]. This difference is likely explained by several factors. First, PE was likely underdiagnosed in our cohort during the initial phase of the outbreak due to the exponential growth of cases, unforeseen high risk until evidence emerged and practical limitations. Secondly, most of our events were diagnosed in a general ward, where incidence is undoubtedly lower than in the ICU. Lastly, the very high compliance with the recommended LMWH protocol and escalating doses might have been effective in reducing events, and in our ICU VTE screening was low due to early initiation of reduced-empirical anticoagulation in many patients.

Isolated arterial events were rare (in accordance with a previous study including 1400 patients from Madrid [56]), but they were diagnosed earlier in the course of the disease and were clinically very relevant. The incidence of IS was 1,1%, also similar to other series [57], mainly affecting large arteries. We reviewed the incidence of IS and ACS during the same 2-month period for the previous 4 years. There was an age-adjusted 6-fold higher incidence of in-hospital IS during the COVID-19 outbreak, but fewer ACS cases than in previous years. A similar discrepancy has been reported [36,58]. Although IS and ACS share risk factors and pathophysiology, hypercoagulability has been linked to a higher risk of IS rather than MI [59,60]. We might have underdiagnosed coronary events though, as an electrocardiogram was performed on admission but only repeated if there were clinical signs of ACS or arrythmia. Reported incidence of ACS in other series has been higher [61].

We found a non-negligible number of concomitant arterial and venous events compared to other studies [36,56]. Scarce reports have described concurrent events [39,62,63], mostly IS and PE, in the absence of classical associated conditions. This probably translates

microthrombi formation not only in the pulmonary microcirculation, but also in cerebral vessels, possibly facilitated by SARS-CoV-2 neurotropism.

Surprisingly, isolated VTE-diagnosed patients showed a very low mortality rate, probably because most of PE cases were peripheral due to microthrombosis in situ. Thrombotic event diagnosis was not associated with increased mortality in the general cohort, in contrast to other similar series [61], but in the thrombotic study group suffering an arterial event conferred an 18-times higher risk of death compared to VTE.

Non-survivors were diagnosed with thrombosis earlier in the course of the illness, possibly reflecting a more rapidly-progressing systemic disease, or perhaps influenced by the fact that the type of event (arterial in most non-survivors) was clinically more patent than venous episodes.

4.2. Mechanisms of thrombosis in COVID-19

An acquired syndrome known as COVID-19-associated coagulopathy has emerged and appears to follow Virchow's Triad [64]. It represents an example of the close interconnection between the immune and coagulation systems [65,66]. Reported underlying mechanisms include a variety of well-established VTE risk factors [9,67], including immobility and severe hypoxemia. However, the high number of episodes, concurrent arteriovenous complications, atypical thrombosis including aortic thrombi or portal thrombosis [62,68,69], as in our cohort, clearly suggest that the prothrombotic state is more intense than in other acute and viral illnesses. It is very difficult to define the primary physiopathological event initiating this prothrombotic phase of the disease [66,70]. Endothelitis might be the key triggering factor [71–74], but cytokine-mediated activation of platelets and of the coagulation cascade, decrease of natural anticoagulants or humoral immune-mediated factors such as lupus anticoagulant, might play partial roles.

Hemostatic abnormalities and increased D-dimer have been associated with poor prognosis. Accordingly, we found higher peak D-dimer levels among non-survivors even comparing a subgroup of patients with thrombosis, but without meaning significance. A very small proportion of patients fulfilled ISTH DIC criteria. However, mean initial ISTH score was higher among non-survivors. Multivariate analysis showed that using a cut-off value of ≥ 3, patients were 7 times more likely to die. Moreover, median pre-event CRP was also higher among non-survivors. Therapies targeting the cytokine storm might probably reduce the severity of coagulopathy [64].

4.3. Thromboprophylaxis

The best thromboprophylactic approach is still unclear [75], evidence is lacking and international guidelines still recommend standard prophylactic dose [76]. In our study 90% of the patients suffered the thrombotic episode despite prophylaxis (39% even being on higher-than-standard dose) and the remaining 10% at presentation. From our accumulated experience during the outbreak, we truly believed that higher LMWH doses were required to treat the likely influence of pulmonary microthrombosis on severe hypoxemia and to prevent thrombotic events.

A recently published retrospective study from New York of over 3300 patients reported an incidence of 16% and 11,5% of any thrombotic event in the general cohort and in the non-ICU cohort, respectively. Screening was not standard, similar to our approach, but low-dose-standard-thromboprophylaxis was used [61]. In our study, incidence was clearly lower, but we were only able to obtain indirect data suggesting a beneficial effect of a higher LMWH dose in reducing events and other factors likely played a role.

Our study has several limitations. Its retrospective nature, coming from a single-center cohort, and the changing practicing conditions during different phases of the outbreak, that influenced the diagnostic, prophylactic and therapeutic protocols. VTE incidence was probably underestimated as DVT screening was limited to PE diagnosed cases or patients with clinical signs of DVT, PE risk was initially unrecognized, and there was no active search in the ICU due to escalated-thromboprophylaxis and procedural constraints. We were unable to properly analyze the potential effect of LMWH dosing on thrombosis incidence and mortality. After implementing the new protocol, dose was variable in some patients depending on the clinical situation and there were too many potential confounders (fewer admissions/day, higher steroid use, optimized ventilator-support circuit, accumulated experience, etc.) that could affect outcomes and for which we could not adjust.

5. Conclusions

We demonstrated the occurrence of typical and atypical arterial and venous thrombotic events, despite quasi-universal optimized or even escalated thromboprophylaxis, in a large cohort of COVID-19 patients. Arterials events tend to appear early in the course of the illness and they confer poor prognosis. Even in patients with proven thrombotic events, DIC is not common, but an ISTH DIC score ≥ 3 at presentation was identified as a potential predictor of mortality. Levels of CRP and D-dimer, reflecting the hyperinflammatory and thrombogenic phases of the disease, were higher among non-survivors. A high-dose thromboprophylactic protocol seemed to reduce the rate of thrombotic events and might have played a role in lowering mortality among other factors, with a low incidence of hemorrhagic complications. Therefore, patients with severe COVID-19 may benefit from severity-adjusted thromboprophylaxis and multicenter randomized controlled trials are eagerly awaited (NCT04372589, NCT04367831, NCT04345848, and NCT04366960).

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Authorship details

N. M-R, A. A-M and J. Ch were responsible for the study design, collected data and wrote the manuscript. B. M-G, F. S—H, C. C—C, R. ML-R, P. A-G, A. F-M, E. M-G, C. M-F, S. A-G, J. R, T. S—V, A. S—D, P. R, E. M-M and J.A. M-N participated in data collection and figure/table design. J.A. H-R, J. T-M, J. R, F. S—H, C. C—C and B. M-G reviewed the paper. All authors have read and approved the manuscript for submission.

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Declaration of competing interest

The authors declare they have no conflict of interest.

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