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.

COVID-19 and Multiorgan Response

Sevim Zaim[†], Jun Heng Chong, BSc (Hons)[†], Vissagan Sankaranarayanan[†], and Amer Harky, MBChB, MSc, MRCS*

Abstract: Since the outbreak and rapid spread of COVID-19 starting late December 2019, it has been apparent that disease prognosis has largely been influenced by multiorgan involvement. Comorbidities such as cardiovascular diseases have been the most common risk factors for severity and mortality. The hyperinflammatory response of the body, coupled with the plausible direct effects of severe acute respiratory syndrome on body-wide organs via angiotensin-converting enzyme 2, has been associated with complications of the disease. Acute respiratory distress syndrome, heart failure, renal failure, liver damage, shock, and multiorgan failure have precipitated death. Acknowledging the comorbidities and potential organ injuries throughout the course of COVID-19 is therefore crucial in the clinical management of patients. This paper aims to add onto the ever-emerging landscape of medical knowledge on COVID-19, encapsulating its multiorgan impact. (Curr Probl Cardiol 2020;45:100618.)

Introduction

A novel coronavirus, designated the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late December 2019 from a cluster of pneumonia cases epidemiologically linked to a wet market in Wuhan, China.[1] The disease, now known as COVID-19, has since spread rampantly leading to a worldwide pandemic which has precipitated draconian measures to limit its transmission.

† Authors contributed equally to this work.
Conflict of Interest: There are no conflicts of interest or sources of support.
Curr Probl Cardiol 2020;45:100618
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100618

COVID-19 has demonstrated a wide spectrum of clinical manifestations, from asymptomatic or paucisymptomatic forms, to severe viral pneumonia with respiratory failure, multiorgan and systemic dysfunctions in terms of sepsis and septic shock, and death.[2,3] This paper aims to encapsulate the multiorgan impact of COVID-19 reported since its outbreak.

Literature Search

A comprehensive literature search was done on PubMed, SCOPUS, Embase, Cochrane database, google scholar and Ovid to identify the articles that discussed the novel corona virus, COVID-19 and its implications on different organs of human body. Key words used were "COVID," "SARS-CoV-2," "SARS-CoV," "2019-nCoV," "COVID-19," "Novel Corona virus." The search terms were used as key words and in combination as MeSH terms to maximize the output from literature findings. A staged literature search was done, whereby a separate literature search was performed for each section within this article and all the relevant studies were identified and summarized separately. If a paper is reporting on many aspects of the COVID-19, then the results have been shared between different parts of this review. The relevant articles are cited and referenced within each section separately. No limit placed on publication time or language of the article.

All the relevant articles were identified and screened by 3 authors; the results are summarized in narrative manner in each relevant section within the text of this review. A summary table of each section is provided where appropriate.

Background

Epidemiology

A timeline of the outbreak is summarized in Table 1. As of April 11, 2020, 1,610,909 confirmed cases worldwide have been reported.[4]

Early investigations reported a basic reproductive number (R_0) ranging between 1.4 and 3.9, while a mean incubation period of 5.2 days[5] ranging between 1 and 14 days.[6] According to the World Health Organization,[4] the current estimated global mortality is 99,690 (6.19% of confirmed cases) (Fig), the proportion of which may vary based on demographics of a location. All ages are susceptible to infection, and viral shedding may occur in asymptomatic individuals.[7] The risk factors for poor prognosis include advancing age and comorbidities,[8] while mortality is associated

Table 1. Timeline of COVID-19 outbreak[4]

December 31, 2019	Emergence of a cluster of pneumonia of unknown etiology in Wuhan, Hubei Province, China
January 7, 2020	Virus isolated for genome sequencing
January 11	First death reported in China
January 12	Genetic sequence available to the WHO facilitating diagnostic PCR tests
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 1,000000
April 11	Global confirmed case count of 1,610,909

PCR, polymerase chain reaction; WHO, World Health Organisation.

with age, high Sequential Organ Failure Assessment score, and D-dimer levels of >1 μg/mL on admission.[9]

Virology

SARS-CoV-2 is an enveloped, positive-sense RNA virus, and belongs to the β-coronavirus genus (*sarbecovirus* subgenus, *orthonavirinae* subfamily).[1] It represents the seventh member of the Coronaviridae family known to infect humans. Its counterparts include 4 strains of low pathogenicity (229E, OC43, NL63 and HKU1), as well as 2 other β-coronaviruses which caused the previous outbreaks of severe and potentially fatal respiratory

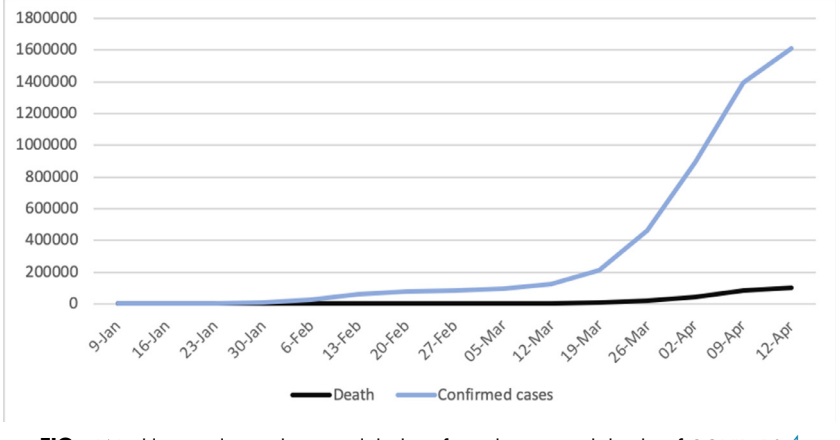

FIG . Weekly cumulative data on global confirmed cases and deaths of COVID-19.[4]

tract infections—SARS-CoV and Middle East respiratory syndrome-CoronaVirus (MERS-CoV).[10]

SARS-CoV-2 more closely resembles SARS-CoV (79% sequence identity) than MERS-CoV (50% sequence identity).[11] It also shares the same cellular receptor as SARS-CoV which is the angiotensin-converting enzyme 2 (ACE2) receptor.[12] ACE2 receptors are enriched in alveolar epithelial type II cells of lung tissues,[13] as well as extrapulmonary tissues such as the heart, endothelium, kidneys, and intestines,[14,15] which might play a role in the multi-organ effects of COVID-19.

Origin and Route of Transmission

Current evidence indicates an initial animal-to-human transmission from wild animals traded at the Huanan seafood market in Wuhan. The origin and mechanism of which remain to be clarified—while some genomic studies suggested bats as the natural reservoir,[16] others suggested pangolins.[17] As the outbreak progressed, person-to-person transmission remains the main mode of spread. This is through (1) respiratory droplets released via coughing or sneezing, (2) aerosol, typically during aerosol-generating clinical procedures, and (3) mucosal membrane contact with fomites.[18,19] Faecal-oral transmission has been speculated,[20] given the detection of viral RNA in stools, reported gastrointestinal (GI) symptoms, and ACE2 expression along the GI-tract.[21] No evidence of intrauterine or transplacental transmission has been reported.[22-24]

Respiratory Involvement of COVID-19

Initial Presentation

In a study that analyzed 138 COVID-19 patients,[25] the most common clinical features were fever (99%), fatigue (70%), dry cough (59%), anorexia (40%), myalgias (40%), dyspnea (31%), and sputum production (27%). Other cohort studies have reported a similar range of clinical findings.[3,26-28] However, fever might not be a universal finding, with 1 study reporting only 20% of their patients with very low grade fever (<100.4˚F/38˚C) and another[2] reporting fever in 44% of patients. Headache, sore throat and rhinorrhea have also been noted as less common symptoms.[29] Although not highlighted in the aforementioned studies, anosmia and dysgeusia (smell and taste disorders) have been reported as well (Table 2).[29]

Table 2. Clinical syndromes associated with COVID-19 in adults[73]

Mild illness	Resembles upper respiratory tract infection. May have nonspecific symptoms such as fever, fatigue, cough, (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea, and vomiting.
Pneumonia	Pneumonia present but no signs of severe pneumonia and no requirements for supplemental oxygen.
Severe pneumonia	Fever or suspected respiratory infection, plus one of the following: respiratory rate $>$ 30 breaths/min; severe respiratory distress or SpO2 $\leq$ 93% on room air.
Acute Respiratory Distress Syndrome (ARDS)	Within 1 week of known clinical insult or worsening respiratory symptoms. Chest radiographs show bilateral opacities which cannot be fully explained by volume overload, lobar or lung collapse, or nodules. Cardiac failure and fluid overload must be ruled out, need objective assessment (eg, echocardiography) to exclude hydrostatic causes if no risk factors are present. • Mild ARDS: 200 mm Hg $<$ PaO2/FiO2 a $\leq$ 300 mm Hg (with PEEP or CPAP $\geq$ 5 cmH2O, or nonventilated) • Moderate ARDS: 100 mm Hg $<$ PaO2/FiO2 $\leq$ 200 mm Hg (with PEEP $\geq$ 5 cmH2O, or nonventilated) • Severe ARDS: PaO2/FiO2 $\leq$ 100 mm Hg (with PEEP $\geq$ 5 cmH2O, or nonventilated) • When PaO2 is not available, SpO2/FiO2 $\leq$ 315 suggests ARDS (including in nonventilated patients)
Sepsis	Life-threatening organ dysfunction caused by dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: difficult or fast breathing, low oxygen saturation, altered mental status, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of thrombocytopenia, high lactate, coagulopathy, acidosis or hyperbilirubinemia.
Septic shock	Persisting hypotension despite fluid resuscitation, requiring vasopressors to maintain mean arterial pressure (MAP). MAP $\geq$ 65 mm Hg and serum lactate level $>$ 2 mmol/L.

ARDS, Acute Respiratory Distress Syndrome; CPAP, continuous positive airway pressure therapy; MAP, Mean Arterial Pressure; PEEP, positive end-expiratory pressure.

Disease Progression

The most frequent, serious manifestation of COVID-19 infection seems to be pneumonia, which is characterized by cough, fever, dyspnea and bilateral infiltrates displayed on radiographic chest imaging. Unfortunately, there are no specific clinical features that discern COVID-19 from other viral respiratory illnesses.[29] Although most patients will only experience mild symptoms of the disease, some patients will experience rapid

Table 3. Summarized interpretations of median time data obtained from Wang et al and Huang et al[3,25]

	Median time taken to develop clinical feature/complication from illness onset (days)					Conclusions
Study and number of patients	Dyspnea	Requiring hospital admission	ARDS	Requiring mechanical ventilation	Requiring ICU admission	
Wang et al. 2020 (n = 138)	5	7	8 Developed in 20% of patients after 8 days.	N/A Implemented in 12.3% of patients.	N/A 26.1% of patients required ICU admission.	Both studies suggest that ARDS manifests shortly after the onset of dyspnea.
Huang et al 2020 (n = 41)	7	8	9	10.5	10.5	

ARDS, Acute Respiratory Distress Syndrome; ICU, intensive care unit.

progression of their symptoms over the span of a week (Table 3).[3,25] One study[30] found that 17% of their patients developed Acute Respiratory Distress Syndrome (ARDS) and among these, 65% rapidly worsened and died from multiple organ failure. In a study focusing on the associated risk factors,[31] it was reported that ARDS was greatly associated with older age (>65 years old), diabetes mellitus, and hypertension. For most cases, bilateral lower zone consolidation (identified through chest x-ray) peaked at 10-12 days from symptom onset.[32]

Radiological Manifestations

COVID-19 infection shares similar radiological features[33] to those of other viral pneumonia.[34] The hallmarks of COVID-19 on computed topography imaging are bilateral and peripheral ground-glass opacities, and consolidative pulmonary opacities. Crazy paving patterns have also been observed.[27] A staging system for using computed topography images has been reported[33] and is summarized in Table 4.

Interestingly, the development of pleural effusions and progression to a mixed pattern of ground-glass opacities and consolidative opacities have been reported in late-stages.[35]

Cardiovascular Involvement of COVID-19

COVID-19 and Pre-Existing Cardiovascular Disease

Patients with existing cardiovascular disease (CVD) are at a greater risk of suffering from severe COVID-19 and having poorer prognosis. A

Table 4. Stages of COVID-19 infection based on CT images[33]

Ultra-early	Refers to the stage without clinical manifestations, patients are often asymptomatic, but normally is seen 1-2 weeks after COVID-19 exposure. Main imaging manifestations are single or multifocal GGO, patchy consolidative opacities, pulmonary nodules encircled by GGO and air bronchograms.
Early	Refers to an early symptomatic presentation, 1-3 days after clinical manifestations. This is the most observed stage through radiological imaging (54%). Main imaging manifestations are single or double GGO combined with interlobular septal thickening. Pathological processes during this stage are dilatation and congestion of the alveolar septal capillary, interlobular interstitial edema and exudation of fluid in alveolar cavity.
Rapid progression	Refers to 3-7 days after clinical manifestations, where the pathological features of this stage are accumulation of exudates in the alveolar cavity, vascular expansion and exudation in the interstitium. These pathological features lead to the further aggravation of alveolar and interstitial edema. Fibrous exudation forms bonds between each alveolus through the interstitial space to form a fusion state. Main radiological manifestations are large, light consolidative opacities with air bronchograms.
Consolidation	Refers to the second week after initial symptomatic presentation. Main pathological features are fibrous exudation of the alveolar cavity and the reduction of capillary congestion. CT imaging can show multiple consolidations reducing in size and density, compared to before.
Dissipation	Refers to 2-3 weeks after onset of symptoms. CT imaging can show dispersed, patchy consolidative opacities, reticular opacities, bronchial wall thickening and interlobular septal thickening.

GGO, ground glass opacities.

meta-analysis comprising of 46,248 patients with confirmed COVID-19 found that the most common co-morbidities were hypertension (17%), diabetes (8%), and CVD (5%).[36] CVD and hypertension have also been more prevalent in the severe patient group as compared to non-severe cases (odds ratio of 3.42 and 2.36, respectively).[36] Existing CVD is also associated with higher mortality which is summarized in Table 5.[16]

Table 5. Association between CVD and risk of mortality from COVID-19 as reported by Zhou et al[16]

	Survivors	Nonsurvivors
Coronary heart disease	8%	24%
Hypertension (CVD risk factor)	30%	48%
DM (CVD risk factor)	13.9%	31.4%
Smoking (CVD risk factor)	4.4%	9.3%

CVD, cardiovascular disease; DM, diabetes mellitus.

On the other hand, it is widely agreed that COVID-19 can also have adverse effects on cardiovascular health itself, causing or aggravating damage to the heart. There are reports of cardiogenic involvement in patients without known CVD[37] as well as cases with solely cardiac presentations.[38,39]

Mechanism of Cardiovascular Involvement

The exact mechanism of cardiovascular involvement in COVID-19 is not yet well understood, however elevated cardiac biomarker levels are commonly seen. In a study by Wang et al, 7.2% of patients had either elevated troponin levels or new electrocardiography or echocardiography abnormalities suggestive of cardiac injury.[25]

ACE2 is highly expressed in the heart, providing opportunity for ACE2-dependent myocardial infection. Cytokine storm from systemic inflammation and the hypoxic state from ARDS inducing excessive extracellular calcium levels leading to myocyte apoptosis are also possible mechanisms of damage.[40] Surge in cytokine levels due to hyperinflammatory response or secondary hemophagocytic lymphohistiocytosis and increased myocardial demand in the setting of acute infection can lead to atherosclerotic plaque instability and myocardial injury, increasing the risk of acute myocardial infarction.[41] Blood pressure abnormalities can also be seen in response to the illness.[41] Additionally, palpitations due to arrhythmia have been observed.[41,42] The type of arrhythmias are variable and etiology can be multi-factorial, ranging from hypoxic state due to ARDS to myocarditis.[41] Hu et al and Zeng et al also reported patients with reduced ejection fraction and heart enlargement.[39,43] Therefore, possible long-term effects of COVID-19 on cardiovascular system such as risk of heart failure should be considered and further investigated.

Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19

Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers on COVID-19 susceptibility and prognosis have been controversial. Some evidence suggests that increasing ACE2 expressions facilitate COVID-19 infection,[44] while others

Table 6. Data on AKI in patients with COVID-19 from major clinical cohort studies

Paper	Study population	Risk of AKI	Need for CRRT	Comorbid conditions
Guan et al[2]	n = 1099 552 Hospitals 30 Regions in China	6 (0.5%)*	0.8%	DM: 7.4% HTN: 15% CKD: 0.7%
Huang et al[3]	n = 41 Jinyintan Hospital Wuhan	3 (7%)	Not reported	DM: 20% HTN: 15% CKD: 10% (defined as creatine > 1.5mg/dL on admission)
Chen et al[26]	n = 99 Jinyintan Hospital Wuhan	3 (3%)	9%	CVD: 40% DM: 12%
Wang et al[25]	n = 221 Single center Zhongnan Hospital, Wuhan	5 (3.6%)	1.45%	DM: 10% HTN: 31% CKD: 2.9%
Chen et al[73]	n = 274 Tongji Hospital Wuhan	29 (11%)	1%	DM: 17% HTN: 34% CKD: 1%
Cheng et al[74]	n = 701 Tongji Hospital Wuhan	36 (5%)* Stage 1: 2% Stage 2: 1% Stage 3: 2%		With ≥ 1 co-morbidity: 43% DM: 14% HTN: 33% CKD: 2%
Arentz et al[75]	n = 21 Critically ill patients Evergreen Hospital, Seattle	4 (19%)*	Not reported	With ≥ 1 co-morbidity: 86% CKD: 0.7% ESKD: 10%
Zhou et al[16]	n = 191 Jinyintan and Wuhan Hospitals Wuhan	28 (15%)	5%	DM: 19% HTN: 30%

AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESKD, end stage kidney disease; HTN, hypertension.

General comments: The incidence of AKI ranges from 0.5% to 19%, however the study that reported the upper value[75] only reported data from critically ill patients, thus explaining the very high incidence rate. Most of the patients included in these studies presented with normal kidney function, with no underlying CKD. In terms of median time for developing AKI from hospital admission, Zhou et al. reports a median of 15 days, whereas Cheng et al. reports most patients developing AKI within 7 days of admission.[16,74]

*Used KDIGO criteria for AKI definitions.

suggest potential beneficial effects of reducing lung injury.[45] Therefore, changes to their standard indications on the basis of COVID-19 is not currently recommended.[40]

Renal Involvement of COVID-19

Renal Manifestations

Acute kidney injury (AKI) is the abrupt loss of kidney function that develops within 7 days. Its incidence has been observed with SARS and MERS-CoV.[46] The reported data of AKI in COVID-19 patients are compiled in Table 6.

Although the exact pathogenesis of kidney involvement in COVID-19 infection is unclear, it is reported that AKI in COVID-19 accompanies sepsis, multiorgan failure and shock, suggesting the cause of AKI to be acute tubular necrosis.[29] Alternatively, a study based on single-cell transcriptome analysis[47] proved ACE2 receptor expression in kidney cells, suggesting the plausibility of direct renal cellular damage from SARS-CoV-2. This is further supported by the recent detection of SARS-CoV-2 in a urine sample from an infected patient.[46] Findings of one of the first systematic investigations of kidney function in COVID-19 patients[48] are summarized in Table 7.

Role of Kidney Replacement Theory

In some patients, the metabolic consequences of AKI cannot be adequately controlled with conservative management; hence renal replacement therapy (RRT) can be required. There is little to no evidence that the starting time,[49] modality[50] and dose[51] of RRT has any difference in outcomes. However, convection therapies are known to cause filter clots and use consumables (eg, tubing and dialysate and/or replacement solution bags), which can increase costs and exacerbate the issues faced by an overwhelmed hospital. Continuous RRT (CRRT) has been successfully applied in the treatment of SARS,[52] MERS,[53] and sepsis.[46] A hemofiltration dose of 6 L/min removed proinflammatory cytokines and improved Sequential Organ Failure Assessment score at day 7 in septic patients,[54] suggesting the effectiveness of CRRT in the management of renal manifestations in COVID-19.

Gastrointestinal Involvement of COVID-19

Gastrointestinal Symptoms

A significant number of patients reported GI symptoms such as diarrhea, nausea, vomiting, and abdominal pain, with some reporting these symptoms as their sole presenting complaint.[32] The incidence of GI

Table 7. Summarized findings and interpretations of a systematic review of COVID-19 patients with renal dysfunction[48]

	Results	General comments
Number of patients included (n = 193)	128 nonsevere 65 severe	55 (28%) developed AKI (used KDIGO criteria).
Alterations in renal function indicators on admission	BUN: 27 (14%) SCr: 20 (10%)	Suggests that renal dysfunction occurred before or at admission, indicating that viral replication of SARS-CoV-2 might play a role in the destruction of renal cells.
Exhibition of proteinuria and hematuria	Proteinuria: 88 (60%) Hematuria: 71 (48%)	Significant number of patients presented with these exhibitions, offering a potential time window for starting interventions to protect kidney function.
Exhibition of elevated level of BUN	59 (31%)	Median time from onset of admission to presence of BUN increase was 2 days.
Exhibition of elevated level of SCr	43 (22%)	Median time from onset of admission to presence of SCr increase was 5 days.
Exhibition of radiographic abnormalities of kidneys (N = 110)	106 (96%)	CT images of the 2 groups (severe and non-severe) are clearly distinguishable, suggesting a presence of renal dysfunction in COVID-19.
Difference in mortality risk of COVID-19 patients with and without AKI	Estimated hazard ratio indicates that the mortality risk of COVID-19 patients with AKI is ~5.3x ($P < 0.001$) higher than the mortality risk of COVID-19 patients without AKI.	

AKI, acute kidney injury; BUN, blood urea nitrogen; KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine.

Conclusions: BUN and SCr are key predictors of AKI and they were found to be significantly higher in non-severe cases of COVID-19 compared to other commonly known pneumonia. Both high levels of BUN and SCr were commonly observed in severe and deceased cases across the course of COVID-19. Unlike BUN, for other pneumonia cases, there were no reported elevated SCr levels. Occurrence of kidney dysfunction in COVID-19 patients could be due to kidney-lung crosstalk[76] for the following reasons: renal cells have the potential to be target sites for SARS-CoV-2 and inflammatory responses following lung impairments could damage the kidney, where this kidney-lung crosstalk could lead to a "cytokine storm" that acutely induces multi-organ failure and death. Furthermore, direct renal cellular damage is consistent with another report[77] which found acute renal tubular damage in 6 COVID-19 cases from the histological analysis of renal cell autopsies.

symptoms, alongside the detection of SARS-CoV-2 RNA in stool samples of infected patients,[55] suggest that ACE2 receptors highly expressed in the GI tract are another target for SARS-CoV-2 infection.

Liver Injury in COVID-19 Patients

Mild and transient liver injury, as well as severe liver damage can occur in COVID-19. Wong et al indicated that 14.8-53.1% of COVID-19 patients had abnormal levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin during the course of the disease, with bilirubin showing the smallest elevation. Furthermore, they reported that severity of liver damage is proportional to that of COVID-19.[32] Gamma-glutamyl transferase was elevated in 54% of patients in 1 cohort study that included 56 COVID-19 patients.[56]

Immune System Response

The immune response is undeniably one of the key determiners of the susceptibility and severity of the disease. While weakened immune system can increase the risk of severe COVID-19, hyperinflammatory response to the infection can be responsible for the commonly seen complications by causing organ damage.

The surge in inflammatory parameters like IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α can be caused by an imbalanced immune response leading to cytokine storm or secondary hemophagocytic lymphohistiocytosis.[57] Along with typical cardinal features like hyperferritinaemia, cytopenia, and unremitting fever; pulmonary and cardiac involvement including ARDS and acute coronary syndrome can also result from hypercytokinaemia.[57,58]

Moreover, accumulating evidence suggests that this hyperinflammatory state can be predictors of morbidity and mortality in a significant subgroup of patients.[57] In a multicenter retrospective study, it was found that ferritin and IL-6 levels were more elevated in the non-survivor group as compared to the survivors.[59] This is also supported by findings of Qin et al who recently discovered that severe cases had higher neutrophil-lymphocyte ratio, lower percentages of basophils, eosinophils, and monocytes, as well as elevated inflammatory biomarkers and cytokines. Additionally, the number of suppressor and helper T cells, B cells, and NK

cells were decreased in the severe group.[60] Septic shock is also reported in 4%-8% of patients in several case series.[61]

Therefore, it is paramount for all patients with severe COVID-19 to be screened for hyperinflammation using ferritin levels, platelet count, and erythrocyte sedimentation rate along with the HScore.[57,62] Once identified, therapeutic approach is to suppress the immune system. However, it is a difficult decision to determine whether anti-inflammatory effects of treatment outweigh the risk of impairing the immune system that is trying to fight the infection. In addition to the options of steroids and intravenous immunoglobulins, IL-6 receptor antagonist monoclonal antibodies like tocilizumab and sarilumab, anakinra, Janus kinase inhibitor and CC chemokine receptor 5 antagonists are also in the clinical trial stage for treatment of cytokine release syndrome in COVID-19.[61]

Other Organ Involvement

The Nervous System

It has been suggested that viral invasion of the central nervous system by SARS-CoV2 is possible by the synapse-connected route observed with other coronaviruses such as SARS-CoV and can lead to several neurological complications including ataxia, seizures, neuralgia, unconsciousness, acute cerebrovascular disease and encephalopathy.[61,63] Mao et al reported that 36.4% of their cohort had neurologic manifestations, the severe group being more likely to have acute cerebrovascular disease, impaired consciousness and skeletal muscle injury.[64] Furthermore, Li et al proposed that this potential viral invasion might play a partial role in the pathophysiology of acute respiratory failure in COVID-19 patients.[63]

The Coagulation Cascade

Disseminated intravascular coagulation is another common complication of COVID-19 reported in 71.4% of nonsurvivors compared to only 0.6% of survivors.[65] It has also been found that use of anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin improved outcomes in severe cases with coagulopathy.[66]

Rhabdomyolysis as a Potential Complication of COVID-19

One case of rhabdomyolysis as a potential late complication of COVID-19 has been reported in China. The possibility of under-diagnosis

due to muscle pains being a common symptom of COVID-19 as well as creatine kinase and myoglobin levels not being routinely tested is also highlighted in the letter.[67]

Clinical Management

Current interventions are supportive, as effective antiviral treatment has not yet been identified. The clinical management of adult patients are guided by international guidelines as well as local experience and regional outcomes.[68,69]

Patients with signs of pneumonia and those of the high-risk group are indicated for hospitalization. Those with mild flu-like symptoms are discharged, supplemented with symptomatic treatment and advised to return in case of illness worsening.

Oxygen and/or Respiratory Support

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

Management of Nonrespiratory Organ Failure

Upon recognition of sepsis, standard care[72] is to be commenced as soon as possible. This includes initiation of fluid bolus and vasopressors for hypotension. Prophylaxis against venous thromboembolism is strongly recommended, LMWH preferred over unfractionated heparin, as well as nonpharmacological modalities such as intermittent pneumatic compression stockings. As mentioned above, AKI can be managed by CRRT. Intermittent RRT has been suggested to be as effective.[72] Cardiac support can be managed with direct input from the cardiology team and inotropic support if required.

Pharmacotherapy

Routine corticosteroids are not recommended, unless for trial purposes or for other indications such as adrenal insufficiency, asthma, or Chronic Obstrcutive Pulmonary Disease.

Conclusion

Multiorgan involvement has been apparent since the emergence of COVID-19—the rapidity of disease progression is widely influenced by the presence of comorbidities and of extrapulmonary organ injuries. ARDS, heart failure, renal failure, shock, and multiorgan failure precipitate death. Full attention to the comorbidities and potential organ injuries is therefore crucial in the implementation of preventative and protective measures. Acknowledging this could help in triaging the management of individual patients, minimizing the risk of decompensation. Alongside the rapid pace at which scientific results are shared, this paper hopes to add onto the ever-emerging landscape of medical knowledge on COVID-19.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China [published online ahead of print, 2020 Feb 28]. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMoa2002032. NEJMoa2002032.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. *Lancet* 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
4. 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. Assessed April 12, 2020.
5. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199–207. https://doi.org/10.1056/NEJMoa2001316.
6. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *Euro Surveill* 2020;25:2000062. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062.

7. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: what we know [published online ahead of print, 2020 Mar 11]. *Int J Infect Dis* 2020. https://doi.org/10.1016/j.ijid.2020.03.004.
8. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention [published online ahead of print, 2020 Feb 24]. *JAMA* 2020. https://doi.org/10.1001/jama.2020.2648.
9. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. *Lancet* 2020;395:1014–5. https://doi.org/10.1016/S0140-6736(20)30633-4.
10. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology* 2018;23:130–7. https://doi.org/10.1111/resp.13196.
11. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565–74. https://doi.org/10.1016/S0140-6736(20)30251-8.
12. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020;63:457–60. https://doi.org/10.1007/s11427-020-1637-5.
13. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. *bioRxiv*. 2020. https://doi.org/10.1101/2020.01.26.919985.
14. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 2004;203:622–30. https://doi.org/10.1002/path.1560.
15. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004;203:631–7. https://doi.org/10.1002/path.1570.
16. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. *Lancet* 2020;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.
17. Zhang T, Wu Q, Zhang Z. Probable Pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. *Curr Biol* 2020;30. https://doi.org/10.1016/j.cub.2020.03.022. 1346−1351.e2.
18. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020;109:102433. https://doi.org/10.1016/j.jaut.2020.102433.
19. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1 [published online ahead of print, 2020 Mar 17]. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMc2004973. NEJMc2004973.

20. Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol* 2020;5:335–7. https://doi.org/10.1016/S2468-1253(20)30048-0.
21. Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *bioRxiv*. 2020. https://doi.org/10.1101/2020.01.30.927806.
22. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). *Front Pediatr* 2020;8:104. https://doi.org/10.3389/fped.2020.00104. Published 2020 Mar 16.
23. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records [published correction appears in Lancet. 2020 Mar 28;395 (10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. *Lancet* 2020;395:809–15. https://doi.org/10.1016/S0140-6736(20)30360-3.
24. Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes [published online ahead of print, 2020 Mar 17]. *Arch Pathol Lab Med* 2020;10. https://doi.org/10.5858/arpa.2020-0901-SA. 5858/arpa.2020-0901-SA.
25. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7]. *JAMA* 2020:e201585. https://doi.org/10.1001/jama.2020.1585.
26. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.
27. Pan F., Ye T., Sun P., et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia [published online ahead of print, 2020 Feb 13]. Radiology. 2020;200370. doi:10.1148/radiol.2020200370
28. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;20:425–34. https://doi.org/10.1016/S1473-3099(20)30086-4.
29. McIntosh, K.Coronavirus disease 2019 (COVID-19): epidemiology, virology, clinical features, diagnosis, and prevention. UpToDate. Available at: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-epidemiology-virology-clinical-features-diagnosis-and-prevention. Published 2020. Accessed April 13, 2020.
30. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China [published online ahead of print, 2020 Mar 19]. *J Infect* 2020. https://doi.org/10.1016/j.jinf.2020.03.004.
31. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [published online ahead of print, 2020 Mar 13]. *JAMA Intern Med* 2020: e200994. https://doi.org/10.1001/jamainternmed.2020.0994.
32. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system [published online ahead of print, 2020 Mar 25]. *J Gastroenterol Hepatol* 2020. https://doi.org/10.1111/jgh.15047.

33. Jin YH, Cai L, Cheng ZS, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020;7:4. https://doi.org/10.1186/s40779-020-0233-6. Published 2020 Feb 6.
34. Robles A, San Gil A, Pascual V, et al. Viral vs bacterial community-acquired pneumonia: radiologic features. *Eur. Respir. J* 2011;38:2507.
35. Shi H, Han X, Zheng C. Evolution of CT manifestations in a patient recovered from 2019 novel coronavirus (2019-nCoV) pneumonia in Wuhan, China. *Radiology* 2020;295:20. https://doi.org/10.1148/radiol.2020200269.
36. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis [published online ahead of print, 2020 Mar 12]. *Int J Infect Dis* 2020. https://doi.org/10.1016/j.ijid.2020.03.017. S1201-9712(20)30136-3.
37. Khan IH, Zahra SA, Zaim S, Harky A. At the heart of COVID-19. *J Card Surg* 2020. https://doi.org/10.1111/jocs.14596. [Epub ahead of print] Review. PubMed PMID:32369872.
38. Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19 [published online ahead of print, 2020 Apr 3]. *Circulation* 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.047164.
39. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin [published online ahead of print, 2020 Mar 16]. *Eur Heart J* 2020. https://doi.org/10.1093/eurheartj/ehaa190. ehaa190.
40. Aggarwal G, Cheruiyot I, Aggarwal S, et al. Association of Cardiovascular Disease with Coronavirus Disease 2019 (COVID-19) Severity: A Meta-Analysis. *Curr Prob Cardiology* 2020:100617. https://doi.org/10.1016/j.cpcardiol.2020.100617.
41. Khashkhusha TR, Chan JSK, Harky A. ACE inhibitors and COVID-19: We don't know yet. *J Card Surg* 2020. https://doi.org/10.1111/jocs.14582.
42. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province [published online ahead of print, 2020 Feb 7]. *Chin Med J (Engl)* 2020. https://doi.org/10.1097/CM9.0000000000000744.
43. Zeng JH, Liu YX, Yuan J, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights [published online ahead of print, 2020 Apr 10]. *Infection* 2020. https://doi.org/10.1007/s15010-020-01424-5.
44. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020;8:e21. https://doi.org/10.1016/S2213-2600(20)30116-8.
45. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020;9:757–60. https://doi.org/10.1080/22221751.2020.1746200.
46. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys [published online ahead of print, 2020 Mar 7]. *Kidney Int* 2020. https://doi.org/10.1016/j.kint.2020.03.001.
47. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective

case series [published correction appears in BMJ. 2020 Feb 27;368:m792]. *BMJ* 2020;368:m606. https://doi.org/10.1136/bmj.m606. Published 2020 Feb 19.
48. Li Z, Wu M, Yao J, et al. Caution on kidney dysfunctions of COVID-19 patients. *medRxiv*. 2020. https://doi.org/10.1101/2020.02.08.20021212.
49. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016;375:122–33. https://doi.org/10.1056/NEJMoa1603017.
50. Liang KV, Sileanu FE, Clermont G, et al. Modality of RRT and recovery of kidney function after AKI in patients surviving to hospital discharge. *Clin J Am Soc Nephrol* 2016;11:30–8. https://doi.org/10.2215/CJN.01290215.
51. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, et al. Intensity of renal support in critically ill patients with acute kidney injury [published correction appears in N Engl J Med. 2009 Dec 10;361(24):2391]. *N Engl J Med* 2008;359:7–20. https://doi.org/10.1056/NEJMoa0802639.
52. Chu KH, Tsang WK, Tang CS, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int* 2005;67:698–705. https://doi.org/10.1111/j.1523-1755.2005.67130.x.
53. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014;160:389–97. https://doi.org/10.7326/M13-2486.
54. Ghani RA, Zainudin S, Ctkong N, et al. Serum IL-6 and IL-1-ra with sequential organ failure assessment scores in septic patients receiving high-volume haemofiltration and continuous venovenous haemofiltration. *Nephrology (Carlton)* 2006;11:386–93. https://doi.org/10.1111/j.1440-1797.2006.00600.x.
55. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020;382:929–36. https://doi.org/10.1056/NEJMoa2001191.
56. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020;5:428–30. https://doi.org/10.1016/S2468-1253(20)30057-1.
57. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.
58. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality [published online ahead of print, 2020 Mar 27]. *JAMA Cardiol* 2020. https://doi.org/10.1001/jamacardio.2020.1105.
59. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China [published online ahead of print, 2020 Mar 3] [published correction appears in Intensive Care Med. 2020 Apr 6;:]. *Intensive Care Med* 2020:1–3. https://doi.org/10.1007/s00134-020-05991-x.
60. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China [published online ahead of print, 2020 Mar 12]. *Clin Infect Dis* 2020. https://doi.org/10.1093/cid/ciaa248. ciaa248.

61. Beeching N, F T, Fowler R. Coronavirus disease 2019 (COVID-19). *BMJ Best Practice* 2020. Available at https://bestpractice.bmj.com/topics/en-gb/3000168/emergingtxs PublishedUpdated Apr 2020Accessed April 11, 2020.
62. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;66:2613–20. https://doi.org/10.1002/art.38690.
63. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients [published online ahead of print, 2020 Feb 27]. *J Med Virol* 2020. https://doi.org/10.1002/jmv.25728.
64. Mao L, Wang MD, Chen SH, et al. Neurological manifestation of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *medRxiv* 2020. https://doi.org/10.1101/2020.02.22.20026500.
65. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844–7. https://doi.org/10.1111/jth.14768.
66. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy [published online ahead of print, 2020 Mar 27]. *J Thromb Haemost* 2020. https://doi.org/10.1111/jth.14817.
67. Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19 [published online ahead of print, 2020 Mar 20]. *Emerg Infect Dis* 2020;26. https://doi.org/10.3201/eid2607.200445.
68. WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Published2020. Available at: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf[Accessed April 13, 2020].
69. NHS. Clinical guide for the management of critical care for adults with COVID-19 during the coronavirus pandemic. Published2020. Available at: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/C0216_Specialty-guide_AdultCritiCare-and-coronavirus_V2_-8-April.pdf[Accessed April 13, 2020].
70. NHS. Clinical guide for the optimal use of oxygen therapy during the coronavirus pandemic. Specialty guides for patient management during the coronavirus (COVID-19) pandemic. Published2020. Available at: https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/04/C0256-specialty-guide-oxygen-therapy-and-coronavirus-9-april-2020.pdf[Accessed April 13, 2020].
71. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–68. https://doi.org/10.1056/NEJMoa1214103.
72. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304–77. https://doi.org/10.1007/s00134-017-4683-6.
73. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study [published correction appears in BMJ.

2020 Mar 31;368:m1295]. *BMJ* 2020;368:m1091. https://doi.org/10.1136/bmj.m1091. Published 2020 Mar 26.
74. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19 [published online ahead of print, 2020 Mar 20]. *Kidney Int* 2020. https://doi.org/10.1016/j.kint.2020.03.005. S0085-2538(20)30255-6.
75. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State [published online ahead of print, 2020 Mar 19]. *JAMA* 2020:e204326. https://doi.org/10.1001/jama.2020.4326.
76. Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. *Nat Rev Nephrol* 2016;12:48–60. https://doi.org/10.1038/nrneph.2015.158.
77. Diao B, Feng Z, Wang C, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.04.20031120.