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***Title***

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

***Running Title***

Extra-pulmonary complications and COVID-19

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## 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

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pandemic and public health problem in almost all countries.<sup>1-3</sup> 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.<sup>4</sup> 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.<sup>5</sup> The ACE2 receptor is highly expressed in lungs, kidneys, gastrointestinal tract, liver, vascular endothelial cells and arterial smooth muscle cells.<sup>6</sup> Thus, all of these organs and systems with high expression of ACE2 receptors might be speculated targets for SARS-CoV-2 infection.<sup>7</sup>

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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.<sup>8,9</sup> 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).<sup>10-12</sup> 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.<sup>13</sup> 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

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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.<sup>14,15</sup> Initially, corticosteroids were not recommended for routine use as their usage may be associated to delayed viral clearance.<sup>16</sup> 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.<sup>17</sup> (For the latest updated treatment and management of severe COVID-19 see<sup>15</sup>). The incidence of acute respiratory distress syndrome (ARDS) in COVID-19 patients is reported to be 15% ~ 30%.<sup>18-20</sup> 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;<sup>21,22</sup> the median duration from ICU admission to death for non-survivors is approximately 7 days.<sup>23</sup> 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 see<sup>24</sup>).

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## 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.<sup>18-20,23</sup> 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.<sup>25,26</sup> 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.<sup>27</sup>

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%.<sup>20,21,28</sup> 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.<sup>21</sup> 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.<sup>20</sup> 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.<sup>28</sup> In a case series of 85 patients with severe SARS-CoV-2 infection, AKI occurred in 23 (27.1%) patients.<sup>29</sup> 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.<sup>24</sup> 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.<sup>30-32</sup> 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.<sup>33</sup> Other autopsy investigations have reported that the endothelium is affected in the kidneys, and is responsible for the proteinuria.<sup>34</sup> SARS-CoV-2 particles in renal endothelial cells may suggest viremia

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as a possible cause of renal endothelial damage resulting in AKI.<sup>29</sup> More recently, Sun et al. have reported the occurrence of subclinical AKI as reflected by increased urinary levels of  $\beta$ 2-microglobulin,  $\alpha$ 1-microglobulin, N-acetyl- $\beta$ -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.<sup>35</sup> In addition, the severity of kidney tubular damage was also greater in severe COVID-19 patients than in less severely affected patients.<sup>30</sup> 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.

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Collectively, therefore, it is recommended that physicians who treat COVID-19 patients should pay special attention to acute changes in patients' kidney function.<sup>36,37</sup> 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.<sup>38</sup> 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.<sup>11</sup> 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).<sup>23</sup> 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.<sup>39</sup> 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.<sup>40</sup> 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,<sup>41</sup> 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.<sup>39,40</sup> 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

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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.<sup>42</sup> 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.<sup>20</sup> 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.<sup>19,43</sup> However, due to the retrospective nature of these

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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.<sup>44</sup>

#### *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.<sup>20</sup> 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

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myocarditis had normal cardiac function.<sup>45-48</sup> 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.<sup>42,49-51</sup>

### **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.<sup>19</sup> Similar results were also confirmed by Wang et al. in a study of

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138 critically ill COVID-19 patients without pre-existing chronic liver diseases, who were admitted to ICU.<sup>20</sup> 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.<sup>21</sup> 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.<sup>52</sup> 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.<sup>23</sup>

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.<sup>53</sup> Several studies showed that in patients with chronic liver diseases,<sup>54-59</sup> especially in those with preexisting cirrhosis,<sup>60,61</sup> there is an increased risk of greater COVID-19 illness and in-hospital mortality, which

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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.<sup>62-64</sup> 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.<sup>63</sup> 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.<sup>65</sup> 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.<sup>66</sup> With limited

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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.<sup>21</sup> However, among SARS-CoV-2 infected patients who had developed atypical clinical presentations, a substantial portion of these patients had GI symptoms.<sup>67</sup> 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

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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.<sup>8</sup>

## **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.<sup>18,20,21</sup> 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.<sup>68</sup> 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.<sup>20</sup>

### *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

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cytokine release syndrome caused by an acute immune response.<sup>18,69-71</sup> 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%).<sup>20</sup> 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.<sup>21</sup> 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.<sup>19</sup> 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%.<sup>70</sup> 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.

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Therefore, special attention should be paid to early diagnosis and treatment of these acute hematological conditions in order to improve patient survival.<sup>72</sup>

### *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.<sup>70,71,73-76</sup> 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.<sup>75,77</sup> VTE occurs approximately in 25% of severe COVID-19 patients, while thrombotic complications occur in 31% of those requiring ICU.<sup>73,74</sup> 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%).<sup>73</sup> 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  $\geq 4$  (40.0% vs. 64.2%,  $p = 0.029$ ).<sup>76</sup> As

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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.<sup>78</sup> 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,<sup>15</sup> 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.<sup>78</sup>

#### *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

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“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.<sup>79</sup> 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

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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.<sup>80</sup> Patients with severe COVID-19 were more likely to develop neurologic symptoms, such as acute cerebrovascular disease, impaired consciousness and skeletal muscle injury.<sup>80,81</sup>

### **COVID-19: psychological disorders**

The adverse psychological effects (post-traumatic stress, confusion and anger) of quarantine during infectious outbreak have been well documented.<sup>82-87</sup> Three years after the SARS epidemic in 2003, two studies have reported alcohol abuse or dependency symptoms, as long-term effects in quarantined healthcare workers.<sup>88,89</sup> 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

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quarantine.<sup>90</sup> Interestingly, healthcare workers reported more severe symptoms of post-traumatic stress when compared to controls (non-healthcare workers) after being quarantined.<sup>91</sup> 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,<sup>92</sup> it is generally accepted that longer duration of quarantine is more likely to induce poorer psychological outcomes and mental health conditions.<sup>88,91,92</sup> Other factors attributable to adverse psychological effects include fear of infection (directed at self-condition or transmitting to others),<sup>83,90-96</sup> adverse reactions to confinement or isolation,<sup>91-94,96-100</sup> lack of sufficient information from authorities (regarding to wellbeing and duration of quarantine),<sup>93,96,98,99,101,102</sup> and fear of financial loss.<sup>86,90,94,102,103</sup>

### *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.<sup>104</sup> For normal individuals, the

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outbreak of COVID-19 has been reported to cause anxiety and fear.<sup>105,106</sup> Because the negative effects of infectious outbreak and quarantine are numerous, substantial and can be often felt months and sometimes years later,<sup>84,90</sup> 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.<sup>107</sup>

### **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

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to non-pregnant women, possibly due to concomitant changes in the immune response.<sup>108-111</sup> According to a previous report of 10 pregnant SARS-infected patients in Hong Kong,<sup>112</sup> it has been proposed that the COVID-19 may be associated with poorer perinatal outcomes, including spontaneous abortion, maternal death, and preterm birth.<sup>113</sup>

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.<sup>114</sup> 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

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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.

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**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. <sup>29</sup> | Retrospective study of 91 patients | 23 patients (defined as a decline of eGFR by at least 30% of the baseline value on admission) | n/a               | n/a                 | n/a               | n/a          | n/a          | 6 (6.6%) patients |

|                            |                                            | on or below 90 mL/min on admission)                                                                         |                                                                                   |     |                                                                    |                                                 |     |                      |
|----------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----|--------------------------------------------------------------------|-------------------------------------------------|-----|----------------------|
| Chen et al. <sup>18</sup>  | 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. <sup>28</sup> | Prospective study of 701 Chinese patients  | 36 (5.1%) patients with acute kidney injury: 13                                                             | n/a                                                                               | n/a | n/a                                                                | n/a                                             | n/a | 113 (16.1%) patients |

|                           |                                                                             | (stage I)<br>9<br>(stage II)<br>14<br>(stage III)<br><br>Diagnosed and staged according to the KDIGO criteria |     |     |     |                                                   |                                                                                            |                    |
|---------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----|-----|-----|---------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------|
| Guan et al. <sup>21</sup> | Retrospective multi-centered (552 hospitals) study of 1099 Chinese patients | 6 patients (defined by increase in serum creatinine levels by 0.3 mg/dl or greater (26.5                      | n/a | n/a | n/a | 12 patients, (as defined by WHO interim guidance) | 1 patient with disseminated intravascular coagulation (as defined by WHO interim guidance) | 15 (1.3%) patients |

|                                      |                                                |                                                                                                                                                                                                                                                                                                           |                                                              |     |     |                                      |     |                           |
|--------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-----|-----|--------------------------------------|-----|---------------------------|
|                                      |                                                | $\mu\text{mol/l}$<br>or<br>greater)<br>within<br>48<br>hours;<br>or<br><br>increas<br>e in<br>serum<br>creatini<br>ne<br>levels<br>to 1.5<br>times<br>of the<br>baselin<br>e level<br>or<br>greater;<br><br>or<br>urine<br>volume<br>of<br>below<br>0.5<br>ml/kg/<br>h for 6<br>consec<br>utive<br>hours) |                                                              |     |     |                                      |     |                           |
| Hua<br>ng<br>et<br>al. <sup>19</sup> | Retrospe<br>ctive<br>study of<br>41<br>Chinese | 3<br>patient<br>s<br>(define<br>d by                                                                                                                                                                                                                                                                      | 5 patients<br><br>(defined as<br>increase in<br>serum levels | n/a | n/a | 3<br>patients,<br><br>(as<br>defined | n/a | 6<br>(14.6<br>%)<br>patie |

|                            | patients (13 patients in ICU vs 28 non-ICU)           | KDIG O criteria ) | of troponin I above the 99th percentile of upper reference limit, or new abnormalities were shown in electrocardiography and echocardiography) |     |     | by WHO interim guidance)       |                                                                                                                           | nts                 |
|----------------------------|-------------------------------------------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|--------------------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------|
| Klokk et al. <sup>74</sup> | Retrospective study of 184 Dutch (Caucasian) patients | n/a               | n/a                                                                                                                                            | n/a | n/a | n/a                            | 25 patients with pulmonary embolism; 3 ischemic strokes; 1 deep vein thrombosis of the leg; 2 catheter related thrombosis | 23 (12.5%) patients |
| Zhen et al. <sup>27</sup>  | Retrospective multi-centered study of 193             | 55 patients (     | 24 patients (diagnosis undefined)                                                                                                              | n/a | n/a | 35 patients (as defined by WHO | n/a                                                                                                                       | 32 (16.6%) patients |

|  |                  |                                                                                                                                                                                                                                                                              |  |  |  |                   |  |  |
|--|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|-------------------|--|--|
|  | Chinese patients | defined as any of the following: (1) increase in serum creatinine by $\geq 0.3$ mg/dl ( $\geq 26.5$ $\mu\text{mol/l}$ ) within 48 hours; or (2) increase in serum creatinine to $\geq 1.5$ times of baseline, which is known or presumed to have occurred within the prior 7 |  |  |  | interim guidance) |  |  |
|--|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|-------------------|--|--|

|                           |                                                      |                                                                                  |                                                                                                                        |     |     |                       |     |                     |
|---------------------------|------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----|-----|-----------------------|-----|---------------------|
|                           |                                                      | days;<br>or (3)<br>urine<br>volume<br>< 0.5<br>ml/kg/<br>hour<br>for 6<br>hours) |                                                                                                                        |     |     |                       |     |                     |
| Ruan et al. <sup>43</sup> | Retrospective multi-centered of 150 Chinese patients | No                                                                               | 49 patients (defined by increase in serum level of cardiac troponin, myoglobin, C-reactive protein, and interleukin-6) | n/a | n/a | n/a                   | n/a | 68 (45.3%) patients |
| Sun et al. <sup>35</sup>  | 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. <sup>20</sup> | Retrospective, study of 138 patients                 | 10 patients (define                                                              | 10 patients (defined by increased serum                                                                                | n/a | n/a | 12 (diagnosis undefin | n/a | 6 (4.3%) patients   |

|                           |                                                   |                                                                 |                                                                                                                                                       |                                |                                                             |                                      |                                              |                     |
|---------------------------|---------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------|--------------------------------------|----------------------------------------------|---------------------|
|                           | (36 ICU patients vs 102 non-ICU patients)         | d by KDIGO criteria )                                           | troponin I were above the 99th percentile upper reference limit or abnormalities indicated on electrocardiography or echocardiography)                |                                |                                                             | ed)                                  |                                              | nts                 |
| Yang et al. <sup>23</sup> | 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 of the reference range or >28 pg/mL) | n/a                            | 15 patients (defined by increased serum ALT and AST levels) | n/a                                  | n/a                                          | 32 (61.5%) patients |
| Zhou et al. <sup>40</sup> | Retrospective multi-centered study of 191         | 28 patients, (defined by KDIGO                                  |                                                                                                                                                       | 44 patients with heart failure |                                                             | 38 patients (according to 2016 Third | 37 patients (defined as a 3-second extension | 54 (28.2%) patients |

|                               | patients                                                     | O<br>criteria<br>) |  |  |                                                                                                 | Internat<br>ional<br>Consen<br>sus<br>Definiti<br>on for<br>Sepsis<br>and<br>Septic<br>Shock) | of pro<br>thrombin<br>time or a<br>5-second<br>extension<br>of<br>activated<br>partial<br>thrombop<br>lastin<br>time) |                    |
|-------------------------------|--------------------------------------------------------------|--------------------|--|--|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------|
| Qi<br>et<br>al. <sup>61</sup> | Retrospe<br>ctive<br>multi-cen<br>tered of<br>21<br>patients | 1<br>patient       |  |  | 1 patient<br>with<br>acute-on-c<br>hronic<br>liver<br>failure, 5<br>patients<br>with<br>ascites | 3<br>patients                                                                                 |                                                                                                                       | 15<br>patie<br>nts |

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.

