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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Acute arterial and deep venous thromboembolism in COVID-19 patients: Risk factors and personalized therapy

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ABSTRACT

Background: The Lombardy region suffered severely during the acute phase of the coronavirus disease 2019 outbreak in Italy (Mar–Apr 2020) with 16,000 diagnosed coronavirus disease 2019–related deaths (49% of the total coronavirus disease 2019–related deaths in Italy). In the area surrounding Pavia during the critical stage of the outbreak (Mar–Apr 2020), 1,225 of the documented 4,200 deaths were related to coronavirus disease 2019 infection, with a mortality rate of 181/100,000 inhabitants and an increase in deaths of 138% compared with the same period during previous years. Our aim was to report the experience of the Department of Vascular Surgery of Pavia (Lombardy, Italy), including the lessons learned and future perspectives regarding the management of coronavirus disease 2019 patients who developed severe acute ischemia with impending lower limb loss or deep vein thrombosis.

Materials and Methods: We carried out a retrospective data collection of coronavirus disease 2019 patients with severe acute ischemia of the lower limbs or deep vein thrombosis, which we observed in our department during the period March 1, 2020, to April 30, 2020. Primary outcomes of the analysis were postoperative mortality for all patients and amputation rates only in those coronavirus disease 2019 patients suffering from acute lower limb ischemia. Secondary outcomes were the prevalence of the disease among admitted coronavirus disease 2019 patients, and any possible correlation among inflammatory parameters, thrombolytic status, and the presence of acute ischemia or deep vein thrombosis.

Results: We observed 38 patients (28 male) with severe coronavirus disease 2019 infection (6 with lower limb arterial thrombosis and 32 with deep vein thrombosis). The median patient age was 64 years (range 30–94 y). In the arterial group, 3 had thrombosis on plaque and 3 on healthy arteries ("simple" arterial thrombosis). All underwent operative or hybrid (open/endo) revascularization; 1 patient died from major organ failure and 1 patient underwent major amputation. In the deep vein thrombosis group, 9 (28%) patients died from major organ failure, despite aggressive medical therapy. In patients with simple arterial thrombosis and those with deep vein thrombosis, we observed a decrease in inflammatory parameters (C-reactive protein) and in D-dimer and fibrinogen after aggressive therapy ($P < .001$).

Conclusion: Our study confirms that critically ill, coronavirus disease 2019 patients who develop arterial and deep vein thrombosis have a high risk of mortality, but, if treated properly, there is an improvement in overall survival, especially in patients of 60 years of age or younger.

Introduction

As of July 9, 2020, more than 34,000 deaths from coronavirus disease 2019 (COVID-19) were identified in Italy. The critical phase

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of the outbreak seemed to be in Italy, as well as in other European countries (eg, Spain and England). The Lombardy region suffered severely during the acute phase of the outbreak (Mar–Apr 2020), with 16,000 diagnosed COVID-19–related deaths (49% of all COVID-19–related deaths in Italy). During the acute phase of the outbreak (Mar–Apr), in the area surrounding Pavia, 1,225 of the documented 4,200 deaths were related to COVID-19 infection, with a mortality rate of 181/100,000 inhabitants and an increase in deaths of 138% in comparison with the same period during previous years[1] The mean age of patients dying from the disease was 81 y, and 70% were older than 75 y. The median age of the patients who died was 20 years older than the median age of infected patients (61 y). Mortality was greater in patients with associated cardiac morbidities (arterial hypertension in 66% of patients who died, coronary artery disease in 28%, atrial fibrillation in 23%, and congestive heart failure in 16%), renal failure (20% of patients), and cancer (16% of patients). The mortality rate increased from 14% in patients with only 1 comorbidity to 61% in patients with 3 or more comorbidities.[1] In the elderly population, the simultaneous occurrence of the COVID-19 infection and the presence of diffuse atherosclerotic disease were of course a common clinical scenario, specifically in the Lombardy region, where the outbreak was severe and overwhelming and a high proportion of the population is elderly.[2,3] Since the end of May 2020, there has been a steady and marked decrease in rates of infection and mortality in Pavia and in Italy as a whole.

The high mortality rate in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can also be attributed to the non-respiratory complications of COVID-19, although the mechanism by which the virus migrates to these other locations remains poorly understood. Furthermore, COVID-19 predisposes patients to both venous and arterial thromboembolic disease because of high-grade inflammation, hypoxia, immobilization, and diffuse intravascular coagulation, but direct damage to the endothelium by the virus has not yet been demonstrated.[4]

The aim of our analysis was to report our experience in the Department of Vascular Surgery of Pavia (Lombardy, Italy), focusing on the lessons learned and future perspectives regarding the management of COVID-19 patients who developed severe acute ischemia with impending lower limb loss or deep vein thrombosis (DVT).

Material and Methods

A general lockdown with strict social isolation rules for the general population and health care workers was established in Italy in March 2020, when the high spread/contagiousness and virulence of the virus became apparent. Unfortunately, the dangerous characteristics of the virus were immediately evident attributable to not only the high number of admissions of infected patients in poor general condition but also to an unexpectedly inadequate health care system overwhelmed with COVID-19 cases. This pandemic exposed the poor capacity with respect to hospital and intensive care unit beds and to workforces worldwide, not only in Italy. After initial organizational problems, hospitals were divided into sections devoted to COVID-19 patients only. Admissions to hospitals were decreased, thereby precluding non-urgent conditions and deferrable elective operations.[5-7] Our activity as vascular surgeons had been reduced dramatically, and we were required to perform other duties in the pneumology departments and emergency departments for COVID-19–positive patients, in addition to our consultancy activities. Table I presents the number of vascular procedures performed in our department during the lockdown period in comparison with the year 2019. Only those emergency procedures which could not be deferred and could not be transported to another COVID-free hospital were performed.

Table I
Operative vascular procedures at the Vascular Surgery Department of Fondazione IRCCS Policlinico San Matteo of Pavia, Italy, during phase 1 of the COVID versus the same period of 2019

	March 1–April 30, 2020		March 1–April 30, 2019	
	Emergency	Elective	Emergency	Elective
AAA				
EVAR	2	0	4	12
Open	0	0	5	18
Carotid				
CAS	0	0	0	3
CEA	0	0	5	27
PAD				
PTA/Stent	9	0	8	18
Open	6	0	6	12
Acute thrombosis	6	0	8	0
Amputation	4	0	3	9

AAA, abdominal aortic aneurysm; *EVAR*, endovascular aortic repair; *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *PAD*, peripheral arterial disease; *PTA*, percutaneous transluminal angioplasty.

We carried out a retrospective data collection of COVID-19 patients with severe acute ischemia of the lower limbs or DVT observed at the Vascular Surgery Unit of the Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, during the period of March 1, 2020, to April 30, 2020. All patients gave written consent. The study was approved by the local ethical committee. Primary outcomes of the analysis were postoperative mortality and amputation rate only in those COVID-19 patients suffering from acute lower limb ischemia. Secondary outcomes were the prevalence of the disease among admitted COVID-19 patients, and any possible correlation between inflammatory parameters, thrombolytic status, and the presence of acute ischemia or DVT.

Statistical analysis

We used the Statistical Package for Social Sciences software version 14.0 (SPSS Inc, Chicago, IL, USA) for Windows to prepare the database and to perform descriptive analysis. The results are presented in Tables. Categorical variables are expressed as frequencies and percentages. Continuous variables with normal distribution are expressed as mean and standard deviation, and those with non-normal distribution as median and interquartile range. The Student's *t*-test and the χ^2 test were used when appropriate.

Results

Arterial occlusion related to COVID-19 infection

Admitted to our department were 6 patients (4 male, 2 female) with acute ischemia of the lower limbs. The median age was 71 years (range 49–83 y). In all 6 patients, the limb was at risk, and the only alternative was a major amputation. Cases 1, 2, and 5 (3 patients) reported previous symptoms of claudication and computed tomography-angiography posed the diagnosis of acute "superimposed" thrombosis over atherosclerotic occlusive disease. The remaining 3 patients (cases 3, 4, and 6) had no clinical evidence of chronic, obstructive, lower limb disease. The occlusion was related to acute "simple" thrombosis of the aortoiliac system with distal embolization and confirmed by computed tomography-angiography.

Table II
COVID19 patients who had emergency surgery for acute thrombosis of lower limb arteries

Surgery	Age/sex	Comorbidities	Oxygen therapy	CRP (mg/dL)	Discharge conditions
			Survival with arterial patency		
1—Embolectomy iliac-femoral-popliteal + iliac stenting	81/F	3	Y/high flow	1.3 (A) 0.3 (B) 0.3 (C)	Arterial patency improved general conditions
2—Embolectomy iliac-femoral-popliteal + popliteal PTA	82/M	4	Y/high flow	2.6 (A) 0.6 (B) 0.5 (C)	Arterial patency improved general conditions
3—Embolectomy iliac-femoral-popliteal	83/F	3	Y/high flow	1.5 (A) 5.4 (B) 1.0 (C)	Arterial patency improved general conditions
4—Embolectomy iliac-femoral-popliteal	49/M	3	Invasive mechanical ventilation	20 (A) 11 (B) 9 (C)	Arterial patency improved general conditions
			Survival with arterial re-thrombosis		
5—Embolectomy iliac-femoral-popliteal + popliteal PTA	67/M	3	Noninvasive mechanical ventilation	12 (A) 5.6 (B) 10 (C)	Re-thrombosis 5 days after initial successful surgery. New embolectomy. Amputation. Improved general conditions
			No survival		
6—Embolectomy iliac-femoral-popliteal	62/M	3	Invasive mechanical ventilation	8 (A) 24 (B) 28 (C)	Re-thrombosis 1 day after initial successful surgery. Died 30 days later (MOF).

(A) Denotes the day after surgery. (B) Denotes the day before surgery. (C) Denotes 2–3 days after surgery.
CRP, C-reactive protein; *MOF*, multiple organ failure; *PTA*, percutaneous transluminal angioplasty.

All patients tested positive for COVID-19 and all had general clinical symptoms, including fever and dyspnea at rest.

All 6 patients underwent urgent revascularization (embolectomy in 3 cases and hybrid open/endo procedures in the others). Postoperatively, all patients started heparin therapy with enoxaparin 0.5 mg/kg twice daily with the first dose given 6 h postoperatively and combined with acetylsalicylic acid 75 mg in the case of embolectomy or acetylsalicylic acid plus clopidogrel 75 mg in the case of simultaneous angioplasty.

In the group of 3 patients with occlusion from "superimposed" arterial thrombosis, 1 patient suffered from early thrombosis postoperatively, noted on day 2, and eventually required above-the-knee amputation. The mean hospital stay was 9 days, and all patients left the hospital in generally good clinical conditions. In the 3 patients with occlusion from "simple" arterial thrombosis, the superficial femoral artery was involved to the common iliac artery; clinical and diagnostic studies supported the hypothesis of an acute "simple" parietal aortoiliac thrombosis with distal embolization. In this group, proximal and distal embolectomy was performed through the femoral artery with initial success. One patient entered the hospital with critical hemodynamic conditions and disseminated intravascular coagulation and required immediate mechanical ventilation (pH = 7.437, lactate = 5.5 mmol/L, sO_2 = 76.4%, PO_2 = 44.8 mmHg, pCO_2 = 24.7 mmHg, calculate pO_2/FiO_2 ratio = 44.8 mmHg). A new femoral embolectomy was required from re-occlusion one day postoperatively. Unfortunately, this patient died a month later from multiple organ failure (MOF). The remaining 2 patients left the hospital in generally good condition. Laboratory parameters varied considerably among patients. Patients with "simple" arterial thrombosis tended to have more increased levels of serum D-Dimer, C-reactive protein (CRP), and a decreased platelet count as compared with patients with "superimposed arterial thrombosis." In the 2 patients with early re-occlusion (1 with simple thrombosis and the other with superimposed thrombosis), these parameters were more altered in comparison with the other 2 patients in each group who had eventual successful arterial revascularization (Table II).

DVT related to COVID-19 infection

The number of requests for in-hospital consultation for patients with DVT increased by more than 100% in comparison with previous years. During this period, 32 hospitalized patients, all of whom were in critical condition (24 male, 8 female) with severe COVID-19 infection (fever, pulmonary complications requiring assisted ventilation), were diagnosed with DVT at a mean of 393 hours after admission on the basis of clinical evidence (edema) confirmed by non-invasive tests and had been evaluated prospectively. The median age was 63 years (range 30–94 y). Of the 32 patients, 9 (28%) died from MOF despite aggressive medical therapy with high doses of selective and non-selective anti-inflammatory agents, full anticoagulation, and antibiotic therapy; 23 patients survived and left the hospital in generally good condition, and, at 1-month follow-up, none of these patients complained of major symptoms..

Treatment of these patients on admission included aggressive supportive management of acute hypoxic respiratory failure and of hemodynamic instability, use of antibiotic therapy, and the correction of the fluid-electrolyte and metabolic unbalances. All patients received prophylaxis with low molecular weight heparin (LMWH) and anti-inflammatory therapy. At the time of diagnosis of DVT, patients began full anticoagulation, and the dosage of anti-inflammatory therapy was increased. Table III presents the laboratory parameters at admission and at diagnosis. In all patients, there were alterations in hemostatic and inflammatory parameters at hospitalization, and, on univariate analysis, advanced age (70 years or older) and associated specific comorbidities (coronary artery disease, diabetes, renal failure) as well as high levels of D-dimers (15,000 or more), fibrinogen, lactate dehydrogenase, and creatine kinase were statistically significant risk factors for mortality ($P < .0001$). Such an aggressive approach to therapy allowed for a 72% survival, involving these patients in critical clinical condition and with high risk parameters. Moreover, we observed that a lack of increase in several laboratory parameters, including CRP values subsequent to initial treatment, levels of D-dimers, and fibrinogen, after full anticoagulation and aggressive anti-inflammatory therapy, represented a good prognostic factor ($P < .001$). The persistence of high systemic

Table III
Mortality in hospitalized COVID19 patients with deep vein thrombosis

	Mortality (9 patients)	No mortality (23 patients)	
Sex (M/F)	8/1	16/7	
Age, y (mean; range)	71.2 (62–83)	58.8 (30–94)	$P < .05$
Comorbidities (mean)	4 (3–5)	3 (2–4)	
Oxygen therapy			
High flow	-	4	
Noninvasive mechanical ventilation	4	7	
Invasive mechanical ventilation	5	12	
Localization thrombosis			
Lower limb proximal	5	7	
Lower limb distal	2	10	
Upper limb	2	6	
Evidence pulmonary embolism	4	4	
Padua score (mean; range)	3.6 (3–4)	3.2 (3–4)	
Platelet (mean: range)			
At admission	222 (154–289)	255 (63–526)	
At diagnosis	272 (112–669)	242 (139–324)	
Fibrinogen			
At admission	599 (367–700)	450 (219–775)	$P < .05$
At diagnosis	418 (122–657)	397 (172–717)	
PT			
At admission	72.2 (51–83)	74.8 (49–93)	
At diagnosis	57.6 (37–74)	75.7 (36–118)	$P < .05$
aPTT	25 (20–34)	25 (20–43)	
D-dimers			
At admission	13,875 (1712–35,000)	6,682 (488–35,000)	$P < .001$
At diagnosis	25,270 (10,800–35,000)	14,430 (985–35,000)	$P < .001$
LDH	482 (276–778)	437 (250–876)	
Creatine kinase	362 (15–2264) (100)	124 (15–842) (78)	
CRP			
At admission	15.9 (7.3–27.0)	20.2 (5.4–37.4)	
At diagnosis	26.3 (1.4–100)	16.7 (0.1–33.6)	$P < .05$
WBC			
At admission	8.9 (6.0–14.7)	10.9 (2.1–29.0)	
At diagnosis	10.4 (1.4–21.3)	10.6 (3.7–18)	

Laboratory values refer to the time of diagnosis unless otherwise specified.
CRP, C-reactive protein (mg/dL) platelet ($\times 10^3$/ mcL); *PT*, prothrombin time (%); *aPTT*, activate thromboplastin time (%); *D-Dimers* (mcg/L); *LDH*, lactate dehydrogenase (mU/mL); *creatine kinase* (mU/mL); *WBC*, white blood count.

levels of CRP and of altered laboratory parameters—despite full anticoagulation and increased dosage anti-inflammatory therapy—was associated with increased mortality rates and was more evident in patients aged 70 years or older with associated diabetes and/or renal failure, who might have had impaired immunologic defenses. Conversely, decreased systemic levels of CRP after therapy for the DVT increased the possibilities for survival and preceded normalization of hemostatic parameters.

Discussion

COVID-19 can lead to acute respiratory disease syndrome, multiorgan involvement, and shock.[8-10] The review of clinical, laboratory, and imaging findings demonstrated an increased risk of thrombotic events in COVID-19 patients.[11] The precise incidence of thrombosis in these patients has not been determined. In a retrospective study of 138 patients, of whom 16.7% of were in a critical condition, 17.3% of these patients were diagnosed with DVT at 3 to 18 days after admission despite the use of guideline-recommended thromboprophylaxis.[12] The prevalence of DVT has been demonstrated to vary 16%–49% in patients with COVID-19 admitted to intensive care, and 40% in autopsy studies.[10,13,14]

Arterial thrombosis has also been reported, and, since the beginning of the pandemic, there have been reports of cases of ischemia (ischemic stroke, myocardial infarction, or systemic arterial embolism). Arterial thrombosis accounts for about 4% of thromboembolic complications during COVID-19.[15]

COVID-19 patients with severe clinical conditions present characteristics of a systemic inflammatory condition associated with hemostatic abnormalities. There is now evidence that some patients respond to COVID-19 with a “cytokine storm” responsible for a hypercoagulability state.[8,9] COVID-19 hospitalized patients displayed hypercoagulability via 3 possible mechanisms: (1) the formation of pro-inflammatory cytokines, which are mediators of atherosclerosis, contributing directly to the rupture of the atherosclerotic plaque by local inflammation, (2) the induction of procoagulant factors, and (3) hemodynamic changes that predispose to ischemia and thrombosis[4]; these thrombotic events contribute to the severity of infections, creating a vicious circle. There is no readily available evidence on any potential therapy or prophylaxis that may provide clinical benefits in patients with severe COVID-19 infections as defined by marked tachypnea with respiratory rate $\geq$30 breaths per minute, hypoxemia with oxygen saturation $\leq$93%, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300, and lung infiltrates >50% of the lung field involved within 24 to 48 h).[16] Moreover, clinical trials have not confirmed a clear efficacy of antimalarial (hydroxychloroquine or chloroquine) with or without azithromycin and anti-retroviral drugs (lopinavir/ritonavir/remdesivir). Currently, several immunomodulating therapies, including glucocorticoids, convalescent plasma, and anti-cytokine therapy, are being investigated.[17,18] LMWH is recommended for all hospitalized patients, unless there are contraindications.[19–22]

In our experience with COVID-19 critically ill patients with acute arterial and DVT, we observed systemic abnormalities in

hemostatic and inflammatory parameters. An aggressive medical and surgical therapeutic approach with anticoagulation, anti-inflammatory agents (selective and non-selective), and antibiotic therapy resulted in a survival of 74% (28/38) in these very critical conditions.[14,19,23,24] In this specific clinical setting, our analysis of the initial abnormalities in hemostatic and inflammatory parameters, demonstrated that these abnormities appeared to be similar in both patients who survived and in those who did not. Even patients with markedly altered parameters recovered after aggressive medical or surgical treatment. Despite the small number of patients in the arterial group of our study, it appears that surgical revascularization in this clinical setting is beneficial for several reasons: 4 of the 6 patients had their legs saved and survived the severe COVID-19 infection. Moreover, in these 4 patients we found a decrease in CRP levels, improved platelet counts, and decreased levels of D-dimers. These data support the possibility that early distal revascularization might reduce the inflammatory storm. The improvement of these parameters was not observed in the 2 patients who suffered from early re-thrombosis postoperatively. We believe that early interventions aimed at decreasing the systemic inflammation may help to prevent thrombosis and its complications. Moreover, although specific or broad-spectrum anti-inflammatory drugs, such as aspirin, decrease the inflammatory condition, their use has been the source of a number of debates. In severe COVID-19 infection a low platelet count is often evident. In the 3 patients with acute "simple" thrombosis, despite 2 patients having a normal platelet count, distal embolization suggests an abnormality in platelet function and adhesion. Conceptually, selective inflammatory inhibitors may prevent the complications related to the simultaneous platelet inhibition; however, in the unregulated and overwhelming inflammatory storm associated with severe COVID-19 infection, alternative activation of other pro-inflammatory cytokines is highly probable.[25,26] These possibilities support the use of anti-inflammatory inhibitors, either selective or non-selective, according to the specific stage and level of the infection.

We observed the same phenomenon in patients affected by DVT in whom early thromboprophylaxis and anti-inflammatory therapy had been established. In particular, in relation to the known high incidence of DVT (25–31%) despite adequate prophylaxis,[27] we preferred to use an escalated dose of LMWH with enoxaparin 0.5 mg/kg twice daily, especially in patients with high levels of D-dimers or fibrinogen being treated in the intensive care unit. We reserved unfractionated heparin for patients who developed severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2). Patients with atrial fibrillation or mechanical cardiac valves continued their full-dose anticoagulation. Furthermore, we extended prophylactic anticoagulation for a duration of 30 days after discharge. Alternatively, those who were low risk could receive only low-dose aspirin prophylaxis (aspirin 81 mg twice daily) for no less than 4 weeks duration after discharge.[28]

Finally, there are little data available on the use of recombinant tissue plasminogen activator in severely hypoxemic patients who do not respond to therapeutic dose anticoagulation or in the case of arterial thrombosis.[29]

In conclusion, we observed that the most important prognostic factor in this specific group of patients was the response to therapy. Improvements in inflammatory and hemostatic parameters soon after the initiation of therapy were correlated to a greater probability for survival. Acute arterial and DVT may worsen the inflammatory condition with endothelial damage. Resolution of the acute thrombosis may overcome the vicious circle of inflammation and -coagulopathy. The results of our study support the use of high doses of anti-inflammatory agents from the initial phase of severe COVID-19 infection and underline the importance of aggressive, anti-thrombosis prevention and treatment. The findings of our study confirm that critically ill COVID-19 patients who develop arterial and DVT are at high risk of mortality. Nevertheless, if properly treated with surgical treatment (in the case of arterial thrombosis), high doses of anti-inflammatory agents, and full anticoagulation and large-spectrum antibiotics, there is an overall survival of 74% (28/38) and of 100% in patients 60 y of age or younger in this large group of patients.

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