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COVID-19 and Multiorgan Response: The Long-Term Impact

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Abstract: In late December 2019, severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) was discovered following a cluster of pneumonia cases in Wuhan, China. During the early stages of the COVID-19 pandemic in 2020, it was unclear how this virus would manifest into a multiorgan impacting disease. After over 750 million cases worldwide, it has become increasingly evident that SARS-CoV-2 is a complex multifaceted disease we continue to develop our understanding of the pathophysiology of COVID-19 and how it affects these systems has many theories, ranging from direct viral infection via ACE2 receptor binding, to indirect coagulation dysfunction, cytokine storm, and pathological activation of the complement system. Since the onset of the pandemic, disease presentation, management, and manifestation have changed significantly. This paper intends to expand on the long-term impacts of COVID-19 on the cardiovascular, respiratory, urinary, gastrointestinal, and vascular systems of

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the body and the changes in clinical management. It is evident that the pharmacological, nonpharmacological and psychological management of COVID-19 patients require clearer guidelines to improve the survival odds and long-term clinical outcomes of those presenting with severe disease. (Curr Probl Cardiol 2023;48:101756.)

Introduction

Severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) was discovered in late December 2019 in Wuhan, China following a cluster of pneumonia cases linked to a wholesale seafood market.[1,2] Three years on, this disease has spread rapidly with over 750 million cases recorded worldwide, setting new societal norms to prevent disease transmission across the globe.[3] Since the outbreak, new strains including the Omicron variant have been established with new symptoms of the acute virus being recognized. However, the longer-term implications are still being determined. This paper aims to expand on the multiorgan manifestations of COVID-19 across the cardiovascular, respiratory, urinary, gastrointestinal, and vascular systems of the body since the onset of the pandemic.

Respiratory Involvement of COVID-19

In the early stages of the COVID-19 pandemic, a study of 138 patients in Wuhan, China[4] indicated that the presenting features were most commonly: fever (99%), fatigue (67%) and dry cough (60%). However, findings via the ZOE COVID study[5] following the discovery of the Omicron variant, identify sore throat (69%) and runny nose (83%) as additional top presenting features. These symptoms have since been recognized by the National Health Service in the United Kingdom and have been added to the list of features to screen for when suspicious of a COVID-19 infection.[6] It is likely this list will continue to develop over time with the discovery of future strains.

The long-term manifestations of the COVID-19 disease have become known as "long-COVID" with the pulmonary systems being one of the most common systems to have long-term sequelae reported. The World Health Organization has defined long COVID[7] as: "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other

explanation." The symptoms of which include fatigue, dyspnea, and cognitive dysfunction. The risk of developing long COVID has also been linked to the variant causing the infection with data showing the risk to be lower with the Omicron variant.[8] A community study in England, UK of over 600,000 people estimates the incidence of long COVID to be approximately 15%.[9] The most reported respiratory long-COVID symptoms are dyspnea and a persistent cough.[10] Lung function tests have also shown a decrease in lung diffusion capacity for carbon monoxide (DLCO) in 53% (30 of 57) patients[11] 3 months following onset of infection.

Radiologically, acute COVID-19 demonstrates a similar appearance to viral pneumonia, displaying peripherally distributed ground glass opacity on computerized tomography (CT) imaging.[12] A study by Han et al[13] following up 114 patients 6 months following onset of infection with COVID-19, found that fibrotic-like changes remained persistent in over a third of patients (40/114). Additionally, these changes had further associations with longer hospital stays, older age, and acute respiratory distress syndrome (ARDS). An alternative study in Spain by Tarraso et al.[14] followed up patients twelve months on. The study found fibrotic-like sequelae in 22.7% (102/448) of patients who had radiological features at admission. These fibrotic changes were defined as traction bronchiectasis, honeycombing, or presence of parenchymal bands.

The long-term respiratory sequelae of COVID-19, including pulmonary fibrosis, will require consideration of further treatment as the burden will remain a challenge for health care providers in both primary and secondary care.

Cardiovascular Involvement of COVID-19

Whilst respiratory disease is the most dominant feature of COVID-19, cardiovascular comorbidities have been shown to increase the risk of severe COVID-19 and having poorer prognosis.[2] A meta-analysis completed by Bea et al.[15] including 51 studies and 48,317 patients, concluded that the overall relative risk of developing severe COVID-19 was significantly higher in those with cardiovascular disease (odds ratio 3.11) including risk factors of hypertension and diabetes (odds ratio 2.50 and 2.25 respectively). Severity included the development of acute respiratory distress syndrome (ARDS), hospitalization and the progression of further complications or death. This risk was increased across all age cohorts however, younger patients had an overall lower prevalence of cardiovascular comorbidities.[15]

The mechanism by which SARS-CoV-2 involves the cardiovascular system is thought to be due to the angiotensin-converting enzyme-2 (ACE2) mechanism of the infection.[16] The virus binds to ACE2 to enter cells by endocytosis to induce cellular damage. ACE2 is heavily prevalent in the respiratory and cardiovascular system, expressed in cardiomyocytes, cardiac fibroblasts, and coronary artery endothelial cells, allowing for the virus to initiate cardiac damage.[17] Cytokines released during the acute infection can also induce myocardial injury, increasing the risk of a myocardial infarction.[18]

Cardiovascular manifestations of the SARS-CoV-2 virus include raised troponin-I of above the 99th percentile in 20% of patients.[19] Further studies[20] on cardiac biomarkers have indicated that raised levels of Troponin-T are linked to poorer outcomes following infection, suggesting that early investigation of cardiac troponin may be a useful tool for risk stratification and 30-day mortality predictions in COVID-19.[21]

Long term cardiac sequelae from COVID-19 include ongoing chest pain which in one study was shown to be present in 21% of survivors after 60 days,[22] and in another study at 6 months, present in 5%.[23] Additionally, the occurrence of arrhythmias has been identified in the 6 month follow up with 9.3% (154/1655) of previous COVID-19 patients reporting ongoing palpitations. A further retrospective cohort study[24] has concluded that survivors of COVID-19 had substantially higher incidence of cardiovascular diseases including atrial fibrillation, myocarditis, ischemic cardiomyopathy, heart failure and thromboembolic disorders. The risk of heart failure and myocardial infarction could be increased by 72% and 63%[25] respectively, following infection with COVID-19. Further studies with prolonged follow up periods are paramount to determine the long-term effects of these risks and the management required to overcome them.

Renal Involvement of COVID-19

Though the lungs are the most commonly affected organ by SARS-CoV-2, several reviews and clinical evidence have pointed to kidney involvement as a serious consequence of COVID-19. Acute kidney injury (AKI) is a common renal complication of SARS-CoV-2 infection, carrying an estimated incidence of 10% in hospitalized patients although some studies have reported these figures to be as high as 28.6%.[26,27] The pathophysiology of COVID-19 AKI remains controversial with some studies pointing to direct viral infection with the renal tropism of the virus and others describing endothelial injury and activation of the

renin-angiotensin-aldosterone system as the most pertinent mechanisms of injury.[28] Critically ill patients were found to have the worst baseline kidney measures, likely due to the cumulative effects of hypotension, hypoxia, and low cardiac output on tubular function.[28] Acute tubular injury was the most common finding in COVID-19 patients' biopsies, followed by de novo collapsing glomerulopathy and thrombotic microangiopathy. Two series of renal biopsy reports from Columbia University Medical Center and Northwell Hospital Systems found that despite the presence of rhabdomyolysis and myoglobin casts, patients' COVID-19 symptomatology was not severe enough to cause de novo acute tubular injury. This suggests that COVID-19 may potentiate endothelial injury in patients with pre-existing conditions.[29] Other studies have actually proposed direct cellular infection as a more plausible pathophysiological mechanism of COVID-induced AKI, stating that SARS-CoV-2 penetrates through angiotensin-converting enzyme to which is very densely concentrated in the proximal tubular epithelial cells of the kidney.[30] Despite the lack of viral particles detected on renal biopsies in these studies, researchers have suggested that AKI develops in later stages in critically ill patients and that it is a marker of long-term multiple organ dysfunction caused by COVID-19.[31] The majority of mechanisms, however, are likely to overlap with each other and work synergistically to decrease kidney function, making them difficult to distinguish from each other.

The most common clinical finding of COVID-19 AKI is frequently reported to be heavy proteinuria followed by hematuria and increased serum creatinine.[30] In patients with both de novo AKI and a history of renal disease, SARS-CoV-2 was associated with worse clinical outcomes than AKI patients without COVID-19.[29] AKI incidence undeniably increases the fatality rate amongst COVID-19 patients, ranging from 33.3% up to 86.4% in ICU patients compared to the 5.6%-9.3% mortality range in COVID-19 ICU patients without AKI.[30] In surviving patients, COVID-induced AKI is associated with impaired long-term kidney function, demonstrating a consistent 125% baseline serum creatinine elevation at 180 and 365 days postdiagnosis compared to COVID patients without AKI. This was especially common in men, older patients, and those with a past medical history of hypertension and ischemic heart disease.[32]

Despite the severity of concomitant AKI and COVID-19, treatment is largely supportive without a specific management strategy. Hypovolemia should be corrected first whereas electrolyte disturbances, notably hyperkalemia, should be managed with potassium binders alongside standard hospital protocol. In the most critically unwell patients who fail to

respond to conservative management and/or presenting with hemodynamic instability, renal replacement therapy (RRT) has offered adequate organ support and prevention of disease progression. However, the long-term effects of RRT on COVID-19 patients has yet to be studied; further longitudinal studies are warranted to study the full effect of RRT and other potential treatments targeted towards COVID-19 AKI patients.[31,33]

Gastrointestinal Involvement of COVID-19

Gastrointestinal (GI) symptoms such as nausea, vomiting, diarrhea, anorexia, and abdominal pain are the second most common set of clinical symptoms in COVID-19 patients after the respiratory sequelae. The GI system, particularly the absorptive enterocytes of the ileum and the colon and the esophageal epithelium, is rich in ACE2 receptors for the SARS-CoV-2 pathogen to bind to, explaining the prevalence of GI symptoms upon infection.[34] Furthermore, a study by Ling et al. suggested the possibility of faecal-oral transmission of COVID-19 after finding that 82% of COVID-confirmed cases had viral RNA in their stool despite negative nasopharyngeal swabs. If true, faecal-oral transmission presents a new challenge for healthcare workers who must handle stool samples of infected patients with extreme caution to prevent more infections.[35]

Apart from its pivotal role in the renin-angiotensin-aldosterone system, ACE2 is a known tryptophan regulator of the GI system that is adversely affected upon SARS-CoV-2 infection. During COVID-19, the inefficient absorption of tryptophan by ACE2 leads to pathological antimicrobial peptide secretion and altered gut microbiota, disturbing the steady state of intestinal flora and further exacerbating the inflammatory response.[36] Another pathological mechanism of concern is the presence of COVID-induced GI bleeding, thought to be caused by excessive inflammation and hypoperfusion leading to thrombotic injury. Damaged, dysfunctional intestinal flora is a serious medical concern that can cause further multi organ damage due to the presence of the gut-lung axis and which must be dealt with appropriately. Despite this, GI involvement in COVID-19 has not been associated with increased mortality rates in clinical practice; the main areas of concern were delayed patient rehabilitation and increased infection rates.[37]

Vascular Involvement of COVID-19

Several studies have reported that COVID-19 patients often have vascular involvements. For example, a study by Wichmann et al.[38] found

that 58% of COVID-19 patients had evidence of thromboembolic events, including pulmonary embolism and deep vein thrombosis. Another study by Llitjos et al.[39] reported that 14% of COVID-19 patients had acute coronary syndrome, and 25% had elevated troponin levels, indicating myocardial injury. These findings suggest that COVID-19 can have serious effects on the cardiovascular system (Table 2).

Many mechanisms have been proposed to explain the vascular involvement seen in COVID-19 patients. One mechanism is direct viral invasion of endothelial cells, which can cause endothelial dysfunction and lead to thrombosis.[40] Another mechanism is an excessive immune response, which can cause cytokine storm and systemic inflammation, leading to vascular injury.[41] A third mechanism is hypoxia, which can lead to pulmonary vasoconstriction and pulmonary embolism.[42] These

TABLE 1. Timeline of key events during the COVID-19 pandemic[95-97]

December 31, 2019	Emergence of a cluster of pneumonia of unknown etiology in Wuhan, China
January 7, 2020	Virus isolated for genome sequencing
January 11	First death reported in China
January 30	WHO declared the outbreak as a public health emergency of international concern (PHEIC)
February 2	1st death reported outside China (Philippines)
February 11	WHO announced name for disease—COVID-19
March 11	WHO declared COVID-19 a pandemic
April 4	Global confirmed cases exceeded 1,000,000
April 10	Global death toll exceeded 100,000
April 23	Vaccine trials begin in Oxford, UK
July 22	Global confirmed cases exceeded 15,000,000
September 29	Global death toll exceeded 1,000,000
December 8	UK administers first doses of Pfizer/BioNTech vaccine outside of clinical trials
December 30	Oxford-AstraZeneca vaccine approved for use in UK
January 29, 2021	EU authorizes Oxford-AstraZeneca vaccine for use in over 18-year-olds
February 20	200 million coronavirus vaccines delivered worldwide
November 26	New B.1.1.529 Covid variant named Omicron
December 12	WHO announces Omicron variant is more transmissible than the delta variant but causes milder symptoms.
December 17	UK reports daily record in number of cases since beginning of pandemic with over 93,000 new cases
January 4, 2022	US report record of 1,000,000 new cases in one day
January 8	UK announces total of 150,000 COVID-19 related deaths since start of pandemic
March 6	Global death toll exceeded 6,000,000
February 28, 2023	69.7% of the world's population has received at least a single dose of a COVID-19 vaccine. 13.31 Billion doses administered globally

TABLE 2. Data on vascular involvement in patients with COVID-19 from major clinical cohort studies

Study	Study design	Sample size	Main findings	Title
Klok et al.[98]	Retrospective cohort study	184 ICU patients with COVID-19	31% of patients experienced thrombotic complications, with a higher incidence in those receiving prophylactic anticoagulation compared to therapeutic anticoagulation.	Incidence of thrombotic complications in critically ill ICU patients with COVID-19
Lodigiani et al.[43]	Retrospective cohort study	388 hospitalized patients with COVID-19	9.3% of patients experienced arterial thrombotic events, 11.3% experienced venous thrombotic events, and 3.7% experienced both. Higher rates were observed in ICU patients and those with D-dimer levels > 3 times the upper limit of normal.	Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy
Middeldorp et al.[99]	Retrospective cohort study	198 hospitalized patients with COVID-19	27% of patients experienced thrombotic complications, with higher rates in ICU patients and those with D-dimer levels > 6 times the upper limit of normal.	Incidence of venous thromboembolism in hospitalized patients with COVID-19
Llitjos et al.[39]	Retrospective cohort study	26 anticoagulated severe COVID-19 patients	22% of patients experienced venous thromboembolic events, with higher rates in ICU patients and those with high D-dimer levels.	High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients
Bilaloglu et al.[100]	Retrospective cohort study	3334 hospitalized patients with COVID-19	11.1% of patients experienced arterial thrombotic events, 6.2% experienced venous thrombotic events, and 16% experienced both. Higher rates were observed in those with cardiovascular risk factors and elevated D-dimer levels.	Thrombosis in hospitalized patients with COVID-19 in a New York City health system
Wichmann et al.[101]	Retrospective cohort study	12 ICU deceased patients who had COVID-19	Cause of death in 4 patients was PE and an autopsy showed 58% of the patients had DVT in whom VTE was never suspected.	Autopsy findings and venous thromboembolism in patients with COVID-19
Li et al.[44]	Retrospective cohort study	1527 patients in total	81 hospitalized patients with COVID-19. 8% of patients experienced ischemic stroke, with higher rates in those with severe disease and elevated D-dimer levels.	Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China

(*continued*)

TABLE 2. (*continued*)

Study	Study design	Sample size	Main findings	Title
Beyrouti et al.[102]	Retrospective cohort study	6 patients	48% of patients had large vessel occlusion, with higher rates in those with severe disease and elevated D-dimer levels.	Characteristics of ischaemic stroke associated with COVID-19
Oxley et al., 2020[103]	Retrospective cohort study	5 patients	79% of patients had large vessel occlusion, with higher rates in those with severe disease and elevated D-dimer levels.	Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

mechanisms may all contribute to the vascular involvement seen in COVID-19 patients.

The vascular involvement of patients with COVID-19 has been a topic of much research and study. Studies have reported a significant prevalence of thromboembolic events, acute coronary syndrome, and myocardial injury in COVID-19 patients.[43] These findings suggest that COVID-19 can have serious effects on the cardiovascular system.[44] Several mechanisms have been proposed to explain the vascular involvement seen in COVID-19 patients, including direct viral invasion, an excessive immune response, and hypoxia.[45]

The clinical presentation of vascular involvement in COVID-19 patients can vary depending on the type and severity of the vascular complication. Thromboembolic events, such as pulmonary embolism and deep vein thrombosis, may present with symptoms such as dyspnea, chest pain, and swelling in the extremities.[39] Acute coronary syndrome may present with symptoms such as chest pain, shortness of breath, and diaphoresis.[39] Myocardial injury may present with elevated troponin levels and abnormal electrocardiogram findings.[39]

The epidemiology of vascular involvement in COVID-19 patients has been studied in several populations. For example, a study by Lodigiani et al.[43] found that the incidence of thromboembolic events in hospitalized COVID-19 patients was 16%, and that the incidence increased with age and severity of illness. Another study by Guan et al.[46] reported that 25.1% of COVID-19 patients had cardiovascular disease at baseline, and that these patients had a higher risk of mortality compared to those without cardiovascular disease. These findings suggest that vascular involvement is a common and serious complication of COVID-19, particularly in older and sicker patients.

Immune System Response

The immune response to COVID-19 plays a critical role in determining disease severity, with both impaired and hyperinflammatory responses leading to complications. Recent research has revealed the importance of T cells in the immune response to COVID-19.[47] Studies have found that T cells play a crucial role in both clearing the virus and preventing reinfection, and a strong T cell response is associated with better clinical outcomes.[48,49]

Innate immune cells, particularly neutrophils, have also been found to play a significant role in the development of hyperinflammatory responses in severe COVID-19 cases.[47] Elevated neutrophil-to-lymphocyte ratios have been found in patients with more severe disease, suggesting a role for neutrophils in the cytokine storm associated with severe COVID-19.[50,51] This has led to investigations into the use of neutrophil-targeted therapies as a potential treatment for COVID-19.

Recent developments in treatments targeting the immune response include the use of steroids and monoclonal antibodies targeting IL-6.[52] New therapies, such as Janus kinase inhibitors and CC chemokine receptor 5 antagonists, are also in clinical trials for the treatment of cytokine release syndrome in COVID-19.[53]

The cellular immune response to COVID-19 involves the activation of T cells, which are responsible for recognizing and killing virus-infected cells. Recent research has shown that patients with severe COVID-19 have lower levels of T cells and reduced function of these cells compared to patients with mild disease.[54] CD8+ T cells, which are responsible for killing virus-infected cells, have been found to be particularly important in controlling the virus.[55] However, the virus has developed strategies to evade the immune response, such as by suppressing T cell activation and inducing T cell exhaustion.[56]

The molecular immune response to COVID-19 involves the activation of innate immune sensors, such as Toll-like receptors (TLRs) and inflammasomes, which recognize viral components and trigger the production of proinflammatory cytokines. Recent research has shown that patients with severe COVID-19 have higher levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), compared to patients with mild disease.[57] This excessive cytokine response, known as a cytokine storm, can lead to tissue damage and multiorgan failure. The virus has also been shown to modulate the immune response by inhibiting the production of type I interferons, which are important antiviral cytokines.[58]

Other Organ Involvement

COVID-19 is a multiorgan disease with significant extrapulmonary involvement, including but not limited to the central nervous system (CNS), the hematopoietic system, the bone marrow, and the liver.[59] COVID-19 has been shown to alter the permeability of the blood-brain barrier, allowing viral particles to attach to neuronal ACE2 receptors and provoke an inflammatory response, causing symptoms such as headaches, dizziness, and altered sense of taste and smell.[60] In the most severe cases, COVID-associated neurological conditions include encephalitis and demyelinating diseases, thought to be mediated by the cytokine storm and glial cell overactivation.[60] Neurological manifestations are the most common sequelae seen in "long COVID," with mood disturbances, severe fatigue, cognitive impairment, and sleep disorders being of significant concern.[61] These symptoms, though independent of disease severity and unrelated to long-term mortality, significantly affect quality of life and have no specific treatment guidelines. The reversibility of these neurological findings remains unknown as not enough literature on long-term patient follow-up exists.[62]

Hematological complications of COVID-19 are of particular concern, too. COVID-19 is a known cause of significant lymphopenia and CD8+ T-cell exhaustion, leading to a weakened immune system and a cytokine storm. Of particular worry is COVID-induced neutrophilia that comes with a significantly increased mortality risk likely due to bacterial superinfection with opportunistic organisms. Neutrophilia and lymphopenia have been reported in up to 75% of critically ill COVID-19 patients in ICU with those who died presenting with continually decreasing lymphocyte counts until death. Thrombocytopenia has been correlated with disease severity, with some meta-analyses suggesting that low platelet count is associated with a nearly 5-fold augmented risk for severe COVID-19 development. Direct bone marrow toxicity as a result of viral infection, as well as mechanical ventilation-induced endothelial damage and pathological platelet activation, are thought to be the primary mechanisms behind the thrombocytopenia seen during COVID, although the extent of each mechanism is unclear and they are thought to all work together synergistically. Furthermore, endothelial injury and patient immobility are risk factors for hypercoagulability, explaining why COVID-19 patients in ICU commonly develop acute thrombotic events that subsequently lead to acute stroke, venous thromboembolism, and acute limb ischemia. COVID-19 patients, especially those who are older and more frail, must undergo complete blood counts and inflammatory marker checks both at

the beginning of their disease and throughout their ICU stay as early identification of severe hematological malignancy could decrease mortality and morbidity rates.[63]

COVID-associated liver damage is another multiorgan manifestation that must be given careful consideration. Though the majority of COVID-related liver damage has been reported to be very mild, even a mild loss of liver function can adversely affect patients, including but not limited to altered therapeutic efficacy of antiviral drugs that are metabolized through the liver and altered production of acute phase reactants, coagulation factors, and albumin.[64] Patients with a past medical history of liver disease, such as hepatic cirrhosis, hepatocellular carcinoma, and HBV/HCV hepatitis, are particularly vulnerable to COVID-19 infection and thus a worse clinical prognosis. Although larger cohort studies are needed to determine this finding, several smaller case reports have found a correlation between hepatic injury and the development of acute respiratory distress syndrome in COVID patients, leading to higher morbidity and mortality in these patients.[65,66]

Clinical Management

Patients with signs of pneumonia and those of the high-risk group are indicated for hospitalisation.[67] Those with mild flu-like symptoms are discharged, supplemented with symptomatic treatment, and advised to return if the illness worsens.[68] Symptomatic treatment includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen for fever, cough suppressants, and hydration.[68,69,70]

Noninvasive oxygenation is generally not recommended in hypoxemic COVID-19 patients, particularly the use of high nasal flow oxygen.[69,71] Noninvasive ventilation with continuous positive airway pressure (CPAP), rather than bilevel positive airway pressure, is preferred. A target peripheral oxygen saturation (SpO2) of 92%-96% has been suggested.[72] Endotracheal intubation is indicated upon acute deterioration or failure of response towards standard oxygen therapy.[68,70] Higher, instead of lower, positive end-expiratory pressure (PEEP) is recommended.[69] For severe acute respiratory distress syndrome (ARDS), prone ventilation for 16 hours/day is suggested.[73] Additional rescue interventions include extracorporeal membrane oxygenation (ECMO).[72,74,75]

Upon recognition of sepsis, standard care is to be commenced as soon as possible. This includes initiation of fluid bolus and vasopressors for hypotension.[76] Prophylaxis against venous thromboembolism (VTE) is strongly recommended, with low molecular weight heparin (LMWH)

preferred over unfractionated heparin.[67] Nonpharmacological modalities such as intermittent pneumatic compression stockings are also recommended.[76] Acute kidney injury (AKI) can be managed by continuous renal replacement therapy (CRRT), while intermittent RRT has been suggested to be as effective.[67] Cardiac support can be managed with direct input from the cardiology team and inotropic support if required.[67,72,76]

Routine corticosteroids are not recommended unless for trial purposes or other indications such as adrenal insufficiency, asthma, or chronic obstructive pulmonary disease. Remdesivir, a broad-spectrum antiviral drug, has been approved by the US Food and Drug Administration (FDA) for the treatment of hospitalized patients with COVID-19.[71,73] Tocilizumab, a monoclonal antibody, has been approved in some countries for the treatment of COVID-19 patients with severe cytokine release syndrome.[72] In addition, the FDA has issued an Emergency Use Authorization for the use of convalescent plasma in hospitalized patients with COVID-19.[71,73]

How Patients Might Benefit From Further Interventions

The COVID-19 pandemic has challenged healthcare systems worldwide.[77] With millions of confirmed cases and hundreds of thousands of deaths, there is an urgent need for effective interventions to prevent and treat the disease.[77] While significant progress has been made in clinical management of COVID-19 (Table 3), there is still a need for further interventions to help patients infected with COVID-19.[77]

Pharmacological interventions have been widely used to manage COVID-19 patients. Several drugs have been repurposed to treat COVID-19, including antivirals, corticosteroids, and immunomodulators.[78] Remdesivir is an antiviral drug that has been shown to reduce recovery time in hospitalized COVID-19 patients.[79] Corticosteroids such as dexamethasone have also been found to reduce mortality in patients with severe COVID-19 (RECOVERY Collaborative Group, 2021).[80,81] Furthermore, the combination of baricitinib and remdesivir has been found to reduce recovery time and accelerate clinical improvement in COVID-19 patients, particularly those receiving high-flow oxygen or noninvasive ventilation.[82] Although the effectiveness of these drugs in treating COVID-19 patients varies, they remain an important part of the management of COVID-19.[83]

Nonpharmacological interventions have also been used to manage COVID-19 patients. These interventions include respiratory support, such as oxygen therapy and mechanical ventilation, and extracorporeal

TABLE 3. Systematic reviews on clinical management of COVID-19

Reference	Key findings
Beigel et al.[79]	Remdesivir was associated with faster recovery and lower mortality in hospitalized COVID-19 patients with lower respiratory tract infection.
Horby et al.[81]	Dexamethasone reduced mortality in hospitalized COVID-19 patients receiving respiratory support.
Kalil et al.[82]	Baricitinib and remdesivir combined were better than remdesivir alone in treating Covid-19 patients, especially those needing high-flow oxygen or noninvasive ventilation.
RECOVERY Collaborative Group (2021)[80]	Tocilizumab reduced mortality and the need for mechanical ventilation in hospitalized COVID-19 patients with hypoxia and systemic inflammation.
Siemieniuk et al.[104]	There was insufficient evidence to support the use of antiviral agents, corticosteroids, or interleukin-6 inhibitors in COVID-19 patients.
Sterne et al.[105]	Dexamethasone reduced mortality in hospitalized COVID-19 patients receiving respiratory support.
WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group (2020)[105]	Hydroxychloroquine, lopinavir/ritonavir, and interferon beta-1a did not reduce mortality or the need for mechanical ventilation in hospitalized COVID-19 patients.

membrane oxygenation (ECMO) for patients with severe respiratory failure.[72,84,85] Proning, the process of turning a patient onto their stomach, has also been found to improve oxygenation in COVID-19 patients with acute respiratory distress syndrome (ARDS).[86] Furthermore, the use of convalescent plasma, monoclonal antibodies, and hyperimmune globulin has shown promise in treating COVID-19 patients.[87]

The COVID-19 pandemic has had a significant impact on mental health, with many individuals experiencing anxiety, depression, and post-

TABLE 4. Potential interventions to benefit COVID - 19 patients

Intervention	Possible benefit
Monoclonal Antibodies[106,107]	Reduce viral load and decrease hospitalization rates
High-Flow Oxygen Therapy[108,109]	Improve oxygenation and prevent intubation
Convalescent Plasma[87,110]	Boost immunity and reduce mortality rates
Anticoagulation Therapy[111,112]	Prevent blood clots and improve survival
Remdesivir[79,113]	Shorten recovery time and decrease need for supplemental oxygen
Dexamethasone[80]	Reduce mortality rates in severe cases
Baricitinib[82,114]	Accelerate clinical improvement and reduce recovery time
Vaccination[115,86]	Prevent infection and reduce transmission rates

traumatic stress disorder (PTSD).[88] Psychological interventions, such as cognitive-behavioral therapy (CBT) and mindfulness-based interventions, have been found to be effective in reducing anxiety and depression in COVID-19 patients.[89] Additionally, online and telehealth interventions have been developed to provide psychological support to COVID-19 patients and healthcare workers (Fig 1).[90]

Vaccination

Vaccination has been an essential tool in controlling the COVID-19 pandemic. The development and distribution of vaccines have been critical in preventing severe illness, hospitalization, and death caused by the virus (Fig 2).

Large-scale clinical trials and real-world data have consistently demonstrated that COVID-19 vaccines are highly effective in preventing severe illness, hospitalization, and death caused by the virus. Studies have shown that vaccines from Pfizer-BioNTech, Moderna, Johnson & Johnson, and AstraZeneca have efficacy rates ranging from 66%-95% in preventing symptomatic COVID-19.[91] Furthermore, recent studies have shown that vaccination reduces the risk of hospitalization, ICU admission, and death by more than 90%.[91]

Several studies have reported the effectiveness of COVID-19 vaccines against new variants of the virus.[92] The Pfizer-BioNTech vaccine has shown a 91% effectiveness against the Delta variant, while the Moderna vaccine has shown a 76% effectiveness.[92] The AstraZeneca vaccine has shown a 67% effectiveness against the Delta variant after 2 doses, and the Johnson & Johnson vaccine has shown a 71% effectiveness against severe disease caused by the Delta variant.[92]

COVID-19 vaccines can cause side effects, but the vast majority of these are mild to moderate and resolve within a few days. The most common side effects include pain and swelling at the injection site, fatigue, headache, fever, and chills. Serious side effects, such as anaphylaxis, have been reported but are rare. The benefits of vaccination far outweigh the risks of potential side effects.

Current evidence suggests that COVID-19 vaccination is highly effective in preventing severe illness, hospitalization, and death caused by the virus.[93] The vaccines also appear to be effective against emerging variants of the virus, although their efficacy may be slightly reduced.[94] Recent studies have shown that the protection provided by the vaccines against severe illness and hospitalization can last for at least 6 months.[92] Long-term safety data are still needed to fully evaluate the potential risks

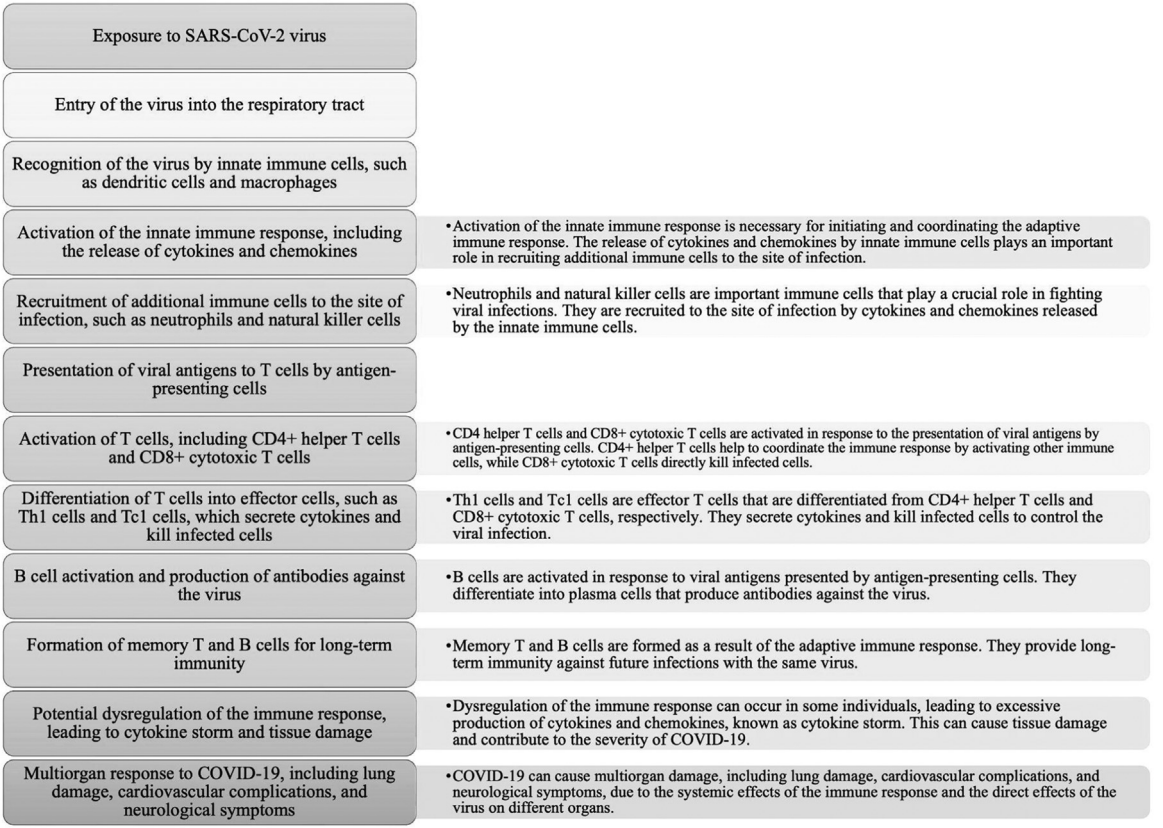

FIG 1. Flow diagram on the immune response pathway for COVID-19.

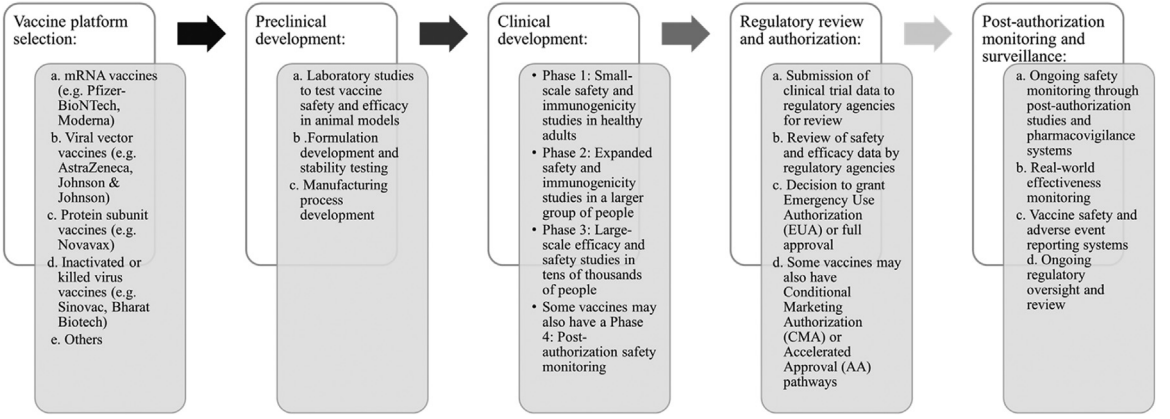

FIG 2. COVID-19 vaccine development and authorization process flowchart.

of vaccination, although current data suggest that serious adverse events are rare.

Conclusion

Though it is frequently thought of as a pulmonary disease, COVID-19 is a serious multiorgan pathology that can affect several organ systems including the cardiovascular, renal, hematological, central nervous, and gastrointestinal in the most severe cases. Several theories exist with regards to COVID-19 pathophysiology in all these organs, ranging from direct viral infection via ACE2 receptor binding to indirect methods such as coagulation dysfunction, cytokine storm, and pathological activation of the complement system. Clearer guidelines need to be implemented for COVID-19 patients presenting with multiorgan failure to improve their survival odds and long-term clinical outcomes.

Declaration of Competing Interest

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

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33. https://doi.org/10.1056/NEJMoa2001017.
2. Khan IH, Zahra SA, Zaim S, Harky A. At the heart of COVID-19. *J Card Surg* 2020;35:1287–94. https://doi.org/10.1111/jocs.14596. Accessed February 26, 2023.
3. Who coronavirus (COVID-19) dashboard [Internet]. World Health Organization. World Health Organization; Available at: https://covid19.who.int/
4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus−infected pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061.
5. Iacobucci G. Covid-19: UK adds sore throat, headache, fatigue, and six other symptoms to official list. *BMJ* 2022;377:o892. https://doi.org/10.1136/bmj.o892. Accessed February 26, 2023.
6. NHS choices. NHS; [cited 2023 Feb28]. Available at: https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/main-symptoms/#:~:text=a%20new%2C%20continuous%20cough%20%E2%80%93%20this,feeling%20tired%20or%20exhausted.
7. Post covid-19 condition (long covid) [Internet]. World Health Organization. World Health Organization; 2023 Available at: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition. Accessed February 26, 2023.

8. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long covid associated with delta versus omicron variants of SARS-COV-2. *Lancet North Am Ed* 2022;399(10343):2263–4.
9. Whitaker M, Elliott J, Chadeau-Hyam M, Riley S, Darzi A, Cooke G, et al. Persistent covid-19 symptoms in a community study of 606,434 people in England. *Nature Communications* 2022;13(1):1957.
10. Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long covid: a review. *J R Soc Med* 2021;114(9):428–42.
11. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respiratory Research* 2020;21(1):163.
12. Elicker BM. What are the long-term pulmonary sequelae of COVID-19 infection? *Radiology* 2022;304(1):193–4.
13. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month follow-up chest CT findings after severe Covid-19 pneumonia. *Radiology* 2021;299(1):E177–86.
14. Tarraso J, Safont B, Carbonell-Asins JA, Fernandez-Fabrellas E, Sancho-Chust JN, Naval E, et al. Lung function and radiological findings 1 year after COVID-19: A prospective follow-up. *Respiratory Research* 2022;23(1):242.
15. Bae SA, Kim SR, Kim M-N, Shim WJ, Park S-M. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with covid-19 according to age: a systematic review and meta-analysis. *Heart* 2020;107(5):373–80.
16. Zhu H, Zhang L, Ma Y, Zhai M, Xia L, Liu J, et al. The role of sars-cov-2 target ACE2 in cardiovascular diseases. *J Cell Mol Med* 2021;25(3):1342–9.
17. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. *J Biol Chem* 2000;275(43):33238–43.
18. Libby P. The heart in covid-19. *JACC* 2020;5(5):537–42.
19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395 (10223):497–506.
20. García de Guadiana-Romualdo L, Morell-García D, Rodríguez-Fraga O, Morales-Indiano C, María Lourdes Padilla Jiménez A, Gutiérrez Revilla JI, et al. Cardiac troponin and Covid-19 severity: Results from Biocovid Study. *European Journal of Clinical Investigation* 2021;51(6):e13532.
21. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19—a systematic review. *Life Sci* 2020;254:117788. https://doi.org/10.1016/j.lfs.2020.117788.
22. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324(6):603.
23. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet North Am Ed* 2021;397(10270):220–32.
24. Wang W, Wang C-Y, Wang S-I, Wei JC-C. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: a retrospective cohort study from the TriNetX US Collaborative Networks. *eClinicalMedicine* 2022;53:101619.

25. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28(3):583–90.
26. Liakopoulos V, Roumeliotis S, Papachristou S, Papanas N. COVID-19 and the kidney: time to take a closer look. *International Urology and Nephrology* 2021;54 (5):1053–7.
27. Sabaghian T, Kharazmi AB, Ansari A, Omidi F, Kazemi SN, Hajikhani B, et al. COVID-19 and Acute Kidney Injury: A Systematic Review. *Frontiers in Medicine* 2022;9:705908.
28. Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, et al. Pathophysiology of COVID-19-associated acute kidney injury. *Nature Reviews Nephrology* 2021;17:751–64. Accessed March 3, 2023.
29. Kapp ME, Fogo AB, Roufouse C, et al. Renal Considerations in COVID-19. *ASAIO Journal* 2021;67(10):1087–96. https://doi.org/10.1097/mat.0000000000001530. Accessed March 3, 2023.
30. Głowacka M, Lipka S, Młynarska E, Franczyk B, Rysz J. Acute kidney injury in COVID-19. *Int J Mol Sci* 2021;22(15):8081. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8347536/ Accessed March 3, 2023.
31. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *The Lancet Respiratory Medicine* 2020;8(7):738–42.
32. Tan BWL, Tan BWQ, Tan ALM, Schriver ER, Gutiérrez-Sacristán A, Das P, et al. Long-term kidney function recovery and mortality after COVID-19-associated acute kidney injury: an international multi-centre observational cohort study. 2023;55:101724. Available at: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00454-0/fulltext.
33. Selby NM, Forni LG, Laing CM, Horne KL, Evans RD, Lucas BJ, et al. Covid-19 and acute kidney injury in hospital: summary of NICE guidelines. *BMJ* 2020;369: m1963.
34. Groff A, Kavanaugh M, Ramgobin D, McClafferty B, Aggarwal CS, Golamari R, et al. Gastrointestinal manifestations of COVID-19: a review of what we know. *Ochsner J* 2021;21(2):177–80.
35. Ling Y, Xu S-B, Lin Y-X, Tian D, Zhu Z-Q, Dai F-H, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)* 2020;133(9):1039–43.
36. Chen F, Dai Z, Huang C, Chen H, Wang X, Li X. Gastrointestinal Disease and COVID-19: A Review of Current Evidence. *Digestive Diseases* 2021. [Internet]. Accessed March 3, 2023.
37. Zhang H, Shao B, Dang Q, Chen Z, Zhou Q, Luo H, et al. Pathogenesis and Mechanism of Gastrointestinal Infection With COVID-19. *Frontiers in Immunology* 2021;12:674074. Accessed March 3, 2023.
38. Wichmann D, Sperhake 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):268–77.

39. Llitjos J, Leclerc M, Chochois C, Monsallier J, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *Journal of Thrombosis and Haemostasis* 2020;18:1743–6.
40. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *The Lancet* 2020;395(10234). [Internet]. Accessed March 18, 2023. Available from: https://www.sciencedirect.com/science/article/pii/S0140673620309375.
41. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews Immunology* 2020;20(6):1–12. [Internet]. Accessed March 20, 2023.
42. Karmouty-Quintana H, Thandavarayan RA, Keller SP, Sahay S, Pandit LM, Akkanti B. Emerging mechanisms of pulmonary vasoconstriction in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) and potential therapeutic targets. *Int J Mol Sci* 2020;21(21):8081.
43. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan. Italy: Thrombosis Research; 2020.
44. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clinical Research in Cardiology: Official Journal of the German Cardiac Society* 2020;109(5):531–8. [Internet]. Accessed March 16, 2023.
45. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *New England Journal of Medicine* 2020;383(4):334–46. https://doi.org/10.1056/NEJMoa2021680.
46. Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J* 2020;55(5):2000547.
47. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* 2020;584(7821):457–62. [Internet] Aug 1. Accessed March 26, 2023.
48. Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell* 2020;183(4):996–1012.e19. Accessed March 22, 2023.
49. Kaneko N, Kuo H-H, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, et al. Loss of Bcl-6-Expressing T Follicular Helper Cells and Germinal Centers in COVID-19. *Cell* 2020;183(1):143–157.e13. Accessed March 22, 2023.
50. Zhou Y, Fu B, Zheng X, et al. Aberrant Pathogenic GM-CSF+ T Cells and Inflammatory CD14+CD16+ Monocytes in Severe Pulmonary Syndrome Patients of a New Coronavirus. *bioRxiv* 2020;7(6):998–1002. Feb 12Accessed March 24, 2023.
51. Del Valle DM, Kim-Schulze S, Huang H-H, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nature Medicine* 2020;26(10):1636–43. [Internet] Oct 1Accessed March 24, 2023.

52. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect* 2020;81(1):e6–12.
53. Roschewski M, Lionakis MS, Sharman JP, Roswarski J, Goy A, Monticelli MA, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol* 2020;5(48):eabd0110.
54. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature* 2020;587 (7833):270–4. [Internet] Nov 1Accessed March 28, 2023.
55. Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* 2020;369(6508):eabc8511.
56. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). *Frontiers in Immunology* 2020;11:827. [Internet] May 1. Accessed March 28, 2023.
57. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet North Am Ed* 2020;395(10223):497–506.
58. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, et al. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. *Cell Host & Microbe* 2020;27(6):883–890.e2. Accessed March 29, 2023.
59. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multi-Organ Response. *Current Problems in Cardiology* 2020;45(8):100618. https://doi.org/10.1016/j.cpcardiol.2020.100618.
60. Nagu P, Parashar A, Behl T, Mehta V. CNS implications of COVID-19: a comprehensive review. *Rev Neurosci* 2020;32(2):219–34.
61. Whittaker A, Anson M, Harky A. Neurological Manifestations of COVID-19: A systematic review and current update. *Acta Neurologica Scandinavica* 2020;142(1):14–22. https://doi.org/10.1111/ane.13266. Accessed March 5, 2023.
62. Hingorani KS, Bhadola S, Cervantes-Arslanian AM. COVID-19 and the brain. *Trends in Cardiovascular Medicine* 2022;32(6):323–30. Accessed March 5, 2023. Available from: https://www.sciencedirect.com/science/article/pii/S1050173822000640.
63. Erdinc B, Sahni S, Gotlieb V. Hematological manifestations and complications of COVID-19. *Adv Clin Exp Med* 2021;30(1):101–7.
64. Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver International: Official Journal of the International Association for the Study of the Liver* 2021;41 (1):20–32. Jan 1Accessed March 8, 2023.
65. Wang X, Lei J, Li Z, Yan L. Potential Effects of Coronaviruses on the Liver: An Update. *Frontiers in Medicine* 2021;8:651658.
66. Kariyawasam JC, Jayarajah U, Abeysuriya V, Riza R, Seneviratne SL. Involvement of the Liver in COVID-19: A Systematic Review. *The American Journal of Tropical Medicine and Hygiene* 2022;106(4):1026–41.

67. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. *The Journal of Clinical Investigation* 2020;130(4):1545–8. Accessed March 31, 2023. Available from: https://www.jci.org/articles/view/138003.
68. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection. Centres for Disease Control and Prevention; 2020. [Internet] Accessed March 29, 2023. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.htm.
69. Information on COVID-19 Treatment, Prevention and Research [Internet] . COVID-19 Treatment Guidelines. Accessed March 29, 2023. Available from: https://www.covid19treatmentguidelines.nih.gov/
70. Clinical management of COVID-19 [Internet]. www.who.int. Accessed March 29, 2023. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19
71. Commissioner O of the. Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19. FDA; 2020. [Internet] Accessed March 29, 2023. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19.
72. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Medicine* 2020;46:854–87. Accessed March 31, 2023.
73. Research C for BE and. Investigational COVID-19 Convalescent Plasma. U.S. Food and Drug Administration; 2021. [Internet]. Accessed March 30, 2023 Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent-plasma.
74. Zaidi S, Nguyen D, Harky A. COVID-19, ECMO, and respiratory infection: a new triad? *J Card Surg* 2022;37:3619–22. https://doi.org/10.1111/jocs.16910.
75. Haiduc AA, Alom S, Melamed N, Harky A. Role of extracorporeal membrane oxygenation in COVID-19: a systematic review. *J Card Surg* 2020;35:2679–87. https://doi.org/10.1111/jocs.14879.
76. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clinical Infectious Diseases* 2020:ciaa478. Accessed March 31, 2023.
77. WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19—Interim WHO Solidarity Trial Results. *New England Journal of Medicine* 2020;384:497–511.
78. Hussain N, Yoganathan A, Hewage S, Alom S, Harky A. The effect of antivirals on COVID-19: a systematic review. *Expert Review of Anti-Infective Therapy* 2020;19 (4):473–86. https://doi.org/10.1080/14787210.2021.1823832.
79. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine* 2020;383:1813–26.

80. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2021;397(10285):1637–45. [Internet]. Accessed March 31, 2023; Available from: https://www.sciencedirect.com/science/article/pii/S0140673621006760?via%3Dihub.
81. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* 2020;384(8):693–704.
82. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *New England Journal of Medicine* 2020;384(9):795–807.
83. Gordon AC. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *New England Journal of Medicine* 2021;385(12):1147–9. https://doi.org/10.1056/NEJMc2108482.
84. Savarimuthu S, BinSaeid J, Harky A. The role of ECMO in COVID-19: can it provide rescue therapy in those who are critically ill? *J Card Surg* 2020;35:1298–301. https://doi.org/10.1111/jocs.14635.
85. Alom S, Haiduc AA, Melamed N, Axiaq A, Harky A. Use of ECMO in patients with coronavirus disease 2019: does the evidence suffice? *J Cardiothorac Vasc Anesth* 2021;35:1256–62. https://doi.org/10.1053/j.jvca.2020.07.070.
86. Venus K, Munshi L, Fralick M. Prone positioning for patients with hypoxic respiratory failure related to COVID-19. *Can Med Assoc J* 2020;192(47):201201. cmaj.
87. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. *New England Journal of Medicine* 2021;384:1015–27.
88. Xiong J, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, et al. Impact of COVID-19 Pandemic on Mental Health in the General population: a Systematic Review. *Journal of Affective Disorders* 2020;277(1):55–64. [Internet]. Accessed March 31, 2023.
89. Shan Y, Ou J, Wang D, Zeng Z, Zhang S, Guan D, et al. Impacts of COVID-19 and fiscal stimuli on global emissions and the Paris Agreement. *Nature Climate Change* 2020;11(3):200–6.
90. Bäuerle A, Teufel M, Musche V, Weismüller B, Kohler H, Hetkamp M, et al. Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany. *Journal of Public Health* 2020;42(4):672–8. Accessed March 31, 2023.
91. Mohammed I, Nauman A, Paul P, Ganesan S, Chen K-H, Jalil SMS, et al. The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. *Human Vaccines & Immunotherapeutics* 2022;18:2027160. https://doi.org/10.1080/21645515.2022.2027160. Accessed April 1, 2023.
92. Hayawi K, Shahriar S, Serhani MA, Alashwal H, Masud MM. Vaccine versus Variants (3Vs): Are the COVID-19 Vaccines Effective against the Variants? A Systematic Review. *Vaccines* 2021;9:1305.. https://doi.org/10.3390/vaccines9111305. Accessed April 1, 2023.

93. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. Science Brief: COVID-19 Vaccines and Vaccination. PubMed 2020. Accessed April 1, 2023. https://www.ncbi.nlm.nih.gov/books/NBK570435/.
94. Song Z, Zhang X, Patterson LJ, Barnes CL, Haas DA. Racial and Ethnic Disparities in Hospitalization Outcomes Among Medicare Beneficiaries During the COVID-19 Pandemic. *JAMA Health Forum* 2021;2(12):e214223. Accessed March 31, 2023.
95. WHO. Coronavirus-19 (COVID-19) situation report—82. 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200411-sitrep-82-covid-19.pdf?sfvrsn=74a5d15_2. Accessed February 26, 2023.
96. Aspinall E. Covid-19 timeline. British Foreign Policy Group; 2022. [Internet] [cited 2023Feb26]. Available from: https://bfpg.co.uk/2020/04/covid-19-timeline/.
97. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Giattino C, Hasell J, et al. Coronavirus (COVID-19) vaccinations [Internet] *Our World in Data* 2020;5(7):947–53. [cited 2023 Feb 28] Available from: https://ourworldindata.org/covid-vaccinations.
98. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research* 2020;191:145–7. [Internet]. Accessed March 13, 2023.
99. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *Journal of Thrombosis and Haemostasis* 2020;18(8):1995–2002. Accessed March 15, 2023.
100. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA* 2020;324(8):799. [Internet]. [cited 2020 Nov 3] Accessed March 15, 2023. Available from: https://jamanetwork.com/journals/jama/fullarticle/2768715.
101. Wichmann D. Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med* 2020;173(12):1030.
102. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *Journal of Neurology, Neurosurgery & Psychiatry* 2020. [Internet]. Accessed March 16, 2023; Available from: https://jnnp.bmj.com/content/early/2020/04/30/jnnp-2020-323586.full.
103. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020;382(20):e60.
104. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Pardo-Hernandez H, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ (Clinical research ed)* 2020;370:m2980. [Internet]. Accessed March 31, 2023. Available from: https://pubmed.ncbi.nlm.nih.gov/32732190/.
105. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. *JAMA* 2020;324(13):1330–41.

106. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *New England Journal of Medicine* 2020;384:238–51. Accessed March 31, 2023.
107. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *N Engl J Med* 2021;384(5):437–50. https://doi.org/10.1056/NEJMoa2022116. Accessed March 31, 2023.
108. Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. *New England Journal of Medicine* 2015;372(23):2185–96. [Internet]. Accessed March 31, 2023; Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1503326.
109. Gragueb-Chatti I, Lopez A, Hamidi D, Guervilly C, Loundou A, Daviet F, et al. Impact of dexamethasone on the incidence of ventilator-associated pneumonia and blood stream infections in COVID-19 patients requiring invasive mechanical ventilation: a multicenter retrospective study. *Annals of Intensive Care* 2021;11(1):87
110. Li Y, Xie Z, Lin W, Cai W. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med* 2020;1:105–13. Accessed March 31, 2023.
111. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;135:2033–40. Accessed March 31, 2023.
112. Lemos ACB, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thrombosis Research* 2020;196:359–66. Accessed March 31, 2023.
113. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. *JAMA* 2020;324(11):1048–57. Accessed March 31, 2023.
114. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine* 2020;383(27):2603–15. [Internet]. Accessed March 31, 2023. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa2034577.
115. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet* 2020;397(10269):99–111. [Internet]. Accessed March 31, 2023.