

# COVID-19 Stroke and Blood Clot Medical Journals Scan

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# Venous Thromboembolism in Critically Ill Patients with Covid-19: Results of a Screening Study for Deep Vein Thrombosis

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## Objectives

To determine the prevalence of venous thromboembolic events (VTE) in critically ill patients with Covid-19, using lower limbs venous ultrasonography screening.

## Methods

Since March 8th, we enrolled 25 patients, who were admitted to the intensive care unit (ICU) with confirmed SARS-CoV-2 infections. The presence of lower extremity deep vein thrombosis (DVT) was systematically assessed by ultrasonography, between day 5 and 10 after admission. The data reported here are those available up until May 9th 2020.

## Results

The mean ( $\pm$ SD) age of the patients was  $68\pm 11$  years, 64% were men. No patients had a history of VTE. During the ICU stay, 8 patients (32%) suffered from VTE; 6 (24%) proximal DVT, 5 (20%) pulmonary embolism. The rate of symptomatic VTE was 24%, while 8% of patients had screen-detected DVT. Only those patients with a documented VTE received a therapeutic anticoagulant regimen. As of May 9th, 2020; 5 patients died (20%), 2 remain in the ICU (8%), and 18 were discharged (72%).

## Conclusions

In critically ill patients with SARS-CoV-2 infections, DVT screening at day 5-10 of admission, yielded a 32% prevalence of VTE. 75% of events occurred before screening. Earlier screening might be effective in optimizing care in ICU patients with Covid-19.

## Incidence of venous thromboembolism in hospitalized patients with COVID-19

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### Abstract

Coronavirus disease 2019 (COVID-19) can lead to systemic coagulation activation and thrombotic complications. We investigated the incidence of objectively confirmed venous thromboembolism (VTE) in 198 hospitalized patients with COVID-19 in a single-center cohort study. Seventy-five patients (38%) were admitted to the intensive care unit (ICU). At time of data collection, 16 (8%) were still hospitalized and 19% had died. During a median follow-up of 7 days (IQR, 3-13), 39 patients (20%) were diagnosed with VTE of whom 25 (13%) had symptomatic VTE, despite routine thrombosis prophylaxis. The cumulative incidences of VTE at 7, 14 and 21 days were 16% (95% CI, 10-22), 33% (95% CI, 23-43) and 42% (95% CI 30-54) respectively. For symptomatic VTE, these were 10% (95% CI, 5.8-16), 21% (95% CI, 14-30) and 25% (95% CI 16-36). VTE appeared to be associated with death (adjusted HR, 2.4; 95% CI, 1.02-5.5). The cumulative incidence of VTE was higher in the ICU (26% (95% CI, 17-37), 47% (95% CI, 34-58), and 59% (95% CI, 42-72) at 7, 14 and 21 days) than on the wards (any VTE and symptomatic VTE 5.8% (95% CI, 1.4-15), 9.2% (95% CI, 2.6-21), and 9.2% (2.6-21) at 7, 14, and 21 days). The observed risk for VTE in COVID-19 is high, particularly in ICU patients, which should lead to a high level of clinical suspicion and low threshold for diagnostic imaging for DVT or PE. Future research should focus on optimal diagnostic and prophylactic strategies to prevent VTE and potentially improve survival.

# Deep Vein Thrombosis in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome

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## Background

To investigate deep vein thrombosis (DVT) in hospitalized patients with coronavirus disease 2019 (COVID-19), we performed a single institutional study to evaluate its prevalence, risk factors, prognosis, and potential thromboprophylaxis strategies in a large referral and treatment center.

## Methods

We studied a total of 143 patients with COVID-19 from January 29 to February 29, 2020. Demographic and clinical data, laboratory data, including ultrasound scans of the lower extremities, and outcome variables were obtained, comparisons were made between DVT and non-DVT groups.

## Results

Of the 143 patients hospitalized with COVID-19 (aged  $63 \pm 14$  years; 74 [51.7%] man), 66 patients developed lower extremity DVT (46.1%, included 23 [34.8%] with proximal DVT and 43 [65.2%] with distal DVT). Compared with patients who with no DVT, patients with DVT were older and had a lower oxygenation index, a higher rate of cardiac injury, and worse prognosis including an increased proportion of deaths (23 [34.8%] vs 9 [11.7%],  $P = 0.001$ ) and a decreased proportion of patients discharged (32 [48.5%] vs 60 [77.9%],  $P < 0.001$ ). Multivariate analysis only showed an association between CURB-65 score 3-5 (OR = 6.122,  $P = 0.031$ ), Padua prediction score  $\geq 4$  (OR = 4.016,  $P = 0.04$ ), and D-dimer  $>1.0$  ( $\mu\text{g/ml}$ ) (OR = 5.818,  $P < 0.014$ ) and DVT in this cohort, respectively. The combination of a CURB-65 score 3-5, a Padua prediction score  $\geq 4$ , and D-dimer  $> 1.0$  ( $\mu\text{g/ml}$ ) has a sensitivity of 88.52% and a specificity of 61.43% for screening for DVT. In the subgroup of patients with a Padua prediction score  $\geq 4$  and whose ultrasound scans were performed  $>72$  hours after admission, DVT was present in 18 (34.0%) of the subgroup receiving venous thromboembolism prophylaxis vs 35 (63.3%) in the nonprophylaxis group ( $P = 0.010$ ).

## Conclusions

The prevalence of DVT is high and is associated with adverse outcomes in hospitalized patients with COVID-19. Prophylaxis for venous thromboembolism may be protective in patients with a Padua protection score  $\geq 4$  after admission. Our data seem to suggest that COVID-19 is probably an additional risk factor for DVT in the hospitalized patients.

# Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Published May 21<sup>st</sup>, 2020

<https://www.nejm.org/doi/full/10.1056/NEJMoa2015432>

## Background

Progressive respiratory failure is the primary cause of death in the coronavirus disease 2019 (Covid-19) pandemic. Despite widespread interest in the pathophysiology of the disease, relatively little is known about the associated morphologic and molecular changes in the peripheral lung of patients who die from Covid-19.

## Methods

We examined 7 lungs obtained during autopsy from patients who died from Covid-19 and compared them with 7 lungs obtained during autopsy from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1) infection and 10 age-matched, uninfected control lungs. The lungs were studied with the use of seven-color immunohistochemical analysis, micro-computed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression.

## Results

In patients who died from Covid-19–associated or influenza-associated respiratory failure, the histologic pattern in the peripheral lung was diffuse alveolar damage with perivascular T-cell infiltration. The lungs from patients with Covid-19 also showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes. Histologic analysis of pulmonary vessels in patients with Covid-19 showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were 9 times as prevalent in patients with Covid-19 as in patients with influenza ( $P<0.001$ ). In lungs from patients with Covid-19, the amount of new vessel growth — predominantly through a mechanism of intussusceptive angiogenesis — was 2.7 times as high as that in the lungs from patients with influenza ( $P<0.001$ ).

## Conclusions

In our small series, vascular angiogenesis distinguished the pulmonary pathobiology of Covid-19 from that of equally severe influenza virus infection. The universality and clinical implications of our observations require further research to define. (Funded by the National Institutes of Health and others.)

## Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19

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Between February and March 2020, the Journal of Thrombosis and Haemostasis has published four papers addressing the intricate, complex, and still little understood relation between COVID-19 and thrombogenesis.

SARS-Cov-2 induces in severe cases a cytokine storm that ultimately leads to the activation of coagulation cascade, causing thrombotic phenomena.<sup>5</sup> There is a further strong link between abnormal coagulation parameters (D-dimer and fibrin degradation products) and mortality. Tang et al described that 71.4% of nonsurvivors and 0.6% of survivors showed evidence of disseminated intravascular coagulation (DIC), suggesting that DIC is a frequent occurrence in severe COVID-19.<sup>4</sup> The frequency of DIC in these patients is much higher than that reported for severe SARS.

There are ongoing widespread discussions among intensivists on the possible use of anticoagulant therapy, especially in severe patients with elevated D-dimer levels. Tang et al showed that the use of heparin for 7 days or more resulted in decreased mortality in severe cases, especially in those with a sepsis-induced coagulopathy score >4 or D-dimer >6 fold of upper normal limit.

A pathological substrate confirming the presence and frequency of pulmonary thrombi in severe COVID-19, to provide more rationale to therapeutic management, is missing. Although the number of fatalities is in the range of tens of thousands worldwide, autopsy studies are scarce and limited to a few organs.<sup>7, 8</sup> It is understandable that few autopsy descriptions have been presented so far. Few centers have skilled pathologists to perform autopsies, not to mention the great risk of contagion during the procedure and the need for special security facilities in the autopsy rooms. In China, for instance, where the disease started, Zhu et al described that, since 2000, almost no autopsies have been performed in 8 hospitals in large Chinese cities.<sup>9</sup> Mostly a neglected procedure, the autopsy rapidly regains its importance when novel diseases arise and can be extremely useful in revealing patterns of tissue damage, systemic involvement, and for further research on the pathogenesis of the disease.

São Paulo is the epicenter of COVID-19 cases in Brazil, with 304 deaths through April 6, 2020. Our large tertiary academic Clinical Hospital of the Faculty of Medicine of the University of São Paulo has allocated all of its 900 beds to receive patients with COVID-19 and, unfortunately, it is expected that a large number of deaths will still occur. Since February 2020, our group has performed minimally invasive autopsies in fatal cases of COVID-19 to characterize the pathology and pathogenesis of this new disease. We have developed a procedure for performing ultrasound-based minimally invasive autopsies that samples tissues from several organs and, at the same time, reduces the risks of the autopsy procedure. In fact, ultrasound-based minimally invasive autopsies was applied during the recent 2018 yellow fever epidemic in Sao Paulo, Brazil, and showed full diagnostic agreement with conventional autopsy.<sup>10</sup> For COVID-19 cases, we analyze histological samples from lungs, kidneys, heart, liver, spleen, brain, skin, and skeletal muscle. The procedure was approved by the institution's ethics board and was performed after informed consent from the next of kin. Here, we present some preliminary autopsy results that may provide new insights into the relation between COVID-19 and DIC.

To date, we have studied 10 fatal cases, 5 men and 5 women, with a mean age of 67.8 years (33-83 years). Eight patients were older than age 60 years and seven had comorbidities, including arterial



hypertension, diabetes mellitus, ischemic heart disease, and chronic obstructive pulmonary disease. The average hospital stay was 5.4 days (0-15 days).

The general pulmonary histological picture in fatal cases of COVID-19 is exudative/proliferative diffuse alveolar damage, with intense epithelial viral cytopathic effects involving alveolar and small airway epithelium, and little lymphocytic infiltration (Figure 1A). We observed a variable number of small fibrinous thrombi in small pulmonary arterioles in areas of both damaged and more preserved lung parenchyma in 8 of 10 cases (Figure 1B-D). Endothelial tumefaction and a large number of pulmonary megakaryocytes in the pulmonary capillaries are other indicators of activation of the coagulation cascade. In addition, small fibrinous thrombi were rarely found in the glomeruli and superficial dermal vessels. There were few and small foci of alveolar hemorrhage, and pulmonary infarctions were not observed. Signs of secondary bacterial pneumonia were observed in six cases. Because these are postmortem transthoracic biopsies, we do not have access to large vessels and therefore cannot exclude or confirm pulmonary embolisms.

In summary, our pathological observations support the current concept of hypercoagulative status in these critically ill patients, showing that the frequency of pulmonary microthrombosis is high. Hopefully, these findings may shed light on the complex therapeutic decisions on this subject.

# Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels

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## Summary

Thirty-two of 106 (30%, [95%CI 22-40%]) patients with COVID-19 infection were positive for acute pulmonary embolus on pulmonary CT angiograms.

## INTRODUCTION

Reports of acute pulmonary embolism associated with COVID-19 have emerged in the literature. For example, Chen et al. described 25 pulmonary CT angiograms examinations from 1008 COVID-19 patients; 10 were positive for pulmonary embolism mostly as segmental or sub-segmental APE [1]. In addition, D-dimer levels have been reported as elevated in patients with COVID-19 [2; 3] with the suggestion of an independent association between the severity of the disease and the level of D-dimer [4]. The purpose of this report is to describe the rate of pulmonary embolus in patients classified as COVID-19 infection and who underwent chest CT at a tertiary referral centre.

## Materials and Methods

### Patient Population

The local ethics committee of Strasbourg University Hospital approved this retrospective study and waived the need of informed consent. Full methods are provided in Appendix E1 (online). From March 1st to March 31st, medical records of all consecutive patients who underwent a CT examination 1) including the chest and 2) performed for either suspicion or follow-up of SARS-CoV-2 infection at one of our 2 hospital sites (Nouvel Hôpital Civil and Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, France) were evaluated. CT examinations that included pulmonary CT angiographic images were evaluated for further study. Clinical and demographic parameters for patients with and without pulmonary embolus in CT pulmonary angiogram were evaluated.

### CT Pulmonary Angiography

CT angiograms were acquired on 64 row or greater scanners after injection of 50 to 75 mL of high concentration iodine contrast media, with the use of a bolus-tracking technique and a threshold of 160 HU to 250 HU in the main pulmonary artery. Images were reconstructed with a slice-thickness of 1 mm in mediastinal and parenchymal windows. A single reader (ILL) classified pulmonary embolism location as main pulmonary arteries, lobar, segmental or subsegmental based on the location of the most proximal luminal defect.

### Laboratory Analysis

Fibrinogen and D-dimer levels were recorded for all patients who had pulmonary CT angiography. All patients with pulmonary CT angiography were evaluated for reverse transcriptase polymerase chain reaction (RT-PCR) results for SARS-CoV-2. All initial samples were obtained by nasopharyngeal swab; some patients had second or third sampling using sputum or bronchoalveolar lavage. Any positive result was classified as confirmed COVID-19 infection. When RT-PCR was negative, chest CT was reviewed by a senior chest radiologist (MO, with 14 years of experience) to look for characteristic COVID-19 lung parenchyma lesions. When CT images were considered typical (i.e. extensive bilateral and peripheral ground glass opacities and/or alveolar consolidation) and clinical data were compatible, the patient was also adjudicated as having COVID-19 [4; 5].

## RESULTS

A flowchart of all patients with CT scans performed from March 1st to March 31st, 2020 is shown in Figure 1. During this period, 1696 patients had CT for suspicion or follow-up of COVID-19 infection. Dedicated pulmonary CT angiograms were performed in 135/1696 (8%) patients, 25 additional patients had pulmonary arterial phase images included in the chest/ abdomen/ pelvic CT scan (total, 160 patients). Of these 160 patients, 106 patients were classified as COVID-19 infection (97 patients by RT-PCR and 9 patients with positive CT and negative RT-PCR test). The reason for CT angiography in these patients was suspicion of pulmonary embolus in 67/106 (63%) patients and other CT indication in 39/106 (37%) patients.

## Endothelial cell infection and endotheliitis in COVID-19

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Cardiovascular complications are rapidly emerging as a key threat in coronavirus disease 2019 (COVID-19) in addition to respiratory disease. The mechanisms underlying the disproportionate effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with cardiovascular comorbidities, however, remain incompletely understood.

SARS-CoV-2 infects the host using the angiotensin converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells. Whether vascular derangements in COVID-19 are due to endothelial cell involvement by the virus is currently unknown. Intriguingly, SARS-CoV-2 can directly infect engineered human blood vessel organoids *in vitro*. Here we demonstrate endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19 (further case details are provided in the appendix).

Patient 1 was a male renal transplant recipient, aged 71 years, with coronary artery disease and arterial hypertension. The patient's condition deteriorated following COVID-19 diagnosis, and he required mechanical ventilation. Multisystem organ failure occurred, and the patient died on day 8. Post-mortem analysis of the transplanted kidney by electron microscopy revealed viral inclusion structures in endothelial cells (figure A, B). In histological analyses, we found an accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies, in the heart, the small bowel (figure C) and lung (figure D). An accumulation of mononuclear cells was found in the lung, and most small lung vessels appeared congested.

Patient 2 was a woman, aged 58 years, with diabetes, arterial hypertension, and obesity. She developed progressive respiratory failure due to COVID-19 and subsequently developed multi-organ failure and needed renal replacement therapy. On day 16, mesenteric ischaemia prompted removal of necrotic small intestine. Circulatory failure occurred in the setting of right heart failure consequent to an ST-segment elevation myocardial infarction, and cardiac arrest resulted in death. Post-mortem histology revealed lymphocytic endotheliitis in lung, heart, kidney, and liver as well as liver cell necrosis. We found histological evidence of myocardial infarction but no sign of lymphocytic myocarditis. Histology of the small intestine showed endotheliitis (endothelialitis) of the submucosal vessels.

Patient 3 was a man, aged 69 years, with hypertension who developed respiratory failure as a result of COVID-19 and required mechanical ventilation. Echocardiography showed reduced left ventricular ejection fraction. Circulatory collapse ensued with mesenteric ischaemia, and small intestine resection was performed, but the patient survived. Histology of the small intestine resection revealed prominent endotheliitis of the submucosal vessels and apoptotic bodies (figure C).

We found evidence of direct viral infection of the endothelial cell and diffuse endothelial inflammation. Although the virus uses ACE2 receptor expressed by pneumocytes in the epithelial alveolar lining to infect the host, thereby causing lung injury, the ACE2 receptor is also widely expressed on endothelial cells, which traverse multiple organs. Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction associated with apoptosis (figure D).

The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is indispensable for the regulation of vascular tone and the maintenance of vascular homeostasis. Endothelial dysfunction is a principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a pro-coagulant state.

Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19-endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilise the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins. This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19.

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## COVID-19: the vasculature unleashed

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On the basis of emerging evidence from patients with COVID-19, we postulate that endothelial cells are essential contributors to the initiation and propagation of severe COVID-19. Here, we discuss current insights into the link between endothelial cells, viral infection and inflammatory changes and propose novel therapeutic strategies.

Coronavirus disease 2019 (COVID-19), caused by the betacoronavirus SARS-CoV-2, is a worldwide challenge for health-care systems. The leading cause of mortality in patients with COVID-19 is hypoxic respiratory failure from acute respiratory distress syndrome (ARDS)<sup>1</sup>. To date, pulmonary endothelial cells (ECs) have been largely overlooked as a therapeutic target in COVID-19, yet emerging evidence suggests that these cells contribute to the initiation and propagation of ARDS by altering vessel barrier integrity, promoting a pro-coagulative state, inducing vascular inflammation (endotheliitis) and mediating inflammatory cell infiltration<sup>2,3</sup>. Therefore, a better mechanistic understanding of the vasculature is of utmost importance.

An established feature of severe COVID-19 is the activation of coagulation pathways with potential development of DIC. This is also related to EC activation and dysfunction because the disruption of vascular integrity and EC death leads to exposure of the thrombogenic basement membrane and results in the activation of the clotting cascade<sup>7</sup>. Moreover, ECs activated by IL-1 $\beta$  and TNF initiate coagulation by expressing P-selectin, von Willebrand factor and fibrinogen, to which platelets bind<sup>2</sup>. In turn, ECs release trophic cytokines that further augment platelet production. Platelets also release VEGF, which triggers ECs to upregulate the expression of tissue factor, the prime activator of the coagulation cascade, which is also expressed by activated pericytes<sup>2</sup>. In response, the body mounts countermeasures to dissolve fibrin-rich blood clots, explaining why high levels of fibrin breakdown products (D-dimers) are predictive of poor patient outcome. As a result of the DIC and clogging/congestion of the small capillaries by inflammatory cells, as well as possible thrombosis in larger vessels, lung tissue ischaemia develops, which triggers angiogenesis<sup>2</sup> and potential EC hyperplasia. While the latter can aggravate ischaemia, angiogenesis can be a rescue mechanism to minimize ischaemia. However, the newly formed vessels can also promote inflammation by acting as conduits for inflammatory cells that are attracted by activated ECs<sup>2</sup>.

Many patients with severe COVID-19 show signs of a cytokine storm<sup>8</sup>. The high levels of cytokines amplify the destructive process by leading to further EC dysfunction, DIC, inflammation and vasodilation of the pulmonary capillary bed. This results in alveolar dysfunction, ARDS with hypoxic respiratory failure and ultimately multi-organ failure and death. EC dysfunction and activation likely co-determine this uncontrolled immune response. This is because ECs promote inflammation by expressing leukocyte adhesion molecules<sup>2</sup>, thereby facilitating the accumulation and extravasation of leukocytes, including neutrophils, which enhance tissue damage. Moreover, we hypothesize that denudation of the pulmonary vasculature could lead to activation of the complement system, promoting the accumulation of neutrophils and pro-inflammatory monocytes that enhance the cytokine storm. This is based on the observation that during influenza virus infection, pulmonary ECs induce an amplification loop, involving interferon-producing cells and virus-infected pulmonary epithelial cells<sup>9</sup>. Moreover, ECs seem to be gatekeepers of this immune response, as modulation of the sphingosine 1 phosphate receptor 1 (S1PR1) in pulmonary ECs dampens the cytokine storm in influenza infection<sup>9</sup>. This raises the question whether

pulmonary ECs have a similar function in the COVID-19 cytokine storm and whether S1PR1 could represent a therapeutic target. Another unexplained observation is the excessive lymphopenia in severely ill patients with COVID-19 and whether this relates to the recruitment of lymphocytes away from the blood by activated lung ECs.

Additional circumstantial evidence suggests a link between ECs, pericytes and COVID-19. First, risk factors for COVID-19 (old age, obesity, hypertension and diabetes mellitus) are all characterized by pre-existing vascular dysfunction with altered EC metabolism<sup>10</sup>. As hijacking of the host metabolism is essential for virus replication and propagation, an outstanding question is whether EC subtypes or other vascular cells in specific pathological conditions have a metabolic phenotype that is more attractive to SARS-CoV-2. Second, occasional clinical reports suggest an increased incidence of Kawasaki disease, a vasculitis, in young children with COVID-19. Third, severe COVID-19 is characterized by multi-organ failure, raising the question how and to what extent the damaged pulmonary endothelium no longer offers a barrier to viral spread from the primary infection site. Additionally, whether infected pericytes can promote coagulation remains to be studied. As such, the consequences of SARS-CoV-2 on the entire vasculature require further attention.

The proposed central role of ECs in COVID-19 disease escalation prompts the question whether vascular normalization strategies during the maladapted immune response could be useful. Indeed, a clinical trial (NCT04342897) is exploring the effect of targeting angiotensin 2 in patients with COVID-19, based on the rationale that circulating levels of angiotensin 2 correlate with increased pulmonary oedema and mortality in patients with ARDS. Several other clinical trials (NCT04344782, NCT04275414 and NCT04305106) are investigating bevacizumab, a monoclonal antibody that binds to VEGF and counteracts its vessel-permeabilizing effect, in patients with COVID-19. Normalization of the vascular wall through metabolic interventions could be considered as an additional route of intervention<sup>10</sup>. For instance, ECs treated with drugs targeting key metabolic enzymes of the glycolytic pathway adopt a 'normalized' phenotype with enhanced vascular integrity and reduced ischaemia and leakiness<sup>10</sup>. Although the hypothetical role and therapeutic targetability of the vasculature in COVID-19 require further validation, the possibility that ECs and other vascular cells are important players paves the way for future therapeutic opportunities.

## COVID-19 update: Covid-19-associated coagulopathy

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<https://link.springer.com/article/10.1007/s11239-020-02134-3>

The Covid-19 pandemic has introduced an array of organ-specific and systemic phenotypes- some previously observed in viral infections, including severe acute respiratory syndrome (SARS) and others that appear to be unique to SARS-coronavirus (CoV)-2. Rapidly emerging information from clinical observations, autopsy-based findings, extrapolations from in vitro and ex vivo studies and dynamic modeling are informing management guidelines; however, many questions remain unanswered and clinical trials that are required to provide evidence have not been completed in most areas. Among the many questions that require careful thought, reflection and investigation are the mechanism(s) underlying the development of a systemic coagulopathy and acquired thrombophilia characterized in a majority of cases by a proclivity for venous, arterial and microvascular thrombosis.

The following review summarizes emerging insights into the pathobiology, mechanism(s), diagnosis, management, foundations for research and either planned or ongoing clinical trials for Covid-19-associated coagulopathy. [Full text available using link above].



## Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19

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<https://www.sciencedirect.com/science/article/pii/S0735109720352189?via%3Dihub>

The novel coronavirus 2019 (COVID-19) has affected nearly every country worldwide. Reports note increased thromboembolic events among hospitalized patients (1,2) and anecdotal observations of improved outcomes with systemic anticoagulation (AC). However the specific role of AC in disease management remains unclear (3,4). We assessed association between administration of in-hospital AC and survival in a large cohort of hospitalized patients with COVID-19. This work was approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai (#20-03271).

Between March 14 and April 11, 2020, 2,773 patients were hospitalized with laboratory-confirmed COVID-19 within the Mount Sinai Health System in New York City. We used a Cox proportional hazards model to evaluate the effect of treatment-dose systemic AC (including oral, subcutaneous, or intravenous forms) on in-hospital mortality. We adjusted for age, sex, ethnicity, body mass index, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, AC use prior to hospitalization, and admission date. To adjust for differential length of stay and initiation of AC treatment, AC treatment duration was used as a covariate while intubation was treated as a time-dependent variable.

Among 2,773 hospitalized COVID-19 patients, 786 (28%) received systemic AC during their hospital course. The median (IQR) hospitalization duration was 5 days (3-8 days). Median (IQR) time from admission to AC initiation was 2 days (0-5 days). Median (IQR) duration of AC treatment was 3 days (2-7 days). In-hospital mortality for patients treated with AC was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients who did not receive AC (Figure 1A). Patients who received AC were more likely to require invasive mechanical ventilation (29.8% vs 8.1%,  $p < 0.001$ ). Overall, we observed significantly increased baseline prothrombin time, activated partial thromboplastin time, lactate dehydrogenase, ferritin, C reactive protein, and D-dimer values among individuals who received in-hospital AC as compared to those who did not. These differences were not observed, however, among mechanically ventilated patients. In patients who required mechanical ventilation (N=395), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with AC as compared to 62.7% with a median survival of 9 days in patients who did not receive AC (Figure 1B). In a multivariate proportional hazards model, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89,  $p < 0.001$ ).

We also explored the association of systemic AC administration with bleeding events. Major bleeding was defined as 1) hemoglobin  $< 7$  g/dL and any red blood cell transfusion, 2) at least two units of red blood cell transfusion within 48 hours or 3) a diagnosis code for major bleeding including intracranial hemorrhage, hematemesis, melena, peptic ulcer with hemorrhage, colon, rectal, or anal hemorrhage, hematuria, ocular hemorrhage, and acute hemorrhagic gastritis. Among those who did not receive AC, 38 (1.9%) individuals had bleeding events, compared to 24 (3%) among those who received AC ( $p = 0.2$ ). Of the 24 patients who had bleeding events on AC, 15 (63%) had bleeding events after starting AC and 9 (37%) had bleeding events before starting AC. Bleeding events were more common among patients intubated (30/395; 7.5%) than among non-intubated patients (32/2378; 1.35%).

Although limited by its observational nature, unobserved confounding, unknown indication for AC, lack of metrics to further classify illness severity in the mechanically ventilated subgroup, and indication bias, our

findings suggest that systemic AC may be associated with improved outcomes among patients hospitalized with COVID-19. The potential benefits of systemic AC, however, need to be weighed against the risk of bleeding and therefore should be individualized. The association of in-hospital AC and mechanical ventilation likely reflects reservation of AC for more severe clinical presentations. Interestingly, there was an association with AC and improved survival after adjusting for mechanical ventilation.

These data, derived from a large United States cohort, provide clinical insights for consideration in the management of patients hospitalized with COVID-19. Prospective randomized trials are needed to determine whether systemic AC confers a survival benefit in hospitalized patients with COVID-19.

## Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis

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<https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.16725>

Coronavirus disease 2019 (COVID-19) is widely spread and poses a critical threat to global health.<sup>1</sup> Prominent changes in coagulation function in severe patients of COVID-19 have been reported in a recent study.<sup>2</sup> Therefore, we conducted this quantitative meta-analysis to explore the difference in blood coagulation parameters between severe and mild cases of COVID-19.

Literature published from December 1, 2019 to March 30, 2020 was searched systematically using PubMed and Embase without language limits. The keywords were: coronavirus ,laboratory , clinical manifestations , clinical characteristics , and clinical features . All documents comparing information on coagulation parameters between mild and severe cases of COVID-19 patients were finally referred to in our meta-analysis. The pooled standardised mean difference (SMD) and 95% confidence interval (CI) were computed by applying the random-effect model using Stata software (STATA 14.0, Stata Corp, College Station, TX, USA). The study quality was measured by adopting an 11-item checklist, which was suggested by the Agency for Healthcare Research and Quality (AHRQ).

Table I displays the main characteristics of the included studies. Nine studies, including one study from medRxiv, with 1105 patients were eventually included for detailed evaluation. Platelet count (PLT), activated partial thromboplastin time (APTT), prothrombin time (PT) and D-dimer (D-D) levels were available in five, six, six and eight studies, respectively. All the studies were conducted in China. Quality score varied from 3 to 7 points, with a mean of 5.4 (Table I). All the studies were of moderate quality, except one of low quality.

The main difference in coagulation function between severe and mild COVID-19 patients is shown in Fig 1. Pooled results revealed that PT and D-D levels were significantly higher in patients with severe COVID-19 (0.68, 95% CI = 0.43–0.93, I<sup>2</sup> = 53.7%; 0.53, 95% CI = 0.22–0.84, I<sup>2</sup> = 78.9%, respectively). However, no significant difference in PLT and APTT values between severe and mild patients was observed (–0.08, 95% CI = –0.34 to 0.18, I<sup>2</sup> = 60.5%; –0.03, 95% CI = –0.40 to 0.34, I<sup>2</sup> = 79.5%, respectively). Increasing values of D-D and PT support the notion that disseminated intravascular coagulation (DIC) may be common in COVID-19 patients.<sup>2</sup> In addition, the rise of D-D level also indicates secondary fibrinolysis conditions in these patients. According to Berri et al. ,<sup>3</sup> fibrin clot formation helps people to fight against influenza virus infections. Hence, fibrinolysis may potentially induce following severe COVID-19 infection. Future studies should aim to discover more biomarkers of severe cases of COVID-19, and studies exploring the underlying mechanism of deranged coagulation function in COVID-19 are urgently needed. The haemostatic system might be explored for underlying treatment against coronavirus.

Due to the lack of sufficient study data, we cannot perform a more thorough analysis to prove beneficial screening parameters for PLT, APTT, PT and D-D for prediction of severity of COVID-19. However, we suggest that clinical practitioners pay attention to the changes in coagulation function in COVID-19 patients on a daily basis.

## COVID-19 as a cardiovascular disease: the potential role of chronic endothelial dysfunction

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As the SARS-CoV-2 pandemic evolves, there is mounting evidence that the cardiovascular system plays a role in the pathophysiology of COVID-19 disease. In their interesting recent article, Chen *et al.* propose that pericytes, with high expression of angiotensin-converting enzyme 2 (ACE2; the receptor for this virus), are the potential target cardiac cells for SARS-CoV-2 infection.<sup>1</sup> Endothelial cells are also known to express ACE2, representing a potential target for infection.<sup>2</sup> In addition to viral factors, other host-dependent cardiovascular factors could contribute to the severity of COVID-19 disease in some patients.

Epidemiological studies show that COVID-19 patients admitted to hospital or to an intensive care unit (ICU) present frequently with accompanying conditions such as advanced age, hypertension, diabetes, and cardiovascular diseases.<sup>3</sup> These conditions are associated with chronic endothelial dysfunction.<sup>4</sup> The endothelium plays major roles in the response to infection: endothelial cells release chemokines to guide leucocytes to the infected tissue and cytokines that activate inflammatory responses. Patients with chronic endothelial dysfunction present major alterations at the glycocalyx, intercellular junctions, and endothelial cells, resulting in enhanced leucocyte adhesion and extravasation, and also in the induction of a procoagulant and antifibrinolytic state.<sup>4</sup> Prior endothelial dysfunction could thus predispose to the development of severe COVID-19.

Chronic endothelial dysfunction and/or direct viral infection of endothelial cells could translate into a dysfunctional endothelial response during SARS-CoV-2 infection, which could contribute to the pathogenesis of pneumonia and acute respiratory syndrome at the respiratory level, and induce microcirculation disorders/myocardial injury in the heart, as detailed in *Figure 1*.<sup>1</sup> Lymphopenia and hypoalbuminaemia, which are frequent events in patients with severe COVID-19, could be explained, at least in part, by the disruption of endothelial barrier integrity at the vascular or lymphatic capillaries (*Figure 1*).<sup>5</sup> The dysfunctional endothelial response to the infection could also induce activation of the coagulation pathway(s), as denoted by the presence of high levels in plasma of D-dimer in severe COVID-19, which represents a risk factor for mortality.<sup>6</sup> It could explain the increased incidence of thrombotic complications in this disease<sup>7</sup> (*Figure 1*). Finally, dysfunctional endothelial responses during COVID-19 could involve not only the continuous non-fenestrated vascular endothelium (such as that present in the lungs or in the heart) (*Figure 1*), but also the continuous fenestrated endothelium (kidney) or the discontinuous/sinusoidal endothelium (liver), contributing to induction of tissue damage also at these levels.

Endothelial dysfunction in COVID-19. In a patient unable to control the virus, viral infection could induce direct damage to the endothelial cells. Along with viral factors, the existence of prior endothelial dysfunction due to ageing and chronic diseases could favour the development of a dysfunctional response to the infection, with the production of cytokines by the patient's own endothelial cells, pneumocytes, or neutrophils, reactive oxygen species (ROS), and neutrophil extracellular traps (NETs). This dysfunctional response would translate into increased apoptosis of endothelial cells and disruption of the intercellular junctions, leading to capillary leakage of fluid, leucocytes, and proteins, which could interfere with the O<sub>2</sub>/CO<sub>2</sub> exchange in the lungs and induce microcirculatory disorders in the heart. Cytokines, destabilized coronary plaque, severe hypoxia, and viral infection of pericytes (green cell in the lower panel) could also contribute to induce myocardial damage. Endothelial dysfunction would promote

formation of microthrombi and emboli. Finally, dysfunction of endothelial cells in the lymphatic vessels could translate into lymphocyte leakage and lymphopenia. DM, diabetes mellitus; HBP, high blood pressure; CVD, cardiovascular disease; EC, endothelial cell; GCX, glycocalyx; PT, prothrombin time; CK, creatine kinase. Images of representative cells were taken from 'Smart Servier Medical Art' (<https://smart.servier.com/>).

Monitoring endothelial dysfunction biomarkers in aged patients and patients with underlying chronic diseases could help in the early identification of those individuals at risk of suffering severe complications during the course of COVID-19 illness. Designing therapies aimed to prevent endothelial deterioration and/or improve endothelial function could help improve outcomes of this disease.

## Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation

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<https://link.springer.com/article/10.1007/s00134-020-06059-6>

Current management guidelines for COVID-19 reflect the assumption that critically ill patients infected with SARS-CoV-2 develop acute respiratory distress syndrome (ARDS). However, emerging data and clinical reports increasingly suggest an alternative view that severe COVID-19 reflects a confluence of vascular dysfunction, thrombosis, and dysregulated inflammation.

### **Severe COVID-19 is distinct from ARDS and cytokine-release syndromes**

Published data [1, 2], anecdotal observations, and discussions with colleagues worldwide indicate that COVID-induced respiratory phenotypes are distinct from typical ARDS in several ways [2]. COVID-19 patients develop profound hypoxemia early in their disease course. However, overt respiratory dysfunction at these early stages is unusual. Pulmonary compliance in intubated COVID-19 patients appears to be only modestly decreased, and patients are therefore relatively easy to ventilate [1]. Gattinoni et al. [1] described hyperperfusion of poorly ventilated lung, perhaps due to vasodilation and the loss of hypoxic vasoconstriction. While benefit from low-to-moderate levels of PEEP and prone positioning have been noted, these authors suggest that they result more from hemodynamics effects than lung recruitment [1]. Later in the course of COVID-19, some patients develop a phenotype more consistent with ARDS [1, 2].

The reported inflammatory response in COVID-19 is also not consistent with either typical ARDS or cytokine-release syndromes (CRS) or “cytokine storm.” Qin et al. [3] report mean interleukin-6 levels were 25 (SD: 10–55) pg/mL (normal range: 7 pg/mL). Other smaller COVID-19 reports have ranged from 7 to 125 pg/mL. These findings contrast with interleukin-6 elevations seen in typical ARDS and in CRS. Sinha et al. report mean interleukin-6 levels of 282 (111–600) pg/mL in “hypoinflammatory” ARDS [9] and 1618 (517–3205) pg/mL in hyperinflammatory ARDS [4], 10- to 60-fold higher than reported in the Wuhan data. Among CRS patients, mean interleukin-6 levels are frequently as high as 10,000 pg/mL [5]. Other inflammatory cytokines (e.g., interleukin-8, interleukin-1 $\beta$ ) demonstrate similar patterns. In summary, COVID-19 is associated with only mild inflammatory cytokine elevation and demonstrates physiology and immunology that are difficult to reconcile with ARDS or CRS. An alternative mechanism of disease therefore seems likely.

### **Vasculopathy and dysregulated inflammation in COVID-19**

The combination of observed physiology and emerging pathologic evidence points toward a vascular disease process as contributing factor in COVID-19 pathogenesis. Pulmonary shunting is consistent with intense vasodilation and endothelial dysfunction. The observation that 89% of hospitalized patients in Rome showed subsegmental vascular enlargement on their admission computed tomography scan supports this view [6]. Reports of increased respiratory dead space suggest lung-vascular thrombosis from thrombotic microangiopathy or pulmonary embolism. The latter was recently reported in up to 40% of hospitalized COVID-19 patients [7]. Autopsies performed on patients who died early on were indeed notable for lung-vascular congestion [8]. Vascular disease may also explain massive D-dimer elevations, while antiphospholipid antibodies were recently reported in COVID-19 [9]. A constellation of multi-system organ involvement, low-grade inflammation, lymphopenia, hypercoagulability, and heterogenous microvascular dysfunction is a classic description of many systemic vasculopathies, such as vasculitides (Supplement Table).

Reported findings indicate that immunosuppression, endothelial activation, and direct viral-mediated tissue damage, rather than hyperinflammatory injury, mediate COVID-induced organ dysfunction. For example, a recent autopsy study found no renovascular or interstitial inflammation, but noted endothelial activation, occasional frank necrosis, and copious virions in renal tissue [10]. If direct infection drives injury, vascular tissue is expected to be quite susceptible as it highly expresses angiotensin-converting enzyme-2 (ACE-2), which is essential for coronavirus uptake.

SARS-CoV-2 initiates cellular infection by binding ACE-2 on the surface of human cells, including endothelial cells (Fig. 1) [11]. Attachment promotes disordered cytokine paracrine signaling, including both pro- and anti-inflammatory molecules, and pro-apoptotic mediators [12]. Chemokine-mediated lymphocyte recruitment and subsequent infection of lymphocytes, which also express ACE-2, likely contribute to lymphocyte apoptosis, natural killer and B cell suppression, and T cell exhaustion, as noted by Qin et al. [3]. These findings are consistent with clinical lymphopenia, which correlates with mortality [3]. Viral injury, disordered cytokine release, and damage-associated molecular patterns (DAMPs) induce localized microvascular inflammation, which triggers endothelial activation, leading to vasodilation and pro-thrombotic conditions.

Angiotensin-II (AngII) is primarily metabolized by endothelial ACE-2 to the vasodilatory and anti-inflammatory peptide angiotensin (1–7). In the early phases of infection, ACE-2 consumption by viral entry would be predicted to increase local AngII concentration. Among the known effects of AngII are vasoconstriction, endothelial activation, and pro-inflammatory cytokine release. Platelet activation by AngII may further enhance a pro-thrombotic milieu. AngII also has potent chemotactic effects that may accelerate lymphocyte recruitment and suppression. Importantly, admission AngII levels in COVID-19 patients are reportedly twice the normal levels [13]. In addition, pulmonary vascular inflammation specifically leads to a phenomenon known as ACE-1 “shedding,” where endothelial surface-bound ACE-1 is released into the interstitium [14]. This phenomenon initially produces a sharp increase in local AngII that gradually decreases until concentrations are well below physiologic levels [14]. Because AngII downregulates ACE-2 expression, transition to a state of AngII deficiency is consistent with the increased ACE-2 expression noted at autopsy [10]. Of note, AngII reportedly increases microvascular permeability under basal conditions but decreases permeability during inflammation, an effect attributed to the inflammation-induced shift from type-1 to type-2 receptor expression [15].

### **Implications for therapeutics and research**

Postulating that COVID-19 is a vascular and hypoinflammatory disease has important implications for ongoing research. However, more evidence is needed to explore vascular injury through biomarkers, imaging, and histology. If COVID-19 is indeed primarily a vascular disorder, early invasive mechanical ventilation should be initiated cautiously. Investigations should examine the impact of liberal versus restrictive invasive mechanical ventilation strategies.

We reiterate that there is no evidence that COVID-19 patients develop “cytokine storm.” This finding suggests that the use of cytokine-blockade agents should meet with skepticism in the absence of randomized evidence. However, anticoagulation should be a key priority for investigation. Similarly, given the putative role of AngII deficiency, a randomized trial of angiotensin-II treatment in COVID-19 patients who have progressed to shock is warranted. Illness progression may also be an effect modifier, with potential benefits of anti-inflammation and angiotensin blockade earlier in critical disease and harms at later time points.

**Conclusion**

COVID-induced respiratory failure involves physiologic, clinical, and immunologic phenotypes that are not consistent with either ARDS or cytokine-release syndromes. COVID-19 instead reflects immunosuppression and features compatible with vascular disease.



## COVID-19 Critical Illness Pathophysiology Driven by Diffuse Pulmonary Thrombi and Pulmonary Endothelial Dysfunction Responsive to Thrombolysis

Published April 21st, 2020

<https://doi.org/10.1101/2020.04.17.20057125>

### **Abstract**

Patients with severe COVID-19 disease have been characterized as having the acute respiratory distress syndrome (ARDS). Critically ill COVID-19 patients have relatively well-preserved lung mechanics despite severe gas exchange abnormalities, a feature not consistent with classical ARDS but more consistent with pulmonary vascular disease. Patients with severe COVID-19 also demonstrate markedly abnormal coagulation, with elevated D-dimers and higher rates of venous thromboembolism. We present five cases of patients with severe COVID-19 pneumonia with severe respiratory failure and shock, with evidence of markedly elevated dead-space ventilation who received tPA. All showed post treatment immediate improvements in gas exchange and/or hemodynamics. We suspect that severe COVID-19 pneumonia causes respiratory failure via pulmonary microthrombi and endothelial dysfunction. Treatment for COVID-19 pneumonia may warrant anticoagulation for milder cases and thrombolysis for more severe disease.

## COVID-19 and Dysfunctional Endothelium: The Mexican Scenario

Published May 15<sup>th</sup>, 2020

<https://doi.org/10.1016/j.arcmed.2020.05.004>

The pandemic of a new coronavirus started in December 2019 in Wuhan China and is the cause of a high percentage of the world population infected with symptoms of the Severe Acute Respiratory Syndrome (SARS), now SARS-CoV-2. The World Health Organization (WHO) named it COVID19 disease and alerted countries with vulnerable health systems to establish an urgent response (1). The clinical conditions detected in infected patients are quite similar to those observed during previous pandemics, SARS-CoV in 2003 and MERS-CoV in 2012. Age of people infected with COVID-19 ranges from 20–80 years old although most deaths occur in patients older than 60 yearold. Moreover, death is associated with chronic diseases such as hypertension, diabetes and vascular diseases (2). However, after the pandemic spreads in America, it has been observed, particularly in Mexico, that deaths occur in patients at a mean of 40–59 years old (3). According to the WHO, Mexico is between the world leading ranks in terms of chronic diseases and the consequent endothelial dysfunction. Is there an explanation for this apparent earlier age for death in Mexican patients? It has been reported that patients with COVID-19 may present venous thromboembolic disease or disseminated intravascular coagulopathy, events involving hemostatic elements as wells as the innate immune response (4). Endothelial dysfunction leads to platelet and leukocyte activation, abnormalities in the anticoagulant and fibrinolytic mechanisms and the resulting abnormalities of the blood coagulation tests and increased plasma D-dimer, circulating thrombin and activated protein C, closely associated to endothelial dysfunction, there is also increased inflammatory cytokines in which tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) has a predominant role. Patients with recurrent unprovoked venous thromboembolic disease also have both, endothelial dysfunction recognized from the early endothelial colony-forming cells (a subpopulation of circulating endothelial progenitor cells), and increased TNF- $\alpha$  synthesis which induces a chronic inflammatory state that may resemble the cytokine storm identified in patients with COVID-19 (5). It seems quite apparent that SARS-CoV-2 may induce endothelial dysfunction as suggested by the increased expression of the human angiotensin-converting enzyme type 2 (ACE2), a receptor necessary for the entry of the virus (6). Perhaps, deaths occurring in Mexico at younger age as compared with other countries may be related to the high frequency of vascular risk factors and the consequent endothelial dysfunction (Figure 1). Such chronic conditions may worsen as soon as the virus infects a young patient with chronic endothelial dysfunction. An old epidemic with a new face?

## Endothelial compromise by SARS-CoV-2

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<https://www.univadis.co.uk/viewarticle/endothelial-compromise-by-sars-cov-2-718723>

SARS-CoV-2 facilitates endotheliitis in several organs, in addition to the host's inflammatory response, according to results from a case series (n=3) reported in the Lancet. Two of the patients died.

According to current literature, SARS-CoV-2 infects the host through angiotensin-converting enzyme 2 (ACE2) receptors which are present in lung, heart, kidney, intestinal and endothelial tissues. Upon microscopic examination of these tissues from each subject, the investigators found viral elements within endothelial cells and accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. This evidence suggests that SARS-CoV-2 facilitates endotheliitis in several organs in addition to the host's inflammatory response. The authors also propose that induction of apoptosis and pyroptosis could be associated with the endothelial cell injury they observed. Therefore, endotheliitis caused by COVID-19 could underlie the systemically impaired microcirculation and some of the clinical manifestations seen in this disease.

These findings could support the use of endothelium-stabilising therapies that can also impact viral replication, such as anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins. Such an approach could be particularly useful for patients at high-risk for COVID-19 (males, smokers, hypertensives, diabetics, obese, and individuals with cardiovascular disease) that tend to have endothelial dysfunction.

# Coronavirus Disease 2019 and Stroke: Clinical Manifestations and Pathophysiological Insights

Published May 12<sup>th</sup>, 2020

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7214348/>

## Highlights

- Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Some COVID-19 patients have exhibited widespread neurological manifestations including stroke.
- Acute ischemic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis have been reported in patients with COVID-19.
- COVID-19-associated coagulopathy is likely caused by inflammation.
- Resultant ACE2 down-regulation causes RAS imbalance, which may lead to stroke.

## Abstract

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global health threat. Some COVID-19 patients have exhibited widespread neurological manifestations including stroke. Acute ischemic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis have been reported in patients with COVID-19. COVID-19-associated coagulopathy is increasingly recognized as a result of acute infection and is likely caused by inflammation, including inflammatory cytokine storm. Recent studies suggest axonal transport of SARS-CoV-2 to the brain can occur via the cribriform plate adjacent to the olfactory bulb that may lead to symptomatic anosmia. The internalization of SARS-CoV-2 is mediated by the binding of the spike glycoprotein of the virus to the angiotensin-converting enzyme 2 (ACE2) on cellular membranes. ACE2 is expressed in several tissues including lung alveolar cells, gastrointestinal tissue, and brain. The aim of this review is to provide insights into the pathophysiological stroke mechanisms in COVID-19 patients. SARS-CoV-2 can down-regulate ACE2 and, in turn, over-activate the classical renin-angiotensin system (RAS) axis and decrease the activation of the alternative RAS pathway in the brain. The consequent imbalance in vasodilation, neuroinflammation, oxidative stress, and thrombotic response may contribute to the pathophysiology of stroke during SARS-CoV-2 infection.

## Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists

Published April 1st, 2020

<https://svn.bmj.com/content/early/2020/05/07/svn-2020-000382.full>

### **Abstract**

Coronavirus disease 2019 (COVID-19) has become a pandemic disease globally. Although COVID-19 directly invades lungs, it also involves the nervous system. Therefore, patients with nervous system involvement as the presenting symptoms in the early stage of infection may easily be misdiagnosed and their treatment delayed. They become silent contagious sources or 'virus spreaders'. In order to help neurologists to better understand the occurrence, development and prognosis, we have developed this consensus of prevention and management of COVID-19. It can also assist other healthcare providers to be familiar with and recognise COVID-19 in their evaluation of patients in the clinic and hospital environment.

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## Stroke in patients with SARS-CoV-2 infection: case series

Published May 20th, 2020

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### Abstract

#### Background

Italy is one of the most affected countries by the coronavirus disease 2019 (COVID-19). The responsible pathogen is named severe acute respiratory syndrome coronavirus (SARS-CoV-2). The clinical spectrum ranges from asymptomatic infection to severe pneumonia, leading to intensive care unit admission. Evidence of cerebrovascular complications associated with SARS-CoV-2 is limited. We herein report six patients who developed acute stroke during COVID-19 infection.

#### Methods

A retrospective case series of patients diagnosed with COVID-19 using reverse-transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs, who developed clinical and neuroimaging evidence of acute stroke during SARS-CoV-2 infection.

#### Results

Six patients were identified (5 men); median age was 69 years (range 57–82). Stroke subtypes were ischemic (4, 67%) and hemorrhagic (2, 33%). All patients but one had pre-existing vascular risk factors. One patient developed encephalopathy prior to stroke, characterized by focal seizures and behavioral abnormalities. COVID-19-related pneumonia was severe (i.e., requiring critical care support) in 5/6 cases (83%). Liver enzyme alteration and lactate dehydrogenase (LDH) elevation were registered in all cases. Four patients (67%) manifested acute kidney failure prior to stroke. Four patients (67%) had abnormal coagulation tests. The outcome was poor in the majority of the patients: five died (83%) and the remaining one (17%) remained severely neurologically affected (mRS: 4).

#### Conclusions

Both ischemic and hemorrhagic stroke can complicate the course of COVID-19 infection. In our series, stroke developed mostly in patients with severe pneumonia and multiorgan failure, liver enzymes and LDH were markedly increased in all cases, and the outcome was poor.

## SARS2-CoV-2 and Stroke in a New York Healthcare System

Published May 20<sup>th</sup>, 2020

<https://doi.org/10.1161/STROKEAHA.120.030335>

### Abstract

#### Background and Purpose:

With the spread of coronavirus disease 2019 (COVID-19) during the current worldwide pandemic, there is mounting evidence that patients affected by the illness may develop clinically significant coagulopathy with thromboembolic complications including ischemic stroke. However, there is limited data on the clinical characteristics, stroke mechanism, and outcomes of patients who have a stroke and COVID-19.

#### Methods:

We conducted a retrospective cohort study of consecutive patients with ischemic stroke who were hospitalized between March 15, 2020, and April 19, 2020, within a major health system in New York, the current global epicenter of the pandemic. We compared the clinical characteristics of stroke patients with a concurrent diagnosis of COVID-19 to stroke patients without COVID-19 (contemporary controls). In addition, we compared patients to a historical cohort of patients with ischemic stroke discharged from our hospital system between March 15, 2019, and April 15, 2019 (historical controls).

#### Results:

During the study period in 2020, out of 3556 hospitalized patients with diagnosis of COVID-19 infection, 32 patients (0.9%) had imaging proven ischemic stroke. Cryptogenic stroke was more common in patients with COVID-19 (65.6%) as compared to contemporary controls (30.4%,  $P=0.003$ ) and historical controls (25.0%,  $P<0.001$ ). When compared with contemporary controls, COVID-19 positive patients had higher admission National Institutes of Health Stroke Scale score and higher peak D-dimer levels. When compared with historical controls, COVID-19 positive patients were more likely to be younger men with elevated troponin, higher admission National Institutes of Health Stroke Scale score, and higher erythrocyte sedimentation rate. Patients with COVID-19 and stroke had significantly higher mortality than historical and contemporary controls.

#### Conclusions:

We observed a low rate of imaging-confirmed ischemic stroke in hospitalized patients with COVID-19. Most strokes were cryptogenic, possibly related to an acquired hypercoagulability, and mortality was increased. Studies are needed to determine the utility of therapeutic anticoagulation for stroke and other thrombotic event prevention in patients with COVID-19.

## Call to Action: SARS-CoV-2 and Cerebrovascular Disorders (CASCADE)

Published May 7<sup>th</sup>, 2020

<https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104938>

### **Abstract**

#### **Background and Purpose**

The novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), now named coronavirus disease 2019 (COVID-19), may change the risk of stroke through an enhanced systemic inflammatory response, hypercoagulable state, and endothelial damage in the cerebrovascular system. Moreover, due to the current pandemic, some countries have prioritized health resources towards COVID-19 management, making it more challenging to appropriately care for other potentially disabling and fatal diseases such as stroke. The aim of this study is to identify and describe changes in stroke epidemiological trends before, during, and after the COVID-19 pandemic.

#### **Methods**

This is an international, multicenter, hospital-based study on stroke incidence and outcomes during the COVID-19 pandemic. We will describe patterns in stroke management, stroke hospitalization rate, and stroke severity, subtype (ischemic/hemorrhagic), and outcomes (including in-hospital mortality) in 2020 during COVID-19 pandemic, comparing them with the corresponding data from 2018 and 2019, and subsequently 2021. We will also use an interrupted time series (ITS) analysis to assess the change in stroke hospitalization rates before, during, and after COVID-19, in each participating center.

#### **Conclusion**

The proposed study will potentially enable us to better understand the changes in stroke care protocols, differential hospitalization rate, and severity of stroke, as it pertains to the COVID-19 pandemic. Ultimately, this will help guide clinical-based policies surrounding COVID-19 and other similar global pandemics to ensure that management of cerebrovascular comorbidity is appropriately prioritized during the global crisis. It will also guide public health guidelines for at-risk populations to reduce risks of complications from such comorbidities.



## Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

Published April 28th, 2020

[https://www.nejm.org/doi/full/10.1056/NEJMc2009787#article\\_citing\\_articles](https://www.nejm.org/doi/full/10.1056/NEJMc2009787#article_citing_articles)

To rapidly communicate information on the global clinical effort against Covid-19, the Journal has initiated a series of case reports that offer important teaching points or novel findings. The case reports should be viewed as observations rather than as recommendations for evaluation or treatment. In the interest of timeliness, these reports are evaluated by in-house editors, with peer review reserved for key points as needed.

We report five cases of large-vessel stroke in patients younger than 50 years of age who presented to our health system in New York City. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all five patients.

Cough, headache, and chills lasting 1 week developed in a previously healthy 33-year-old woman (Patient 1) (Table 1). She then had progressive dysarthria with both numbness and weakness in the left arm and left leg over a period of 28 hours. She delayed seeking emergency care because of fear of Covid-19. When she presented to the hospital, the score on the National Institutes of Health Stroke Scale (NIHSS) was 19 (scores range from 0 to 42, with higher numbers indicating greater stroke severity), and computed tomography (CT) and CT angiography showed a partial infarction of the right middle cerebral artery with a partially occlusive thrombus in the right carotid artery at the cervical bifurcation. Patchy ground-glass opacities in bilateral lung apices were seen on CT angiography, and testing to detect SARS-CoV-2 was positive. Antiplatelet therapy was initiated; it was subsequently switched to anticoagulation therapy. Stroke workup with echocardiography and magnetic resonance imaging of the head and neck did not reveal the source of the thrombus. Repeat CT angiography on hospital day 10 showed complete resolution of the thrombus, and the patient was discharged to a rehabilitation facility.

Over a 2-week period from March 23 to April 7, 2020, a total of five patients (including the aforementioned patient) who were younger than 50 years of age presented with new-onset symptoms of large-vessel ischemic stroke. All five patients tested positive for Covid-19. By comparison, every 2 weeks over the previous 12 months, our service has treated, on average, 0.73 patients younger than 50 years of age with large-vessel stroke.

On admission of the five patients, the mean NIHSS score was 17, consistent with severe large-vessel stroke. One patient had a history of stroke. Other pertinent clinical characteristics are summarized in Table 1.

A retrospective study of data from the Covid-19 outbreak in Wuhan, China, showed that the incidence of stroke among hospitalized patients with Covid-19 was approximately 5%; the youngest patient in that series was 55 years of age.<sup>1</sup> Moreover, large-vessel stroke was reported in association with the 2004 SARS-CoV-1 outbreak in Singapore.<sup>2</sup> Coagulopathy and vascular endothelial dysfunction have been proposed as complications of Covid-19.<sup>3</sup> The association between large-vessel stroke and Covid-19 in young patients requires further investigation.

Social distancing, isolation, and reluctance to present to the hospital may contribute to poor outcomes. Two patients in our series delayed calling an ambulance because they were concerned about going to a hospital during the pandemic.

## Testing for blood clotting abnormalities reveals which critically ill COVID-19 patients are at risk for thrombotic events and need hemodialysis

Published May 15h, 2020

<https://www.facs.org/media/press-releases/2020/blood-clotting-051520>

CHICAGO (May 15, 2020): When researchers from the University of Colorado Anschutz Medical Campus, Aurora, used a combination of two specific blood-clotting tests, they found critically ill patients infected with Coronavirus Disease 2019 (COVID-19) who were at high risk for developing renal failure, venous blood clots, and other complications associated with blood clots, such as stroke. Their study, which was one of the first to build on growing evidence that COVID-19-infected patients are highly predisposed to developing blood clots, linked blood clotting measurements with actual patient outcomes. The research team is now participating in a randomized clinical trial of a drug that breaks down blood clots in COVID-19-infected patients. "This is an early step on the road to discovering treatments to prevent some of the complications that come with this disease," said Franklin Wright, MD, FACS, lead author of the research article and an assistant professor of surgery at the University of Colorado School of Medicine. Their research is published as an "article in press" appearing on the *Journal of the American College of Surgeons* website ahead of print.

Patients who are critically ill regardless of cause can develop a condition known as disseminated intravascular coagulation (DIC). The blood of these patients initially forms many clots in small blood vessels. The body's natural clotting factors can form too much clot or eventually not be able to effectively form any clot leading to issues of both excessive clotting and excessive bleeding. However, in patients with COVID-19 the clotting appears to be particularly severe and—as evidenced by case studies in China and elsewhere<sup>1</sup>—clots in COVID-19 patients do not appear to dissipate, explained Dr. Wright.

Trauma acute care surgeons and intensive care physicians who treat trauma, transplant, and cardiothoracic surgery patients at UCHHealth University of Colorado Hospital saw the potential of using a specialized coagulation test to examine clotting issues in COVID-19 patients. Thromboelastography (TEG) is a whole blood assay that provides a broad picture of how an individual patient's blood forms clots, including how long clotting takes, how strong clots are, and how soon clots break down. TEG is highly specialized and used primarily by surgeons and anesthesiologists to evaluate the efficiency of blood clotting; it is not widely used in other clinical settings. "The COVID pandemic is opening doors for multidisciplinary collaboration so trauma acute care surgeons and intensivists can bring the tools they use in their day-to-day lives and apply them in the critical care setting to new problems," Dr. Wright said.

The researchers evaluated outcomes for all patients who had a TEG assay as part of their treatment for COVID-19 infection as well as other conventional coagulation assays, including ones that measure D-dimer levels. D-dimer is a protein fragment that is produced when a blood clot dissolves. D-dimer levels are elevated when large numbers of clots are breaking down.

A total of 44 patients treated for COVID-19 infection between March 22 and April 20 were included in the analysis. Those whose bodies were not breaking down clots most often required hemodialysis and had a higher rate of clots in the veins. These patients were identified by TEG assays showing no clot breakdown after 30 minutes and a D-dimer level greater than 2600 ng/mL. Eighty percent of patients with both affirmative test findings were placed on dialysis compared with 14 percent who tested for neither finding. Patients with affirmative test findings also had a 50 percent rate of venous blood clots compared with 0 percent for those patients with neither finding.

"These study results suggest there may be a benefit to early TEG testing in institutions that have the technology to identify COVID-19 patients who may need more aggressive anticoagulation therapy to prevent complications from clot formation," Dr. Wright said.

A clinical trial of one form of treatment is already underway. The Denver Health and Hospital Authority is leading a multi-center study that includes UHealth University of Colorado Hospital, National Jewish Health-St Joseph Hospital, Beth Israel Deaconess Medical Center, and Long Island Jewish Hospital in conjunction with Genentech, Inc., enrolling patients with COVID-19 infection in a randomized clinical trial of tissue plasminogen activator (tPA). This drug is a clot-busting, thrombolytic medicine that was first approved by the U.S. Food and Drug Administration in 1987 for the treatment of heart attack and later approved for acute massive pulmonary embolism and acute ischemic stroke.<sup>2\*</sup> The trial will assess the efficacy and safety of intravenous tPA in improving respiratory function and management of patients with aggressive blood clotting.

"This study suggests that testing whole blood clotting measurements may allow physicians to identify and treat patients with COVID-19 more effectively to prevent complications and encourage further research into therapies to prevent blood clots in these patients," Dr. Wright said.

## Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases

Published June 2020

<https://doi.org/10.1016/j.trsl.2020.04.007>

Acute respiratory failure and a systemic coagulopathy are critical aspects of the morbidity and mortality characterizing infection with severe acute respiratory distress syndrome-associated coronavirus-2, the etiologic agent of Coronavirus disease 2019 (COVID-19). We examined skin and lung tissues from 5 patients with severe COVID-19 characterized by respiratory failure ( $n=5$ ) and purpuric skin rash ( $n=3$ ). COVID-19 pneumonitis was predominantly a pauci-inflammatory septal capillary injury with significant septal capillary mural and luminal fibrin deposition and permeation of the interalveolar septa by neutrophils. No viral cytopathic changes were observed and the diffuse alveolar damage (DAD) with hyaline membranes, inflammation, and type II pneumocyte hyperplasia, hallmarks of classic acute respiratory distress syndrome, were not prominent. These pulmonary findings were accompanied by significant deposits of terminal complement components C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL)-associated serine protease (MASP)2, in the microvasculature, consistent with sustained, systemic activation of the complement pathways. The purpuric skin lesions similarly showed a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d in both grossly involved and normally-appearing skin. In addition, there was co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in the interalveolar septa and the cutaneous microvasculature of 2 cases examined. In conclusion, at least a subset of sustained, severe COVID-19 may define a type of catastrophic microvascular injury syndrome mediated by activation of complement pathways and an associated procoagulant state. It provides a foundation for further exploration of the pathophysiologic importance of complement in COVID-19, and could suggest targets for specific intervention.

# Incidence of thrombotic complications in critically ill ICU patients with COVID-19

Published June 2020

<https://www.sciencedirect.com/science/article/pii/S0049384820301201>

## Abstract

### Introduction

COVID-19 may predispose to both venous and arterial thromboembolism due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation. Reports on the incidence of thrombotic complications are however not available.

### Methods

We evaluated the incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism in all COVID-19 patients admitted to the ICU of 2 Dutch university hospitals and 1 Dutch teaching hospital.

### Results

We studied 184 ICU patients with proven COVID-19 pneumonia of whom 23 died (13%), 22 were discharged alive (12%) and 139 (76%) were still on the ICU on April 5th 2020. All patients received at least standard doses thromboprophylaxis. The cumulative incidence of the composite outcome was 31% (95%CI 20-41), of which CTPA and/or ultrasonography confirmed VTE in 27% (95%CI 17-37%) and arterial thrombotic events in 3.7% (95%CI 0-8.2%). PE was the most frequent thrombotic complication ( $n = 25$ , 81%). Age (adjusted hazard ratio (aHR) 1.05/per year, 95%CI 1.004-1.01) and coagulopathy, defined as spontaneous prolongation of the prothrombin time  $> 3$  s or activated partial thromboplastin time  $> 5$  s (aHR 4.1, 95%CI 1.9-9.1), were independent predictors of thrombotic complications.

### Conclusion

The 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high. Our findings reinforce the recommendation to strictly apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU, and are strongly suggestive of increasing the prophylaxis towards high-prophylactic doses, even in the absence of randomized evidence.

## COVID-19-Related Stroke

Published May 7<sup>th</sup>, 2020

<https://link.springer.com/article/10.1007/s12975-020-00818-9>

### **Abstract**

The COVID-19 pandemic is associated with neurological symptoms and complications including stroke. There is hypercoagulability associated with COVID-19 that is likely a “sepsis-induced coagulopathy” and may predispose to stroke. The SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2) present on brain endothelial and smooth muscle cells. ACE2 is a key part of the renin angiotensin system (RAS) and a counterbalance to angiotensin-converting enzyme 1 (ACE1) and angiotensin II. Angiotensin II is proinflammatory, is vasoconstrictive, and promotes organ damage. Depletion of ACE2 by SARS-CoV-2 may tip the balance in favor of the “harmful” ACE1/angiotensin II axis and promote tissue injury including stroke. There is a rationale to continue to treat with tissue plasminogen activator for COVID-19-related stroke and low molecular weight heparinoids may reduce thrombosis and mortality in sepsis-induced coagulopathy.

Although the precise incidence is not known, stroke is emerging as a complication of the COVID-19 pandemic. The clinical course of COVID-19 is most severe in elderly patients, in men, and in patients with comorbidities such as hypertension, diabetes, heart disease, and obesity, all risk factors for stroke. [1]. Neurological symptoms are common in COVID-19 including anosmia and hypogeusia, seizures, and strokes. In a retrospective study of 214 hospitalized COVID-19 patients from Wuhan, China, 5.7% of the severe patients suffered a stroke [2].

## Pulmonary Arterial Thrombosis in COVID-19 With Fatal Outcome

Published May 23rd, 2020

<https://www.practiceupdate.com/content/pulmonary-arterial-thrombosis-in-covid-19-with-fatal-outcome/100843>

### TAKE-HOME MESSAGE

- This single-center, prospective autopsy study examined pathologic cardiovascular changes in 11 patients with COVID-19. The patients, 73% of whom were men, were a mean age of 80.5 years. No patients had venous thromboembolism clinically suspected antemortem. Prophylactic anticoagulant therapy use was common (in 91% of patients). Signs of diffuse alveolar damage at various stages were common. All patients had thrombosis of small and mid-sized pulmonary arteries. These thromboses were associated with bronchopneumonia (6 patients) and infarction (8 patients). All patients exhibited Kupffer cell proliferation. Multiple liver changes were noted, as well as changes in other organ systems. Polymerase chain reaction was used to test for the SARS-CoV-2 virus, and it was detected in pharyngeal, bronchial, and colonic mucosa.
- Although this study included only 11 patients, it provides important information about pathologies in patients with COVID-19 and suggests that pulmonary arterial thrombosis is an important cause of death even when patients receive prophylactic anticoagulation.

These two studies address the prominence of vascular complications in COVID-19.<sup>1,2</sup> All respiratory viruses predominantly infect lung epithelial cells, with varying proclivity for different cell types (eg, ciliated vs secretory cells) and different regions of the respiratory tract (eg, nose, bronchi, alveoli). After initial infection of a localized region, respiratory viruses typically spread laterally from cell to cell within the epithelium. With some notable exceptions, respiratory viruses generally do not productively penetrate the epithelium both because of its barrier function and because receptors for viral entry are not expressed in internal cell types. Although SARS-CoV-2 infection results in a clinical course that in most ways is typical of moderately virulent respiratory viruses such as influenza and paramyxoviruses, a relatively high rate of vascular complications has been noted with SARS-CoV-2. Thrombotic complications can occur in any severe pneumonia, bacterial or viral, within the lungs or at distal sites, resulting from tissue damage and inflammation.

However, these two autopsy series both find a notably high rate of vascular thrombosis and microvascular injury within the lungs of COVID-19 patients. The study of Ackermann et al includes a comparator group of patients with influenza pneumonia, and alveolar capillary microthrombi were nine times as prevalent in patients with COVID-19.<sup>1</sup> The study of Lax et al, although similarly finding microthrombi, also noted a high prevalence of thrombi in small to mid-sized pulmonary arteries, often associated with distal lung infarction.<sup>2</sup> Besides being expressed on the apical surface of lung epithelial cells, the receptor for SARS-CoV-2, ACE2, is also expressed on endothelial cells. Ackermann et al noted extensive endothelial injury with the presence of viral particles within endothelial cells and a higher rate of reparative angiogenesis than in influenza patients.

Together, these studies suggest that a relatively unique feature of COVID-19 is the translocation of virus across the respiratory epithelium with infection of endothelial cells, resulting in microvascular and arterial thrombosis that may contribute to pathogenesis beyond the diffuse alveolar damage characteristic of other viral pneumonias.

## Venous Thromboembolism in SARS-CoV-2 Patients: Only a Problem in Ventilated ICU Patients, or Is There More to It?

Published May 12, 2020

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7236825/>

### Short abstract

The insidious VTE seems mainly a problem in the ICU ventilated patients, while patients in the general ward, treated with thromboprophylaxis (0.5 mg/kg), had a low incidence of insidious VTE.

### To the editors

Venous thromboembolism (VTE) is a well-known complication in hospitalised patients [1–5]. Risk factors include older age, obesity, immobilisation, active malignancy, systemic inflammatory response syndrome (SIRS), (major) surgery, thrombophilia, and a history of thromboembolism [2, 5]. Rudolph Virchow first described in 1884 its underlying pathophysiological mechanism and consists of endothelial cell dysfunction/inflammation, low blood flow, and blood hypercoagulability. Current guidelines recommend the use of thromboprophylaxis in acutely ill medical patients who are at high risk for VTE (Padua score $\geq$ 4, IMPROVE score $\geq$ 2) [6]. However, in medical practice, less than half of the patients at risk receive adequate thromboprophylaxis [4]. In light of the current worldwide SARS-CoV-2 outbreak, medical wards are confronted with increased numbers of acute severely ill patients. It is estimated that one in five SARS-CoV-2 infected patients require hospitalisation with a median stay of 11 days [7]. Together with older age (>65 years) and higher SOFA-score (>4), elevated D-dimer levels (>1  $\mu$ g/mL) are associated with in-hospital death [7]. D-dimer levels are a well-known but non-specific biomarker for VTE, and they could indicate hypercoagulability. Elevated D-dimer levels also indicate inflammation. D-dimer levels are elevated in many other conditions than VTE, and its specificity for VTE diagnosis is low [7]". Among hospitalised SARS-CoV-2 patients, 68% had D-dimer levels above the upper limit of normal, suggesting hypercoagulability in these patients [7]. Up to now, there is no clear association between SARS-CoV-2 infection and the presence of VTE besides a few case reports [9, 10]. Nevertheless, it seems that these patients are at increased risk for VTE. Firstly, elevated levels of pro-inflammatory cytokines are found in patients infected with SARS-CoV-2 leading to a highly inflammatory state in these patients [7]. Secondly, similar to the previous SARS-coronavirus epidemic, angiotensin receptor 2 has been identified as a receptor SARS-CoV-2 uses for cellular entry [11]. This receptor is highly expressed on the membrane of endothelial cells, and this could lead to endothelial cell-specific inflammation/dysfunction due to viral replication in these cells [12].

We assessed all patients hospitalised in the intensive care unit (ICU) and non-ICU ward of our center the April 3rd, 2020. At that time in Belgium, 7297 patients were hospitalised due to SARS-CoV-2, the province Limburg had the highest incidence, 2607 infected patients, corresponding with 3 infected patients per 1000 inhabitants. Patients in a palliative phase and/or not contributive, mostly due to agitation or impaired mental status, were excluded. Insidious VTE was investigated using a doppler echography of the upper and lower limbs. ICU patients daily received 2 $\times$ 40 mg enoxaparin. Patients above 100 kg received 2 $\times$ 60 mg enoxaparin. In the non-ICU population, patients daily received 1 $\times$ 40 mg enoxaparin. Patients above 100 kg received 1 $\times$ 60 mg enoxaparin. None of the patients was on unfractionated heparin. For the statistical analysis, where appropriate, Mann-Whitney or Chi-squared test was used for the analysis of patient's characteristics using GraphPad Prism version 5.0.



In total 82 patients were screened, 52 in the general ward, and 30 in ICU. In ICU, 21 out of 30 patients were ventilated, none was on extracorporeal membrane oxygenation (ECMO); the other 9 patients received nasal high flow oxygen (Optiflow™). In total 6 patients (7.3%) had an insidious VTE (flowchart). In the ICU, four patients had insidious VTE; all of these patients were ventilated. Among the 52 patients from the general ward, two patients had an insidious VTE, of which 1 had a risk factor (active stage IV cancer). If we consider the 49 patients (out of the 52) who benefited of prophylaxis, only 1 of them developed VTE (1/49=2%), compared to the incidence of VTE of 4/30 (13%) in ICU ward. None of the patients who accidentally (n=2) did not receive thromboprophylaxis, developed a VTE. The patient demographics were comparable between the ICU and non-ICU (table 1). In both groups, overweight seems a clinically relevant issue in hospitalisation SARS-CoV-2. Patients in ICU had lower renal clearance at admission. No difference in D-dimer levels and cardiac enzymes were observed between both groups. Hypertension and diabetes were more prevalent in the cohort, without a difference between both groups. Mortality in the ICU group was until 22th April 4 out of 30 patients (13%) and in the non-ICU ward 5 out of 52 (9.6%).

The current observation confirms a possible problem of thromboembolic events in SARS-CoV-2 critically ill ventilated patients. The insidious VTE seems mainly a problem in the ICU ventilated patients, while patients in the general ward, treated with thromboprophylaxis, had a low incidence of insidious VTE. In our cohort, two patients had an insidious VTE in the non-ICU population, and both had an apparent predisposing risk factor. One other patient had a tiny clot in the left internal jugular vein. This is also described in another viral disease like influenza A [13], although in this case, without any findings of thrombosis in neither one of the lower limbs. Cultures were negative, no signs of sepsis. Control after 3 days was negative for any VTE.

VTE with adequate thromboprophylaxis is prevalent in 5 to 15% of critically ill patients in an ICU [14]. In this cohort, we describe 13%, in line with previous data. Thromboprophylaxis failure (n=5) in our cohort (ICU and non-ICU) was 6.1%, comparable with landmark studies MEDODOX [15] for non-critical ill patients and PROTECT [16] for critically ill patients where thromboprophylaxis failure of 5–6% is reported. In the ventilated SARS-CoV-2 population, 4/21 (19%) developed VTE. Until now, no clear correlation with the underlying disease is found. These results were somewhat lower than previously published studies. In the Cui *et al.* study, authors reported an incidence of VTE in 25% of the patients, while they did not receive thromboprophylaxis [17]. In the Klok *et al.* study, authors reported that 27% developed VTE, with inclusion of pulmonary embolism [18]. As a remark should we address that the incidence in our study of VTE is possibly underestimated since we only looked at VTE in the lower and upper limbs. Due to practical reasons and disease severity, no CTscan was performed in all patients. As so, pulmonary embolism was not included in this study.

D-dimer levels at presentation seem to be no clear marker for the development of insidious VTE or outcome in our cohort, probably due to the evaluated levels that we detect in our whole SARS-CoV-2 population. The VTE cohort (n=6) is too small to do adequate analysis and draw a conclusion on the patients with VTE and the predictive value of d-dimer levels. Further, as previously described in other cohorts, overweight, hypertension, and diabetes are risk factors for hospitalisation due to SARS-CoV-2 [19].

In conclusion, we believe these single-center data could be relevant as preliminary data on a hot topic as thromboprophylaxis in the SARS-CoV-2 population. Further data and follow-up data are needed to confirm if SARS-CoV-2, as a risk factor for thromboembolic events.

## D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19

Published April 19<sup>th</sup>, 2020

<https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14859>

### **Abstract**

#### **Background**

The outbreak of the coronavirus disease 2019 (Covid-19) has shown a global spreading trend. Early and effective predictors of clinical outcomes are urgently needed to improve management of Covid-19 patients.

#### **Objective**

The aim of the present study was to evaluate whether elevated D-dimer levels could predict mortality in patients with Covid-19.

#### **Methods**

Patients with laboratory confirmed Covid-19 were retrospective enrolled in Wuhan Asia General Hospital from January 12, 2020, to March 15, 2020. D-dimer levels on admission and death events were collected to calculate the optimum cutoff using receiver operating characteristic curves. According to the cutoff, the subjects were divided into two groups. Then the in-hospital mortality between two groups were compared to assess the predictive value of D-dimer level.

#### **Results**

A total of 343 eligible patients were enrolled in the study. The optimum cutoff value of D-dimer to predict in-hospital mortality was 2.0 µg/mL with a sensitivity of 92.3% and a specificity of 83.3%. There were 67 patients with D-dimer ≥2.0 µg/mL, and 267 patients with D-dimer <2.0 µg/mL on admission. 13 deaths occurred during hospitalization. Patients with D-dimer levels ≥2.0 µg/mL had a higher incidence of mortality when comparing with those who with D-dimer levels <2.0 µg/mL (12/67 vs 1/267, P < .001; hazard ratio, 51.5; 95% confidence interval, 12.9-206.7).

#### **Conclusions**

D-dimer on admission greater than 2.0 µg/mL (fourfold increase) could effectively predict in-hospital mortality in patients with Covid-19, which indicated D-dimer could be an early and helpful marker to improve management of Covid-19 patients. (Chinese Clinical Trial Registry: ChiCTR2000031428).

## Coronaviruses and the cardiovascular system: acute and long-term implications

Published March 18<sup>th</sup>, 2020

<https://academic.oup.com/eurheartj/article/41/19/1798/5809453>

### **Abstract**

The recent outbreak of coronavirus disease 2019 (COVID-19) provides a further challenge in the battle against outbreaks of novel virus infections and has been declared a public health emergency of international concern. Much has been learnt in the course of preceding epidemics, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza, and it is now recognized that their overall health burden may be under-estimated since extra-pulmonary manifestations are frequent.<sup>1</sup> Acute and chronic cardiovascular complications of pneumonia are common and result from various mechanisms, including relative ischaemia, systemic inflammation, and pathogen-mediated damage. There is, however, only limited published data concerning cardiovascular presentations in the wake of viral epidemics. The present COVID-19 outbreak emphasizes the need for greater awareness of the immediate and long-term cardiovascular implications of viral infection and the significant gaps in knowledge that future research will need to address.

# Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

Published April 24<sup>th</sup>, 2020

<https://www.sciencedirect.com/science/article/pii/S0049384820301407>

## Highlights

- COVID-19 is characterized by coagulation activation and endothelial dysfunction. Few data are available on thromboembolic complications.
- We studied symptomatic patients with laboratory-proven COVID-19 admitted to a university hospital in Milan, Italy (13.02-10.04.2020).
- Venous and arterial thromboembolic events occurred in 8% of hospitalized patients (cumulative rate 21.0%) and 50% of events were diagnosed within 24 h of hospital admission.
- Forty-four (11% of total) patients underwent VTE imaging tests; 16 were positive (36% of tests), suggesting underestimation of thromboembolic complications.
- There is an urgent need to investigate VTE diagnostic strategies and the impact of thromboprophylaxis in ambulatory COVID-19 patients.

## Abstract

### Background

Few data are available on the rate and characteristics of thromboembolic complications in hospitalized patients with COVID-19.

### Methods

We studied consecutive symptomatic patients with laboratory-proven COVID-19 admitted to a university hospital in Milan, Italy (13.02.2020–10.04.2020). The primary outcome was any thromboembolic complication, including venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS)/myocardial infarction (MI). Secondary outcome was overt disseminated intravascular coagulation (DIC).

### Results

We included 388 patients (median age 66 years, 68% men, 16% requiring intensive care [ICU]). Thromboprophylaxis was used in 100% of ICU patients and 75% of those on the general ward. Thromboembolic events occurred in 28 (7.7% of closed cases; 95%CI 5.4%–11.0%), corresponding to a cumulative rate of 21% (27.6% ICU, 6.6% general ward). Half of the thromboembolic events were diagnosed within 24 h of hospital admission. Forty-four patients underwent VTE imaging tests and VTE was confirmed in 16 (36%). Computed tomography pulmonary angiography (CTPA) was performed in 30 patients, corresponding to 7.7% of total, and pulmonary embolism was confirmed in 10 (33% of CTPA). The rate of ischemic stroke and ACS/MI was 2.5% and 1.1%, respectively. Overt DIC was present in 8 (2.2%) patients.

### Conclusions

The high number of arterial and, in particular, venous thromboembolic events diagnosed within 24 h of admission and the high rate of positive VTE imaging tests among the few COVID-19 patients tested suggest that there is an urgent need to improve specific VTE diagnostic strategies and investigate the efficacy and safety of thromboprophylaxis in ambulatory COVID-19 patients.

## Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening

Published April 22<sup>nd</sup>, 2020

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7175449/>

The COVID-19 outbreak in Wuhan city, China, in December 2019 has rapidly spread up to the level of Pandemia at the beginning of March 2020. A recent report from China has identified high inflammatory status as a predictor of adverse outcome, suggesting that mortality might be due to virally driven hyper-inflammation status [1].

There is a well-established link between inflammation and increased risk of deep vein thrombosis (DVT). A potential explanation is that vessel wall inflammation initiates thrombus formation, through the activation of endothelial cells, platelets, and leukocytes that trigger the coagulation pathway [2, 3]. Additionally, procoagulant state has long been recognized also as part of ARDS pathophysiology, demonstrated by the identification of diffuse pulmonary endothelial injury associated with platelets' activation, macro- and micro-thrombi thought to be either embolic, formed in situ or both [4]. Moreover, the interaction pathway among platelets, neutrophils, and endothelial cells' dysfunction in ARDS has been associated with deep vein thrombosis development [2]. High prevalence of acute pulmonary embolism (APE) has been recently reported in patients admitted with COVID-19-related pneumonia [5].

We report the prevalence of venous thrombotic events in patients consecutively admitted to the ICU of a Hub Hospital for SARS-CoV-2 since the beginning of the Italian outbreak infection on February 21, 2020. Informed consent was collected following the *ad hoc* procedures defined by the Ethics Committee for the COVID-19 pandemic.

All patients were sedated, mechanically ventilated and treated with prophylactic low-molecular-weight heparin (LMWH) adjusted on body weight since the admission.

Eight out of 54 patients (14.8%) were diagnosed with deep vein thrombosis, 6 of which were central catheter-related. Additionally, one patient had a thrombotic formation attached to the tricuspid valve in the absence of predisposing factors. Sub-segmental pulmonary embolism was found in two patients examined with computed tomography pulmonary angiography (CTPA) and one patient died of cardiac arrest with pulseless electrical activity (PEA) as presentation rhythm and sudden right ventricular dilatation.

In our experience 22.2% of patients (83% male, 68±7 years old; BMI 29.3±4.4 kg/m<sup>2</sup>; C-reactive protein 25.7±9.2 mg/dl, fibrinogen 657.1±200.6 mg/dl) admitted to ICU due to SARS-CoV-2 interstitial pneumonia had venous thrombotic events (Fig. 1).

ICU admission and ARDS are considered both predisposing factors for a number of reasons, including the need for prolonged immobilization and hyper-inflammatory state. The prevalence of vein thrombosis in patients admitted with ARDS is currently unknown.

A recent report showed that 10 out of 25 patients admitted with pneumonia due to COVID-19 presented sub-segmental APE, assessed with CPTA. No associated deep vein thrombosis was reported as the authors did not perform ultrasound screening.

Because of the pathophysiological link between inflammation and thrombosis development [3], especially in critically ill patients, the hyper-inflammatory status of patients with COVID-19 [1] and the high

prevalence of APE [5] and of vein thrombotic events found in our population, we strongly suggest that a close vein ultrasound screening and monitoring should be performed in all patients hospitalized due to SARS-CoV-2-related infection. Additionally, right ventricular dilatation/dysfunction should trigger the suspicion of APE.

## Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2

Published April 20th, 2020

<https://pubmed.ncbi.nlm.nih.gov/32311843/>

### **Abstract**

In March 2020, the global healthcare system is overwhelmed by patients infected with SARS-CoV-2, which is the cause of the coronavirus pandemic (Covid-2019). A large number of these patients end up in the intensive care units (ICU) with critical illness requiring mechanical ventilation. One of the most important clinical features of the infection is a profound coagulopathy. In a recent cohort study 71% of patients who eventually died matched the ISTH criteria for disseminated intravascular coagulation (DIC), while this percentage was only 0.6% in patients who survived.

## Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

Published May 6<sup>th</sup>, 2020

<https://doi.org/10.7326/M20-2003>

### **Abstract**

#### **Background:**

The new coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS–CoV-2), has caused more than 210 000 deaths worldwide. However, little is known about the causes of death and the virus's pathologic features.

#### **Objective:**

To validate and compare clinical findings with data from medical autopsy, virtual autopsy, and virologic tests.

#### **Design:**

Prospective cohort study.

#### **Setting:**

Autopsies performed at a single academic medical center, as mandated by the German federal state of Hamburg for patients dying with a polymerase chain reaction–confirmed diagnosis of COVID-19.

#### **Patients:**

The first 12 consecutive COVID-19–positive deaths.

#### **Measurements:**

Complete autopsy, including postmortem computed tomography and histopathologic and virologic analysis, was performed. Clinical data and medical course were evaluated.

Results: Median patient age was 73 years (range, 52 to 87 years), 75% of patients were male, and death occurred in the hospital (n = 10) or outpatient sector (n = 2). Coronary heart disease and asthma or chronic obstructive pulmonary disease were the most common comorbid conditions (50% and 25%, respectively). Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients. Postmortem computed tomography revealed reticular infiltration of the lungs with severe bilateral, dense consolidation, whereas histomorphologically diffuse alveolar damage was seen in 8 patients. In all patients, SARS–CoV-2 RNA was detected in the lung at high concentrations; viremia in 6 of 10 and 5 of 12 patients demonstrated high viral RNA titers in the liver, kidney, or heart.

#### **Limitation:**

Limited sample size.

#### **Conclusion:**

The high incidence of thromboembolic events suggests an important role of COVID-19–induced coagulopathy. Further studies are needed to investigate the molecular mechanism and overall clinical incidence of COVID-19–related death, as well as possible therapeutic interventions to reduce it.



# High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients

Published April 22<sup>nd</sup>, 2020

<https://doi.org/10.1111/jth.14869>

## **Abstract**

### **Background**

Coagulopathy is a common abnormality in patients with COVID-19. However, the exact incidence of venous thromboembolic event is unknown in anticoagulated, severe COVID-19 patients.

### **Objectives**

Systematic assessment of venous thromboembolism (VTE) using complete duplex ultrasound (CDU) in anticoagulated COVID-19 patients.

### **Patients and methods**

We performed a retrospective study in 2 French intensive care units (ICU) where CDU is performed as a standard of care. A CDU from thigh to ankle at selected sites with Doppler waveforms and images was performed early during ICU stay in patients admitted with COVID-19. Anticoagulation dose was left to the discretion of the treating physician based on the individual risk of thrombosis. Patients were classified as treated with prophylactic anticoagulation or therapeutic anticoagulation. Pulmonary embolism was systematically searched in patients with persistent hypoxemia or secondary deterioration.

### **Results**

From March 19 to April 11, 2020, 26 consecutive patients with severe COVID-19 were screened for VTE. Eight patients (31%) were treated with prophylactic anticoagulation, whereas 18 patients (69%) were treated with therapeutic anticoagulation. The overall rate of VTE in patients was 69%. The proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared with the other group (100% vs 56%, respectively,  $P = .03$ ). Surprisingly, we found a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation, with 56% of VTE and 6 pulmonary embolisms.

### **Conclusion**

Our results suggest considering both systematic screening of VTE and early therapeutic anticoagulation in severe ICU COVID-19 patients.

## High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Published May 4<sup>th</sup>, 2020

<https://pubmed.ncbi.nlm.nih.gov/32367170/>

### **Abstract**

**Purpose:** Little evidence of increased thrombotic risk is available in COVID-19 patients. Our purpose was to assess thrombotic risk in severe forms of SARS-CoV-2 infection.

**Methods:** All patients referred to 4 intensive care units (ICUs) from two centers of a French tertiary hospital for acute respiratory distress syndrome (ARDS) due to COVID-19 between March 3rd and 31st 2020 were included. Medical history, symptoms, biological data and imaging were prospectively collected. Propensity score matching was performed to analyze the occurrence of thromboembolic events between non-COVID-19 ARDS and COVID-19 ARDS patients.

**Results:** 150 COVID-19 patients were included (122 men, median age 63 [53; 71] years, SAPSII 49 [37; 64] points). Sixty-four clinically relevant thrombotic complications were diagnosed in 150 patients, mainly pulmonary embolisms (16.7%). 28/29 patients (96.6%) receiving continuous renal replacement therapy experienced circuit clotting. Three thrombotic occlusions (in 2 patients) of centrifugal pump occurred in 12 patients (8%) supported by ECMO. Most patients (> 95%) had elevated D-dimer and fibrinogen. No patient developed disseminated intravascular coagulation. Von Willebrand (vWF) activity, vWF antigen and FVIII were considerably increased, and 50/57 tested patients (87.7%) had positive lupus anticoagulant. Comparison with non-COVID-19 ARDS patients (n = 145) confirmed that COVID-19 ARDS patients (n = 77) developed significantly more thrombotic complications, mainly pulmonary embolisms (11.7 vs. 2.1%,  $p < 0.008$ ). Coagulation parameters significantly differed between the two groups.

**Conclusion:** Despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. Higher anticoagulation targets than in usual critically ill patients should therefore probably be suggested.

## Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past

Published April 9<sup>th</sup>, 2020

<https://www.sciencedirect.com/science/article/pii/S1386653220301049>

### **Abstract**

Coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus strain disease, has recently emerged in China and rapidly spread worldwide. This novel strain is highly transmittable and severe disease has been reported in up to 16% of hospitalized cases. More than 600,000 cases have been confirmed and the number of deaths is constantly increasing. COVID-19 hospitalized patients, especially those suffering from severe respiratory or systemic manifestations, fall under the spectrum of the acutely ill medical population, which is at increased venous thromboembolism risk. Thrombotic complications seem to emerge as an important issue in patients infected with COVID-19. Preliminary reports on COVID-19 patients' clinical and laboratory findings include thrombocytopenia, elevated D-dimer, prolonged prothrombin time, and disseminated intravascular coagulation. As the pandemic is spreading and the whole picture is yet unknown, we highlight the importance of coagulation disorders in COVID-19 infected patients and review relevant data of previous coronavirus epidemics caused by the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV).

## Sex-Specific SARS-CoV-2 Mortality: Among Hormone-Modulated ACE2 Expression, Risk of Venous Thromboembolism and Hypovitaminosis D

Published April 22<sup>nd</sup>, 2020

<https://www.mdpi.com/1422-0067/21/8/2948>

### **Abstract**

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) disease (COVID-19) appears to have a higher mortality rate in presence of comorbidities and in men. The latter suggests the presence of a possible sex-dependent susceptibility. An enzymatic system involved in this different predisposition could be represented by angiotensin converting enzyme 2 (ACE2). ACE2 is activated and down-regulated by the spike protein of the virus and allows the penetration of SARS-CoV-2 into epithelial cells and myocardium. Data on the experimental animal have shown that 17 $\beta$ -estradiol increases the expression and activity of ACE2 in both adipose tissue and kidney. Spontaneously hypertensive male mice have a higher myocardial ACE2 expression than females and its levels decrease after orchiectomy. In addition to this first aspect, the recent evidence of an increased frequency of venous thromboembolism in patients with COVID-19 (a clinical element associated with a worse prognosis) calls the attention on the safety of treatment with testosterone, in particular in hypogonadal men with greater genetic predisposition. Evidence that sex hormones are able to modulate the expression of ACE2 could help in interpreting epidemiological results and in designing more appropriate intervention strategies. Moreover, the vitamin D deficiency in elderly men may be worthy of further study regarding the epidemiological aspects of this different susceptibility and lethality between sexes.

## Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia

Published April 9<sup>th</sup>, 2020

<https://pubmed.ncbi.nlm.nih.gov/32271988/>

### **Abstract**

**Background:** Three months ago, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan, China, and spread rapidly around the world. Severe novel coronavirus pneumonia (NCP) patients have abnormal blood coagulation function, but their venous thromboembolism (VTE) prevalence is still rarely mentioned.

**Objectives:** To determine the incidence of VTE in patients with severe NCP.

**Methods:** In this study, 81 severe NCP patients in the intensive care unit (ICU) of Union Hospital (Wuhan, China) were enrolled. The results of conventional coagulation parameters and lower limb vein ultrasonography of these patients were retrospectively collected and analyzed.

**Results:** The incidence of VTE in these patients was 25% (20/81), of which 8 patients with VTE events died. The VTE group was different from the non-VTE group in age, lymphocyte counts, activated partial thromboplastin time (APTT), D-dimer, etc. If 1.5 µg/mL was used as the D-dimer cut-off value to predicting VTE, the sensitivity was 85.0%, the specificity was 88.5%, and the negative predictive value (NPV) was 94.7%.

**Conclusions:** The incidence of VTE in patients with severe NCP is 25% (20/81), which may be related to poor prognosis. The significant increase of D-dimer in severe NCP patients is a good index for identifying high-risk groups of VTE.

## Coagulation Abnormalities and Thrombosis in Patients With COVID-19

Published June 8<sup>th</sup>, 2020

<https://www.practiceupdate.com/c/101558/75/24/?elsca1=>

### TAKE-HOME MESSAGE

- This is a short review that focuses on the coagulation abnormalities in patients with COVID-19. Summarizing the latest data, the authors suggest that the coagulopathy associated with COVID-19 is a combination of low-grade disseminated intravascular coagulation and localized pulmonary thrombotic microangiopathy.
- The authors suggest routine monitoring of prothrombin time, platelet count, and D-dimer levels every 2–3 days and encourage the use of thromboprophylaxis.

### Abstract

Although most patients with coronavirus disease 2019 (COVID-19) predominantly have a respiratory tract infection, a proportion of patients progress to a more severe and systemic disease, characterised by treatment-resistant pyrexia, acute lung injury with acute respiratory distress syndrome (ARDS), shock, and multiple organ dysfunction, associated with substantial mortality.<sup>1</sup> Many patients with severe COVID-19 present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy, but COVID-19 has distinct features.<sup>2</sup> Coagulopathy in patients with COVID-19 is associated with an increased risk of death.<sup>3</sup> Furthermore, the relevance of COVID-19-coagulation abnormalities are becoming increasingly clear as a substantial proportion of patients with severe COVID-19 develop, sometimes unrecognised, venous and arterial thromboembolic complications.<sup>4,5</sup> In this Comment we summarise the characteristics of COVID-19 coagulopathy, coagulation laboratory findings in affected patients, the prohaemostatic state and incidence of thromboembolic events, and potential therapeutic interventions.

## Venous Thrombosis Among Critically Ill Patients With COVID-19

Published June 8<sup>th</sup>, 2020

<https://www.practiceupdate.com/c/101556/75/24/?elsca1=>

### TAKE-HOME MESSAGE

- In this study, 34 consecutive COVID-19 patients admitted to an intensive care unit in France had lower-extremity venous ultrasounds on admission and at 48 hours. Of the total patients, 22 (65%) had deep vein thrombosis (DVT) on admission, and 27 patients (79%) had DVT by 48 hours. The population also had elevated D-dimer, fibrinogen, and C-reactive protein levels.
- With 15% of patients developing VTE within 48 hours of admission while on thromboprophylaxis, this small single-center study adds to accumulating evidence of hypercoagulability in COVID-19 patients.

### Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) was identified as a new coronavirus causing pneumonia and acute respiratory distress syndrome. It has become a pandemic, spreading particularly quickly across Europe and the US. Most deaths are related to severe acute respiratory distress syndrome, but other organ failures, such as acute kidney failure and acute cardiac injury, seem also related to the disease.<sup>1</sup> Inflammatory response is highly increased in coronavirus disease 2019 (COVID-19) infection, and inflammation is known to favor thrombosis. High dimerized plasmin fragment D (D-dimer) levels and procoagulant changes in coagulation pathways were reported among patients with severe COVID-19.<sup>2,3</sup> An elevated rate of venous and arterial thrombotic events associated with COVID-19 infection has also been reported.<sup>4,5</sup> This case series reports a systematic assessment of deep vein thrombosis among patients in an intensive care unit (ICU) in France with severe COVID-19.

## Delays in Stroke Onset to Hospital Arrival Time in COVID-19

Published June 5<sup>th</sup>, 2020

<https://www.practiceupdate.com/c/101136/75/24/?elsca1=>

### TAKE-HOME MESSAGE

- This retrospective, single-center compared the characteristics of 73 patients with TIA or stroke during the COVID-19 pandemic with those of 89 patients who experienced TIA or stroke prior to the pandemic during the same weeks in 2019. The two groups of patients were similar in terms of age, gender, stroke severity, and vascular risk factors. The median stroke onset-to-door time was 154 minutes for the COVID-19 group and 95 minutes for the pre-COVID-19 group ( $P = .12$ ). Compared with the pre-COVID-19 group, a significantly lower proportion of individuals in the COVID-19 group had an onset-to-door time less than 4.5 hours. Referrals to the TIA clinic were similar during the pre-COVID-19 and COVID-19 periods. During the COVID-19 period, fewer patients presented to the hospital with TIA than during the pre-COVID-19 period.
- These data suggest that some patients experienced delays in obtaining treatment for stroke and TIA and that there is a need to encourage patients to seek treatment when needed.

### BACKGROUND AND PURPOSE

The current coronavirus disease 2019 (COVID-19) pandemic represents a global public health crisis, disrupting emergency healthcare services. We determined whether COVID-19 has resulted in delays in stroke presentation and affected the delivery of acute stroke services in a comprehensive stroke center in Hong Kong.

### METHODS

We retrospectively reviewed all patients with transient ischemic attack and stroke admitted via the acute stroke pathway of Queen Mary Hospital, Hong Kong, during the first 60 days since the first diagnosed COVID-19 case in Hong Kong (COVID-19: January 23, 2020-March 24, 2020). We compared the stroke onset to hospital arrival (onset-to-door) time and timings of inpatient stroke pathways with patients admitted during the same period in 2019 (pre-COVID-19: January 23, 2019-March 24, 2019).

### RESULTS

Seventy-three patients in COVID-19 were compared with 89 patients in pre-COVID-19. There were no significant differences in age, sex, vascular risk factors, nor stroke severity between the 2 groups ( $P > 0.05$ ). The median stroke onset-to-door time was  $\approx 1$ -hour longer in COVID-19 compared with pre-COVID-19 (154 versus 95 minutes,  $P = 0.12$ ), and the proportion of individuals with onset-to-door time within 4.5 hours was significantly lower (55% versus 72%,  $P = 0.024$ ). Significantly fewer cases of transient ischemic attack presented to the hospital during COVID-19 (4% versus 16%,  $P = 0.016$ ), despite no increase in referrals to the transient ischemic attack clinic. Inpatient stroke pathways and treatment time metrics nevertheless did not differ between the 2 groups ( $P > 0.05$  for all comparisons).

### CONCLUSIONS

During the early containment phase of COVID-19, we noted a prolongation in stroke onset to hospital arrival time and a significant reduction in individuals arriving at the hospital within 4.5 hours and presenting with transient ischemic attack. Public education about stroke should continue to be reinforced during the COVID-19 pandemic.



# Treatment of Acute Ischemic Stroke Due to Large Vessel Occlusion With COVID-19

Published June 15<sup>th</sup>, 2020

<https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.030574>

## TAKE-HOME MESSAGE

Among 10 patients with COVID-19 treated for acute ischemic stroke due to large-vessel occlusion, 7 had no symptoms or mild symptoms of COVID-19 at the onset of the stroke. There was a median time of 6 days from COVID-19 symptoms to stroke onset. Within 3 hours of symptoms, all patients had brain imaging, and 5 patients had multi-territory large-vessel occlusion. All patients had mechanical thrombectomy, and 5 patients received alteplase therapy; 9 patients had successful recanalization. None of the patients experienced any neurological improvement early on, and 60% of the patients died in the hospital.

In patients with COVID-19, the best medical care resulted in poor outcomes. Taking into account inflammatory and coagulation disorders associated with COVID-19, a different pharmacological approach may be needed to treat these patients.

## BACKGROUND AND PURPOSE:

Higher rates of strokes have been observed in patients with coronavirus disease 2019 (COVID-19), but data regarding the outcomes of COVID-19 patients suffering from acute ischemic stroke due to large vessel occlusion (LVO) are lacking. We report our initial experience in the treatment of acute ischemic stroke with LVO in patients with COVID-19.

## METHODS:

All consecutive patients with COVID-19 with acute ischemic stroke due to LVO treated in our institution during the 6 first weeks of the COVID-19 outbreak were included. Baseline clinical and radiological findings, treatment, and short-term outcomes are reported.

## RESULTS:

We identified 10 patients with confirmed COVID-19 treated for an acute ischemic stroke due to LVO. Eight were men, with a median age of 59.5 years. Seven had none or mild symptoms of COVID-19 at stroke onset. Median time from COVID-19 symptoms to stroke onset was 6 days. All patients had brain imaging within 3 hours from symptoms onset. Five patients had multi-territory LVO. Five received intravenous alteplase. All patients had mechanical thrombectomy. Nine patients achieved successful recanalization (mTICI2B-3), none experienced early neurological improvement, 4 had early cerebral reocclusion, and a total of 6 patients (60%) died in the hospital.

## CONCLUSION:

Best medical care including early intravenous thrombolysis, and successful and prompt recanalization achieved with mechanical thrombectomy, resulted in poor outcomes in patients with COVID-19. Although our results require further confirmation, a different pharmacological approach (antiplatelet or other) should be investigated to take in account inflammatory and coagulation disorders associated with COVID-19.

## Coagulation, thromboembolic complications and the use of heparin in COVID-19 Pneumonia

Published May 22<sup>nd</sup>, 2020

[https://www.jvsvenous.org/article/S2213-333X\(20\)30342-5/fulltext?dgcid=raven\\_jbs\\_aip\\_email](https://www.jvsvenous.org/article/S2213-333X(20)30342-5/fulltext?dgcid=raven_jbs_aip_email)

### ABSTRACT

The SARS-CoV-2 (COVID-19) is causing a pandemic and potentially fatal disease, actually of global public health concern. Viral infections are known to be associated with coagulation impairment thus thrombosis, hemorrhage, or both, may occur. Understanding the pathophysiological mechanisms underlying the development of coagulation disorders during viral infection is essential for the development of therapeutic strategies. Coagulopathy in COVID-19 infection is emerging as a precipitant factor for severe respiratory complications and death. An increase in coagulation markers such as fibrinogen and D-Dimer has been found in severe COVID-19 cases. Heparin, clinically used as an anticoagulant, has also anti-inflammatory properties including binding of inflammatory cytokines, inhibition of neutrophil chemotaxis, protection of endothelial cells and a potential antiviral effect. We hypothesized that low molecular weight heparin (LMWH) may attenuate cytokine storm in COVID-19 patients therefore LMWH could be a valid adjunctive therapeutic drug for the treatment of COVID-19 pneumopathy. In this paper we review potential mechanisms involved in coagulation impairment following viral infection and the possible role of heparin in the treatment of COVID-19 patients

## COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up

Published June 23<sup>rd</sup>, 2020

<https://www.onlinejacc.org/content/75/23/2950>

### **ABSTRACT**

Coronavirus disease-2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), may predispose patients to thrombotic disease, both in the venous and arterial circulations, because of excessive inflammation, platelet activation, endothelial dysfunction, and stasis. In addition, many patients receiving antithrombotic therapy for thrombotic disease may develop COVID-19, which can have implications for choice, dosing, and laboratory monitoring of antithrombotic therapy. Moreover, during a time with much focus on COVID-19, it is critical to consider how to optimize the available technology to care for patients without COVID-19 who have thrombotic disease. Herein, the authors review the current understanding of the pathogenesis, epidemiology, management, and outcomes of patients with COVID-19 who develop venous or arterial thrombosis, of those with pre-existing thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic.

# Clinical Characteristics of Acute Lower Extremity Deep Venous Thrombosis Diagnosed by Duplex in Patients Hospitalized for Coronavirus Disease (COVID-19)

Published 25<sup>th</sup> June, 2020

[https://www.jvsvenous.org/article/S2213-333X\(20\)303486/fulltext?dgcid=raven\\_jbs\\_aip\\_email](https://www.jvsvenous.org/article/S2213-333X(20)303486/fulltext?dgcid=raven_jbs_aip_email)

## ABSTRACT

### Objective

Little is known about coronavirus disease (COVID-19)-associated hypercoagulability. We sought to characterize patients with deep venous thrombosis (DVT) identified after admission for COVID-19.

### Methods

All adult patients admitted to Montefiore Medical Center (MMC) from March 1, 2020 to April 10, 2020 and undergoing lower extremity venous duplex for DVT evaluation were included. Patients admitted with suspicion of COVID-19 were divided into severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive and SARS-CoV-2 negative groups based on in-hospital test results. Patients without clinical suspicion for COVID-19 were not tested. A retrospective case-control study design was used to identify potential risk factors for DVT in patients with COVID-19. Demographic, radiographic and laboratory values were abstracted and analyzed.

### Results

During the study period, 3,404 patients with confirmed COVID-19 were admitted to the hospital. Of the 135 SARS-CoV-2 patients who underwent duplex scanning, there were 18 (13.3%) noted to have DVT compared to 72 of the 711 patients (10.1%) who were either SARS-CoV-2 negative or untested. The odds ratio for DVT in COVID-19 was 1.35 (95% CI 0.78 – 2.34,  $p=0.289$ ). Baseline characteristics for COVID-19 patients with and without DVT were overall similar. COVID-19 patients with DVT had an elevated median first D-dimer (18.88 mcg/mL [IQR 7.79, 20.00] versus 2.55 mcg/mL [IQR 1.45, 6.28],  $p=0.002$ , reference range  $<0.5$  mcg/mL), average in-hospital D-dimer (median 11.93 mcg/mL [IQR 8.25, 16.97] versus 3.54 mcg/mL [IQR 2.05, 8.53],  $p<0.001$ ) and median fibrinogen level (501.0 [IQR 440.0, 629.0] versus 654.5 [IQR 535.8, 780.0],  $p=0.002$ , reference range 187-502 mg/dL). There was a trend to significance for COVID-19 patients with DVT compared to without DVT in median D-dimer levels at the time of the duplex (13.61 mcg/mL [IQR 4.04, 19.97] versus 3.58 mcg/mL [IQR 2.51, 9.62],  $p=0.055$ ) and median ferritin levels (1,679.0 ng/mL [IQR 1,168.0, 2,577.0] versus 1,103.0 ng/mL [IQR 703.5, 2,076.5],  $p=0.055$ , reference 25-270 ng/mL). Twelve of the 18 patients with COVID who developed DVT did so despite chemical thromboprophylaxis, and two developed DVT in spite of therapeutic anticoagulation.

### Conclusions

We found only a modestly increased risk of DVT in patients with COVID-19, likely underestimated due to limitations in duplex testing early in the epidemic. Elevated D-dimer and a less elevated fibrinogen are associated with DVT in patients with COVID-19 who appear to form thrombus despite conventional chemical thromboprophylaxis. Additionally, an increasing D-dimer over time may be a reflection of the development of DVT in patients with COVID-19.

## Bleeding and Thrombotic Manifestations of SARS-CoV2 Infection

Published 17<sup>th</sup> June, 2020

<https://www.practiceupdate.com/content/bleeding-and-thrombotic-manifestations-of-sars-cov2-infection/101941#collapse1>

### TAKE-HOME MESSAGE

- This is a multicenter retrospective study of 400 COVID-19 patients who were admitted to a hospital, receiving standard-dose prophylactic anticoagulation. Confirmed venous thromboembolism occurred in 4.8%; overall and major bleeding rates were 4.8% and 2.3%, respectively.
- Although there is accumulating evidence emphasizing the prothrombotic state associated with COVID-19, this study also provides some insight into the bleeding risk.

### ABSTRACT:

Patients with coronavirus disease 2019 (COVID-19) have elevated D-dimer levels. Early reports describe high venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC) rates, but data are limited. This multicenter, retrospective study described the rate and severity of hemostatic and thrombotic complications of 400 hospital-admitted COVID-19 patients (144 critically ill) primarily receiving standard-dose prophylactic anticoagulation. Coagulation and inflammatory parameters were compared between patients with and without coagulation-associated complications. Multivariable logistic models examined the utility of these markers in predicting coagulation-associated complications, critical illness, and death. The radiographically-confirmed VTE rate was 4.8% (95% CI, 2.9-7.3%) and the overall thrombotic complication rate was 9.5% (6.8-12.8%). The overall and major bleeding rates were 4.8% (2.9-7.3%) and 2.3% (1.0-4.2%). In the critically ill, radiographically-confirmed VTE and major bleeding rates were 7.6% (3.9-13.3%) and 5.6% (2.4-10.7%). Elevated D-dimer at initial presentation was predictive of coagulation-associated complications during hospitalization [D-dimer >2,500 ng/mL, adjusted OR for thrombosis, 6.79 (2.39-19.30), adjusted OR for bleeding, 3.56 (1.01-12.66)], critical illness, and death. Additional markers at initial presentation predictive of thrombosis during hospitalization included platelet count >450×10<sup>9</sup>/L [adjusted OR, 3.56 (1.27-9.97)], C-reactive protein (CRP) >100 mg/L [adjusted OR, 2.71 (1.26-5.86)], and erythrocyte sedimentation rate >40 mm/h [adjusted OR, 2.64 (1.07-6.51)]. ESR, CRP, fibrinogen, ferritin, and procalcitonin were higher in patients with thrombotic complications than those without. DIC, clinically-relevant thrombocytopenia, and reduced fibrinogen were rare and were associated with significant bleeding manifestations. Given the observed bleeding rates, randomized trials are needed to determine any potential benefit of intensified anticoagulant prophylaxis in COVID-19 patients.

## Endotheliopathy in COVID-19–Associated Coagulopathy

Published 21<sup>st</sup> July, 2020

<https://www.practiceupdate.com/content/endotheliopathy-in-covid-19-associated-coagulopathy/103508>

### TAKE-HOME MESSAGE

- In this single-center, cross-sectional study of 68 COVID-19 patients, the authors compare markers of endothelial cell and platelet activation. Elevated levels of von Willebrand factor (VWF) antigen and soluble thrombomodulin had a significant correlation with mortality. Other factors including VWF antigen and soluble P-selectin were significantly elevated in ICU patients compared with non-ICU patients.
- This work contributes to growing evidence implicating endotheliopathy as a contributor to COVID-19 coagulation disorders

### ABSTRACT:

#### BACKGROUND

An important feature of severe acute respiratory syndrome coronavirus 2 pathogenesis is COVID-19-associated coagulopathy, characterised by increased thrombotic and microvascular complications. Previous studies have suggested a role for endothelial cell injury in COVID-19-associated coagulopathy. To determine whether endotheliopathy is involved in COVID-19-associated coagulopathy pathogenesis, we assessed markers of endothelial cell and platelet activation in critically and non-critically ill patients admitted to the hospital with COVID-19.

#### METHODS

In this single-centre cross-sectional study, hospitalised adult ( $\geq 18$  years) patients with laboratory-confirmed COVID-19 were identified in the medical intensive care unit (ICU) or a specialised non-ICU COVID-19 floor in our hospital. Asymptomatic, non-hospitalised controls were recruited as a comparator group for biomarkers that did not have a reference range. We assessed markers of endothelial cell and platelet activation, including von Willebrand Factor (VWF) antigen, soluble thrombomodulin, soluble P-selectin, and soluble CD40 ligand, as well as coagulation factors, endogenous anticoagulants, and fibrinolytic enzymes. We compared the level of each marker in ICU patients, non-ICU patients, and controls, where applicable. We assessed correlations between these laboratory results with clinical outcomes, including hospital discharge and mortality. Kaplan-Meier analysis was used to further explore the association between biochemical markers and survival.

#### FINDINGS

68 patients with COVID-19 were included in the study from April 13 to April 24, 2020, including 48 ICU and 20 non-ICU patients, as well as 13 non-hospitalised, asymptomatic controls. Markers of endothelial cell and platelet activation were significantly elevated in ICU patients compared with non-ICU patients, including VWF antigen (mean 565% [SD 199] in ICU patients vs 278% [133] in non-ICU patients;  $p < 0.0001$ ) and soluble P-selectin (15.9 ng/mL [4.8] vs 11.2 ng/mL [3.1];  $p = 0.0014$ ). VWF antigen concentrations were also elevated above the normal range in 16 (80%) of 20 non-ICU patients. We found mortality to be significantly correlated with VWF antigen

( $r = 0.38$ ;  $p=0.0022$ ) and soluble thrombomodulin ( $r = 0.38$ ;  $p=0.0078$ ) among all patients. In all patients, soluble thrombomodulin concentrations greater than 3.26 ng/mL were associated with lower rates of hospital discharge (22 [88%] of 25 patients with low concentrations vs 13 [52%] of 25 patients with high concentrations;  $p=0.0050$ ) and lower likelihood of survival on Kaplan-Meier analysis (hazard ratio 5.9, 95% CI 1.9-18.4;  $p=0.0087$ ).

## **INTERPRETATION**

Our findings show that endotheliopathy is present in COVID-19 and is likely to be associated with critical illness and death. Early identification of endotheliopathy and strategies to mitigate its progression might improve outcomes in COVID-19.

## Risk of Ischemic Stroke in Patients With COVID-19 vs Patients With Influenza

22 July, 2020

<https://jamanetwork.com/journals/jamaneurology/fullarticle/2768098>

### TAKE-HOME MESSAGE

- In this cohort study, 1916 patients with emergency department visits or hospitalizations with COVID-19 had an elevated risk of ischemic stroke compared with 1486 patients with emergency department visits or hospitalizations with influenza.
- Patients with COVID-19 appear to have a heightened risk of acute ischemic stroke compared with patients with influenza.

### ABSTRACT

**Importance** It is uncertain whether coronavirus disease 2019 (COVID-19) is associated with a higher risk of ischemic stroke than would be expected from a viral respiratory infection.

**Objective** To compare the rate of ischemic stroke between patients with COVID-19 and patients with influenza, a respiratory viral illness previously associated with stroke.

**Design, Setting, and Participants** This retrospective cohort study was conducted at 2 academic hospitals in New York City, New York, and included adult patients with emergency department visits or hospitalizations with COVID-19 from March 4, 2020, through May 2, 2020. The comparison cohort included adults with emergency department visits or hospitalizations with influenza A/B from January 1, 2016, through May 31, 2018 (spanning moderate and severe influenza seasons).

**Exposures** COVID-19 infection confirmed by evidence of severe acute respiratory syndrome coronavirus 2 in the nasopharynx by polymerase chain reaction and laboratory-confirmed influenza A/B.

**Main Outcomes and Measures** A panel of neurologists adjudicated the primary outcome of acute ischemic stroke and its clinical characteristics, mechanisms, and outcomes. We used logistic regression to compare the proportion of patients with COVID-19 with ischemic stroke vs the proportion among patients with influenza.

**Results** Among 1916 patients with emergency department visits or hospitalizations with COVID-19, 31 (1.6%; 95% CI, 1.1%-2.3%) had an acute ischemic stroke. The median age of patients with stroke was 69 years (interquartile range, 66-78 years); 18 (58%) were men. Stroke was the reason for hospital presentation in 8 cases (26%). In comparison, 3 of 1486 patients with influenza (0.2%; 95% CI, 0.0%-0.6%) had an acute ischemic stroke. After adjustment for age, sex, and race, the likelihood of stroke was higher with COVID-19 infection than with influenza infection (odds ratio, 7.6; 95% CI, 2.3-25.2). The association persisted across sensitivity analyses adjusting for vascular risk factors, viral symptomatology, and intensive care unit admission.

**Conclusions and Relevance** In this retrospective cohort study from 2 New York City academic hospitals, approximately 1.6% of adults with COVID-19 who visited the emergency department or were hospitalized



experienced ischemic stroke, a higher rate of stroke compared with a cohort of patients with influenza. Additional studies are needed to confirm these findings and to investigate possible thrombotic mechanisms associated with COVID-19.

## Utility of D-dimer for diagnosis of deep vein thrombosis in COVID-19 infection

20<sup>th</sup> July 2020

[https://www.jvsvenous.org/article/S2213-333X\(20\)30420-0/fulltext?dgcid=raven\\_jbs\\_aip\\_email](https://www.jvsvenous.org/article/S2213-333X(20)30420-0/fulltext?dgcid=raven_jbs_aip_email)

### ABSTRACT

#### Objective

The objective of this study was to investigate the clinical utility of D-dimer in excluding a diagnosis of deep vein thrombosis (DVT) in patients with COVID-19 infection, potentially limiting the need for venous duplex ultrasonography (US).

#### Methods

We retrospectively reviewed consecutive patients admitted to our institution with confirmed COVID-19 status by PCR between March 1, 2020 and May 13, 2020 and selected those who underwent both D-dimer and venous duplex US. This cohort was divided into two groups, those with and without DVT based on duplex US. These groups were then compared to determine the value of D-dimer in establishing this diagnosis.

#### Results

A total of 1170 patients were admitted with COVID-19, of which 158 were selected as our study. Of the 158, there were 52 patients with DVT and 106 without DVT. There were no differences in gender, age, race, or ethnicity between groups. Diabetes and routine hemodialysis were less commonly seen in the group with DVT. Over 90% of patients in both groups received prophylactic anticoagulation, but the use of LMWH or subcutaneous heparin prophylaxis was not predictive of DVT. All patients had elevated acute-phase D-dimer levels using conventional criteria, and 154/158 (97.5%) had elevated levels with age-adjusted criteria (mean D-dimer  $16,163 \pm 5,395$  ng/mL). Those with DVT had higher acute-phase D-dimer levels than those without DVT (median  $13,602$  [6,616-36,543 ng/mL] vs.  $2,880$  [1,030-9,126 ng/mL],  $p < 0.001$ ). An optimal D-dimer cutoff of  $6,494$  ng/mL was determined to differentiate those with and without DVT (sensitivity 80.8%, specificity 68.9%, negative predictive value 88.0%). Wells DVT criteria was not found to be a significant predictor of DVT. Elevated D-dimer as defined by our optimal metric was a statistically significant predictor of DVT in both univariate and multivariable analyses when adjusting for other factors (OR 6.12, 95%CI [2.79-13.39],  $p < 0.001$ ).

#### Conclusion

D-dimer levels are uniformly elevated in COVID-19 patients. While standard predictive criteria failed to predict DVT, our analysis showed a D-dimer of less than  $6,494$  ng/mL may exclude DVT, therefore potentially limiting the need for venous duplex ultrasonography.

## Deep vein thrombosis in non–critically ill patients with coronavirus disease 2019 pneumonia: deep vein thrombosis in non–intensive care unit patients

6th September, 2020

[https://www.jvsvenous.org/article/S2213-333X\(20\)30466-2/fulltext?dgcid=raven\\_jbs\\_aip\\_email](https://www.jvsvenous.org/article/S2213-333X(20)30466-2/fulltext?dgcid=raven_jbs_aip_email)

### TAKE-HOME MESSAGE

Non–critically ill patients with coronavirus disease 2019 pneumonia have a high risk of lower limb DVT despite correct prophylactic treatment.

### ABSTRACT

#### Background

Venous thromboembolic events have been one of the main causes of mortality among hospitalized patients with coronavirus disease 2019 (COVID-19) pneumonia. The aim of our study was to describe the prevalence of deep vein thrombosis (DVT) in non–critically ill patients with COVID-19 pneumonia and correlate such observations with the thromboprophylaxis received.

#### Methods

We performed a prospective cohort study of 67 patients admitted to the hospital for COVID-19 pneumonia. The diagnosis was confirmed using polymerase chain reaction testing of nasopharyngeal specimens. The deep veins were examined using compression duplex ultrasonography with the transducer on B-mode. The patients were separated into two groups for statistical analysis: those receiving low-molecular-weight heparin prophylaxis and those receiving intermediate or complete anticoagulation treatment. Risk analysis and logistic regression were performed.

#### Results

Of the 67 patients, 57 were included in the present study after applying the inclusion and exclusion criteria; 49.1% were women, and the patient mean age was 71.3 years. All 57 patients had undergone compression duplex ultrasonography. Of these 57 patients, 6 were diagnosed with DVT, for an in-hospital rate of DVT in patients with COVID-19 pneumonia of 10.5%. All the patients who had presented with DVT had been receiving low-molecular-weight heparin prophylaxis. The patients receiving prophylactic anticoagulation treatment had a greater risk of DVT (16.21%; 95% confidence interval, 0.04-0.28;  $P = .056$ ) compared with those receiving intermediate or complete anticoagulation treatment. We also found a protective factor for DVT in the intermediate or complete anticoagulation treatment group (odds ratio, 0.19; 95% confidence interval, 0.08-0.46;  $P < .05$ ).

#### Conclusions

Non–critically ill, hospitalized patients with COVID-19 pneumonia have a high risk of DVT despite receipt of correct, standard thromboprophylaxis.

## A narrative review of venous thrombosis epidemiology, pathophysiology and anticoagulant therapies and trials in SARS-CoV2 infection

8th September, 2020

[https://www.jvsvenous.org/article/S2213-333X\(20\)30468-6/fulltext?dgcid=raven\\_jbs\\_aip\\_email](https://www.jvsvenous.org/article/S2213-333X(20)30468-6/fulltext?dgcid=raven_jbs_aip_email)

### ABSTRACT

#### Objective

Infection with the SARS-CoV2 virus confers a risk of significant coagulopathy with resulting development of venous thromboembolism (VTE), potentially contributing to the morbidity and mortality. The purpose of this review is to evaluate the potential mechanisms that contribute to this increased risk of coagulopathy and the role of anticoagulants in treatment.

#### Methods

A literature review of COVID-19 or SARS-CoV2 and cell-mediated inflammation, clinical coagulation abnormalities, hypercoagulability, pulmonary intravascular coagulopathy, and anticoagulation was performed. The National Clinical Trials database was queried for ongoing studies on anticoagulation/antithrombotic treatment or incidence/prevalence of thrombotic events in SARS-CoV2 infection.

#### Results

The reported rate of VTE amongst critically ill patients infected with SARS-CoV2 is between 21% and 69%. The phenomenon of breakthrough VTE, acute development of VTE despite adequate chemoprophylaxis or treatment dose anticoagulation, occurs with severe infection. The pathophysiology of overt hypercoagulability and development of VTE is likely multifactorial with evidence supporting the role of significant cell mediated responses including neutrophil and monocyte/macrophages, endothelialitis, cytokine release syndrome and dysregulation of fibrinolysis. Collectively, this inflammatory process contributes to the severe pulmonary pathology experienced by patients. As the infection worsens, extreme elevations in D-dimer, significant thrombocytopenia, decreasing fibrinogen, and prolongation of PT and PTT occurs, often associated with deep vein thrombosis, in situ pulmonary thrombi, and/or pulmonary embolism. A new phenomenon, termed pulmonary intravascular coagulopathy (PIC) is associated with morbidity amongst patient with severe infection. Heparin, both unfractionated heparin and low-molecular-weight heparin, have emerged as agents that address viral infection, inflammation and thrombosis in this syndrome.

#### Conclusions

The overwhelming inflammatory response in patients with SARS-CoV2 infection leads to a hypercoagulable state, microthrombosis, large vessel thrombosis, and ultimately death. Early VTE prophylaxis should be used in all admitted patients. Therapeutic anticoagulation maybe beneficial in critically ill patients and is the focus of 39 ongoing trials. Close monitoring for thrombotic complications is imperative, and if confirmed early transition from prophylactic to therapeutic anticoagulation should be instituted. The interplay between inflammation and thrombosis is a hallmark of the SARS-Co2 viral infection.

## Is COVID-19 Primarily a Heart and Vascular Disease?

8th September, 2020

<https://www.infectioncontroltoday.com/view/is-covid-19-primarily-a-heart-and-vascular-diseases>

*Infection preventionists need to be able to articulate to those who feel that the young are safe just because their fatality rate is extremely low, that even in this age group there are major concerns regarding long-term consequences of this virus.*

Several recent studies have supported the growing hypothesis that coronavirus disease 2019 (COVID-19) is primarily a cardiovascular, and not a pulmonary virus. The narrative that those affected are usually asymptomatic and have very mild or no disease may be false. Many of those who are asymptomatic may actually fall victim to myocarditis, a sinister, stealth-like disease, whose resulting disability may take decades to manifest.

Concerns for cardiovascular involvement of SARS-CoV-2 have been present since the early genesis of the pandemic. A research paper from China found that 20% of COVID-19 hospitalized patients developed [heart disease](#) and thromboembolic events happened in 31% of those [in the ICU](#). Another from Germany reported ongoing myocardial inflammation in 60% of 100 recently recovered patients with [COVID-19](#).

However, cardiovascular disease has been assumed by many to be a manifestation of severe COVID-19; and not from direct infection of the virus but instead from small vessel disease caused by the hypercoagulation of the blood.

All of that changed last week with the publication of three reports. The first was from Penn State Health which reported that 15% of Penn State athletes who tested positive for COVID-19 had myocarditis. These were young athletes and included both mildly symptomatic and asymptomatic individuals. As a result of these findings, the Big 10 and Pac 12 postponed their [football season](#).

Myocarditis does not have specific symptoms and most patients can be [asymptomatic](#). Myocarditis can produce fibrosis of the heart which may present years later with heart failure from dilated cardiomyopathy. However, in 50% of cases the cause of dilated cardiomyopathy is unknown, but there is strong evidence that past viral infections [play a role](#). And myocarditis can [occur in children](#).

The second was a study by Perez-Bermejo, et al. which provided evidence that COVID-19 heart disease was a direct effect on the heart by [SARS-CoV-2](#). This was suspected since cardiac myocytes express the ACE2 protein needed for viral entry into the cells. The authors described robust and specific change in cell cultured cardiomyocytes which corresponded to the changes they observed in autopsies of patients with COVID-19. Thus, the virus can also attack and destroy the heart directly, not just indirectly with hemodynamic stress, hypoxemia and small vessel thrombosis.

The third report was by [Reynolds, et al.](#), and offered an explanation for the perplexing clinical finding that COVID-19 asymptomatic patients have no pulmonary symptoms but are still hypoxic, indicating something major may be taking place. This finding is so common, that there was even discussion in the news media regarding pulse oximeters and if they should be purchased to detect infections with SARS-CoV-2.

Reynolds, et al. noted that there is a “disconnect between gas exchange and lung mechanics in COVID-19 pneumonia.” In other words, the patient’s decreased oxygenation does not correspond to the patient’s ability to breathe. Much like what has been observed in asymptomatic patients. The authors drew similarities to what is observed in hepatopulmonary syndrome and using a contrast enhanced doppler they were able to postulate pulmonary vascular dilatation with resultant increased blood flow which could account for the “ventilation-perfusion mismatch and hypoxemia.”

Thus, the once thought asymptomatic patients who luckily dodged a bullet and were spared from the ravages of the disease, may indeed be truly sick. A significant portion of them may develop myocarditis along with vascular vasodilation with resultant hypoxemia. This pathological process could easily be more significant than the pulmonary effects of the virus, since it is present in both symptomatic and asymptomatic patients. And could explain the debilitating symptoms of fatigue and mental fog which “long-haulers” are experiencing, many of which had a mild [initial illness](#).

These findings underscore the utmost importance for infection preventionists to advocate for the identification of asymptomatic COVID-19 carriers. Infection preventionists need to be able to articulate to those who feel that the young are safe just because their fatality rate is extremely low, that even in this age group there are major concerns regarding long-term consequences of this virus. We need to take this virus seriously.

## Incidence of Venous Thromboembolism (VTE) in COVID-19: An Experience From A Single Large Academic Center

Accepted date: 15<sup>th</sup> September, 2020

<https://doi.org/10.1016/j.jvsv.2020.09.006>

### TAKE HOME MESSAGE

Our data represents one of the earliest published US reports on the incidence rate of VTE in COVID-19. Patients with high clinical suspicion and identified risk factors (need for invasive mechanical ventilation, D-dimer on admission > 1,500 ng/mL) can be considered for early VTE testing. Our findings should be confirmed prospectively in future studies.

### ABSTRACT

**Background:** Novel severe acute respiratory coronavirus 2 (SARS-CoV2) has been associated with a hypercoagulable state. Emerging literature from China and Europe has consistently shown an increased incidence of venous thromboembolism (VTE). We aim to identify the VTE incidence and early predictors of VTE at our high-volume tertiary care center.

**Methods:** We performed a retrospective cohort study of patients admitted to Temple University Hospital with COVID-19. We first identified VTE [pulmonary embolism (PE) and deep vein thrombosis (DVT)] incidence in our cohort. VTE and no VTE groups were compared in univariable analysis for demographics, co-morbidities, laboratory data, and treatment outcomes. Subsequently, multivariable logistic regression analysis was performed to identify early predictors of VTE.

**Results:** 147 patients admitted to Temple University Hospital, between April 1<sup>st</sup>, 2020 to April 27<sup>th</sup>, 2020 to designated COVID 19 unit with a high clinical suspicion for acute VTE were tested with either CT pulmonary angiogram and/or extremity venous duplex, representing 20.9% of all admissions. The overall incidence of VTE was 17% (25/147). There were 16 cases of acute PE, 14 cases of acute DVT, and 5 patients with both PE and DVT. The need for invasive mechanical ventilation (adjusted OR 3.19, 95% CI:1.07-9.55), admission D-dimer level > 1,500 ng/mL (aOR 3.55, 95% CI:1.29-9.78) were independent markers associated with VTE occurrence. All-cause mortality in the VTE group was higher (48% vs. 22%,  $p=0.007$ ) than no VTE group.

**Conclusion:** Our data represents one of the earliest published US reports on the incidence rate of VTE in COVID-19. Patients with high clinical suspicion and identified risk factors need for invasive mechanical ventilation, D-dimer on admission > 1,500 ng/mL can be considered for early VTE testing. We did not screen all patients admitted for VTE, therefore it is possible the true incidence of VTE was underestimated. Our findings should be confirmed prospectively in future studies.

## CytoSorb Filter for Survival in a COVID-19 Patient With Cytokine Storm

15<sup>th</sup> September, 2020

### TAKE-HOME MESSAGE

- The CytoSorb filter device, which has been developed and approved in Europe, is currently being trialed in the United States to treat cytokine storm. This is a case report in which this device was used for the management of severe COVID-19 in a 51-year-old man with ARDS. The device was utilized starting on day 11 of hospitalization. He also received azithromycin, hydroxychloroquine, tocilizumab, and convalescent plasma during his hospitalization. He had a protracted hospitalization but was eventually discharged to rehab on hospital day 60.
- CytoSorbents' filters have a potentially interesting mechanism of action in combating severe COVID-19 disease. More research within the constraints of a rigorous clinical trial is needed as it is unclear from this case report the impact of the filter on this patient's clinical course.



# Deep Venous Thrombosis in Hospitalized Patients with Coronavirus Disease 2019

8<sup>th</sup> October 2020

[https://www.jvsvenous.org/article/S2213-333X\(20\)30543-6/fulltext?dgcid=raven\\_jbs\\_aip\\_email](https://www.jvsvenous.org/article/S2213-333X(20)30543-6/fulltext?dgcid=raven_jbs_aip_email)

## ABSTRACT

### Objectives

The pandemic of Coronavirus disease 2019 (COVID-19) has caused devastating morbidity and mortality worldwide. In particular, thromboembolic complications have emerged as a key threat in COVID-19. We assessed our experience with deep venous thrombosis (DVT) in patients with COVID-19.

### Methods

We performed a retrospective analysis of all patients with COVID-19 undergoing upper or lower extremity venous duplex ultrasonography at an academic health system in New York City between March 3 2020 and April 12 2020 with follow-up through May 12 2020. A cohort of hospitalized patients without COVID-19 (non-COVID-19) undergoing venous duplex ultrasonography from December 1 2019 to December 31 2019 was used for comparison. The primary outcome was DVT. Secondary outcomes included pulmonary embolism (PE), in-hospital mortality, admission to intensive care unit, and antithrombotic therapy. Multivariable logistic regression was performed to identify risk factors for DVT and mortality.

### Results

Of 443 patients (188 COVID-19 and 255 non-COVID-19) undergoing venous duplex ultrasonography, patients with COVID-19 had higher incidence of DVT (31% vs. 19%;  $P=0.005$ ), compared to the non-COVID-19 cohort. The incidence of PE was not statistically different between the COVID-19 and non-COVID-19 cohorts (8% vs. 4%;  $P=.105$ ). The DVTs in the COVID-19 group were more distal (63% vs. 29%;  $P<.001$ ) and bilateral (15% vs. 4%;  $P<.001$ ). The result of duplex ultrasonography had a significant impact on the antithrombotic plan; 42 (72%) patients with COVID-19 in the DVT group had their therapies escalated while 49 (38%) and 3 (2%) patients had their therapies escalated and de-escalated in the non-DVT group, respectively ( $P<.001$ ). Within the COVID-19 cohort, the D-dimer was significantly higher in the DVT group at the time of admission (2,746 ng/mL vs 1,481 ng/mL;  $P=.004$ ) and at the time of the duplex exam (6,068 ng/mL vs. 3,049 ng/mL;  $P<0.01$ ). At multivariable analysis, male sex (odds ratio (OR) 2.27; 95% confidence interval (CI), 1.06-4.87;  $P=.035$ ), ICU admission (OR 3.42; 95% CI, 1.02-11.44;  $P=.046$ ) and extracorporeal membrane oxygenation (OR 5.5; 95% CI, 1.01-30.13;  $P=.049$ ) were independently associated with DVT.

### Conclusion

Given the high incidence of venous thromboembolic events in this population, we support the decision to empirically initiate therapeutic anticoagulation in patients with low bleeding risk and severe COVID-19 infection, with duplex ultrasonography reserved for patients with high clinical suspicion of VTE in which anticoagulation may pose a life-threatening consequence. Further study is warranted in patients with COVID-19 to elucidate the etiology of vascular thromboembolic events and guide prophylactic and therapeutic interventions in these patients.

## In-Hospital Cardiac Arrest in Critically Ill Patients With Covid-19

8<sup>th</sup> October 2020

<https://www.practiceupdate.com/content/in-hospital-cardiac-arrest-in-critically-ill-patients-with-covid-19/107591>

### TAKE-HOME MESSAGE

- This multicenter cohort study examined in-hospital cardiac arrest and in-hospital mortality in 5019 critically ill patients with laboratory-confirmed Covid-19. Of the included participants, 14.0% experienced in-hospital cardiac arrest and 57.1% of this subgroup underwent cardiopulmonary resuscitation. Compared with other patients, those who experienced in-hospital cardiac arrest had more comorbidities, were older, and were more likely to be admitted to hospitals with relatively low numbers of intensive care beds. Compared with patients who did not receive cardiopulmonary resuscitation, those who did were younger. Survival was low in patients who underwent cardiopulmonary resuscitation, with 12.0% surviving to discharge and only 7.0% having normal or mildly impaired neurological status at discharge. A higher percentage of patients younger than age 45 versus those aged 80 or older survived to hospital discharge.
- These data show that critically ill patients with Covid-19 commonly experience in-hospital cardiac arrest, which is associated with poor outcomes.

### ABSTRACT

#### Objectives

To estimate the incidence, risk factors, and outcomes associated with in-hospital cardiac arrest and cardiopulmonary resuscitation in critically ill adults with coronavirus disease 2019 (covid-19).

#### Design

Multicenter cohort study.

#### Setting Participants

Intensive care units at 68 geographically diverse hospitals across the United States.

#### Participants

Critically ill adults (age  $\geq 18$  years) with laboratory confirmed covid-19.

#### Main outcome measures

In-hospital cardiac arrest within 14 days of admission to an intensive care unit and in-hospital mortality.

## Results

Among 5019 critically ill patients with covid-19, 14.0% (701/5019) had in-hospital cardiac arrest, 57.1% (400/701) of whom received cardiopulmonary resuscitation. Patients who had in-hospital cardiac arrest were older (mean age 63 (standard deviation 14) v 60 (15) years), had more comorbidities, and were more likely to be admitted to a hospital with a smaller number of intensive care unit beds compared with those who did not have in-hospital cardiac arrest. Patients who received cardiopulmonary resuscitation were younger than those who did not (mean age 61 (standard deviation 14) v 67 (14) years). The most common rhythms at the time of cardiopulmonary resuscitation were pulseless electrical activity (49.8%, 199/400) and asystole (23.8%, 95/400). 48 of the 400 patients (12.0%) who received cardiopulmonary resuscitation survived to hospital discharge, and only 7.0% (28/400) survived to hospital discharge with normal or mildly impaired neurological status. Survival to hospital discharge differed by age, with 21.2% (11/52) of patients younger than 45 years surviving compared with 2.9% (1/34) of those aged 80 or older.

## Conclusions

Cardiac arrest is common in critically ill patients with covid-19 and is associated with poor survival, particularly among older patients.