

Title

Extra-pulmonary complications of COVID-19: a multi-system disease?

Running Title

Extra-pulmonary complications and COVID-19

Authors:

Kenneth I. Zheng, MD;^{1#} Gong Feng, MD;^{2#} Wen-Yue Liu, MD;³ Giovanni Targher, MD;⁴ Christopher D. Byrne, MD;⁵ Ming-Hua Zheng, MD.^{1*}

Affiliations:

¹Department of Infectious Diseases, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

²Xi'an Medical University, Xi'an, China;

³Department of Endocrinology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

⁴Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy;

⁵Southampton National Institute for Health Research Biomedical Research Center, University Hospital Southampton, Southampton General Hospital, Southampton, UK;

#Co-first authors: Kenneth I. Zheng and Gong Feng.

***Corresponding author:**

Ming-Hua Zheng, MD, PhD

Department of Infectious Diseases, the First Affiliated Hospital of Wenzhou Medical

University; No. 2 Fuxue Lane, Wenzhou 325000, China.

E-mail: zhengmh@wmu.edu.cn; fax: (86) 577-55578522; tel: (86) 577-55579622.

Number of figure: 1

Word count: 4752

ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been recently declared a pandemic by the World Health Organization. In addition to its acute respiratory manifestations, SARS-CoV-2 may also adversely affect other organ systems. To date, however, there is very limited understanding of the extent and management of COVID-19-related conditions outside of the pulmonary system. This narrative review provides an overview of the current literature about the extra-pulmonary manifestations of COVID-19 that may affect the urinary, cardiovascular, gastrointestinal, hematological, hematopoietic, neurological, or reproductive systems. This review also describes current understanding of the extra-pulmonary complications caused by COVID-19 in order to improve the management and prognosis of patients with COVID-19.

Keywords: COVID-19; SARS-CoV-2; extra-pulmonary manifestations; management.

Introduction

The spread of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has recently become a global pandemic and public health problem in almost all countries.¹⁻³ SARS-CoV-2 is similar to Severe Acute Respiratory Syndrome Coronavirus (SARS) and Middle East Respiratory Syndrome Coronavirus (MERS) in that these coronavirus infections are responsible for severe and potentially life-threatening acute respiratory syndromes in humans. As of June 16, 2020, a total of more than 7,900,000 confirmed cases and ~434,796 total deaths for COVID-19 had been reported globally.⁴ Unfortunately, there are no targeted drugs for treatment of SARS CoV-2 infection to date, vaccine development is at an early stage, and the number of infected patients is increasing rapidly worldwide. There is a growing body of evidence suggesting that in addition to the common acute respiratory symptoms (such as fever, cough and dyspnea), COVID-19 patients may also have signs and symptoms of injury in many other organ systems (as summarized in **Figure 1**), which may further complicate medical management and adversely affect clinical outcomes of these patients.

SARS-CoV-2 is thought to use cell receptor angiotensin converting enzyme 2 (ACE2) to gain cellular access in humans.⁵ The ACE2 receptor is highly expressed in lungs, kidneys, gastrointestinal tract, liver, vascular endothelial cells and arterial smooth muscle cells.⁶ Thus, all of these organs and systems with high expression of ACE2 receptors might be speculated targets for SARS-CoV-2 infection.⁷

The main purpose of this narrative review article is to provide an overview of the current literature on the extra-pulmonary manifestations and complications of COVID-19 in order to improve the management and prognosis of these patients.

COVID-19: diagnosis, treatment and outcomes

The diagnosis of SARS-CoV-2 infection is currently established with nucleic acid (RNA) testing of suspected patients using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) techniques by oropharyngeal swabs or, in some cases, by stool samples.^{8,9} Initially, a patient was suspected of SARS-CoV-2 infection if he/she had symptoms of cough, fever and/or dyspnea and a history of travel to endemic regions affected by the SARS-CoV-2 outbreak; or have had close contact(s) with individuals with an aforementioned travel history. However, due to the ever-increasing number of COVID-19 cases, physicians are now recommending RT-PCR testing only in all patients showing any evidence of viral pneumonia on chest X-ray or computed tomography (CT) (e.g., ground-glass opacities and exudative lesions).¹⁰⁻¹² In some cases, absence of fever and typical symptoms in the early stages of viral infection hinders the identification of infection in at risk individuals.¹³ To date, the treatment options are scarce, mostly due to the fact that no targeted therapy for SARS-CoV-2 is available. The mainstay of COVID-19 management is the patient's isolation and supportive medical care, as recommended by National Institutes of Health (NIH) of United States of America and China Center for Disease Control and Prevention (CCDC), which includes the use of antiviral, antibacterial medications and

oxygenation therapy as appropriate.^{14,15} Initially, corticosteroids were not recommended for routine use as their usage may be associated to delayed viral clearance.¹⁶ However, the latest trial data demonstrated that low to moderate dosage of dexamethasone may reduce mortality by 20% among critically-ill patients, especially for patients requiring ventilation therapy.¹⁷ (For the latest updated treatment and management of severe COVID-19 see¹⁵). The incidence of acute respiratory distress syndrome (ARDS) in COVID-19 patients is reported to be 15% ~ 30%.¹⁸⁻²⁰ Compared to survivors, patients dying with COVID-19 are more likely to be older, have more severe viral infection, be admitted to intensive care unit (ICU), and are more likely to have comorbidities or develop ARDS. For survivors, the median recovery time from hospital admission to discharge is approximately 12 to 14 days;^{21,22} the median duration from ICU admission to death for non-survivors is approximately 7 days.²³ The discharge criteria for COVID-19 patients after in-hospital treatment varied across the globe, while specific criteria can be quickly evolving (for detailed comparison between guidelines, please see²⁴).

COVID-19: acute kidney injury and renal failure

The kidneys are one of the most frequently affected extra-pulmonary organs in patients infected with SARS-CoV-2; especially, in those patients who are severely ill.^{18-20,23} Previous studies of patients affected by the 2013 SARS outbreak have shown that kidney damage is mainly characterized by tubular injury (as reflected by abnormal urine test results) and increased serum creatinine and urea nitrogen concentrations.^{25,26}

A recent study of 59 patients infected with SARS-CoV-2 (nearly half of whom had a severe illness) showed that mild proteinuria was the commonest kidney abnormality in these patients. In addition, nearly 30% of these patients also had elevated urea nitrogen levels and ~20% had increased serum creatinine levels.²⁷

Currently, the occurrence of acute kidney injury (AKI) among patients with COVID-19 is not consistent across published studies, ranging from 0.1% to 29%.^{20,21,28} Guan et al. reported that in 1,099 confirmed COVID-19 cases from 552 Chinese hospitals, 926 patients had a mild condition and 173 had a severe condition. Amongst patients with severe COVID-19, 4.3% had serum creatinine levels >133 $\mu\text{mol/L}$, and 2.9% had AKI. In contrast, among those with mild COVID-19, only 1% had serum creatinine levels >133 $\mu\text{mol/L}$, and 0.1% had AKI. Another study of 710 COVID-19 patients from Tongji Hospital, Wuhan, China, reported that 44% of these patients had combined proteinuria and hematuria, 26.9% had hematuria alone, 15.5% had elevated serum creatinine, and 14.1% had elevated urea nitrogen levels.²¹ Data from 138 COVID-19 patients from Zhongnan Hospital in Wuhan, China, showed that AKI occurred in 8.3% of patients admitted to ICU *versus* 2% in non-ICU patients.²⁰ In another study, the occurrence of AKI in 58 critically ill COVID-19 patients was as high as 29%, and AKI was also found to be an important risk factor for increased hospital mortality.²⁸ In a case series of 85 patients with severe SARS-CoV-2 infection, AKI occurred in 23 (27.1%) patients.²⁹ In this study, a post-mortem analysis of six patients revealed the presence of severe acute tubular necrosis with accumulation of SARS-CoV-2

nucleocapsid protein antigens.²⁴ This finding suggests that the SARS-CoV-2 might directly infect kidney tubules. Although the underlying virologic mechanisms are not completely understood, it is plausible to speculate that there is binding by the virus to the ACE2 receptor, which is highly expressed in kidney tubules, causing glomerulopathy, acute tubular necrosis and protein leakage in the Bowman's capsule.³⁰⁻³² However, it is also possible to speculate that AKI could be an epiphenomenon of both respiratory distress syndrome-induced hypoxia and septic shock caused by the SARS-CoV-2.³³ Other autopsy investigations have reported that the endothelium is affected in the kidneys, and is responsible for the proteinuria.³⁴ SARS-CoV-2 particles in renal endothelial cells may suggest viremia as a possible cause of renal endothelial damage resulting in AKI.²⁹ More recently, Sun et al. have reported the occurrence of subclinical AKI as reflected by increased urinary levels of β 2-microglobulin, α 1-microglobulin, N-acetyl- β -D-glucosaminidase and retinol binding protein (i.e., all biomarkers of kidney tubular damage) in a sample of 32 confirmed COVID-19 cases without prior chronic kidney disease.³⁵ In addition, the severity of kidney tubular damage was also greater in severe COVID-19 patients than in less severely affected patients.³⁰ Based on the available evidence, we can draw the following considerations: (1) AKI is not uncommon in patients with COVID-19, especially in those with severe COVID-19; patients can present with proteinuria early or at hospital admission, while AKI often develops in later stages of the viral disease (i.e. critically ill patients) and is understood as an early sign of multiple organ dysfunction; (2) AKI could be related to direct effects of the virus, and to other

concomitant virus-related complications, such as hypoxia and shock; (3) the precise incidence of AKI in SARS-CoV-2 infected patients is not known; however, it is reasonable to assume that AKI is more common in critically ill patients than in those with mild COVID-19 disease; and (4) COVID-19 patients with a prior history of chronic kidney disease are more likely to develop AKI; and (5) COVID-19 patients with AKI have a poorer prognosis.

Collectively, therefore, it is recommended that physicians who treat COVID-19 patients should pay special attention to acute changes in patients' kidney function.^{36,37} Volume depletion at hospital admission might be suggestive of subsequent occurrence of AKI, especially when COVID-19 patients are infrequently given pre-hospital fluid resuscitation. In the absence of targeted treatment strategies for SARS-CoV-2 infection, supportive care is the cornerstone in managing COVID-19, and thus, lung-protective ventilation may be used to reduce the risk of AKI by limiting ventilator-induced hemodynamic effects and the cytokine burden on the kidneys.³⁸ It is also recommended to follow Kidney Disease Improving Global Outcomes supportive care guidelines in patients at risk for AKI. In patients with early signs of hyperinflammation and "cytokine storm", possible strategies such as dexamethasone treatment or cytokine removal need to be explored further. However, large clinical trials are needed to test the risks and benefits of rigorous interventions in COVID-19 patients specifically at risk of AKI.

COVID-19: heart disease

Myocardial injury

In a retrospective study of SARS-CoV-2 infected patients, who were quarantined at the Tongji Hospital, Wuhan, China, from January to February 2020, including 24 patients who were critically ill and 126 who were severely ill, Chen et al. reported that approximately 20% of these patients had signs of myocardial injury as reflected by increases in plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) levels.¹¹ Also, in a retrospective study of 52 critically ill COVID-19 patients, 15 (29%) of these patients had increased cTnI levels (i.e. > 28 pg/mL).²³ There is an estimated 12% of COVID-19 patients without pre-existing or known ischemic heart disease had elevated troponin levels or cardiac arrest during the hospitalization.³⁹ Particularly, cTnI levels were shown to be above the 99th centile upper normal limit in 46% of non-survivors, as compared to 1% of survivors.⁴⁰ The rise in cTnI levels together with proinflammatory markers, such as interleukin-6, lactate dehydrogenase and D-dimer, might be indicative of cytokine storm or secondary hemophagocytic lymphohistiocytosis, in addition to isolated myocardial injury. However, based on preliminary data, the probability of fulminant myocarditis and cardiogenic shock is low. In addition to the ACE-2-dependent infection within myocardium as demonstrated in mice models,⁴¹ some investigators have also suggested a potential mechanism of myocardial injury due to COVID-19-induced cytokine storm that is mediated by a mixed T helper cell response in combination to hypoxia-induced excess of intracellular calcium causing cardiac myocyte cell

death.^{39,40} Although it is uncertain whether SARS-CoV-2 may directly damage myocardial tissue and induce a major cardiovascular event, it is currently recommended that physicians should regularly monitor plasma cTnI and NT-proBNP levels in all COVID-19 patients. However, longer-term follow-up studies of cardiac function parameters of these infected patients (also by using transthoracic echocardiographic examination) are needed.

Cardiac arrhythmias

In addition to myocardial injury, arrhythmia is another facet of the cardiac involvement in COVID-19 that ranges from tachycardia to bradycardia and asystole. A study of 121 COVID-19 patients showed that most of these patients had some type of arrhythmia, including 87 (71.9%) with sinus tachycardia unrelated to fever, 18 (14.9%) with bradycardia, and one patient with paroxysmal atrial fibrillation.⁴² Another study has shown that cardiac arrhythmias occurred in 23 (16.7%) of 138 patients with SARS-CoV-2 infection, especially among those admitted to the ICU.²⁰ Another interesting observation was made among the vasoplegic population (comprising a syndrome of pathologically low systemic vascular resistance in the Wuhan cohort, where a higher proportion of critically ill COVID-19 patients/non-survivors had increased blood pressure values, which might contribute to arrhythmia, potentially explaining the pathological activity of SARS-CoV-2 infection.^{19,43} However, due to the retrospective nature of these data, it is difficult to ascertain whether the cause of this observed hypertension is due to physiological

reactions to the viral illness, or it is a consequence of virus-induced derangements in ACE2 expression. Overall, this suggests that arrhythmia may be an important complication among patients with SARS-CoV-2 infection. However, due to the very limited data available, arrhythmia type and corresponding electrocardiogram changes in patients with SARS-CoV-2 infection remain poorly defined. That said, these findings suggest that especially in patients with severe COVID-19, routine electrocardiogram monitoring is needed to closely monitor patients for paroxysmal tachycardias and pulse accelerations that do not match the patient's condition.⁴⁴

Sudden cardiac death

In a study involving 99 SARS-CoV-2 infected patients quarantined at Wuhan Jinyintan Hospital, China, there were 11 (11%) deaths due to sudden cardiac arrest among those patients without a prior history of ischemic heart disease.²⁰ These results suggest that the cause of death might be caused mainly by an imbalance of pulmonary ventilation perfusion ratio and a decrease in capacity of the pulmonary vasculature. While acute myocarditis might contribute to heart failure and some investigators have reported depressed left ventricular ejection fraction due to COVID-19, the majority of COVID-19 patients with uncomplicated lymphocytic myocarditis had normal cardiac function.⁴⁵⁻⁴⁸ The pathophysiologic factors possibly involved include occlusion of microvasculature and reduction of the amount of functional residual gas, which could lead to increased resistance of pulmonary vessels, resulting in subsequent pulmonary hypertension and *cor pulmonale*. Cardiac dysfunction due to direct virus infection or

systemic inflammation might potentially cause coronary microcirculation disruption and downstream myocardial ischemic sequelae, but the relationship between SARS-CoV-2 infection and heart failure remains unclear. Although there is limited understanding of the pathophysiology of sudden cardiac death in patients infected with SARS-CoV-2, it is important to be aware of this condition in order to try and prevent cardiac arrest (especially in patients with a previous history of ischemic heart disease or multiple cardiovascular risk factors), so that appropriate measures may be performed to reduce the risk of death.^{42,49-51}

COVID-19: liver dysfunction and other gastrointestinal complications

Liver dysfunction

Huang et al. first reported that circulating levels of liver function tests, such as serum transaminases, bilirubin, lactate dehydrogenase (LDH) and prothrombin time, were significantly higher in COVID-19 patients admitted to ICU than in non-ICU patients.¹⁹ Similar results were also confirmed by Wang et al. in a study of 138 critically ill COVID-19 patients without pre-existing chronic liver diseases, who were admitted to ICU.²⁰ Also, mild to moderate elevations of serum liver enzymes (mostly increased serum transaminases) were reported in a large multicenter Chinese study of 1,099 COVID-19 patients.²¹ In clinical practice, the liver function test results of patients with mild SARS-CoV-2 infection were relatively unremarkable. Conversely, patients with severe (but non-critically ill) SARS-CoV-2 infection had mild-to-moderate elevations of serum transaminase and LDH levels.⁵² Jaundice is less common and was observed

only in a few SARS-CoV-2 infected patients, who died during hospital admission; however, hypoalbuminemia and a longer prothrombin time (PT) were also observed amongst patients who subsequently died. Liver failure has also been observed with other organ failure in non-survivors of SARS-CoV-2 infection and thus, it is not easy at this time to quantify the excess risk of death attributable to liver failure alone.²³

The current evidence suggests that liver injury occurs more frequently among critically ill patients with COVID-19, who have other coexisting causes of liver damage, such as the use of potentially hepatotoxic therapies and the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia and multiple organ dysfunction.⁵³ Several studies showed that in patients with chronic liver diseases, especially in those with preexisting cirrhosis, there is an increased risk of greater COVID-19 illness and in-hospital mortality,⁵⁴⁻⁵⁹ which suggests specialized intervention strategies in these patients might help avoid a worse outcome.

Management of liver transplant recipients has remained a challenge for physicians during the COVID-19 outbreak. It is recognized that transplant recipients are more susceptible to SARS-CoV2 infection, are more likely to have increased severity of illness, and prolonged viral shedding.⁶⁰⁻⁶² In one case report, a transplant recipient with chronic rejection and COVID-19 quickly developed multiple nosocomial infections during his brief hospital stay despite changes in treatment.⁶¹ The patient eventually failed to be rescued due to septic shock attributable to multiple infections, possibly

worsened by corticosteroid treatment (for the chronic rejection). Another case of a post-transplant patient who successfully recovered from COVID-19 developed nosocomial infections, similar to the previous case.⁶³ However, early discontinuation of immunosuppressive therapy (tacrolimus and mycophenolate) was associated with recovery. In addition, SARS-CoV-2 infection during the peri-operative period may also represent an opportunistic infection for patients treated with immunosuppressive drugs to prevent acute graft rejection, and thus, it is advised to delay the scheduled transplantation procedure. However, there was a reported case where a patient who had COVID-19 prior to liver transplantation, recovered from COVID-19 sixty days after transplantation associated with lowered dosage of immunosuppressant agents.⁶⁴ With limited available evidence, it is conceivable that the primary cause of death for liver transplant recipients is nosocomial infections leading to septic shock, rather than SARS-CoV-2 infection. Therefore, secondary infections should be carefully monitored in post-transplant patients with compromised immune status when treating COVID-19. Excessive immunosuppression can lead to secondary infections, in contrast to acute graft rejection. Therefore, physicians must attentively balance the risks and benefits of adjusting immunosuppressive dosage in liver transplant recipients.

Gastrointestinal tract involvement

Currently, there is little information on the effect of SARS-CoV-2 infection on gastrointestinal (GI) functions. A retrospective study from Wuhan, China, showed that gastrointestinal symptoms were generally uncommon among 1,099 SARS-CoV-2

infected patients, i.e. ~5% had nausea and vomiting, while 3.8% had diarrhea.²¹

However, among SARS-CoV-2 infected patients who had developed atypical clinical presentations, a substantial portion of these patients had GI symptoms.⁶⁵ Song et al. described a SARS-CoV-2 infected patient with diarrhea as the first symptom and suggested that the gastrointestinal tract might be a route of invasion and transmission of the virus. Recently, negative fecal nucleic acid testing has been also added to the criteria for hospital discharge in COVID-19 patients, as recommended by Health Commission of Zhejiang Province, China.⁸

COVID19: immunological and hematological complications

Blood leukocyte abnormalities

At hospital admission, SARS-CoV-2 infected patients often have leucopenia, lymphopenia or elevated levels of peripheral neutrophils.^{18,20,21} However, an exception was reported by Jin et al. in which a SARS-CoV-2 infected patient had increased leukocyte and lymphocyte counts, possibly due to coexisting chronic lymphocytic leukemia masking SARS-CoV-2 infection.⁶⁶ In a nineteen-day comparison of the biochemical profiles of 28 survivors and 5 non-survivors with SARS-CoV-2 infection, most of these patients had lymphopenia, but non-survivors developed more severe lymphopenia from day 7 to 19 with a lymphocyte count ranging from 0.5 to $0.3 \times 10^9/L$. In contrast, higher white blood cell (ranging from 4.2 to $15.0 \times 10^9/L$) and neutrophil counts from days 5 to 19, were reported in non-survivors compared to survivors.²⁰

Septic shock and disseminated intravascular coagulation

Multiple organ failure due to diffuse microvascular damage is an important cause of death in critically ill SARS-CoV-2 infected patients and is associated with cytokine release syndrome caused by an acute immune response.^{18,67-69} In a retrospective study of 138 confirmed COVID-19 cases, the risk of septic shock was nearly 30-fold higher among ICU patients (30.6%) than among non-ICU patients (1%).²⁰ In a multicenter Chinese study of 1,099 COVID-19 patients, Guan et al. reported that septic shock was observed in one (0.1%) patient who was not severely affected and in 11 patients who were severely ill (6.4% most of whom did not survive); disseminated intravascular coagulation (DIC) was also observed in one non-survivor.²¹ In another study involving 99 patients with SARS-CoV-2 infection, septic shock occurred in 17% of non-survivors and in 4% of survivors, respectively; it is also important to note that the occurrence of septic shock among non-survivors often led to multiple organ dysfunction syndrome and death.¹⁹ At present, the occurrence of septic shock, organ dysfunction or organ failure among SARS-CoV-2 infected patients appears to be higher than that of DIC. However, a retrospective analysis of 21 deaths in SARS-CoV-2 infected patients recently reported that 71% of patients who died had DIC with a median time of 4 days from admission to presentation of DIC; whilst the incidence of DIC in surviving patients was 0.6%.⁶⁸ These data suggest that acute coagulation disorders and DIC in severe cases of SARS-CoV-2 infection are common, and acute coagulation disorders and DIC are important risk factors for increased

in-hospital mortality. Therefore, special attention should be paid to early diagnosis and treatment of these acute hematological conditions in order to improve patient survival.⁷⁰

Management for coagulopathy

Patients with moderate and severe COVID-19 illness are more likely to have a hypercoagulable state placing them at high risk for venous thromboembolism (VTE) than end-stage DIC.^{68,69,71-74} Patients with a hypercoagulable state may exhibit normal or increased platelet count with a fairly normal activated partial thromboplastin time, a dramatic increase in fibrinogen and D-dimer levels, increased levels of C-reactive protein, protein C, factor VII and von Willebrand factor, while antithrombin levels may be marginally decreased.^{73,75} VTE occurs approximately in 25% of severe COVID-19 patients, while thrombotic complications occur in 31% of those requiring ICU.^{71,72} Elevations in D-dimer levels may be indicative of thrombosis and can be used as a predictor for VTE (sensitivity: 85%, specificity: 88.5%, negative predictive value: 94.7%).⁷¹ The use of anticoagulants is associated with decreased mortality among severe COVID-19 patients. In a study of 99 severe COVID-19 patients who used low molecular weight heparin (LMWH) for 7 days or longer, the 28-day mortality of heparin users was significantly lower, compared to non-users, especially amongst those with sepsis-induced coagulopathy score of ≥ 4 (40.0% vs. 64.2%, $p = 0.029$).⁷⁴ As per recommendations by the American College of Chest Physicians, in the absence of contraindications, thrombotic prophylaxis is recommended in all

moderate and severe COVID-19 patients, while LMWH is preferred over direct oral anticoagulants.⁷⁶ In patients requiring ICU admission, therapeutic treatment of LMWH can be effective in reducing in-hospital mortality. There is a mixed recommendation for prolonged use of thromboprophylaxis after hospital discharge,¹⁵ although it is generally recommended in COVID-19 patients with proximal deep venous thrombosis or VTE (continued therapy for minimum of three months). In those with recurrent VTE despite anticoagulation by LMWH, increasing the dosage by 25-30% is suggested.⁷⁶

Hemopoietic disorders

Zheng et al. recently described a case of haemaphagocytosis in a severe COVID-19 patient (without any pre-existing hematological diseases) with sustained fever and worsening respiratory symptoms (data not published). In this case report, bone marrow aspiration showed cellular bone marrow with features of haemaphagocytosis that might be characteristic of secondary hemophagocytic lymphohistiocytosis, i.e. an acute condition typically characterized by poor prognosis that is often caused by severe viral infections. Caution is therefore needed with careful monitoring of potentially developing inflammatory cytokine “storm”, which has been reported as playing a key role in the severe immune injury to the lungs caused by T-cell overactivation and subsequent death with severe COVID-19.⁷⁷ Due to our currently limited understanding of COVID-19 immunology, meticulous assessment for other hematologic conditions, including secondary macrophage activation syndrome and

cytokine release syndrome are needed, particularly because the current evidence implies a possible association between the SARS-CoV-2 infection and presence of myelosuppressive effects. It is therefore important that physicians are aware of the possible viral effect on the bone marrow and, if necessary, they should also consider performing a bone marrow examination in some COVID-19 patients.

COVID-19: neurological complications

Neurological symptoms

Little information is available on the possible adverse effects of SARS-CoV-2 infection on the neurological system. The neurological signs and symptoms caused by the SARS-CoV-2 infection can be divided into three main clinical presentations: 1) central nervous system presentations, such as headache, dizziness, disturbance of consciousness, acute cerebrovascular disease, and epilepsy; 2) peripheral nervous system presentations, such as neuralgia and decreased taste, smell, and appetite; and 3) skeletal muscle injury presentations. In a retrospective study of 214 patients diagnosed with SARS-CoV-2, 78 of these patients had some neurological symptoms, accounting for 36.4% of all confirmed COVID-19 patients.⁷⁸ Patients with severe COVID-19 were more likely to develop neurologic symptoms, such as acute cerebrovascular disease, impaired consciousness and skeletal muscle injury.^{78,79}

COVID-19: psychological disorders

The adverse psychological effects (post-traumatic stress, confusion and anger) of

quarantine during infectious outbreak have been well documented.⁸⁰⁻⁸⁵ Three years after the SARS epidemic in 2013, two studies have reported alcohol abuse or dependency symptoms, as long-term effects in quarantined healthcare workers.^{86,87} Increased avoidance behaviors have been described to be common among healthcare workers after quarantine, such as avoiding direct contact with patients and work absence were found significantly associated with increased duration of quarantine.

Factors influencing psychological disorders

Several factors may induce psychological disorders during quarantine. History of psychiatric illness was found to be closely associated with anxiety and anger within two to six months for patients who were subject to release from quarantine.⁸⁸ Interestingly, healthcare workers reported more severe symptoms of post-traumatic stress when compared to controls (non-healthcare workers) after being quarantined.⁸⁹ Unsurprisingly, after quarantine, healthcare workers also felt increased levels of stigmatization, having had more avoidance behaviors, reported higher lost in income, and felt more negatively affected psychologically. Among the various psychological effects include increased worry, anger, fear, frustration, guilt, isolation, loneliness, and nervousness. Although one study showed that a cut-off of 10 days of quarantine duration significantly influenced the outcome of psychological impact,⁹⁰ it is generally accepted that longer duration of quarantine is more likely to induce poorer psychological outcomes and mental health conditions.^{86,89,90} Other factors attributable to adverse psychological effects include fear of infection (directed at self-condition or

transmitting to others),^{81,88-94} adverse reactions to confinement or isolation,^{89-92,94-98} lack of sufficient information from authorities (regarding to wellbeing and duration of quarantine),^{91,94,96,97,99,100} and fear of financial loss.^{84,88,92,100,101}

Recommendations for the current infectious outbreak

With the virus's worrisome transmission rate and the threat to human health, negative emotions are spreading among the general public, and it is expected to be on the same trajectory similar to past experiences.¹⁰² For normal individuals, the outbreak of COVID-19 has been reported to cause anxiety and fear.^{103,104} Because the negative effects of infectious outbreak and quarantine are numerous, substantial and can be often felt months and sometimes years later,^{82,88} it is recommended that authorities should keep the quarantine duration as short as possible. It is also advisable for authorities to properly educate others on the necessary duration length, to keep a clear communication channel between those that are quarantined and actively address those experiencing psychological symptoms, while also adhere to the period of quarantine imposed on individuals by not extending it. Healthcare workers are often quarantined as they serve on the frontline, and thus, special attention should be paid to this group of individuals in order to reduce the negative psychosocial and mental impact during, and after, the infectious outbreak. Overall, limited investigations exist regarding the specific impact of COVID-19 on mental health. However, there is already a call for immediate prioritization to collect high-quality data on the mental health and psychological effects of the current COVID-19 pandemic across multiple disciplinary

networks to promote efficient and rapid collaborations.¹⁰⁵

COVID-19: pregnancy and male reproductive complications

Prior studies have shown that pregnant women with viral respiratory diseases have a higher risk of obstetric complications and adverse perinatal outcomes compared to non-pregnant women, possibly due to concomitant changes in the immune response.¹⁰⁶⁻¹⁰⁹ According to a previous report of 10 pregnant SARS-infected patients in Hong Kong,¹¹⁰ it has been proposed that the COVID-19 may be associated with poorer perinatal outcomes, including spontaneous abortion, maternal death, and preterm birth.¹¹¹

Until now there are no reports of the effects of COVID-19 on the male reproductive system. Previous studies have reported that SARS virus infection may cause orchitis, spermatogenic tubule destruction or male infertility; indeed, viral orchitis can severely damage testicular spermatogenic function, causing oligo-zoospermia and even azoospermia.¹¹² Whether the COVID-19 may also have similar adverse effects on the male reproductive system remains currently not known.

Conclusions

The prevention and control of the COVID-19 outbreak is well underway around the world and efforts must continue to target this virus. The present review article emphasizes that more careful surveillance and management of extra-pulmonary

complications of COVID-19 patients are needed. Indeed, this viral infection appears to adversely affect not only the respiratory system but also several other organ systems, including the urinary, cardiovascular, gastrointestinal and neurological systems. The COVID-19 pandemic has also caused tremendous anxiety and other psychological effects both in suspected and confirmed cases with SARS-CoV-2 infection, while it remains to be clarified if it also causes negative psychological effects on those who have been released from quarantine. However, further research is needed to better understand the underlying mechanisms linking SARS-CoV-2 with the occurrence of multiple extra-pulmonary complications. In the meantime, we believe that the front-line multidisciplinary team should carefully monitor multi-organ functions, which may also be the key to the survival of infected patients. We suggest an improved knowledge of COVID-19 related extra-pulmonary complications will help to develop better medical management strategies for these patients.

Acknowledgements

None.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81500665), High Level Creative Talents from Department of Public Health in Zhejiang Province and Project of New Century 551 Talent Nurturing in Wenzhou. G. T. is supported in part by grants from the School of Medicine, University of Verona,

Verona, Italy. C. D. B. is supported in part by the Southampton NIHR Biomedical Research Centre (IS-BRC-20004), UK.

Role of funder

None.

Conflict of interest statement

All authors have no conflict of interest to disclose.

Reference

1. 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(13):1199-1207.
2. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. 2020;5(5):428-430.
3. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.
4. World Health Organization. Coronavirus disease 2019 (COVID-19): Situation Report—148. Accessed June 17, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200616-covid-19-sitrep-148-draft.pdf?sfvrsn=9b2015e9_2.
5. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273.
6. Santos RAS, Sampaio WO, Alzamora AC, et al. The ACE2/Angiotensin-(1-7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1-7). *Physiological reviews*. 2018;98(1):505-553.
7. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *The Journal of pathology*. 2003;200(3):282-289.
8. Xu K, Cai H, Shen Y, et al. [Management of corona virus disease-19 (COVID-19): the Zhejiang experience]. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2020;49(1):0.
9. Center for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Overview of Testing for SARS-CoV-2. https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fclinical-criteria.html. [Accessed on June 17, 2020]. 2020.

10. Chung M, Bernheim A, Mei X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). *Radiology*. 2020;295((1)):202-207.
11. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imaging*. 2020;47(5):1275-1280.
12. Xu YH, Dong JH, An WM, et al. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. *J Infect*. 2020;80(4):394-400.
13. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med*. 2020;382(10):970-971.
14. China Center for Disease Control and Prevention. Diagnosis and treatment of COVID-19 in China (seventh edition). In Chinese. Published March 5, 2020. Accessed March 13, 2020. http://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_11815/202003/t20200305_214142.html.
15. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed [June 17, 2020].
16. Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)*. 2020;133(9):1039-1043.
17. Ledford H. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. *Nature*. 2020; doi:10.1038/d41586-41020-01824-41585.
18. 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(10223):507-513.
19. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
20. 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):1061-1069.
21. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
22. Zheng KI, Wang XB, Jin XH, et al. A Case Series of Recurrent Viral RNA Positivity in Recovered COVID-19 Chinese Patients. *J Gen Intern Med*. 2020:1-2.
23. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
24. European Center for Disease Prevention and Control. Novel coronavirus (SARS-CoV-2) Technical Report. Discharge criteria for confirmed COVID-19 cases. <https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-Discharge-criteria.pdf>. [Accessed on June 17, 2020].
25. Hui DSC, Zumla A. Severe Acute Respiratory Syndrome: Historical, Epidemiologic, and Clinical Features. *Infect Dis Clin North Am*. 2019;33(4):869-889.
26. Joob B, Wiwanitkit V. Novel Middle East respiratory syndrome and renal failure. *Ren Fail*. 2014;36(1):147.
27. Li Z, Wu M, Guo J, et al. Caution on Kidney Dysfunctions of COVID-19 Patients. 2020. Available at SSRN: <https://ssrn.com/abstract=3559601> or <http://dx.doi.org/10.2139/ssrn.3559601>.
28. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients

- with COVID-19. *Kidney Int.* 2020;97(5):829-838.
29. Bo Diao ZF, Chenhui Wang, Huiming Wang, Liang Liu, Changsong Wang, Rongshuai Wang, Ying Liu, Yueping Liu, Gang Wang, Zilin Yuan, Yuzhang Wu, Yongwen Chen. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. *medRxiv.* 2020;2020.03.04.20031120; doi: 10.1101/2020.03.04.20031120.
 30. Caibin Fan KL, Yanhong Ding, Wei Lu Lu, Jianqing Wang. ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection. *medRxiv* 2020021220022418; doi: 101101/2020021220022418. 2020.
 31. Larsen CP, Bourne TD, Wilson JD, Saqqa O, Sharshir MA. Collapsing Glomerulopathy in a Patient With Coronavirus Disease 2019 (COVID-19). *Kidney Int Rep.* 2020 Apr 9;5(6):935-939. doi: 10.1016/j.ekir.2020.04.002.
 32. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int.* 2020 Apr 9;S0085-2538(20)30369-0. doi: 10.1016/j.kint.2020.04.003.
 33. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol.* 2020;16(6):308-310.
 34. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020;395(10234):1417-1418.
 35. Sun DQ, Wang TY, Zheng KI, et al. Subclinical Acute Kidney Injury in COVID-19 Patients: A Retrospective Cohort Study. *Nephron.* 2020:1-4.
 36. Yang XH, Sun RH, Chen DC. [Diagnosis and treatment of COVID-19: acute kidney injury cannot be ignored]. *Zhonghua yi xue za zhi.* 2020;100(0):E017.
 37. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med.* 2020 May 14;S2213-2600(20)30229-0.
 38. Fanelli V, Cantaluppi V, Alessandri F, et al. Extracorporeal CO(2) Removal May Improve Renal Function of Patients with Acute Respiratory Distress Syndrome and Acute Kidney Injury: An Open-Label, Interventional Clinical Trial. *Am J Respir Crit Care Med.* 2018;198(5):687-690.
 39. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020;17(5):259-260.
 40. 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. *Lancet.* 2020;395(10229):1054-1062.
 41. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest.* 2009;39(7):618-625.
 42. Yu CM, Wong RS, Wu EB, et al. Cardiovascular complications of severe acute respiratory syndrome. *Postgrad Med J.* 2006;82(964):140-144.
 43. 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. *Intensive Care Med.* 2020;46(5):846-848.
 44. Tan ZC, Fu LH, Wang DD, Hong K. [Cardiac manifestations of patients with COVID-19 pneumonia and related treatment recommendations]. *Zhonghua xin xue guan bing za zhi.* 2020;48(0):E005.
 45. Ammirati E, Cipriani M, Moro C, et al. Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis: Multicenter Lombardy Registry. *Circulation.*

- 2018;138(11):1088-1099.
46. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2020 Mar 16;ehaa190. doi: 10.1093/eurheartj/ehaa190.
 47. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020 Mar 27. doi: 10.1001/jamacardio.2020.1096.
 48. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63(3):364-374.
 49. Gao F, Zheng KI, Wang XB, et al. Obesity Is a Risk Factor for Greater COVID-19 Severity. *Diabetes Care*. 2020 May 14;dc200682.
 50. Huang JF, Wang XB, Zheng KI, et al. Letter to the Editor: Obesity hypoventilation syndrome and severe COVID-19. *Metabolism*. 2020;108:154249.
 51. Targher G, Mantovani A, Wang XB, et al. Patients with diabetes are at higher risk for severe illness from COVID-19. *Diabetes Metab*. 2020; May 13;S1262-3636(20)30075-6. doi: 10.1016/j.diabet.2020.05.001.
 52. Hu LL, Wang WJ, Zhu QJ, Yang L. [Novel coronavirus pneumonia related liver injury: etiological analysis and treatment strategy]. *Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese journal of hepatology*. 2020;28(0):E001.
 53. Feng G, Zheng KI, Yan QQ, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. *J Clin Transl Hepatol*. 2020;8(1):18-24.
 54. Gao F, Zheng KI, Wang XB, et al. Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in nondiabetic patients. *J Gastroenterol Hepatol*. 2020.
 55. Targher G, Mantovani A, Byrne CD, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut*. 2020; May 15;gutjnl-2020-321611. doi: 10.1136/gutjnl-2020-321611.
 56. Targher G, Mantovani A, Byrne CD, et al. Detrimental effects of metabolic dysfunction-associated fatty liver disease and increased neutrophil-to-lymphocyte ratio on severity of COVID-19. *Diabetes Metab*. 2020; Jun 4;S1262-3636(20)30088-4. doi: 10.1016/j.diabet.2020.06.001.
 57. Zheng KI, Gao F, Wang XB, et al. Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism*. 2020;108:154244.
 58. Zhou YJ, Zheng KI, Wang XB, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. *J Hepatol*. 2020;S0168-8278(20):30271-30273.
 59. Qi X, Liu Y, Wang J, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut*. 2020; May 20;gutjnl-2020-321666. doi: 10.1136/gutjnl-2020-321666.
 60. Gao F, Zheng KI, Gu JY, George J, Zheng MH. COVID-19 and liver transplantation: Lessons learned from three reported cases. *Transpl Infect Dis*. 2020:e13335.
 61. Huang JF, Zheng KI, George J, et al. Fatal outcome in a liver transplant recipient with COVID-19. *Am J Transplant*. 2020; doi:10.1111/ajt.15909.
 62. Fishman JA, Grossi PA. Novel Coronavirus-19 (COVID-19) in the immunocompromised transplant recipient: #Flatteningthecurve. *Am J Transplant*. 2020; doi:10.1111/ajt.15890.
 63. Liu B, Wang Y, Zhao Y, Shi H, Zeng F, Chen Z. Successful treatment of severe COVID-19

- pneumonia in a liver transplant recipient. *Am J Transplant*. 2020; doi:10.1111/ajt.15901.
64. Qin J, Wang H, Qin X, et al. Perioperative Presentation of COVID-19 Disease in a Liver Transplant Recipient. *Hepatology*. 2020; doi:10.1002/hep.31257.
 65. Gao QY, Chen YX, Fang JY. 2019 Novel coronavirus infection and gastrointestinal tract. *J Dig Dis*. 2020;21(3):125-126.
 66. Jin XH, Zheng KI, Pan KH, Xie YP, Zheng MH. COVID-19 in a patient with chronic lymphocytic leukaemia. *Lancet Haematol*. 2020;7(4):e351-e352.
 67. Jiang H, Liu L, Guo T, et al. Improving the safety of CAR-T cell therapy by controlling CRS-related coagulopathy. *Ann Hematol*. 2019;98(7):1721-1732.
 68. 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(4):844-847.
 69. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629.
 70. Mei H, Hu Y. [Characteristics, causes, diagnosis and treatment of coagulation dysfunction in patients with COVID-19]. *Zhonghua xue ye xue za zhi = Zhonghua xueyexue zazhi*. 2020;41(0):E002.
 71. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421-1424.
 72. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147.
 73. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A Report of Thromboelastography Findings and other Parameters of Hemostasis. *J Thromb Haemost*. 2020; Apr 17. doi: 10.1111/jth.14850.
 74. 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. *J Thromb Haemost*. 2020;18(5):1094-1099.
 75. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. *Ann Clin Microbiol Antimicrob*. 2020;19(1):18.
 76. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. *Chest*. 2020;S0012-3692(20):31625-31621. doi: 31610.31016/j.chest.32020.31605.31559.
 77. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420-422.
 78. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020 Apr 10;e201127.
 79. Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. *Neurology*. 2020; doi:10.1212/WNL.00000000000009673.
 80. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*. 2020;395(10227):912-920.
 81. Bai Y, Lin CC, Lin CY, Chen JY, Chue CM, Chou P. Survey of stress reactions among health care workers involved with the SARS outbreak. *Psychiatr Serv*. 2004;55(9):1055-1057.
 82. Liu X, Kakade M, Fuller CJ, et al. Depression after exposure to stressful events: lessons learned from the severe acute respiratory syndrome epidemic. *Compr Psychiatry*.

- 2012;53(1):15-23.
83. Sprang G, Silman M. Posttraumatic stress disorder in parents and youth after health-related disasters. *Disaster Med Public Health Prep.* 2013;7(1):105-110.
 84. Taylor MR, Agho KE, Stevens GJ, Raphael B. Factors influencing psychological distress during a disease epidemic: data from Australia's first outbreak of equine influenza. *BMC Public Health.* 2008;8:347.
 85. Wu P, Fang Y, Guan Z, et al. The psychological impact of the SARS epidemic on hospital employees in China: exposure, risk perception, and altruistic acceptance of risk. *Can J Psychiatry.* 2009;54(5):302-311.
 86. Marjanovic Z, Greenglass ER, Coffey S. The relevance of psychosocial variables and working conditions in predicting nurses' coping strategies during the SARS crisis: an online questionnaire survey. *Int J Nurs Stud.* 2007;44(6):991-998.
 87. Wu P, Liu X, Fang Y, et al. Alcohol abuse/dependence symptoms among hospital employees exposed to a SARS outbreak. *Alcohol Alcohol.* 2008;43(6):706-712.
 88. Jeong H, Yim HW, Song YJ, et al. Mental health status of people isolated due to Middle East Respiratory Syndrome. *Epidemiol Health.* 2016;38:e2016048.
 89. Reynolds DL, Garay JR, Deamond SL, Moran MK, Gold W, Styra R. Understanding, compliance and psychological impact of the SARS quarantine experience. *Epidemiol Infect.* 2008;136(7):997-1007.
 90. Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS control and psychological effects of quarantine, Toronto, Canada. *Emerg Infect Dis.* 2004;10(7):1206-1212.
 91. Cava MA, Fay KE, Beanlands HJ, McCay EA, Wignall R. The experience of quarantine for individuals affected by SARS in Toronto. *Public Health Nurs.* 2005;22(5):398-406.
 92. Desclaux A, Badji D, Ndione AG, Sow K. Accepted monitoring or endured quarantine? Ebola contacts' perceptions in Senegal. *Soc Sci Med.* 2017;178:38-45.
 93. Maunder R, Hunter J, Vincent L, et al. The immediate psychological and occupational impact of the 2003 SARS outbreak in a teaching hospital. *Cmaj.* 2003;168(10):1245-1251.
 94. Robertson E, Hershenfield K, Grace SL, Stewart DE. The psychosocial effects of being quarantined following exposure to SARS: a qualitative study of Toronto health care workers. *Can J Psychiatry.* 2004;49(6):403-407.
 95. Blendon RJ, Benson JM, DesRoches CM, Raleigh E, Taylor-Clark K. The public's response to severe acute respiratory syndrome in Toronto and the United States. *Clin Infect Dis.* 2004;38(7):925-931.
 96. Braunack-Mayer A, Toohar R, Collins JE, Street JM, Marshall H. Understanding the school community's response to school closures during the H1N1 2009 influenza pandemic. *BMC Public Health.* 2013;13:344.
 97. DiGiovanni C, Conley J, Chiu D, Zaborski J. Factors influencing compliance with quarantine in Toronto during the 2003 SARS outbreak. *Biosecur Bioterror.* 2004;2(4):265-272.
 98. Wilken JA, Pordell P, Goode B, et al. Knowledge, Attitudes, and Practices among Members of Households Actively Monitored or Quarantined to Prevent Transmission of Ebola Virus Disease - Margibi County, Liberia: February-March 2015. *Prehosp Disaster Med.* 2017;32(6):673-678.
 99. Caleo G, Duncombe J, Jephcott F, et al. The factors affecting household transmission

- dynamics and community compliance with Ebola control measures: a mixed-methods study in a rural village in Sierra Leone. *BMC Public Health*. 2018;18(1):248.
100. Pellecchia U, Crestani R, Decroo T, Van den Bergh R, Al-Kourdi Y. Social Consequences of Ebola Containment Measures in Liberia. *PLoS One*. 2015;10(12):e0143036.
 101. Mihashi M, Otsubo Y, Yinjuan X, Nagatomi K, Hoshiko M, Ishitake T. Predictive factors of psychological disorder development during recovery following SARS outbreak. *Health Psychol*. 2009;28(1):91-100.
 102. Zhou X. Psychological crisis interventions in Sichuan Province during the 2019 novel coronavirus outbreak. *Psychiatry research*. 2020;286:112895.
 103. Yao H, Chen JH, Xu YF. Patients with mental health disorders in the COVID-19 epidemic. *Lancet Psychiatry*. 2020;7(4):e21.
 104. Park SC, Park YC. Mental Health Care Measures in Response to the 2019 Novel Coronavirus Outbreak in Korea. *Psychiatry investigation*. 2020;17(2):85-86.
 105. Holmes EA, O'Connor RC, Perry VH, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry*. 2020;7(6):547-560.
 106. Creanga AA, Johnson TF, Graitcer SB, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. *Obstet Gynecol*. 2010;115(4):717-726.
 107. Olgun NS. Viral Infections in Pregnancy: A Focus on Ebola Virus. *Curr Pharm Des*. 2018;24(9):993-998.
 108. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol*. 2004;191(1):292-297.
 109. Alfaraj SH, Al-Tawfiq JA, Alzahrani NA, Altwajiri TA, Memish ZA. The impact of co-infection of influenza A virus on the severity of Middle East Respiratory Syndrome Coronavirus. *J Infect*. 2017;74(5):521-523.
 110. Wong SF, Chow KM, de Swiet M. Severe Acute Respiratory Syndrome and pregnancy. *Bjog*. 2003;110(7):641-642.
 111. Wang X, Zhou Z, Zhang J, Zhu F, Tang Y, Shen X. A case of 2019 Novel Coronavirus in a pregnant woman with preterm delivery. *Clin Infect Dis*. 2020; doi:10.1093/cid/ciaa1200.
 112. Xu J, Qi L, Chi X, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). *Biol Reprod*. 2006;74(2):410-416.
 113. Qi X, Liu Y, Wang J, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut*. 2020. doi:10.1136/gutjnl-2020-321666.

Table 1. Common extra-hepatic complications of COVID-19.

Study	Study design, sample size	Acute kidney injury	Myocardial injury	Cardiac arrhythmias	Liver dysfunction	Septic shock	Coagulopathy	Fatality
Bo et al. ²⁹	Retrospective study of 91 patients	23 patients (defined as a decline of eGFR by at least 30% of the baseline value on admission or below 90 mL/min on admission)	n/a	n/a	n/a	n/a	n/a	6 (6.6%) patients
Chen et al. ¹⁸	Retrospective study of 99 Chinese patients	7 patients had varied degrees of kidney damage, 3 confirmed acute kidney injury (defined by KDIGO criteria)	75 patients had elevated lactate dehydrogenase, 13 had elevated creatinine kinase	n/a	43 patients had (as defined by increased serum ALT and AST levels)	4 patients (as defined by WHO interim guidance)	n/a	11 (11.1%) patients
Cheng et al. ²⁸	Prospective study of 701 Chinese patients	36 (5.1%) patients with acute kidney injury: 13 (stage I) 9 (stage II) 14 (stage III) Diagnosed and staged according to the KDIGO criteria	n/a	n/a	n/a	n/a	n/a	113 (16.1%) patients
Guan	Retrospective	6 patients	n/a	n/a	n/a	12 patients,	1 patient with	15 (1.3%)

et al. ²¹	multi-centered (552 hospitals) study of 1099 Chinese patients	(defined by increase in serum creatinine levels by 0.3 mg/dl or greater (26.5 µmol/l or greater) within 48 hours; or increase in serum creatinine levels to 1.5 times of the baseline level or greater; or urine volume of below 0.5 ml/kg/h for 6 consecutive hours)				(as defined by WHO interim guidance)	disseminated intravascular coagulation (as defined by WHO interim guidance)	patients
Huang et al. ¹⁹	Retrospective study of 41 Chinese patients (13 patients in ICU vs 28 non-ICU)	3 patients (defined by KDIGO criteria)	5 patients (defined as increase in serum levels of troponin I above the 99th percentile of upper reference limit, or new abnormalities were shown in electrocardiography and echocardiography)	n/a	n/a	3 patients, (as defined by WHO interim guidance)	n/a	6 (14.6%) patients
Klok	Retrospective	n/a	n/a	n/a	n/a	n/a	25 patients with	23 (12.5%)

et al. ⁷²	study of 184 Dutch (Caucasian) patients						pulmonary embolism; 3 ischemic strokes; 1 deep vein thrombosis of the leg; 2 catheter related thrombosis	patients
Zhen et al. ²⁷	Retrospective multi-centered study of 193 Chinese patients	55 patients (defined as any of the following: (1) increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 hours; or (2) increase in serum creatinine to ≥ 1.5 times of baseline, which is known or presumed to have occurred within the prior 7 days; or (3) urine volume < 0.5 ml/kg/hour for 6 hours)	24 patients (diagnosis undefined)	n/a	n/a	35 patients (as defined by WHO interim guidance)	n/a	32 (16.6%) patients
Ruan et al. ⁴³	Retrospective multi-centered	No	49 patients (defined by increase in serum	n/a	n/a	n/a	n/a	68 (45.3%) patients

	of 150 Chinese patients		level of cardiac troponin, myoglobin, C-reactive protein, and interleukin-6)					
Sun et al. ³⁵	Retrospective study of 32 patients	32 patients (defined by KDIGO criteria)	n/a	n/a	n/a	n/a	n/a	0 patient
Wang et al. ²⁰	Retrospective, study of 138 patients (36 ICU patients vs 102 non-ICU patients)	10 patients (defined by KDIGO criteria)	10 patients (defined by increased serum troponin I were above the 99th percentile upper reference limit or abnormalities indicated on electrocardiography or echocardiography)	n/a	n/a	12 (diagnosis undefined)	n/a	6 (4.3%) patients
Yang et al. ²³	Retrospective study of 52 critically ill patients	15 patients (as defined by increased serum creatinine and eGFR)	12 patients (defined by increased serum concentration of hypersensitive cardiac troponin I above the upper limit	n/a	15 patients (defined by increased serum ALT and AST levels)	n/a	n/a	32 (61.5%) patients

			of the reference range or >28 pg/mL)					
Zhou et al. ⁴⁰	Retrospective multi-centered study of 191 patients	28 patients, (defined by KDIGO criteria)		44 patients with heart failure		38 patients (according to 2016 Third International Consensus Definition for Sepsis and Septic Shock)	37 patients (defined as a 3-second extension of prothrombin time or a 5-second extension of activated partial thromboplastin time)	54 (28.2%) patients
Qi et al. ¹¹³	Retrospective multi-centered of 21 patients	1 patient			1 patient with acute-on-chronic liver failure, 5 patients with ascites	3 patients		15 patients

Abbreviations: KDIGO, Kidney Disease: Improving Global Outcomes; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WHO, world health organization.

FIGURE LEGEND

Figure 1. Schematic figure showing the potential complications of COVID-19 affecting organ systems.