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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Letter to the Editors-in-Chief

The long haul COVID-19 arterial thrombosis

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The presence of a coexisting hypercoagulable state associated with Covid-19 infection has gained attention and several studies have already described acute limb ischemia (ALI) and peripheral arterial disease in critically ill patients, as well as coronary artery disease and ischemic stroke as manifestations usually associated with respiratory distress. Actually no information is currently available on how long inflammation and thrombotic derangements can last after recovery from Covid-19 symptoms and which patients are prone to develop acute arterial thrombosis.

During the 2nd and 3rd wave of Covid-19 pandemic we experienced a significant increase of Covid-19 infected patients who were admitted to our Vascular Referral Center for ALI or acute visceral ischemia. Moreover we've noted cases of acute arterial thrombosis in patients who had history of recent SARS-CoV-2 infection with complete resumption of symptoms and a negative nasopharyngeal swab at hospital admission.

We evaluated data from 38 consecutive patients admitted for acute ischemic symptoms in our Vascular Referral Center. From 15/12/2020 until 30/4/2021 we faced with 34 ALI and 4 abdominal visceral thrombosis; regarding ALI, the location of ischemia included upper limbs in 18 % of cases (7 patients) and lower extremity in 71 % of cases (27 patients). Visceral ischemic symptoms were caused by a celiac trunk thrombosis in one patient, splenic infarction in 2 patients and splenic infarction combined with left renal artery thrombosis in the remaining case.

The demographic data, comorbidities and thrombosis location are summarized in Table 1.

Among our cohort study, 16 patients were positive at hospital admission for Sars-CoV-2 infection instead 22 had a negative nasopharyngeal swab; among this last group, 6 patients reported a recent demonstrated Sars-CoV-2 infection (with previous nasopharingeal swab negativization approximately15 days before the admission in our Department); another patient had a known Covid-19 exposure approximately 45 days before our visit with an influenza like illness, but she didn't underwent to a nasopharyngeal swab test. In this case, considering that the thrombotic events was unexplained and relying on the high clinical suspicion, antibody testing for SARS-CoV-2 was performed and it showed a significantly high concentration of IgG.

All patients with ALI due to thrombosis of iliac-femoral or femoral-popliteal segment underwent surgical thrombectomy as long as their general and local conditions allowed an arterial revascularization. In case of Rutherford III stage limb ischemia at hospital admission or failure of revascularization attempt, we proceeded to limb amputation. In patients with tibial or forearm vessels occlusion and in those with extremely peripheral arteries' involvement, we used an endovascular approach. In cases of suboptimal results after endovascular revascularization, a Fountain-infusion catheter was placed down into the artery for continuous 48 h infusion of Urokinase or Abciximab. We administered a loading dose of 100,000 UI of Urokinase followed by continuous infusion of 1,200,000 UI/24 h of Urokinase or a maintenance Abciximab infusion of 0.125 μg/kg/min for 12 h. The choice of which drug administer was based on the result, at patient admission, of the nasopharyngeal swabs for SARS-CoV-2 carried out by RT-PCR: if positive, we treated patients by continuous 48 h infusion of Abciximab associated with previous Urokinase shots delivered during endovascular mechanical thrombectomy by an automated pulse-spray infusion pump (Angiodynamics); in patients with negative swab we used continuous Urokinase infusion for 48 h.

After procedure, both open surgical and endovascular, all patients received anticoagulation by continuous intravenous heparin infusion at therapeutic dose, checking aPTT every 6 h to achieve the target dose.

All patients admitted in our department complaining visceral ischemic symptoms were managed conservatively with medical therapy and intravenous unfractionated heparin infusion at therapeutic dose was administrated: this decision was based on critical systemic conditions in one case and on clinical manifestations with mild symptomatology in the other 3 patients.

Operative treatment was performed in 22 cases (21 patients) and was successful in 13 patients (2 with Covid-19 current infection, 3 with a previous history of Covid-19 infection, 8 patient without history of Covid-19 infection).

We performed 5 amputations, 1 primary and 4 secondary.

22 cases of arterial thrombosis, in 17 patients, were treated with medical therapy; among this group 11 patients had a current Covid-19 infection, 4 patients had a recent story of Sars-CoV-2 infection and a negative nasopharingeal swab at hospital admission, the remaining 2 patients hadn't story of current or past Covid-19 infection.

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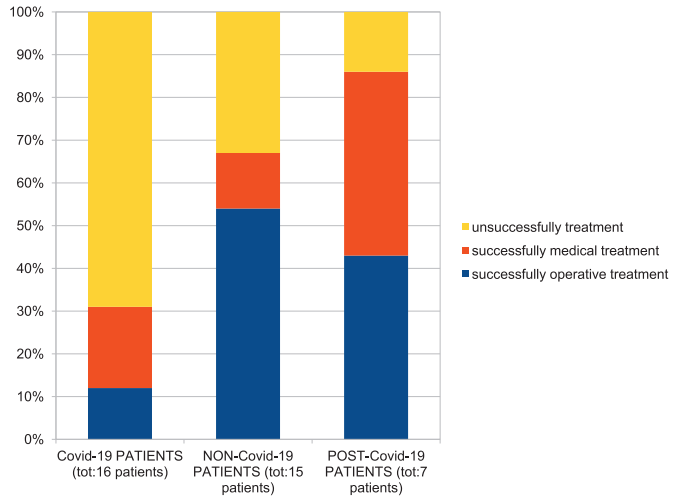
Table 1
Demographic data, comorbidities, thrombosis location and risk factors for entire cohort.

Variables	Value (n = 38)	Percentage (%)
Sex		
- Female	17	45 %
- Male	21	55 %
Age, years		
- 40-49	1	3 %
- 50-59	5	13 %
- 60-69	7	18 %
- 70-79	13	34 %
- >80	12	32 %
Comorbidities		
- Hypertension	24	63 %
- Diabetes	13	34 %
- Peripheral arterial disease	15	40 %
- Coronary artery disease	12	31 %
- Atrial fibrillation	12	31 %
- Smoking	12	31 %
- Dyslipidemia	6	16 %
- Chronic kidney disease	7	18 %
- Malignancy	3	8 %
- BPCO	8	21 %
- Antiphospholipid antibody syndrome	1	3 %
Thrombosis location		
- Lower limbs	27	71 %
- Upper limbs	7	18 %
- Visceral arteries	4	11 %
COVID-19 diagnosis	23	60 %
- Past	7	18 %
- Current	16	42 %
No COVID-19 infection	15	40 %
Anticoagulation therapy before arterial thrombosis	13	34 %
- Past COVID-19 infection	2	15 %
- Current COVID-19 infection	5	39 %
- No COVID-19 infection	6	46 %
Antiplatelet therapy before arterial thrombosis	10	26 %
- Past COVID-19 infection	1	10 %
- Current COVID-19 infection	4	40 %
- No COVID-19 infection	5	50 %

We summarized the outcomes of operative and medical treatment in Graphic 1.

We reported 13 in-hospital deaths, 11 of them occur in Covid-19 patients and all related to severe pneumonia complications.

Bellosta et al. reported a significant increased incidence of acute limb ischemia during Covid-19 pandemia, associated with a higher rate of revascularization failure [1]. Our results confirmed that negative trend, and, among Covid-19 patients, a successful revascularization was lower than expected.



Graphic 1. Operative and medical treatment outcomes.

On the other hand we registered a high rate of successful artery recanalization after operative or medical treatment in post-Covid thrombosis.

The association of Covid-19 disease with coagulopathy is established, but the sequence of events leading to arterial thrombosis hasn't been completely explained.

Chioh et al. [2] investigated the association between vascular injury in post Covid-19 patients and blood levels of circulating endothelial cells (CECs), which are shed from damaged vessel and are considered a biomarker of endothelial dysfunction. The Authors found elevated levels of CECs in patients with a recent story of Covid-19 infection, in particular in those with known comorbidity such as diabetes or hypertension. These evidence is consistent with the hypothesis that Covid-19 patients, especially those with pre-existing cardiovascular risk factors, may present persistent signs of vascular dysfunction even after recovery from viral infection. In fact elevated levels of CECs indicate that blood vessel injury is still apparent after recovering from viral infection. Moreover Authors found that recovered Covid-19 patients continued to produce high level of cytokines, and unusually high numbers of T cells were also present even in the absence of the virus.

The presence of both cytokines and higher levels of immune cells mean that immune system remained activated and this could explain the increasing risk of blood clot formation.

Evidence of post-Covid-19 endothelial dysfunction leading to cardiovascular complication are reported in young people without cardiovascular risk factors [3] and even in children and adolescents [4].

Several studies on thrombotic events associated with Covid-19 have been published, but the real prevalence of arterial thrombosis due to the viral infection remains unknown.

Most of the authors have mainly considered the occurrence of thrombotic events during the acute phase of the disease, while only few studies reported their occurrence after resumption of Covid-19.

Patell et al. [5] conducted a retrospective observational cohort study and they reported 2.5 % of cumulative incidence of overall thrombosis (including arterial and venous events) in post-Covid-19 patient at 30 days after discharge.

In our recent article [6] we reported three cases of arterial delayed vascular complications occurred in patients after completely Covid19 systemic symptoms resumption and with a negative nasopharyngeal swab at hospital admission and without any suspected findings of currently active disease at chest-CT.

Considering the high rates of in-hospital thrombosis in Covid-19 patients, an aggressive thromboprophylaxis is recommended during hospitalization [7].

The International Society on Thrombosis and Haemostasis recommend to administer low molecular-weight heparin (LMWH) to all patients who need to be hospitalized for Covid-19 infection, unless contraindicated [8]. Beyond its anticoagulant action, heparin has also anti-inflammatory, cytoprotective and anti-viral effects: in fact it is able to bind to Sars-CoV-2 and block replication of the virus [9].

Besides LMWH and UFH, direct oral anticoagulants, antiplatelet drugs and fibrinolytic agents are also useful in management of Covid-19 patients.

Abciximab (ReoPro) is a monoclonal antibody against the GPIIb/IIIa receptor, inhibiting platelet aggregation and thrombus formation. Evidence from the coronary literature suggest its use to enhance microperfusion likely because of prevention of downstream microembolization and platelet aggregation. The PROMPT Study, a randomized pilot trial [10], has demonstrated that in patients with ALI who underwent urokinase thrombolysis an adjunctive abciximab infusion resulted in faster thrombus dissolution and improved amputation free-survival.

Our rationale for using adjunctive intra-arterial infusion of abciximab in Covid-19 patients with ALI was based on the histologic analysis

of thrombi extracted in these kind of patients, which revealed platelet-fibrin thrombi and not just simple clot.

Although prophylactic anticoagulation in active Covid-19 patients is largely accepted, there is no agreement on the dosage to be employed. Furthermore, whether and how long the pro-thrombotic state of Covid-19 persists after symptoms resumption is unknown and the utility of post-discharge tromboprophylaxis is debated.

Our analysis underlines that delayed arterial thrombotic sequela of Covid-19 can also occur in susceptible patients after the index infection. From this perspective, vascular screening and followup should be discussed both during and after Covid-19 systemic symptoms resumption, to detect vascular manifestations which could be silent during viral infection.

A better understanding of the coagulopathy in Covid-19 could have an essential role to guide prevention and treatment of arterial thromboembolic events, both during and after the viral infection.

Further investigations are required to establish the type, dose and duration of anticoagulant/antiplatelet therapy not just during but also after Covid-19 infection.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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