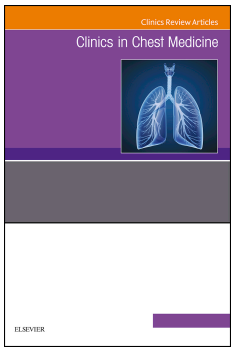
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



Impact of COVID-19 on Non-Pulmonary Critical Illness: Prevalence, Clinical Manifestations, Management, and Outcomes

Mina Pirzadeh, MD, Hallie C. Prescott, MD, MSc

PII: S0272-5231(22)00127-7

DOI: https://doi.org/10.1016/j.ccm.2022.11.011

Reference: CME 1407

To appear in: *CLINICS IN CHEST MEDICINE*

Please cite this article as: Pirzadeh M, Prescott HC, Impact of COVID-19 on Non-Pulmonary Critical Illness: Prevalence, Clinical Manifestations, Management, and Outcomes, *CLINICS IN CHEST MEDICINE* (2022), doi: https://doi.org/10.1016/j.ccm.2022.11.011.

Impact of COVID-19 on Non-Pulmonary Critical Illness: Prevalence, Clinical Manifestations, Management, and Outcomes

Mina Pirzadeh, MD[1,2]. and Hallie C. Prescott, MD, MSc[1,2,3]

hprescot@umich.edu

1- Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA 48109

2- Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan

3- VA Center for Clinical Management Research, University of Michigan, Ann Arbor, MI, USA 48109

Key Words: COVID-19, organ failure, critical illness, sepsis

Key Points:

1) SARS-CoV-2 infection has significant impact on multiple organ systems in the body, a distinctive feature compared to past viral epidemics

2) It is uncommon for hospitalized patients to need non-pulmonary organ support without respiratory failure

3) Nearly every organ failure is independently associated with poorer outcomes in COVID-19 infection

4) Long term outcomes of isolated and multi-organ failure are underway

Synopsis: While respiratory manifestations are the most common driver of hospitalization, SARS-CoV-2 infection has a wide range of manifestations, including

multi-system organ failure in severe cases. This review discusses the prevalence, pathophysiology, clinical manifestations, treatment, and outcomes of non-pulmonary organ dysfunction from SARS-CoV2, including renal, liver, cardiac, neurologic, and coagulation system dysfunction. Management largely focuses on supportive care practices that are applicable regardless of the etiology of organ injury. However, there is emerging evidence to support therapeutic anticoagulation in non-critically ill patients with COVID-19 to mitigate risk for venous thromboembolism.

This manuscript does not represent the views of the Department of Veterans Affairs or the US government. This material is the result of work supported with resources and use of facilities at the Ann Arbor VA Medical Center.

Corresponding Author:
Mina Pirzadeh
2215 Fuller Rd (111G)
Ann Arbor, MI 48105
mpirzad@med.umich.edu
mina.pirzadeh@va.gov
(734) 658- 4346

The authors have no commercial or financial conflicts of interest. HCP has grant funding from VA, AHRQ, and BCBSM, unrelated to this manuscript.

INTRODUCTION

Over the past 2 years, SARS-CoV-2 has infected millions of patients worldwide, contributing to 513 million cases and 6.2 million deaths[1] as of May 1st, 2022. While respiratory manifestations are the most common driver of hospitalization, SARS-CoV-2 infection has a wide range of manifestations, including multi-system organ failure in severe cases (**Figure 1, Table 1**). In this review, we discuss the prevalence, pathophysiology, clinical manifestations, treatment, and outcomes of non-pulmonary organ dysfunction from SARS-CoV2.

Sepsis and Multi-organ Failure

Prevalence

Prior to the COVID pandemic, viral sepsis was an under-recognized cause of sepsis in adults[2]. However, sepsis may result from any type of infection, including viruses such as influenza, MERS, SARS, and SARS-CoV-2[3,4]. In a meta-analysis by Karakike, *et al*. of 151 studies published August 2020-March 2021 including 218,184 patients hospitalized with COVID-19 (mostly in Asia, Europe, and North America), the prevalence of sepsis (inferred by SOFA scoring, acute organ dysfunction, or organ support) was 33% among ward-treated patients, 78% among ICU-treated patients, and 52% overall (**Table 2**).[2] Among ICU-treated patients, the most common organ supports were mechanical ventilation (60%), vasopressor therapy (50%) and renal replacement therapy (20%).[2] Overall, while respiratory support was most common, a large proportion of ICU hospitalizations for COVID-19 required non-pulmonary organ support.

In the Society of Critical Care Medicine (SCCM) VIRUS cohort of 20,608 adult hospitalizations for COVID in 16 countries during February-November 2020, 15,0001 (72.3%) patients required no organ support, 5,005 (24.3%) required invasive mechanical ventilation (IMV), and 602 (2.9%) required vasopressor therapy and/or acute renal replacement therapy (RRT) without IMV. Of the 5,005 who required IMV: 1,1749 (34.9%) required IMV only; 2,032 (40.6%) required IMV and vasopressors; 655 (13.1%) required IMV, vasopressors, and RRT; 180 (3.6%) required IMV and RRT; and 389 (7.8%) underwent extracorporeal membrane oxygenation [5]. Among 5,837 patients in the Health Outcome Predictive Evaluation (HOPE) COVID-19 registry, an international registry of patients hospitalized from March-June 2020 in 8 countries, patients with COVID-19 who developed viral sepsis were older, admitted sooner after symptom onset, and had higher burden of comorbid disease.[6]

Pathophysiology

SARS-COV-2 enters the human host by inhalation. Once viral particles are inhaled, a spike protein on the virus surface attaches to the angiotensin 1 converting enzyme 2 (ACE-2) receptor, then relies on transmembrane protease serine 2 (TMPRSS2) expressed on the surface of respiratory epithelium to enter the cell[7,8]. Once inside the host cell, the virus can replicate. The ACE-2 receptor and TMPRSS2 have been identified in lung alveolar epithelial cells, but also on many other cell types, suggesting that direct viral invasion may be a common mechanism of injury across organs. Beyond direct viral invasion, a number of other mechanisms may be implicated, including

endothelial damage with thrombo-inflammation[9], dysregulation of the immune response via high serum level of pro- inflammatory cytokines such as interleukin (IL) 6 and IL-1 beta, and tumor necrosis factor (TNF)[8,10] , viral sepsis-induced immune paralysis[6], and dysregulation of the renin-angiotensin-aldosterone system (RAAS)[9]. Mechanisms of specific organ dysfunctions are discussed further in sections specific to each organ.

Clinical Manifestations

Respiratory failure is the most common organ dysfunction in COVID-19, and other organ dysfunctions rarely occur without respiratory dysfunction. In the HOPE-COVID-19 registry, patients with COVID-related sepsis had higher levels of D-dimer, procalcitonin, CRP, troponin, transaminases, ferritin, LDH, and creatinine[6]. Prevalence of leukocytopenia and lymphocytopenia, however, were similar among patients with vs without sepsis.[6] The parsimonious HOPE Sepsis Score identified the following risk factors for sepsis during COVID hospitalization: current smoking, respiratory rate, SpO_2, blood pressure, Glasgow Coma Scale, procalcitonin, troponin I, creatinine, and hemoptysis.[6]

Outcomes

Hospital mortality for COVID is strongly associated with the severity and number of acute organ dysfunctions. In the SCCM VIRUS cohort, in-hospital mortality among 5,005 IMV-treated patients was 50% versus 8% among 15,001 patients without organ support[5]. In-hospital mortality increased with additional organ supports, from 41% among IMV-treated patients, to 71.6% among patient receiving IMV, vasopressors, and

RRT (n=655)[5]. In the meta-analysis by Karakike, *et a*l., in-hospital mortality was 33% among ICU-treated patients, and 42% among IMV-treated patients.[2]

Management

Treatment of COVID-related sepsis focuses on resuscitation and supportive therapy, as with other causes of sepsis.[11] While antibacterial therapy is crucial to treatment of bacterial sepsis, anti-SARS-CoV-2 therapies such as antivirals and monoclonal antibodies are most effective in earlier phases of SARS-CoV-2 infection, prior to the onset of acute organ dysfunction.

There has been particular interest in regulating the hyperinflammatory response to SARS-CoV-2 and subsequent viral-induced immunosuppression.[11] High-quality evidence indicate that corticosteroids[12],IL-6 inhibition[13], and JAK inhibition[14] reduce mortality, and these therapies are broadly recommended in COVID treatment guidelines[15]. However, timing of initiation is important, and patients should be initiated on these therapies promptly upon meeting illness severity criteria. Research is ongoing to clarify the optimal dosing regimens and patient populations for these therapies.

Beyond corticosteroids and IL-6 inhibitors, many other therapies under investigation for treatment/mitigation of disease, including stem cell therapy[16], short-chain fatty acids (SCFAs)[17], anakinra[18], infliximab[19], cytokine therapy (i.e.. IL-17 inhibitors)[20], vitamin

D[21], vitamin C[22,23], fecal microbiota transplantation[24], blood filters[25], convalescent plasma[26], plasma exchange[27] and CRP-apheresis[28].

Acute Renal Dysfunction

Prevalence

Renal replacement therapy for acute renal failure is the third most common organ support among patients with COVID. In a cohort of 3,993 patients hospitalized with COVID-19 at 5 hospitals in New York during March-May 2020, 46% had acute kidney injury (AKI, defined by Kidney Disease Improving Global Outcomes criteria[29]), including 76% of ICU-treated patients[30]. 19% of patients with AKI received RRT[30]. In a separate cohort of 5,449 patients hospitalized with COVID-19 at 13 hospitals in New York during March-May 2020, 37% had AKI, including 90% of IMV-treated patients. Renal failure and RRT were largely limited to patients with respiratory failure. Indeed, in the 13-hospital New York cohort, nearly all patients treated with RRT were also receiving IMV[31]. In the meta-analysis by Karakike, *et al*., the pooled prevalence of RRT among ICU patients with COVID-19 was 20%.

Histology and Pathophysiology

The hypothesized mechanisms of COVID-19-related AKI are largely drawn from biopsy and autopsy studies. In a series of 10 patients with COVID-19-related renal failure requiring RRT, the most common histologic finding was acute tubular injury[32], with ACE2 highly expressed on proximal tubular cells[33]. In a series of 63 decedents with

COVID-19 respiratory infection, SARS-CoV-2 RNA was detected in 60%, including 72% of decedents with AKI.[34] Other findings included thrombotic microangiopathy, pauci-immune crescent glomerulonephritis, widespread myoglobin casts.[32] Several studies found evidence of live virus, suggesting direct kidney tropism through angiotensin-converting enzyme-2 receptors expressed on proximal tubule cells and podocytes. [34] Additionally, micro-thrombi formation of the capillaries around the renal tubulars were seen on autopsy, suggesting a hypercoagulable effect.[33,35] Whether from direct viral invasion, hypoxia, or hypercoagulability, there are may be indirect causes for renal injury including hemodynamic instability, mitochondrial dysfunction[36], excessive diuresis, nephrotoxic exposure, cytokine storm, and rhabdomyolysis. [34]

Clinical Manifestations

COVID-related AKI manifests as decreased glomerular filtration, elevated serum creatinine and BUN, frequent proteinuria[30,33,37], and occasional hematuria and leukocyturia.[30] In a cohort of 182 patients hospitalized with COVID-19-associated AKI, serum creatine was similar, proteinuria was more common, and dialysis was more common than in non-COVID-related AKI[38].

Outcomes

The development of COVID-related AKI is associated with worse outcomes, particularly among patients requiring RRT. While AKI is a marker of worse disease, the association persists after adjustment for illness severity, suggesting that renal injury may also directly contribute to worse outcomes. In the 13-hospital New York cohort, development

of AKI was associated with a 3.4-fold increased risk of in-hospital mortality in adjusted analysis, while RRT was associated with 6.4-fold increased risk[39]. In the 5-hospital New York cohort, in-hospital mortality was 50% among patients with COVID-19 and AKI vs 8% among patients without renal injury.[30] Furthermore, among 832 patients with AKI who survived to hospital discharge, 35% had not returned to baseline renal function by discharge.[30] In a single-center telephone follow-up of 300 patients who survived ICU hospitalization for COVID-19 during March-April of 2020 in New York, only 42% survived to 6 months post-discharge. At 6 months post-discharge, AKI recovered in 74% of survivors, including 77% who liberated from dialysis.[40]

Management

Treatment strategies for COVID-related AKI are similar to standard management of AKI from other causes. Management focuses on mitigating further renal injury through avoidance of nephrotoxic medications, renally-dosing medications, and maintaining perfusion to the kidney. The threshold for initiating RRT is similar to non-COVID-related renal failure. Clotting of continuous renal replacement therapy (CRRT) filters has led to significant resource utilization. In a case series of 65 patients who received CRRT for COVID-19-related renal failure at a single U.S. hospital, 85% lost at least one filter, with a median filter life of only 6.5 hours.[41] Studies are underway testing interventions to mitigate progression of renal disease, including oral medications targeting inflammatory pathways (NCT05038488) and treatments such as CRP-apheresis (NCT04898062) (**Table 3**).

Cardiac Dysfunction

Prevalence

The spectrum of cardiac manifestations of COVID-19 includes asymptomatic cardiac biomarker elevation and symptomatic cardiac dysfunction such as heart failure, arrhythmia, and sudden cardiac arrest. Biomarker elevation occurs in approximately 20-35% of patients hospitalized with COVID-19. In a meta-analysis of 35 studies of 22,473 patients hospitalized in 2020 with COVID-19, troponin was elevated in 21% of patients tested on admission[42]. In a cohort of 2,736 patients hospitalized in single system in New York, troponin was elevated in 36%[43]. Symptomatic cardiac dysfunction is present in approximately 10-20% of hospitalized patients. In a study of 748 patients hospitalized in Europe and Australia during January-October 2020, 141 (19%) had an acute cardiac complication, including cardiovascular death (7%), heart failure (5%), pulmonary embolism (5%), sustained supraventricular tachycardia or ventricular arrythmia (4%), cardiac arrest (2%), myocarditis (2%), and acute coronary syndrome (1%).[44]

Pathophysiology/Mechanisms

SARS-COV-2 is hypothesized to cause cardiac injury via endothelial inflammation, immune activation, direct myocardial injury, acute right heart strain secondary to ARDS and/or pulmonary embolism, and hypoxic injury.[45]

Clinical Manifestations

Cardiac biomarkers, including troponin and BNP, may be elevated in up to one-third of patients hospitalized with COVID-19. Cardiac arrhythmias, including atrial fibrillation, bradyarrhythmias, and ventricular arrhythmias, occur in a minority of patients. The extent to which arrhythmias are directly mediated by SARS-CoV-2 versus general acute illness is unclear. Myocarditis may be triggered by a variety of viral infections including SARS-CoV-2, but the prevalence of this manifestation is unknown.[46] Most myocarditis occurs simultaneous to acute respiratory disease, but case reports of delayed myocarditis have been reported.[46] While not common, cardiac manifestations can be the presenting symptom of COVID-19. In a series of 28 patients hospitalized in Italy during February-March 2020 with COVID-19 and ST segment elevation myocardial infarction (STEMI), 24 of 28 patients had the STEMI as the first manifestation of SARS-CoV-2 infection[47]. Seventeen had a culprit lesion and underwent revascularization.[47]

Outcomes

Troponin elevation is indicative of myocardial injury, and consistently associated with worse outcomes.[44,48] In a meta-analysis of 11 studies of patients hospitalized with COVID during 2020, troponin elevation was associated with 2.7-fold increased risk of in-hospital mortality[42] in adjusted analysis. In a study of 416 patients hospitalized with COVID in China in 2020, cardiac biomarker elevation was associated with increased need for IMV.[49] In a meta-analysis of 3 studies of in-hospital cardiac arrest, SARS-CoV 2 infection was associated with lower rates of shockable rhythm (9.6% vs. 19.8%, p<

0.001), lower rates of ROSC (33.9% vs. 52.1%, p< 0.001), and higher 30-day mortality (77.2% vs. 59.7%, p=0.003).[50]

Management/Treatment

Treatment of COVID-19-related cardiac injury is similar to management of cardiac injury from other causes. As of May 1, 2022, 253 phase 2- 4 interventional clinical trials were registered in clinicaltrials.gov to test interventions prevent or mitigate cardiac complications, including trials of colchicine (NCT04510038), anti-platelet and anti-coagulant triple therapy (NCT04333407), angiotensin receptor neprilysin inhibitors (NCT04883528) and anti-IL1b (NCT04365153) antibody therapy.

Liver Dysfunction

Prevalence

Liver enzymes elevations are common in patients requiring hospitalization for COVID-19, but severe liver dysfunction is a rare manifestation of COVID-19. In a study of 2073 patients hospitalized with COVID-19 in China during January-April 2020, 62% of patients had liver enzymes above upper limit of normal (ULN), including 46% on admission. Liver dysfunction was hepatocellular in 40%, cholestatic in 3%, mixed in 12%, and other in 8%. However, liver injury (>2-3x ULN) occurred in only 14%, including 5% on admission.[51] In a U.S. cohort of 834 patients hospitalized with COVID during April 2020, 12% had significant liver injury (5x ULN) during hospitalization.[52] Acute liver

failure (defined as acute liver injury with hepatic encephalopathy) is a rare complication of COVID-19.[51]

Pathophysiology/Mechanisms

Like other solid organs, the liver is susceptible to hypoxic, ischemic, thrombotic, congestive, and direct viral injury. Several therapies for COVID-19, such as remdesivir and tocilizumab can be hepatotoxic, making drug-induced liver injury a potential cause of liver injury during hospitalization. The ACE2 receptor, where the SARS CoV-2 enters the host is expressed in higher amounts on cholangiocytes than hepatocytes[53]. In series of 40 decedents, macrovesicular steatosis was the most common finding (75%), followed by lobular necroinflammation (50%), portal inflammation (50%) and cholestasis (38%)[54].

Clinical Manifestations

Liver enzyme abnormalities in COVID include hepatocellular, cholestatic, and mixed patterns of injury, with most cases being mild (1-2x the upper limit of normal). The 834 patient U.S. cohort found the most common liver abnormalities were AST (63%), ALT (34%), alkaline phosphatase (12%) and total bilirubin (3%)[52]. The median time to peak of AST level was 3 days (IQR 1-6 days) post-admission.[52]

Outcomes

Liver injury due to COVID-19 is associated with worse outcomes. In a meta-analysis of 26 studies of patients hospitalized with COVID-19 in China, baseline AST >ULN was

associated with increased mortality (OR=3.82, p=0.05), ICU admission (OR= 2.98, p=0.06), and non-fatal complications (OR= 2.95, p=0.08)[55]. In study of 565 patients hospitalized with COVID on general medicine wards in Italy during 2020, 58% had abnormal liver function, which was associated with higher rates of ICU transfer (20% vs 8%), AKI (22% vs 13%), need for IMV (14% vs 6%) and mortality (21% vs 11%).[56] Abnormal liver function was independently associated with death and/or transfer to the ICU (aOR=3.5)[56].

Management/Treatment

The management of acute liver injury in COVID-19—including hepatocellular, cholestatic, and mixed liver injury—is consistent with current strategies for management of non-COVID-19 related liver injury, including maintaining perfusion, minimizing hepatotoxic medications, optimizing volume status, and ruling out of other causes of hepatic injury. As of May 1, 2022, there was one interventional clinical trial registered on clinicaltrials.gov targeted specifically at patients with elevated liver enzymes in the setting of COVID-19 (NCT04816682).

Neurologic Dysfunction

Prevalence and Clinical Manifestations

The neurologic manifestations of COVID-19 are varied but can cause severe debility. A meta-analysis of 48 studies published in the 2020, including 2,839 patients with severe/critical COVID and 7,493 with non-severe COVID-19, analyzed neurologic

manifestations and their association with COVID-19 severity.[57] Severe COVID-19 was associated with skeletal muscle injury, delirium or impaired consciousness, and fatigue, and less alteration in smell or taste. Myopathy was associated with prolonged hospitalization,[58] and critical illness neuropathy was more prevalent in COVID-19 cohorts than non-COVID 19 cohorts.[59] In a retrospective cohort of 277 patients admitted with a stroke to a large NYC hospital in March-April 2020, 38% were SARS-CoV-2 positive. The COVID-19-positive patients were more likely to have a cryptogenic stroke etiology, lobar stroke location, admission to the ICU, and in-hospital mortality.[60] The majority (68%) of COVID-19-positive patients with stroke had parenchymal abnormalities on chest imaging, although stroke has been reported as the presenting sign of COVID-19 in patients without respiratory symptoms.[61] A meta-analysis of 29 studies published in 2020 with 43,024 patients found a 2% pooled prevalence of stroke, which is higher than the prevalence in influenza (0.2%)[62].

Delirium is a common manifestation in critical COVID, and known to be associated long-term cognitive impairment.[63] In an international cohort of 2,088 ICU-treated patient during January-April 2020, 82% were comatose, for a median of 10 days, and 54.9% experienced delirium, for a median of 3 days.[64]

Pathophysiology/Mechanisms

The expression of ACE2 receptor is significantly lower in the central and peripheral nervous system compared to other organs but are found in glial cells in the brain and spinal neurons. In vitro models of the human blood brain barrier showed a negative

impact of SARS CoV-2 spike protein and brain endothelial cells showed a distinct proinflammatory response.[65,66] Endothelial dysfunction, coagulation abnormalities, direct viral transmission through olfactory nerve, hypoxic brain injury, and disruption of the blood brain barrier[65] are all postulated to play a role in neurologic manifestation of patients.[8] Loss of taste/smell, meningitis, encephalitis, cerebral vasculitis, and myalgia may all result from direct viral invasion of the nervous system.[16] Encephalopathy from hypoxia, hyper inflammatory response, and hypercoagulability (leading to stroke) are indirect manifestations of COVID-19 infection on the central nervous system.

Outcomes

Like other acute organ dysfunction, neurologic dysfunction is associated with increased mortality. In a meta-analysis of 21 studies, 770 of 2,982 patients with neurologic manifestations died. The pooled prevalence of mortality among patients with neurologic manifestations was 27% (95% CI 19%–35%)[57]. For patients >60 years, any neurologic manifestation was associated with mortality (OR 1.80, 95% CI 1.11–2.91)[57]. Nearly 1 in 50 patients developed a stroke which has been associated with marked increase in risk of mortality.[67] COVID-19 infection is also associated with significant morbidity in ICU survivors. A multi-center Dutch prospective cohort with follow-up to 1 year post-ICU, physical symptoms were reported in 74.3%, mental symptoms in 26.2%, and cognitive symptoms in 16.2% [68]. The most symptoms were weakened condition (38.9%), joint stiffness (26.3%), joint pain (25.5%), muscle weakness (24.8%) and myalgia (21.3%)[68].

Management/Treatment

The management and treatment of neurologic manifestations of COVID-19 mirror strategies used for non-COVID-19 associated symptoms/diseases. Given the known association of delirium and poor outcomes[69], strategies to reduce delirium in mechanically ventilated patients is extremely important. In a large international cohort of 2,088 ICU patients, of which 87.5% undergoing mechanical ventilation at some point in their hospitalization, benzodiazepine use was identified as a modifiable risk factor for the development of delirium while the family visitation was associated with decreased risk for delirium. This information should be considered for sedations protocols as well as hospital policies regarding visitation. The treatment for stroke follows guidelines for non-COVID-19 stroke, but studies are underway to assess the safety, feasibility, and efficacy of thrombectomy for the management of acute ischemia strokes in patients with COVID-19 (NCT04406090). Early mobility and rehabilitation are crucial to reduce the morbidity associated with COVID-19 disease.

Hematologic Abnormalities (Coagulopathy)

Prevalence

Coagulation abnormalities are a common manifestation of severe and critical COVID-19. In a meta-analysis of 24 studies including 2,570 patients with critical COVID-19, the pooled prevalence of clinically-detected VTE was 31%, and increased to 48% if using systematic screening (e.g., for extremity swelling and/or elevated D-dimer)[70]. A subsequent meta-analysis of 19 studies with1,599 patients receiving prophylactic anticoagulation reported pooled prevalences of VTE, DVT, and PE in 30.1%, 27.2% and

18.3%, respectively.[71] Among studies with routine screening, DVT was identified in 48%, versus in 15% with symptom-driven testing (p<.0001)[71]. The frequent occurrence of VTE when not clinically suspected is corroborated on postmortem studies.[72] While rare, aortic thrombosis, occlusion of large vessels, and solid organ infarct have been reported[73]. In the abdomen and pelvis, hemorrhagic complications were more common than thrombotic complications, including hematomas of retroperitoneum and abdominal wall.[73] Overall, rates of VTE among patients hospitalized with COVID-19 are approximately three-fold higher than among historical matched controls[74], whereas rates of arterial thromboembolism are lower.[75]

Pathophysiology and Clinical Manifestations

The balance of coagulation and fibrinolysis is deranged in SARS-CoV-2 infection **(Figure 2)**. Abnormal labs associated with coagulopathy in COVID-19 are summarized in **Table 4**. While the exact mechanism is incompletely understood, endothelial dysfunction is widely regarded as the major driver of the prothrombotic state in COVID-19.[73,76] Most patients hospitalized with COVID-19 have elevated D-dimer, mild prolongation of aPTT and/or PT, and mild thrombocytopenia.[77] It is unclear whether these abnormalities indicate hypercoagulability or consumptive disseminated intravascular coagulation (DIC)[77]. Hypofibrinogenemia is rare[77] and peripheral smears support a hypercoagulable state[78]. However, in prospective cohort of 98 patients hospitalized in ICU with COVID in the US during 2020-2021 at a single U.S. center, thromboelastographic parameters and conventional coagulation parameters suggested a relative consumptive coagulopathy.[79]

Overall, COVID-19 is associated with a prothrombotic profile that may be driven by excessive inflammation, endothelial activation, platelet activation, impaired fibrinolysis, immune-related molecular events, and systemic hypercoagulability.[80]

Outcomes

Thromboembolism is associated with worse outcomes in COVID-19. In a meta-analysis of 42 studies with 8,217 patients hospitalized with COVID-19, the pooled VTE rate in-hospital was 21% (31% among ICU-treated patients) [81]. Pooled in-hospital mortality was 23% vs 13% among patients with versus without thromboembolism. The pooled odds of mortality were 74% higher for patients diagnosed with a thromboembolism (OR 1.74, p=0.04)[81].

Treatment

Several high-quality RCTs have addressed prevention of thrombotic complications in COVID-19. The current evidence supports prophylactic anticoagulation in critically ill patients, but therapeutic anticoagulation in ward patients. An open-label trial[82] that randomized 1207 patients to therapeutic heparin anticoagulation versus heparin thromboprophylaxis was stopped for futility. Patients randomized to therapeutic anticoagulation had fewer organ-support free days (median 1 vs 4 days) and similar survival to discharge (62.7% vs 64.5%)[82]. However, among non-critically patients, full-dose anticoagulation decreased the need for IMV and other organ supports (aOR=1.27), without increasing major bleeding (1.9% vs 0.9%).[83] Similarly, a multi-center U.S. trial evaluated the impact of therapeutic anticoagulation for patients

hospitalized with COVID-19 with elevated D-dimer levels (>4x ULN) or sepsis-induced coagulopathy score of 4 or more. The study found that—among non-critically ill patients—the combined outcome of VTE, arterial thromboembolism (ATE), or mortality was lower (16.7% vs 36.1%, p=0.004) among patients randomized to therapeutic-dose anticoagulation.[75] However, among critically patients, outcomes were similar between arms (51.1 vs 55.3%, p=0.71).[75] A multi-center RCT in Iran randomized 562 patients with critical COVID to intermediate-dose thromboprophylaxis (enoxaparin 1mg/kg daily) vs standard thromboprophylaxis (enoxaparin 40 mg daily).[84] Outcomes, including composite outcome of VTE or ATE, ECMO treatment, and 30-day mortality, were similar among patients randomized to intermediate vs standard enoxaparin dosing. At this time, it is unclear whether continuing anticoagulation post hospital discharge impacts short term or long-term outcomes. However, studies are underway evaluating post-hospitalization direct oral anticoagulants to prevent or reduce long term symptoms associated with COVID-19 infection (NCT04801940).

New biomarkers for tests of coagulation, fibrinolysis, and platelet activation are being studied to support its usefulness for prognostic, diagnostic and management decisions in COVID-19 related thrombosis.[80] (Table 4) Many advocate for the use of personalized protocol-based titration of heparin anticoagulation[85,86], as studies consistently show heparin resistance manifested by subtherapeutic anti-Xa levels compared to standard dosing protocols[87,88] however, the exact biomarker of choice has yet to be determined. In all, the prevalence and severe prognostic implications of thromboembolism should make thrombotic risk assessment and VTE prevention a priority.

Conclusion

While SARS-CoV-2 infection most commonly causes respiratory symptoms and impairment, it can also cause non-pulmonary organ dysfunction, most commonly shock, acute kidney injury, and hypercoagulability. Neurological, cardiac, and, to a lesser degree, liver injury may also occur from SARS-CoV-2. Management of extra-pulmonary organ dysfunction largely focuses on supportive care practices that are applicable regardless of the etiology of organ injury. However, there is emerging evidence to support therapeutic anticoagulation in non-critically ill patients to mitigate risk for VTE.

Clinics Care Points

References

1. Coronavirus World Map: Tracking the Global Outbreak. The New York Times. Updated May 1, 2022. Accessed May 1, 2022, 2022. https://www.nytimes.com/interactive/2021/world/covid-cases.html?smid=url-share

2. Karakike E, Giamarellos-Bourboulis EJ, Kyprianou M, et al. Coronavirus Disease 2019 as Cause of Viral Sepsis: A Systematic Review and Meta-Analysis. *Crit Care Med*. Dec 1 2021;49(12):2042-2057. doi:10.1097/CCM.0000000000005195

3. Shappell CN, Klompas M, Rhee C. Quantifying the Burden of Viral Sepsis During the Coronavirus Disease 2019 Pandemic and Beyond. *Crit Care Med*. Dec 1 2021;49(12):2140-2143. doi:10.1097/CCM.0000000000005207

4. Lopes-Pacheco M, Silva PL, Cruz FF, et al. Pathogenesis of Multiple Organ Injury in COVID-19 and Potential Therapeutic Strategies. Review. *Frontiers in Physiology*. 2021-January-28 2021;12doi:10.3389/fphys.2021.593223

5. Domecq JP, Lal A, Sheldrick CR, et al. Outcomes of Patients With Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med*. Mar 1 2021;49(3):437-448. doi:10.1097/CCM.0000000000004879

6. Abumayyaleh M, Nunez-Gil IJ, El-Battrawy I, et al. Sepsis of Patients Infected by SARS-CoV-2: Real-World Experience From the International HOPE-COVID-19-Registry and Validation of HOPE Sepsis Score. *Front Med (Lausanne)*. 2021;8:728102. doi:10.3389/fmed.2021.728102

7. Loganathan S, Kuppusamy M, Wankhar W, et al. Angiotensin-converting enzyme 2 (ACE2): COVID 19 gate way to multiple organ failure syndromes. *Respir Physiol Neurobiol*. Jan 2021;283:103548. doi:10.1016/j.resp.2020.103548

8. Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G. COVID-19 and multiorgan failure: A narrative review on potential mechanisms. *J Mol Histol*. Dec 2020;51(6):613-628. doi:10.1007/s10735-020-09915-3

9. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. Jul 2020;26(7):1017-1032. doi:10.1038/s41591-020-0968-3

10. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. Apr 2020;8(4):420-422. doi:10.1016/S2213-2600(20)30076-X

11. Olwal CO, Nganyewo NN, Tapela K, et al. Parallels in Sepsis and COVID-19 Conditions: Implications for Managing Severe COVID-19. *Front Immunol*. 2021;12:602848. doi:10.3389/fimmu.2021.602848

12. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. Feb 25 2021;384(8):693-704. doi:10.1056/NEJMoa2021436

13. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. May 1 2021;397(10285):1637-1645. doi:10.1016/S0140-6736(21)00676-0

14. Kramer A, Prinz C, Fichtner F, et al. Janus kinase inhibitors for the treatment of COVID-19. *Cochrane Database Syst Rev*. Jun 13 2022;6:CD015209. doi:10.1002/14651858.CD015209

15. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed August 28th, 2022.

16. Bhalerao A, Raut S, Noorani B, Mancuso S, Cucullo L. Molecular Mechanisms of Multi-Organ Failure in COVID-19 and Potential of Stem Cell Therapy. *Cells*. Oct 25 2021;10(11)doi:10.3390/cells10112878

17. Jardou M, Lawson R. Supportive therapy during COVID-19: The proposed mechanism of short-chain fatty acids to prevent cytokine storm and multi-organ failure. *Med Hypotheses*. Sep 2021;154:110661. doi:10.1016/j.mehy.2021.110661

18. Hellenic Institute for the Study of S. suPAR-Guided Anakinra Treatment for Management of Severe Respiratory Failure by COVID-19. 2021.

19. Jena University H, German Federal Ministry of E, Research, Celltrion. Infliximab in the Treatment of Patients With Severe COVID-19 Disease. 2022.

20. University of Sao P, Conselho Nacional de Desenvolvimento Científico e T, Science Valley Research I. Survival TRial Using CytoKines in COVID-19 (STRUCK Trial). Updated March 31. https://ClinicalTrials.gov/show/NCT04724629

21. Prof. Dr. Jörg L, Cantonal Hosptal B. High Dose Vitamin-D Substitution in Patients With COVID-19: a Randomized Controlled, Multi Center Study. 2021.

22. Hunter Holmes Mcguire Veteran Affairs Medical C, McGuire Research I. Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation. 2020.

23. Université de S, Lotte, John Hecht Memorial F. Lessening Organ Dysfunction With VITamin C. Updated August 15. https://ClinicalTrials.gov/show/NCT03680274

24. Medical University of W, Human Biome Institute P. The Impact of Fecal Microbiota Transplantation as an Immunomodulation on the Risk Reduction of COVID-19 Disease Progression With Escalating Cytokine Storm and Inflammatory Parameters. 2022.

25. ExThera Medical Europe BV, ExThera Medical C, Vivantes Klinikum N. Safety & Effectiveness Evaluation of Seraph 100 in Treatment of Pts With COVID-19. 2022.

26. Helsinki University Central H, Finnish Red C. Convalescent Plasma in the Treatment of Covid-19. 2021.

27. Unicef, Pak Emirates Military Hospital R. Therapeutic Plasma Exchange for Coronavirus Disease-2019 Triggered Cytokine Release Storm. 2020.

28. Bechman K, Yates M, Mann K, et al. Inpatient COVID-19 mortality has reduced over time: Results from an observational cohort. *PLoS One*. 2022;17(1):e0261142. doi:10.1371/journal.pone.0261142

29. 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI). Accessed May 1, 2022. https://kdigo.org/guidelines/acute-kidney-injury/

30. Chan L, Chaudhary K, Saha A, et al. AKI in Hospitalized Patients with COVID-19. *J Am Soc Nephrol*. Jan 2021;32(1):151-160. doi:10.1681/ASN.2020050615

31. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. Jul 2020;98(1):209-218. doi:10.1016/j.kint.2020.05.006

32. Sharma P, Uppal NN, Wanchoo R, et al. COVID-19-Associated Kidney Injury: A Case Series of Kidney Biopsy Findings. *J Am Soc Nephrol*. Sep 2020;31(9):1948-1958. doi:10.1681/ASN.2020050699

33. Yang X, Jin Y, Li R, Zhang Z, Sun R, Chen D. Prevalence and impact of acute renal impairment on COVID-19: a systematic review and meta-analysis. *Crit Care*. Jun 18 2020;24(1):356. doi:10.1186/s13054-020-03065-4

34. Braun F, Lutgehetmann M, Pfefferle S, et al. SARS-CoV-2 renal tropism associates with acute kidney injury. *Lancet*. Aug 29 2020;396(10251):597-598. doi:10.1016/S0140-6736(20)31759-1

35. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. Mar 17 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585

36. Alexander MP, Mangalaparthi KK, Madugundu AK, et al. Acute Kidney Injury in Severe COVID-19 Has Similarities to Sepsis-Associated Kidney Injury: A Multi-Omics Study. *Mayo Clin Proc*. Oct 2021;96(10):2561-2575. doi:10.1016/j.mayocp.2021.07.001

37. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. May 2020;97(5):829-838. doi:10.1016/j.kint.2020.03.005

38. Nugent J, Aklilu A, Yamamoto Y, et al. Assessment of Acute Kidney Injury and Longitudinal Kidney Function After Hospital Discharge Among Patients With and Without COVID-19. *JAMA Netw Open*. Mar 1 2021;4(3):e211095. doi:10.1001/jamanetworkopen.2021.1095

39. Ng JH, Hirsch JS, Hazzan A, et al. Outcomes Among Patients Hospitalized With COVID-19 and Acute Kidney Injury. *Am J Kidney Dis*. Feb 2021;77(2):204-215.e1. doi:10.1053/j.ajkd.2020.09.002

40. Chand S, Kapoor S, Naqvi A, et al. Long-Term Follow up of Renal and Other Acute Organ Failure in Survivors of Critical Illness Due to Covid-19. *J Intensive Care Med*. Dec 17 2021:8850666211062582. doi:10.1177/08850666211062582

41. Endres P, Rosovsky R, Zhao S, et al. Filter clotting with continuous renal replacement therapy in COVID-19. *J Thromb Thrombolysis*. May 2021;51(4):966-970. doi:10.1007/s11239-020-02301-6

42. Zhao B-C, Liu W-F, Lei S-H, et al. Prevalence and prognostic value of elevated troponins in patients hospitalised for coronavirus disease 2019: a systematic review and meta-analysis. *Journal of Intensive Care*. 2020/11/23 2020;8(1):88. doi:10.1186/s40560-020-00508-6

43. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. *Journal of the American College of Cardiology*. 2020/08/04/ 2020;76(5):533-546. doi:https://doi.org/10.1016/j.jacc.2020.06.007

44. Henein MY, Mandoli GE, Pastore MC, et al. Biomarkers Predict In-Hospital Major Adverse Cardiac Events in COVID-19 Patients: A Multicenter International Study. *J Clin Med*. Dec 14 2021;10(24)doi:10.3390/jcm10245863

45. Tanacli R, Doeblin P, Gotze C, et al. COVID-19 vs. Classical Myocarditis Associated Myocardial Injury Evaluated by Cardiac Magnetic Resonance and Endomyocardial Biopsy. *Front Cardiovasc Med*. 2021;8:737257. doi:10.3389/fcvm.2021.737257

46. Farshidfar F, Koleini N, Ardehali H. Cardiovascular complications of COVID-19. *JCI Insight*. Jul 8 2021;6(13)doi:10.1172/jci.insight.148980

47. Stefanini GG, Montorfano M, Trabattoni D, et al. ST-Elevation Myocardial Infarction in Patients With COVID-19: Clinical and Angiographic Outcomes. *Circulation*. Jun 23 2020;141(25):2113-2116. doi:10.1161/CIRCULATIONAHA.120.047525

48. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. Jul 1 2020;5(7):811-818. doi:10.1001/jamacardio.2020.1017

49. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. Jul 1 2020;5(7):802-810. doi:10.1001/jamacardio.2020.0950

50. Bielski K, Makowska K, Makowski A, et al. Impact of COVID-19 on in-hospital cardiac arrest outcomes: An updated meta-analysis. *Cardiol J*. 2021;28(6):816-824. doi:10.5603/CJ.a2021.0168

51. Ding ZY, Li GX, Chen L, et al. Association of liver abnormalities with in-hospital mortality in patients with COVID-19. *J Hepatol*. Jun 2021;74(6):1295-1302. doi:10.1016/j.jhep.2020.12.012

52. Chew M, Tang Z, Radcliffe C, et al. Significant Liver Injury During Hospitalization for COVID-19 Is Not Associated With Liver Insufficiency or Death. *Clin Gastroenterol Hepatol*. Oct 2021;19(10):2182-2191 e7. doi:10.1016/j.cgh.2021.05.022

53. Chai X, Hu L, Zhang Y, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. *bioRxiv*. 2020:2020.02.03.931766. doi:10.1101/2020.02.03.931766

54. Lagana SM, Kudose S, Iuga AC, et al. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol*. Nov 2020;33(11):2147-2155. doi:10.1038/s41379-020-00649-x

55. Ampuero J, Sanchez Y, Garcia-Lozano MR, Maya-Miles D, Romero Gomez M. Impact of liver injury on the severity of COVID-19: a systematic review with meta-analysis. *Rev Esp Enferm Dig*. Feb 2021;113(2):125-135. doi:10.17235/reed.2020.7397/2020

56. Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. *Liver Int*. Oct 2020;40(10):2394-2406. doi:10.1111/liv.14565

57. Misra S, Kolappa K, Prasad M, et al. Frequency of Neurologic Manifestations in COVID-19: A Systematic Review and Meta-analysis. *Neurology*. Dec 7 2021;97(23):e2269-e2281. doi:10.1212/WNL.0000000000012930

58. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19. *The ALBACOVID registry*. 2020;95(8):e1060-e1070. doi:10.1212/wnl.0000000000009937

59. Bocci T, Campiglio L, Zardoni M, et al. Critical illness neuropathy in severe COVID-19: a case series. *Neurol Sci*. Dec 2021;42(12):4893-4898. doi:10.1007/s10072-021-05471-0

60. Dhamoon MS, Thaler A, Gururangan K, et al. Acute Cerebrovascular Events With COVID-19 Infection. *Stroke*. Jan 2021;52(1):48-56. doi:10.1161/STROKEAHA.120.031668

61. Morassi M, Bagatto D, Cobelli M, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol*. Aug 2020;267(8):2185-2192. doi:10.1007/s00415-020-09885-2

62. Merkler AE, Parikh NS, Mir S, et al. Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. *JAMA Neurol*. Jul 2 2020;doi:10.1001/jamaneurol.2020.2730

63. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med*. May 2014;2(5):369-79. doi:10.1016/s2213-2600(14)70051-7

64. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. Mar 2021;9(3):239-250. doi:10.1016/S2213-2600(20)30552-X

65. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood–brain barrier. *Neurobiology of Disease*. 2020/12/01/ 2020;146:105131. doi:https://doi.org/10.1016/j.nbd.2020.105131

66. Whitmore HAB, Kim LA. Understanding the Role of Blood Vessels in the Neurologic Manifestations of Coronavirus Disease 2019 (COVID-19). *Am J Pathol*. Nov 2021;191(11):1946-1954. doi:10.1016/j.ajpath.2021.04.017

67. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke*. Jul 2020;51(7):2002-2011. doi:10.1161/STROKEAHA.120.030335

68. Heesakkers H, van der Hoeven JG, Corsten S, et al. Clinical Outcomes Among Patients With 1-Year Survival Following Intensive Care Unit Treatment for COVID-19. *JAMA*. 2022;327(6):559-565. doi:10.1001/jama.2022.0040

69. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *Jama*. Apr 14 2004;291(14):1753-62. doi:10.1001/jama.291.14.1753

70. Mohamed MFH, Al-Shokri SD, Shunnar KM, et al. Prevalence of Venous Thromboembolism in Critically Ill COVID-19 Patients: Systematic Review and Meta-Analysis. Systematic Review. *Frontiers in Cardiovascular Medicine*. 2021-January-08 2021;7doi:10.3389/fcvm.2020.598846

71. Wu C, Liu Y, Cai X, Zhang W, Li Y, Fu C. Prevalence of Venous Thromboembolism in Critically Ill Patients With Coronavirus Disease 2019: A Meta-Analysis. Systematic Review. *Frontiers in Medicine*. 2021-April-29 2021;8doi:10.3389/fmed.2021.603558

72. Wichmann DS, J.P.; Lütgehetmann, M.; Steurer, S,; Edler, C.; Heinemann, A.; et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Annals of Internal Medicine*. 2020;173(4):268-277. doi:10.7326/m20-2003 %m 32374815

73. Lee EE, Gong AJ, Gawande RS, Fishman EK, Vadvala HV. Vascular findings in CTA body and extremity of critically ill COVID-19 patients: commonly encountered vascular complications with review of literature. *Emergency Radiology*. 2022/01/22 2022;doi:10.1007/s10140-021-02013-1

74. Malato A, Dentali F, Siragusa S, et al. The impact of deep vein thrombosis in critically ill patients: a meta-analysis of major clinical outcomes. *Blood Transfus*. Oct 2015;13(4):559-68. doi:10.2450/2015.0277-14

75. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. *JAMA Intern Med*. Dec 1 2021;181(12):1612-1620. doi:10.1001/jamainternmed.2021.6203

76. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. Jun 4 2020;135(23):2033-2040. doi:10.1182/blood.2020006000

77. Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. *Pathobiology*. 2021;88(1):15-27. doi:10.1159/000512007

78. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res*. Oct 2020;194:101-115. doi:10.1016/j.thromres.2020.06.029

79. Marvi TK, Stubblefield WB, Tillman BF, et al. Serial Thromboelastography and the Development of Venous Thromboembolism in Critically Ill Patients With COVID-19. *Crit Care Explor*. Jan 2022;4(1):e0618. doi:10.1097/CCE.0000000000000618

80. Gorog DA, Storey RF, Gurbel PA, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. *Nature Reviews Cardiology*. 2022/01/13 2022;doi:10.1038/s41569-021-00665-7

81. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine*. Dec 2020;29:100639. doi:10.1016/j.eclinm.2020.100639

82. Investigators R-C, Investigators AC-a, Investigators A, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. *N Engl J Med*. Aug 26 2021;385(9):777-789. doi:10.1056/NEJMoa2103417

83. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. *New England Journal of Medicine*. 2021;385(9):790-802. doi:10.1056/NEJMoa2105911

84. Investigators I. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *JAMA*. 2021;325(16):1620-1630. doi:10.1001/jama.2021.4152

85. Flaczyk A, Rosovsky RP, Reed CT, Bankhead-Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations. *Crit Care*. Sep 16 2020;24(1):559. doi:10.1186/s13054-020-03273-y

86. Farrar JE, Trujillo TC, Mueller SW, et al. Evaluation of a patient specific, targeted-intensity pharmacologic thromboprophylaxis protocol in hospitalized patients with COVID-19. *Journal of Thrombosis and Thrombolysis*. 2021/08/19 2021;doi:10.1007/s11239-021-02552-x

87. Trunfio M, Salvador E, Cabodi D, et al. Anti-Xa monitoring improves low-molecular-weight heparin effectiveness in patients with SARS-CoV-2 infection. *Thromb Res*. Dec 2020;196:432-434. doi:10.1016/j.thromres.2020.09.039

88. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. *Journal of Thrombosis and Thrombolysis*. 2020/08/01 2020;50(2):287-291. doi:10.1007/s11239-020-02145-0

89. Lombardi CM, Carubelli V, Iorio A, et al. Association of Troponin Levels With Mortality in Italian Patients Hospitalized With Coronavirus Disease 2019: Results of a Multicenter Study. *JAMA Cardiology*. 2020;5(11):1274-1280. doi:10.1001/jamacardio.2020.3538

90. Mansory EM, Srigunapalan S, Lazo-Langner A. Venous Thromboembolism in Hospitalized Critical and Noncritical COVID-19 Patients: A Systematic Review and Meta-analysis. *TH Open*. Jul 2021;5(3):e286-e294. doi:10.1055/s-0041-1730967

FIGURE LEGENDS

Figure 1. Non-pulmonary critical organ dysfunctions due to COVID-19 infection

Figure 2. Endotheliopathy in COVID-19 coagulopathy.

From O'Sullivan JM, Gonagle DM, Ward SE, Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. The Lancet Haematology. 2020;7(8):e553-e555..

Table 1. Prevalence of Organ Dysfunction by hospitalization status and association with mortality

Organ Dysfunction	General Prevalence in Hospitalized patients	ICU Prevalence	Association with Mortality
Sepsis[2]	5% (pooled)	Septic Shock 36.4%; Lactate elevated (>2mmol/L) 47.2%	Mortality could not be assessed separately for patients with and without sepsis, since none of the studies reported such outcomes
Cardiac[42,43,89]	21-45% with troponin elevation; 10-20% with symptomatic dysfunction	Troponin elevation more common in patients requiring >50% Fraction of inspired oxygen support	Troponin elevation has 2.7x risk in-hospital mortality and associated with 2x increase in major complications, including sepsis, acute kidney failure, multiorgan failure, pulmonary embolism, and major bleeding
Renal[2,30,31,39]	37% to 46% with AKI defined by KDIGO[29] criteria	28.6% to 76% with AKI; 19% received renal replacement therapy	3.4x risk in-hospital mortality; 50% with AKI vs 8% without AKI

Liver[2,51,56]	14% (>2-3 UNL transaminitis); 58%-62% (>ULN)	20.3 %	Elevation in AST and direct bilirubin on admission associated with 2x increase in hospital mortality
Neurologic[57]	fatigue (31%) and myalgia (30%) more common in hospitalized COVID-19 cases; stroke 2%	Skeletal muscle injury (5%) and disturbances of consciousness more likely in severe than non-severe COVID-19 infection; 50% delirium	In patients ≥60 years of age, the presence of any neurologic manifestations was significantly associated with increased mortality (OR 1.80, 95% CI 1.11–2.91); nonsignificant higher odds of mortality in all patients with neurologic manifestations compared to those without them (OR 1.39)
Coagulopathy[71,81,90]	8% - 21%	Pooled prevalence of VTE 24 - 31%	Pooled odds mortality 74% higher (OR 1.74) for patients with VTE

Table 2. Multi-organ Dysfunction Studies in Detail

Study Author	Study Characteristics; Patient No.	Dates of Study	Findings	Conclusion

Karakike et al[2] (Meta-analysis)	151 studies; 218,184 patients. Forty-seven studies reported results from Asia, mainly China (21 studies), 21 from North America, seven from Central and South America, 73 across Europe, one from Australia, and	104 studies published in 2020 and 47 published in 2021	Sepsis prevalence was 77.9% (95% CI, 75.9-79.8; I2 = 91%; 57 studies) in the ICU, and 33.3% (95% CI, 30.3-36.4; I2 = 99%; 86 studies) in the general ward Pooled prevalence of organ support: vasopressor use 9.5%; Non-invasive ventilation (NIV) 20.9%; Invasive Mechanical Ventilation (IMV) 62.4%; Extracorporeal membrane oxygenation 6.2%; Continuous renal replacement therapy/dialysis 19.9%. Pooled prevalence of organ dysfunction: Septic Shock 36.4%; Lactate elevated (>2mmol/L) 47.2%; Renal Dysfunction 28.6 %; Coagulopathy 17.7 %, Liver Dysfunction 20.3 %, CNS Dysfunction 8.8 %, acute respiratory distress syndrome (ARDS) 87.5 %, Mild ARDS 21.5 %, Moderate ARDS 43.7 %, Severe ARDS 32.1 %	The majority COVID-19 patients hospitalized in the ICU meet Sepsis-3 criteria and present with infection-associated organ dysfunction. Awareness and systematic reporting of COVID 19 viral sepsis is crucial to understand prognostic and treatment implications

	two were international			
Domecq et al.[5] (Registry)	16 countries; 168 hospitals (150 from the United States); 20,608 patients	Patient hospitalized from February 15, 2020, to November 30, 2020	Mean age 60.5 years, 54.3% men; 42.4% were admitted to the ICU Organ Support and Mortality: IMV Only 40.8%; IMV + Vasopressors 53%; IMV+ Vasopressors + RRT 71.6%; ECMO 35%; No organ support 8.2%; All patients 19%	Prognosis varies by age and level of organ support. Interhospital variation in mortality of mechanically ventilated patients was not explained by patient characteristics and requires further evaluation

Table 3. Organ-specific Randomized Control Trials of Therapeutics in COVID-19 Infections*

Organ Function	NCT number	Name of Study
Cardiac	NCT04883528	Protecting with ARNI against cardiac consequences of Coronavirus Disease 2019 with Drug: Sacubitril / Valsartan Oral Tablet [Entresto]
	NCT04365153	Canakinumab to Reduce Deterioration of Cardiac and Respiratory Function in SARSCoV2 Associated Acute Myocardial Injury with Heightened Inflammation (completed)
Renal	NCT04402957	LSALT Peptide vs. Placebo to Prevent ARDS and Acute Kidney Injury in Patients Infected With SARS-CoV-2 (COVID-19)
	NCT04818216	Nicotinamide Riboside in SARS-CoV-2 (COVID-19) Patients for Renal Protection (NIRVANA)
Liver	NCT04816682	Silymarin, phase 4, Does Silymarin Mitigate Clinical Course of COVID-19 in Patients Admitted to an Internal Medicine Ward with Elevated Liver Enzymes?

Neuro	NCT04904536	An International, Investigator Initiated and Conducted, Pragmatic Clinical Trial to Determine Whether 40mg Atorvastatin Daily Can Improve Neurocognitive Function in Adults With Long COVID Neurological Symptoms; Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER)
Coagulopathy	NCT04650087	COVID-19 Post-hospital Thrombosis Prevention Trial: An Adaptive, Multicenter, Prospective, Randomized Platform Trial Evaluating the Efficacy and Safety of Antithrombotic Strategies in Patients With COVID-19 Following Hospital Discharge
	NCT04508023	A Study of Rivaroxaban to Reduce the Risk of Major Venous and Arterial Thrombotic Events, Hospitalization and Death in Medically Ill Outpatients With Acute, Symptomatic Coronavirus Disease 2019 (COVID-19) Infection (PREVENT-HD)

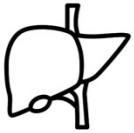
* Partial list of active interventional phase 2-4 randomized control trials

Table 4. Current and Novel Biomarkers of Hypercoagulability in COVID-19 Disease.

Serologic Biomarkers	Current summary of evidence supporting usefulness
C-reactive protein	Strong evidence that levels are associated with disease severity, occurrence of VTE and mortality
IL-6	Strong evidence to guide prognosis but not for prediction of thrombosis
D-dimer	Strong evidence that levels are associated with disease severity and adverse outcomes, including mortality
aPTT/Anti-Xa	Not useful as a marker of COVID-19 severity or prognosis
Neuroendocrine Tumors	Potential use in detecting severe vs. non severe COVID-19, but not in predicting thrombotic risk
Complement Factors	Potentially of use in detecting severe COVID-19, longer-term prognostic utility unknown
ACE2	Discrimination of COVID-19 severity not shown
Calprotectin	Potentially of use in detecting severe COVID-19 and assessing the risk of thrombosis

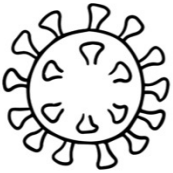
Adapted from Gorog DA, Storey RF, Gurbel PA, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat Rev Cardiol. 2022;19(7):475-495.

Multi-organ Dysfunction
- Viral Sepsis
- Mechanical Organ Support



Liver Dysfunction
- Transaminitis
- Acute Liver Injury

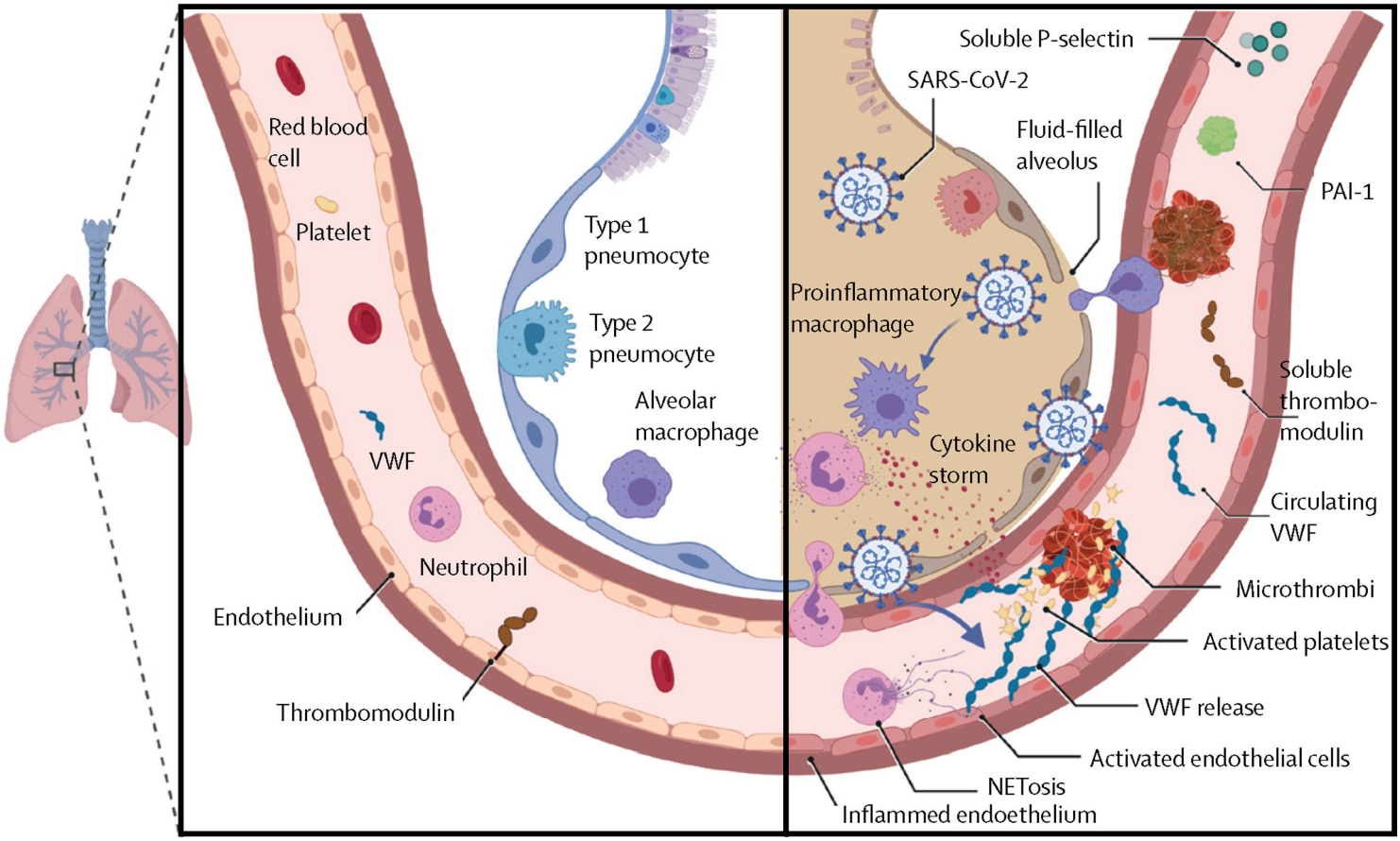
Neurologic Dysfunction
- Skeletal Muscle Injury
- Delirium
- Stroke



Cardiac Dysfunction
- Myocardial Infarction
- Myocarditis
- Arrythmia

Renal Dysfunction
- Acute Kidney Injury
- Renal Replacement Therapy

Hematologic Abnormalities
- Venous Thromboembolism
- Arterial Thromboembolism
- Hemorrhage


Red blood cell
Platelet
VWF
Neutrophil
Endothelium
Thrombomodulin
Type 1 pneumocyte
Type 2 pneumocyte
Alveolar macrophage
Soluble P-selectin
SARS-CoV-2
Fluid-filled alveolus
PAI-1
Proinflammatory macrophage
Cytokine storm
Soluble thrombo-modulin
Circulating VWF
Microthrombi
Activated platelets
VWF release
Activated endothelial cells
NETosis
Inflammed endoethelium