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

Science of the Total Environment 729 (2020) 139021

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Follow-up studies in COVID-19 recovered patients - is it mandatory?

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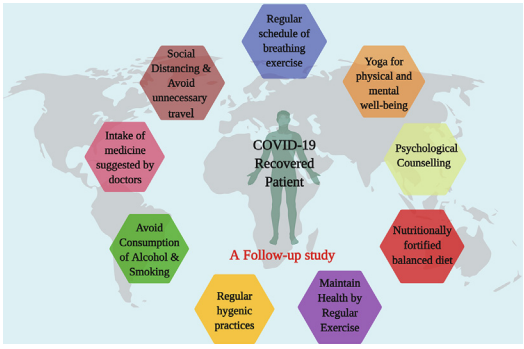
HIGHLIGHTS

- Conduct the longitudinal study to assess the health status of the COVID-19 recovered patient
- COVID-19 may have a possible influence to cause multiorgan damage.
- Follow-up survey of COVID-19 recovered patients will be helpful to evaluate any changes in the other organs in human systems.
- Follow-up study will be useful to design a possible vaccine for this dreadful infection.
- Recommendation for COVID-19 recovered patients

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 15 April 2020
Received in revised form 24 April 2020
Accepted 25 April 2020
Available online xxxx

Editor: Jianmin Chen

ABSTRACT

The novel Coronavirus disease 2019 (COVID-19) is an illness caused due to Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) has declared this outbreak a global health emergency and as on April 24, 2020, it has spread to 213 countries, with 25,91,015 confirmed cases and 742,855 cases have been recovered from COVID-19. In this dreadful situation our team has already published an article in the Science of the Total Environment, which elaborates the various aspects of the SARS-CoV-2 infection. In this situation, it is imperative to understand the possible outcome of COVID-19 recovered patients and determine if they have any other detrimental illnesses by longitudinal analysis to safeguard their life in future. It is necessary

Abbreviations: AKI, Acute kidney injury; ARDS, Acute respiratory distress syndrome; ALT, Alanine aminotransferase; ACE2, Angiotensin-Converting Enzyme 2; AST, Aspartate aminotransferase; CNS, Central Nervous System; CXCL10, Chemokine (C-X-C motif) ligand 10; CXCL9, Chemokine (C-X-C motif) ligand 9; COPD, Chronic obstructive pulmonary disease; CT, Computed tomography; GI, Gastrointestinal tract; Hb, Hemoglobin; IL-12p40, Interleukine-12p40; IL-15, Interleukine-15; IL-6, Interleukine-6; MRI, Magnetic resonance imaging; MERS, Middle East respiratory syndrome; COVID-19, Novel Coronavirus disease 2019; NLRP3, Nucleotide-binding domain (NOD)-like receptor protein 3; SARS, Severe acute respiratory syndrome; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; TMPRSSs, Transmembrane protease, serine 2; TNF-α, Tumour necrosis factor-alpha; UPSIT, University of Pennsylvania Smell Identification Test; WBC, White Blood Cells; WHO, World Health Organization.

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https://doi.org/10.1016/j.scitotenv.2020.139021

Keywords:
COVID-19
SARS-CoV-2
Epidemiological study
Health assessment
Recovered patients
Follow-up studies

to follow-up these recovered patients and performs comprehensive assessments for detection and appropriate management towards their psychological, physical, and social realm. This urges us to suggest that it is highly important to provide counselling, moral support as well as a few recommended guidelines to the recovered patients and society to restore to normalcy. Epidemiological, clinical and immunological studies from COVID-19 recovered patients are particularly important to understand the disease and to prepare better for potential outbreaks in the future. Longitudinal studies on a larger cohort would help us to understand the in-depth prognosis as well as the pathogenesis of COVID-19. Also, follow-up studies will help us provide more information for the development of vaccines and drugs for these kinds of pandemics in the future. Hence, we recommend more studies are required to unravel the possible mechanism of COVID-19 infection and the after-effects of it to understand the characteristics of the virus and to develop the necessary precautionary measures to prevent it.

Contents

1. Introduction

The novel coronavirus 2019 (COVID-19), the unexpected pandemic, has caused severe panic among people worldwide. Many coronaviruses are zoonotic, spreading the disease from animals to humans (Mohammadi et al., 2020). It is a severe illness that has a high attack rate and case fatality rate around the globe. To combat this dramatic situation of COVID-19, our team has provided the importance of Indian traditional medicine as therapeutic approach for COVID-19 (Balachandar et al., 2020a). Previously, after the Severe acute respiratory syndrome (SARS) outbreak, there was an important question that needed to be answered: will patients recovering from SARS have any re-infection chances? Since the SARS (2002−2003) outbreak, no vaccine has been developed so far, but plenty of people have recovered from this infection, and several follow-up studies have been conducted to check their health status (Tang et al., 2011). According to a previous report, it is possible that ongoing active alveolitis during the host immune system response to the SARS-CoV antigen might lead to pulmonary fibrosis in some patients after recovery (Hui et al., 2005). Das et al. (2015) analysed 55 patients who recovered from Middle East respiratory syndrome (MERS) and found that after 1-year, lesions were present in the periphery of the lungs. Even with such a huge mortality rate, there is hope that the COVID-19 patients will recover from this deadly situation. Hospitals and doctors may find it impossible to offer follow-up checks and investigate reinfection and it will be highly beneficial for hospitals and patients if this can be outsourced. At this situation, researchers should overtake their responsibility for regular follow-up survey of COVID-19 recovered patients in the convalescent phase which would be helpful to evaluate any changes in the acquired immune function, blood parameters, psychological factors, biochemical factors, lung, brain, eye, kidney, heart and gastrointestinal (GI) tract functions over the course of time. The drug chloroquine repurposed from a malarial drug has been utilized for COVID-19 and Hydroxychloroquine reduces the pH levels and can interfere with viral replication (Chen et al., 2020).

Reports have suggested that the SARS-CoV-2 mainly affects the people who have had any previous medical conditions related to lungs, kidney, heart and the GI tract (Meredith et al., 2020). In the lungs, the virus-mediated cytokine activation in the alveolar macrophages results in lung fibrosis and damage. In the kidney, activated Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) signalling can cause pyroptosis and cell death. In the heart, this viral infection can rupture the necrotic lipid core forming blood clots resulting in myocardial infarction. In the brain, the olfactory bulb gets infected by SARS-CoV-2, which leads to the inability of smell and might also trigger neurodegenerative diseases in the COVID-19 recovered patients. In the eyes, the tears act as the route of transmission to other organs of the human system through the nasolacrimal system (Qing et al., 2020). Also, the COVID-19 recovered patients may have psychological stress due to their infection and may be ambiguous about their acceptance in society post infection. Hence, it is essential to conduct the follow-up studies in COVID-19 recovered patients to determine if they have any other detrimental illnesses.

According to World Health Organization (WHO), the mortality rate of COVID-19 patients is 3 to 5%, and the remaining affected patients will mostly recover. The Government officials in all countries continue to make efforts to minimize human contact by facilitating countrywide shutdowns of public places as well as various steps have been initiated to ensure the safety of the people, like social distancing and self-quarantine which limits our social interactions. The avoidance of

COVID-19 recovered patients may be due to the fear of contracting the virus. To overcome this situation, an epidemiological survey focusing on the health status of the COVID-19 recovered patients should be carried out by the scientists and researchers for the betterment of society. By knowing the possible complications of its after-effect from the recovered patients will be helpful to ascertain the future disease complications and will provide more information for the development of vaccines and drugs for these kinds of pandemics in the future. More research is required on the diagnostic and therapeutic approaches to develop vaccines and drugs (Mahalaxmi et al., 2020). Hence this review emphasizes to focus the research on various multi-organ damages which could occur due to SARS-CoV-2 infection. Further, we suggest the possible complications faced by the COVID-19 recovered patients and suggestion on dealing with the aftermath by providing counselling and follow-up studies that would be beneficial for them as well as the society.

2. Current Scenario of COVID-19 and recovered patients

In mid-April 2020, when this article was written, the WHO had proclaimed that around 1,914,916 are infected with the disease, totally 123,010 deaths had occurred, and almost 501,758 people have recovered, and the prime minister of India has declared a national lockdown that might extend further to contain the spread of the infection. This shows that the healthcare professional and Government officials have been doing their job efficiently (Balachandar et al., 2020b). Now, we the researchers have to step up and find measures to safeguard the life of affected as well as COVID-19 recovered patients. Though the patients are recovered from the infection, some of the aftereffects of it may have a significant impact on recovered patients in their future. Researchers have asserted that half of the COVID-19 patients who had recovered from the mild symptomatic infection, could still carry the SARS-CoV-2 within their system which could make it even more difficult to control the spread of the diseases. As an alternative the scientists have suggested that carrying out a regular follow-up study and consecutive nucleic acid tests would be beneficial to constrain the infection spread as well as provide peace of mind to the recovered patients (WHO, 2020). It has been observed that the COVID-19 patients might be infectious even after initial recovery, so it is mandatory to monitor the recently recovered patients as prudently as symptomatic patients. In this current scenario, it is necessary to conduct the epidemiological and immunological based studies from COVID-19 recovered patients to monitor their health status for any possible future complications (Kaavya et al., 2020; Venugopal et al., 2020; Mohan Devi et al., 2020). Observational investigation on a larger cohort would help us to understand the in-depth prognosis as well as the pathogenesis of the COVID-19 disease. These kinds of studies would help uncover if COVID-19 recovered patients needed post-acute care to recuperate from any further infections or multi-organ damage. The SARS-CoV-2 mainly affects older, immune deficient people and who had any previous medical conditions (issues related to lungs, kidney, heart and GI tract). Hence, it is imperative to understand the possible outcome of the COVID-19 recovered patients, and if they will develop any other harmful illnesses.

3. Manifestations of SARS-CoV-2 in the multi-organ system

With the global count of infection continuing to rise, it is important to stay vigilant at the wake of the virus. Follow-up examinations of infected individuals can help medical practitioners stay informed of what's to come next. This will help in alerting ourselves as we progress on to the next step of the pandemic. A significant proportion of patients who survive from COVID-19 may have the possibility to get impairment in their overall health status after their recovery. COVID-19 patients may exhibit infections in the GI tract, kidney, heart, brain, eyes and lungs (Fig. 1). Although the multiorgan damage has been established in the condition, the long-term relevance of it remains perplexing. It is too ahead off to comment on the various frailties that the COVID-19 recovered patients, where more studies are needed. Severe pneumonia which could inflame the air sacs in the lungs might also result in the acute respiratory distress syndrome (ARDS). If after a given period of time, there is a sudden surge of associated illness, this will, in turn, overwhelm the medical system. Hence, monitoring individuals on a regular basis can result in many benefits that may be unforeseen even now. This will help ascertain diseases at earlier stages allowing medical intervention at this time. Early medical intervention will help to prevent the conditions altogether or at least ameliorate its prognosis. Here, we discuss the possible organ damage that is associated with COVID-19 and the long-term issues that may stem from them.

3.1. SARS-CoV-2 and its influence in central nervous system

The central nervous system (CNS), is the central processing unit of the human system, which can maintain life and homeostasis. The SARS-CoV-2 can enter the CNS via the nasal route and could reach the olfactory bulb region of the brain to trigger any form of infection (Mathew, 2020). Supporting this, Ling et al. (2020) have also reported that COVID-19 patients do manifest neurological symptoms such as hyposmia, hypogeusia, hypopsia, and headaches. Unfortunately, if there is any acute, tenacious or dormant form of viral infection inside the CNS, its immune system does not react subsequently, which results in neurological disorders. At this point, the brain damage has yet to be demonstrated as a crucial outcome of the COVID-19 infection. In a recent case report from the USA, a 50-year old woman was diagnosed with COVID-19 infection, which also manifested severe neurological symptoms such as acute necrotizing encephalopathy. The neurological report of a woman was confirmed by Computed tomography (CT) scan where the doctors found that there is a blood-brain barrier vessel leakage in the thalamus which could occur due to viral infection (Poyiadji et al., 2020). Another report of a 74-year-old man, who was positive for COVID-19, and had a previous medical history of Parkinson's disease and chronic lung disease also displayed neurological symptoms such as inability to speak and seizures (Filatov et al., 2020). There are theories which suggest that viral infections can trigger a cytokine storm in the brain when the immune system of the host cell overreacts to the virus. This cytokine storm could release various pro-inflammatory cytokines such as Interleukine-6 (IL-6), Interleukine-12p40 (IL-12p40), Interleukine-15 (IL-15), tumour necrosis factor-alpha (TNF-α), chemokine (C-X-C motif) ligand 9 (CXCL9) and chemokine (C-X-C motif) ligand 10 (CXCL10), which can induce demyelination or cell deaths in the nervous system (Puja et al., 2020). SARS-CoV-2 is an acute respiratory infection which may have neurotropic capacities which allow the virus to gain dormancy and inhibits immunological reactions in the host cell. Hence, more studies are required to unravel the possible link between COVID-19 and neurological conditions to understand the neuroinvasion properties of the virus and to develop precautionary measures to prevent it.

3.2. SARS-CoV-2 and Ocular infection

The eyes might have a potent role in the spread of the COVID-19 infection. The eye could also aid as a favourable site for viral replication and routes to the extraocular sites to establish respiratory infection. A recent report suggests that the virus initially enervates the conjunctiva present in the eye, which in turn helps in the spread of the infection to other organs in the human system (Sommer, 2020). The angiotensin-converting enzyme 2 (ACE2) enacts as the functional receptor for the binding of the SARS-CoV-2 to the host cell. The ACE2 is prominently present in retinal pigment epithelial cells of the retina in the eye; hence the lacrimal system could also perform as the route of transmission of the virus inside the human system. Qing et al. (2020) has stated that tears which get renewed in the lacrimal system could

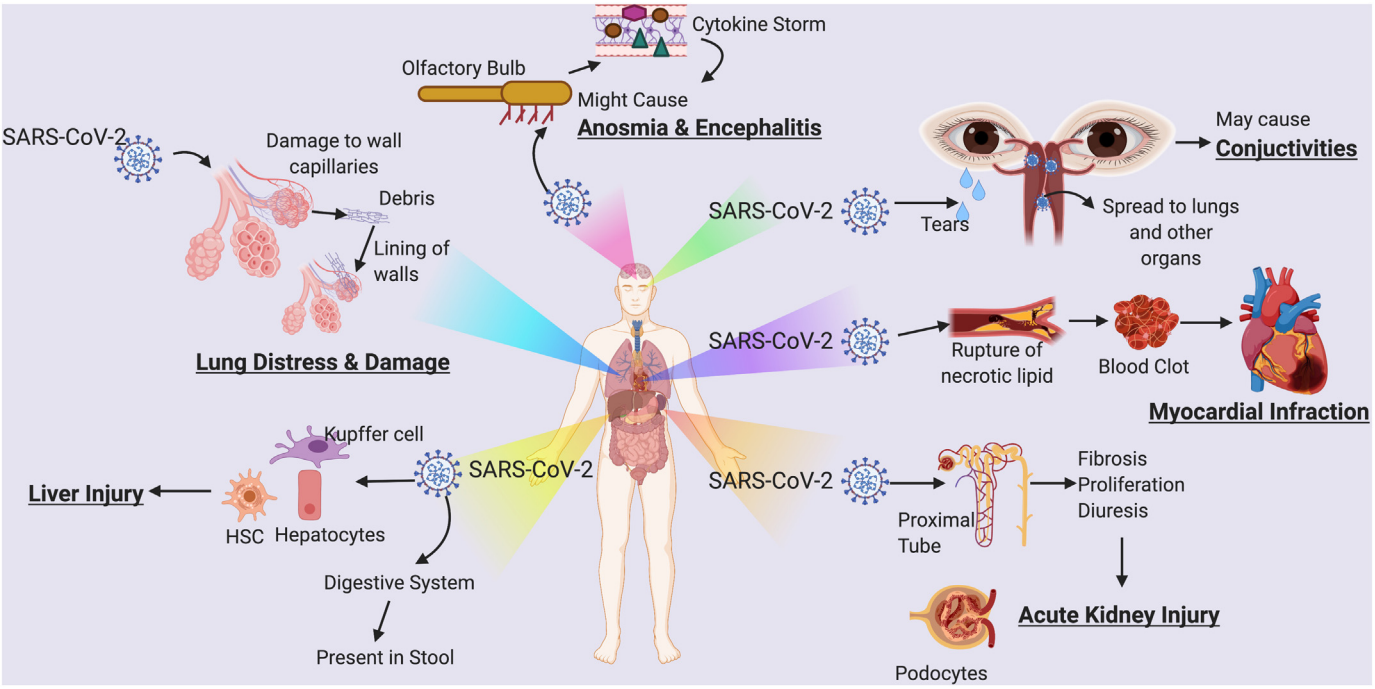

Fig. 1. Effect of SARS-CoV-2 infection on organs in different parts of the body. (Clockwise) Virus enters through the olfactory bulb causing an inflammatory response leading to a cytokine storm. This may cause anosmia and encephalitis. Upon entry into the eyes, the virus can spread through tear and mediate spreading via nasolacrimal system to other organs of the body and may cause conjunctivitis in the eyes. Entry of virus into the heart through the blood, can cause the formation of a necrotic lipid. When the lipid ruptures it can cause blood clots leading to myocardial infraction. In the kidney, the virus enters the proximal tubules and podocytes via the ACE2 receptors. After entry, it causes deposition of extracellular matrix causing fibrosis, diuresis and proliferation of kidney cells leading to acute kidney injury. In the liver, the virus activates kupffer cells mediating an inflammatory response. This causes activation of the hepatic skellate cells and hepatocytes resulting in pyroptosis and fibrosis derived injury. In the lungs, the virus causes damage to the walls of the alveolar cells, this results in the formation of debris. The debris accumulated in the walls of the alveolar cells causing thickening and results in lung distress and damage. This causes shortness of breath the commonly displayed symptom in COVID-19 (This figure was created by Biorender).

carry the viral droplets and might pass via a nasolacrimal duct to the respiratory tract. The patients who have acquired the SARS-CoV-2 infection might also have ocular related symptoms including conjunctivitis, chemosis, swelling of the conjunctiva, epiphora or overflow of tears onto the face. Further the authors also reported that the COVID-19 patients with symptoms related to eye have haematological abnormalities such as increased levels of white blood cells (WBC), neutrophils, prolactin and C-reactive protein when compared with the COVID-19 patients who do not have ocular symptoms (Wu et al., 2020). These studies suggest that aside from the nose or mouth, the eyes can also exist as a transmission route for viral spreading.

3.3. SARS-CoV-2 and inflammation in the lungs

The lung has been the major site of SARS-CoV-2 infection. Abnormal CT scans have emerged as the first few indicators of infection. Interestingly, Chen et al. (2020) performed the biochemical examination of 99 patients with SARS-CoV-2 pneumonia and identified the abnormal phenomenon of Hb-related biochemical indexes of patients. It was further confirmed that the Hb and neutrophil counts of most patients have decreased, and the index values of serum ferritin, erythrocyte sedimentation rate, C-reactive protein, albumin, and lactate dehydrogenase of many patients increased significantly. Recently Cao et al. (2020) conducted the metanalysis, including 31 articles and 46,959 patients and uncovered some major lung associated insights into COVID-19. Among the patients, 28.8% of the individuals exhibited ARDS, when the chest CT was considered, 75.5% of them had double pneumonia, while 20.4% exhibited unilateral pneumonia. The frequently occurring abnormalities consisted of ground-glass opacities, which was found in 69.9% of the patients. Irregular lesions were found in 54.4%, thickening of the bronchovascular bundles was seen in 39.5% of the patients and grid form shadow and hydrothorax were found in 24.4% and 18.5% of the individuals respectively. 31.2% of the patients complained of chest distress, and 3.9% had Chronic obstructive pulmonary disease (COPD) as a comorbid condition (Cao et al., 2020). Although a substantial amount of lung associated disruptions are observed in COVID-19, the long-term significance of it remains unknown. In a diabetic patient with COVID-19, the lung opacities and infection showed improvement after recovery (Han et al., 2020). As subsequent data regarding lung infection after SARS-CoV-2 is very limited, hence the researchers should find out the exact mechanism behind this infection. As, the majority of the pathways associated with COVID-19 might trigger lung fibrosis and damage, making it mandatory to monitor the health status of the recovered patients. This is highly essential to understand the basics and long-term effects of this condition.

3.4. SARS-CoV-2 and its impact on cardiovascular system

In addition to lung injury, COVID-19 patients also have an impact on their cardiovascular systems. The prime most symptom of SARS-CoV-2 infection is pneumonia which could cause inflammation throughout the body; this, in turn, leads to plaque in the arteries to become unstable and can eventually lead to heart attacks. Many reports from various countries such as China, Italy and the USA have confirmed that SARS-CoV-2 can affect the heart muscle causing cardiac failure or myocarditis (Markian, 2020). Myocarditis is caused due to inflammation in the myocardium region of the heart mainly because of viral infection. The entry route of SARS-CoV-2 into the human cells is mainly facilitated by the ACE2, which is an aminopeptidase most commonly expressed in various organs (heart and lungs). The binding of SARS-CoV-2 to the ACE2 receptors in the heart could deviate the normal ACE2 signalling pathways consequentially leading to acute myocardial infarction (Xiong et al., 2020). This alteration in the ACE2 signalling pathway could also arise into acute systemic inflammatory responses and cytokine storm and may cause multiorgan failure or damage in the human system (Huang et al., 2020). The cytokine storm can cause an increase in proliferation

of cardiac muscle cells and might form a fibrous cap on the fatty steak. This results in necrotic lipid core rupture, which forms blood clots resulting in myocardial infarction. The shortness of breath observed in COVID-19 cases could increase the cardiometabolic demand allied with hypoxia which in turn impair the myocardial oxygen demand supply and might lead to myocardial injury (Bansal, 2020). It has been reported that the protein troponin which is present in the heart muscle and regulates the normal function of the heart gets elevated when a person gets infected with SARS-CoV-2 infection (Wang et al., 2020), and this could be used as a diagnostic tool to detect any abnormality in the heart well in advance. Therefore, studies which could describe the general clinical and biochemical characteristics associated with COVID-19 patients could help to rapidly reduce the deteriorating health conditions of the COVID-19 infected as well as recovered patients.

3.5. SARS-CoV-2 and gastrointestinal tract

Patients with COVID-19 have been known to commonly exhibit GI symptoms (Jin et al., 2020; Chen et al., 2020). They include anorexia, vomiting, nausea, abdominal pain and gastrointestinal bleeding. Patients with GI symptoms had increased rates of sore throat, dizziness, fever, headache, fatigue and shortness of breath, showing that GI symptoms may occur at the initial stage of COVID-19. This is conclusive with a study in which a neonate first exhibited GI symptoms, including vomiting and milk refusal (Zhu et al., 2020) before other symptoms of COVID-19 manifested. Viral particles have been isolated from the faecal matter of infected individuals, implicating gastrointestinal conditions in COVID-19 (Tian et al., 2020). According to Zhang et al. (2020), there is a possibility of viral exposure in the liver causing infection in COVID-19 patients (Zhang et al., 2020; Yang et al., 2020). Liver damage can be characterized by a change in levels of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) (Wan et al., 2020; Wang et al., 2020; Liu et al., 2020). A similar increase in enzymes and liver damage was observed in a 55-day old infant infected with SARS-CoV-2 (Cui et al., 2020). In SARS patients, there was an increased proliferation in the liver and associated markers (Chau et al., 2004). Similarly, abnormalities were found in apoptosis-related markers and cytokines in paediatric patients with COVID-19 (Sun et al., 2020). These liver manifestations must be considered while providing therapy for COVID-19 (Rismanbaf and Zarei, 2020). However, if these abnormalities are identified at the preliminary stages, it would be possible to develop precautionary measures. A similar organ injury has been reported in the kidney. More research is required to understand the lasting effects of COVID-19 infection accurately.

3.6. SARS-CoV-2 and the effect of renal injury

Acute kidney injury (AKI) has been reported in SARS-CoV-2 patients (Yang et al., 2020). This is in accordance with the fact that the kidney consists of the ACE2 receptors. Interestingly, the patients displaying AKI in SARS-CoV-2 are significantly higher than that of SARS-CoV; this could be the result of the increased binding of SARS-CoV-2 to its receptor (Perico et al., 2020). Moreover, ACE2 and Transmembrane protease, serine 2 (TMPRSSs) were expressed in the proximal convoluted tubules of the kidney cells of the host (Pan et al., 2020). TMPRSS is known for its proteolytic activity that allows viral entry into the cell (Shen et al., 2017). These factors may provide an improved entry mechanism for SARS-CoV-2. The inflammasome and apoptosis pathways may also have an effect on kidney resulting in inflammation and kidney injury (Li et al., 2019). Hence, it is imperative to do follow-up studies in infected patients to ensure that there are no underlying conditions stemming from COVID-19.

4. How to handle the COVID-19 repercussions

The COVID-19 affected patients have symptoms such as fever, mild respiratory symptoms after infection of 5–6 days and most of them with mild disease will recover. After the recovery, those patients should be careful about their health status and follow-up. In addition to lungs, other organs including kidney, heart, liver, GI tract and eye are the possible sites of infection. A recent study reported that the human kidney is a specific target for SARS-CoV-2 infection (Diao et al., 2020). In the follow-up of SARS recovered patients, addition to the alveolar cells in the lungs, ACE2 expression has been reported in other organs, including the kidney, the heart and the gut (Ye et al., 2006).

People who have recovered from COVID-19 should be more careful in maintaining and monitoring their health status. They have to be in regular monitoring for their future complications that may occur after their recovery. Hence, the recovered patients are recommended to complete a master health check-up to scout for risks for other diseases. Those recovered patients are recommended to get CT, and Magnetic resonance imaging (MRI) scans and University of Pennsylvania Smell Identification Test (UPSIT) to test smell identification, as loss of smell is one of the initial symptoms of neuroinvasion in COVID-19 patients. To identify the ocular complications, slit lamp diagnosis can be recommended to check conjunctivitis. Lung inflammation can be examined by CT scans. The levels of troponin can be analysed for possible inflammation in the heart. To check the GI tract inflammation in COVID-19 patients, endoscopy can be recommended for those recovered patients. The enzymes AST and ALT should be checked for possible liver injury and creatine levels for acute kidney damage (Table 1). These kinds of diagnosis and frequent monitoring of recovered patients will definitely combat the challenges faced by them after recovery and help to reduce their stress levels and make them feel psychologically better.

5. Challenges faced by COVID-19 recovered patients

Most of the COVID-19 recovered patients are experiencing stress for several weeks and this usually disappear within a short period, but the psychophysical symptoms including depression, fear and anxiety may persist for a longer time. The COVID-19 has reached a contagion situation, where the coming months would be full of grim updates about the spread of infection and the homecoming of recovered patients. Time of recovery depends on a person's age and pre-existing conditions before the onset of the infection. According to the WHO, people at the age group of 10–50 are likely to get recovered from the disease since the death rate for this age category is well below 1%. The COVID-19 patients who were hospitalized will be back to resume their normal lives after spending weeks breathing with the help of mechanical ventilators. Some of the recovered patients will still have some lingering effects of the virus as well as of the hospital environment. Such situations would make the recovered patients feel paranoid, and the aftermath of the disease would be persistent in the back of their minds. During the quarantine period, the infected, as well as few recovered patients, are devoid from human contact, which might increase the chances of psychological symptoms. Many rehabilitation services have not been accepting patients recovering from the virus because of the risk of infection and social distancing orders in place. This would make the COVID-19 recovered patients prone to physical, cognitive as well as few psychological problems which could also be termed as post-intensive care syndrome. Unaffected folks being worried about getting the virus from someone who has recovered may try to avoid them, but it is important not to ostracize those who have recovered from the disease. They may also be worried about being stigmatized by the community. Hence, we suggest providing counselling, moral support as well as a few recommended guidelines to the COVID-19 recovered patients returning to normalcy.

Table 1
A complete characteristics details about SARS-CoV-2 in multi-organ system.

Organ	Site of symptom	Manifestation	Confirmative test	Presence of viral nucleic acid	Presence of ACE-2 receptor	Remarks	References
Brain	Olfactory Bulb	Hyposmia, hypogeusia, hypopsia, encephalitis and headache	CT Scan, MRI Scan, UPSIT (University of Pennsylvania Smell Identification Test)	Nasopharyngeal swab	–	- SARS-CoV-2 enroute to the olfactory bulb leading to smell dysfunction and cytokine storm in the thalamus.	Mathew, 2020; Poyiadji et al., 2020; Puja et al., 2020
Eye	Conjunctiva	Conjunctivitis, chemosis, swelling of conjunctiva, epiphora or overflow of tears onto the face	Slit Lamp diagnostics	–	Retina and Retinal pigment epithelium	-SARS-CoV-2 could enters the tears in the droplet form and could transmit the disease to various organs.	Sommer, 2020; Qing et al., 2020; Wu et al., 2020
Lung	Pulmonary lobe Pulmonary nodules Bronchovascular bundles	Bilateral pneumonia, unilateral pneumonia, ground glass opacities, Irregular lesions Thickening	CT Scan	Lung sputum	Transient secretory cells	-Damage of walls and lining cells by SARS-CoV-2 -Inflammasome pathway mediated lung injury and damage	Cao et al., 2020; Han et al., 2020
	Alveolus	Shortness of breath ARDS	Physical symptom				
Heart	Myocardium and Cardiac muscle cell	Cardiac failure or Myocarditis, Myocardial infraction.	Increased levels of Troponin protein	–	Viable myocardium	-Inflammation and cytokine storm mediated myocardial infraction or myocarditis.	Markian, 2020; Huang et al., 2020; Bansal, 2020; Wang et al., 2020
Gastrointestinal system	Stomach and digestive organs	Anorexia, vomiting, nausea, abdominal pain	Physical symptoms	Nasopharynx Throat	Oesophagus, ileum and colon	- GI symptoms may occur at the initial stage of COVID-19	Zhu et al., 2020; Zhang et al., 2020; Cui et al., 2020; Rismanbaf and Zarei, 2020.
	GI tract	Gastrointestinal bleeding	Endoscopy, colonoscopy	Stool			
	Liver	Liver injury	AST, ALT		Cholangiocytes	-Possible drug induced liver injury - Liver fibrosis through AP-1 or inflammasome pathway	
Kidney		Acute Kidney Injury	Creatinine blood test	Urine (Uncommon)	Proximal convoluted tubules Podocytes	-Inflammasome pathway -Multi-organ mediated damage	Yang et al., 2020; Perico et al., 2020; Pan et al., 2020

Footnotes: GI, Gastrointestinal; AST, Aspartate amino transferase; ALT, Alanine aminotransferase; AP-1, Activator protein 1; ARDS, Acute respiratory distress syndrome; CT, Computerized tomography.

6. Recommendations

The COVID-19 symptoms range from various organs dysfunction such as the lungs, heart, eyes, brain and GI tract. Although the SARS-CoV-2 infected persons do get recovered from the preliminary effects, there might be some aftermaths which the recovered patients may have to face. Many recovered patients still might have paranoid feelings about the COVID-19 disease. Therefore, through this review, we provide a few recommendations to safeguard the COVID-19 recovered patients as well as their families from the repercussion of this disease. The recommendations are:

- COVID-19 recovered patients should be treated with the utmost care.
- Tighter supervision of workplace safety should be provided to safeguard the safety of people's lives, along with the COVID-19 recovered patients.
- Rapid follow-up should be recommended for the recovered patients, which should include frequent nucleic acid tests.
- The signs and symptoms (fever and cough) of the recovered patients should be monitored regularly.
- Extensive attempts are to be made to create awareness about the virus to recovered patients.
- The family members of the recovered patients should be trained in empathy skills to relate and communicate with them by encouraging two-way discussions.
- Home monitoring programs for recovered patients can help them to improve their diet and physical activity.
- Advise the recovered patients to drink plenty of water and other fluids to stay well hydrated and to consume nutritious food to improve their immunity.
- Proper counselling and education about the ill-effects of smoking and alcohol consumption must be given to recovered patients.
- Recovered patients should be recommended to cooperate with researchers who are voluntarily involved in conducting and collecting the data for the health status assay.
- Recovered patients should be encouraged to share their feelings about the treatment, quarantine, symptoms of the disease and their experience on the whole to reduce their psychological burden.
- To overcome this psychological stress, it is advised to practice yoga and breathing exercises, which may help in combating the psychological stress caused due to this disease.
- The host genetic predisposition and biomarker genes in different populations with respect to viral infection and persistence will help in understanding the co-evolution of the coronaviruses and other age-old diseases like Malaria etc. This will also help to dissect the genomics of symptomatic and asymptomatic cases.
- The community/society must be educated not to stigmatize or isolate recovered patients.
- Counselling is suggested for the recovered patients periodically not to lose courage and keep themselves mentally strong.
- The one health concept stresses the ecological relationships between human, animal, and environmental health. Understanding the importance of microbiome relationships between the environment-humans-animals opens up the potential for

innovative and integrated approaches to diagnosis, treatment, and intervention of diseases to animals and humans.

7. Concluding remarks

COVID-19 has materialized into a deadly disease affecting people worldwide. Besides the common symptoms that occur in COVID-19. It has recently uncovered into a multifaceted condition known to affect various other organs. This disease appears to be at the hub of various converging pathways. Altogether they exhibit detrimental effects on the individual who have infected with the virus. The severe forms of the conditions have progressed into ARDS, septic shock, coagulation dysfunction and death, while the mild and moderate cases seem to have a positive recovery rate. The maximum number of patients in the world have been recovered and discharged after infection and getting treatment. Although this seems celebratory, the major drawback of COVID-19 included is the speedy transmission capacities. In addition, the long-term effects of COVID-19 remain still unknown. It needs to figure out if the virus-mediated organ damage completely improves on recovery? In order to determine the actual consequences of the condition, it is essential to maintain follow-up studies on patients, and it will help to determine diseases at initial stages and allowing medical intervention in a timely manner. Moreover, this could provide enough comparative data among patients worldwide to determine the effects of COVID-19 on different populations. Analysis focusing on the comparison might shine a light on the similarities and differences between the patients worldwide. It may be beneficial to analyse if a particular population has an added advantage in terms of immunity while combating the virus. Besides the physical manifestations of the conditions, it is relevant to look into the emotional aftermath of the pandemic. Populations worldwide have been living in solidarity and in fear of contracting the virus. Individuals who have recovered from the condition may be stigmatized, contributing to psychological issues like depression and anxiety. As the world recuperates from COVID-19, it is essential to move forward with all the information necessary to be more prepared for a pandemic of its kind in the future. It is necessary to conduct the follow-up studies in the COVID-19 recovered patients and provide the appropriate management of this dreadful disease in terms of psychological physical, and social aspects. More research is required to adequately care for patients post recovery and to provide a framework of possible physical manifestations of the disease. As COVID-19 is causing more panic worldwide, it is crucial to get a comprehensive analysis of the post-recovery states of patients. This might also help the social circle of the patients to attain peace, knowing that their friend or family members are no longer contagious or in danger.

Author contribution

Conceptualization: **VB; NSK; SGC;** Data Curation: **IM; SM; JK; GL; PS; SK** Formal analysis: funding acquisition: **VB; NSK; SGC** investigation: **VB; IM; NSK; SGC** methodology: project administration: **VB; NSK; NA; JKR; GV; SM** resources: software: NSK; **PS; SK** supervision: **VB; SGC; NSK** Validation: visualization: **NA** roles/writing original draft: **IM; SM; JK; GL; JKR; GV** writing/review and editing: **IM; VB; IM; SM; JK; NSK.**

Funding

This work was supported by the Science and Engineering Research Board (SERB), Government of India [ECR/2016/001688]; the Science and Engineering Research Board (SERB), Government of India [ECR/2018/000718]; the DBT, New Delhi sponsored Advanced Level State Biotech Hub (BT/04/NE/2009 Dt.29.082014), Mizoram University. The study was supported by a grant from the National Research Foundation (NRF) funded by the Korean Government (Grant no: 2019M3A9H1030682).

Declaration competing of interest

The authors have no conflicting interest.

Acknowledgements

The author Dr. VB would like to thank Bharathiar University for providing the necessary infrastructure facility and the Science and Engineering Research Board (SERB) (ECR/2016/001688), Government of India, New Delhi for providing necessary help in carrying out this review process in the Neurology aspects of the manuscript and Dr. SMD would like to thank the Science and Engineering Research Board (SERB) (ECR/2018/000718), Government of India, New Delhi for providing necessary help in carrying out this review process Ophthalmology aspects. The Authors wish to thank the Advanced Level State Biotech Hub (BT/04/NE/2009 Dt.29.08.2014), Mizoram University, Aizawl sponsored by the Department of Biotechnology (DBT), New Delhi, Government of India for providing the infrastructural support and facilities. The study was supported by a grant from the National Research Foundation (NRF) funded by the Korean Government (Grant no: 2019M3A9H1030682).

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