Journal of Advanced Research in Medicine
Volume 8, Issue 1 - 2021, Pg. No. 9-18
Peer Reviewed & Open Access Journal

Review Article

Long Term Health Sequelae of COVID-19: A Review

Naresh Kumar[1], Dhiraj Wasnik[2], Harsh Vardhan[3], MK Daga[4]

[1]Professor of Medicine & Head, [3]Senior Resident, Department of Pulmonary Medicine, Maulana Azad Medical College, New Delhi, India.
[2]Resident, [4]Director Professor, Department of Medicine, Maulana Azad Medical College, New Delhi, India.
DOI: https://doi.org/10.24321/2349.7181.202102

I N F O

Corresponding Author:
Naresh Kumar, Department of Pulmonary Medicine, Maulana Azad Medical College, New Delhi, India.
E-mail Id:
drnareshmamc@gmail.com
Orcid Id:
https://orcid.org/0000-0003-4581-609X
How to cite this article:
Kumar N, Wasnik D, Vardhan H, Daga MK. Long Term Health Sequelae of COVID-19: A Review. J Adv Res Med. 2021;8(1):9-18.

Date of Submission: 2021-02-15
Date of Acceptance: 2021-03-26

A B S T R A C T

The outbreak of Coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by World Health Organization (WHO) on 11th March, 2020. COVID-19 infection predominantly manifests as pulmonary symptoms that may progress to acute respiratory distress syndrome. The data on extra-pulmonary manifestations of acute COVID-19 are available. Most patients who have COVID-19 recover well within months. Currently, more than 50 million people have recovered globally. Many reports of patients with persistent severe symptoms and significant end-organ damage after SARS-CoV-2 infection have also been observed. As COVID-19 is a relatively new disease, future sequelae aren't well established. Major adverse outcomes were found to affect different body systems: respiratory system (lung fibrosis and pulmonary thromboembolism), cardiovascular system (cardiomyopathy), and neurological system (sensory dysfunction and stroke). Mental health of COVID-19 patients were also found to be adversely affected. This review describes the effects of SARS-CoV-2 taking into account the previous experiences with SARS-CoV-2 and the Middle East Respiratory Syndrome (MERS) coronavirus that caused SARS in 2003 and MERS in 2012 respectively. This review aims to update on the long-term sequelae of SARS-CoV-2 infection and highlight the necessity for patient monitoring following the acute stage of infection with SARS-CoV-2 to provide ground for the prevention, diagnosis, and management of these potential long-term sequelae and to complete the natural history of COVID-19.

Keywords: COVID-19, SARS-CoV-2, Pulmonary fibrosis, Long Covid, Post-acute COVID-19 syndrome, Post Intensive Care Syndrome

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global pandemic began in Wuhan, China, in December 2019, and has spread worldwide. World Health Organization (WHO) declared a worldwide health emergency on 30th January, 2020 and a COVID-19 pandemic on 11th March, 2020 subsequently. The clinical spectrum of SARS-CoV-2 ranges from mild to severe with the majority of them (81%) having mild symptoms while severe symptoms (defined as respiratory rate ≥ 30/

min, hypoxia: blood oxygen saturation ≤ 90%, PaO2/ FiO2 < 300, and/or pulmonary infiltrates >50% within 24 to 48h) occurring in 14% cases. Critical illness (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure) have been reported in only 5% of the subjects with an overall case fatality rate (CFR) of 2.3%.[1] Now the literature has emerged describing the involvement of other organ systems, including the cardiovascular, gastrointestinal, renal, and neurologic systems. SARS-CoV-2 binds to the ACE2 receptor in humans, similar to SARS-CoV. A unique structural feature of the spike glycoprotein receptor binding domain of SARS-CoV-2 (responsible for virus entry into host cells) has a higher binding affinity for ACE2 on host cells than SARS-CoV-1. Lungs, kidneys, gastrointestinal (GI) tract, liver, vascular endothelial cells, and arterial smooth muscle cells also express ACE2 receptors. Thus, all of these organs and systems with higher expression of ACE2 receptors might be the possible targets for SARS-CoV-2 infection.[2] Various studies have reported that around 70-80% of the patients who recovered from COVID-19 present with persistence of at least 1 or more symptoms (General or system-specific symptoms in the acute phase), even after being declared COVID-free.[3] Now the challenging part is how to manage these COVID-19 sequelae which may vary from mild in terms of fatigue and body aches to severe forms requiring long term oxygen therapy and lung transplantation due to lung fibrosis, significant cardiac abnormalities and stroke leading to significant impairment in the quality of life. The main purpose of this review is to provide a summary of the present literature on the pulmonary and extra-pulmonary complications of COVID-19 to enhance the awareness for the better management and prognostication of these patients.

Method

This brief review outlines the long term sequelae of COVID-19. A literature search of the PubMed and Google Scholar databases was performed from the inception of COVID-19 infection in December 2019 to December 2020 for articles using the keywords COVID-19, SARS-CoV-2, long term sequelae, and post COVID. We included case reports and case series, retrospective and prospective studies, systematic reviews and meta-analyses, clinical guidelines, and narrative reviews.

Long Term Sequelae

Pulmonary Complications

Upper and lower respiratory tracts are the most common sites of SARS-CoV-2 infection as the virus is inhaled, and the severity of lung damage is closely related to the severity of infection.[4] The virus can injure the lungs in 3 ways: Acute Respiratory Distress Syndrome (ARDS) with Diffuse Alveolar Damage (DAD), diffuse thrombotic alveolar microvascular occlusion, and inflammatory mediator-associated airway inflammation, leading to impaired alveolar oxygenation, hypoxemia, and respiratory acidosis.[5] In the absence of effective treatment, the consequences of this poor oxygenation are either death of the patient from respiratory failure, or the sequelae of permanent lung injury if the patient recovers. It has been found that 40% of the patients with COVID-19 develop ARDS, and out of them, 20% are in the severe ARDS category.[6] A substantial proportion of COVID-19 ARDS patients develop residual long-term impairment of lung function and radiological (CT) evidence of pulmonary fibrosis in survivors.[6] 'Post-COVID-19,' or 'chronic COVID,' and the gradual loss of lung function due to pulmonary interstitial fibrosis can have profound effects on the quality of life for people initially believed to have recovered from COVID-19. UK NHS recently described potential long term respiratory complications that include chronic cough, fibrotic lung disease, bronchiectasis in COVID-19 recovered patients.[7]

In one Chinese study of 55 patients with COVID-19, 3 months follow up was done after discharge. 35 (64%) patients had persistent symptoms and 39 (71%) patients had radiologic abnormalities suggestive of pulmonary dysfunction such as interstitial thickening and evidence of fibrosis, while 25% of the patients had decreased diffusion capacity for carbon monoxide (DLCO) on PFT.[8] In another similar study of 57 patients, PFT was performed after 30 days of discharge, in which decreased diffusion capacity for carbon monoxide (DLCO) and diminished respiratory muscle strength were common findings that occurred in 30 patients (53%) and 28 patients (49%), respectively, suggestive of restrictive lung disease.[9] The pathology behind the residual lung dysfunction (decreased diffusion capacity, restrictive and obstructive pattern) might be parenchymal fibrosis leading to alveolar volume reduction and airway narrowing, persistent microvascular thrombosis and persistent low grade alveolitis.

It is very early to find out the actual prevalence of post-COVID-19 lung fibrosis, but at present an analysis of hospital discharged COVID-19 patients has shown that more than a third of recovered patients develop fibrotic abnormalities. Previous studies highlighted that duration of the disease is an important determinant for lung fibrosis post-ARDS. This study showed that 4% of the patients with a disease duration of less than 1 week, 24% of the patients with a disease duration between 1 and 3 weeks, and 61% of the patients with a disease duration of greater than 3 weeks developed fibrosis.[10] Zhou et al. observed that out of 62 COVID-19 patients, 21 patients (33.9%) developed fibrotic changes in the lung. In this study the incidence of fibrosis correlated well with duration of illness as fibrosis was seen more in the patients with advanced-phase of COVID-19 disease (8-14 days after the onset of symptoms)

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

than in the early phase of the disease (<7 days of onset of symptoms).[11] Pan et al. also reported pulmonary fibrosis on CT in 11 patients, out of the total 63 COVID-19 hospitalized patients, early in the disease.[10] Findings confirmed on autopsy included diffuse alveolar damage with areas of consolidation by fibroblastic proliferation and deposition of ECM and fibrin in the alveolar spaces. Reticulation (inter/intralobular septal thickening subpleural irregular line), traction bronchiectasis, architectural destruction, mosaic attenuation, air trapping, and resolving Ground-Glass Opacities (GGOs) were typical post COVID lung changes on HRCT.[12] However, it has been seen in most of the cases that these post COVID changes resolve with time. In one of the studies, a chest CT scan was performed on the last day before discharge, two weeks and four weeks after the discharge. On follow up of these patients, the abnormalities (including focal/ multiple GGO, consolidation, interlobular septal thickening, subpleural irregular lines) in lungs were gradually absorbed in the first and second follow-ups after discharge as compared with the last scan before discharge. The lung lesions of 64.7% of the discharged patients were fully absorbed after a 4-week follow-up. It indicated that the damage to lung tissue by COVID-19 could be reversible for most of the COVID-19 patients.[13]

Risk factors for developing lung fibrosis include older age (> 65 years), severity of the illness (increased LDH level), prolonged ICU stay, history of smoking and chronic alcoholism.[14] This was hypothesised from the previous studies on SARS and MERS outbreak.[11-14] Mechanism for fibrosis by SARS-CoV-2 includes downregulation of ACE-2 receptors, reducing the angiotensin clearance which could upregulate TGF-*B* and connective tissue growth factors.[15]

As of now, no fully proven options are available for the treatment of post COVID-19 pulmonary fibrosis. Various treatment strategies are under evaluation. It has been proposed that prolonged use of anti-viral, anti-inflammatory and anti-fibrotic drugs diminish the probability of the development of lung fibrosis. However, it is yet to be ascertained whether early and prolonged use of antiviral agents may prevent remodelling of the lung or which of the available antiviral agent is more effective. Prolonged low dose corticosteroid may prevent remodelling of the lung in survivors, though the risk-benefit ratio should be assessed prior to its use. Anti-fibrotic drugs like- pirfenidone and nintedanib, have anti-inflammatory effects as well and thus they may be used even in the acute phase of COVID-19 pneumonia.[16] Pirfenidone has anti-fibrotic, anti-oxidative and anti-inflammatory effects. It attenuates ARDS induced lung injury as it reduces LPS-induced acute lung injury and subsequent fibrosis by suppressing NLRP3 inflammation activation.[17] But, there are few concerns regarding the use of these antifibrotics in the acute phase of COVID-19. Many COVID-19 patients have hepatic dysfunction in the form of raised transaminases and both antifibrotics pirfenidone and nintedanib cause hepatotoxicity. As most of the COVID-19 patients are on an anticoagulant, nintedanib might be associated with an increased risk of bleeding.

Lung transplantation could be the only treatment option for the patients with end-stage lung fibrosis due to COVID-19. However, only a few patients received this therapy. Chen et al. reported three patients who received lung transplantation for COVID-19 related lung fibrosis. Two out of them survived.[18] Convalescent plasma also showed beneficial effects in ARDS which could decrease the fibroproliferation.[19] Multipotent mesenchymal stem cells, which have the capacity to replace damaged alveolar cells, secrete anti-inflammatory factors and reduce fibro-proliferation.[20] However, various ongoing clinical trials are investigating their therapeutic use.[21]

Over subsequent months, the number of patients infected by SARS-CoV-2 surviving the acute phase with clinical and CT evidence of pulmonary involvement is predicted to grow exponentially, therefore, the long-term sequelae on lung function shouldn't be overlooked. Surely, some patients may be at risk of developing long-standing lung fibrosis, which can affect the quality of life and survival. With no specific proven effective therapy to prevent lung fibrosis, risk reduction measures must be undertaken.

While several treatment options have been evaluated, none except systemic glucocorticoids have been shown to improve survival in COVID-19. Unfortunately, widespread use of glucocorticoids can lead to secondary bacterial or fungal infections. Invasive pulmonary aspergillosis complicating the course of COVID-19 is widely recognized.[22] However, many case reports had shown that patients developed mucomycosis (pulmonary and rhino-orbital) after prolonged systemic steroid use in the acute phase of COVID-19. Moreover, the immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as tocilizumab could further increase the risk of infections in COVID-19 patients.[23,24]

One alarming observation was the absence of traditional risk factors, such as diabetes mellitus, transplantation, or haematological malignancies, in the case reports. The development of mucormycosis can probably be attributed to the use of glucocorticoids and suggest a need for their judicious use. Thus, the use of glucocorticoids in mild COVID-19 cases (without hypoxemia) or the utilization of higher doses of glucocorticoids should be avoided. Further, in the absence of a clear benefit, drugs targeting immune pathways such as tocilizumab should be discouraged in the absence of any clear benefit.

Cardiovascular Complications

Up to 20-30% of the hospitalized COVID-19 patients have

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

evidence of myocardial involvement with elevated troponin levels.[25] In the previous report, a patient infected with SARS-CoV-2 developed left ventricular dysfunction and pericarditis without any respiratory symptoms. Complications involving the cardiovascular system include MI (7.2%-27.8%), arrhythmias (5.9%-16.7%), shock (1.1%-20%), and heart failure (23%).[25] Coagulation abnormalities and myocarditis have also been reported in various reports.[25] While understanding of the novel virus is continuously evolving, the mechanism through which the SARS-CoV-2 virus leads to cardiovascular manifestations is currently suggested to involve the ACE2 transmembrane protein. In patients with COVID-19, myocardial involvement may initiate inflammation pathway and subsequent fibrosis. In a German study of 100 recovered COVID-19 patients, cardiac MRI performed at a median of 71 days after COVID-19 diagnosis had revealed cardiac involvement in 78% of the patients and ongoing myocarditis in 60% of the patients.[26] Acute myocarditis might contribute to heart failure and some investigators have reported depressed left ventricular ejection fraction due to COVID-19.[27] Cardiac dysfunction due to direct virus infection or systemic inflammation might potentially cause coronary microcirculation disruption and downstream myocardial ischemic sequelae. Indeed, amongst 25 SARS survivors, 40% continued to have cardiovascular abnormalities at 12-year follow-up.[28] Arrhythmia risk in COVID-19 patient is likely to be multifactorial. It may be due to the viral infection, severity of the illness, severity of the cardiac injury, inflammation, or drug treatment with QT-prolonging drugs. A study of 121 COVID-19 patients showed that the majority of those patients had some sort of arrhythmia, including 87 (71.9%) patients with sinus tachycardia unrelated to fever, 18 (14.9%) patients with bradycardia, and one patient with paroxysmal atrial fibrillation.[29] These malignant arrhythmias can be persistent and may increase the risk of sudden cardiac death.

Neurological Complications

SARS-CoV-2 can penetrate brain tissue through ACE2 receptors and also by direct invasion of the olfactory nerve leading to anosmia. The commonest neurological symptoms that occurred during COVID-19 are headache, vertigo, and chemosensory dysfunction (eg, anosmia and ageusia). COVID-19 related anosmia is included in the screening criterion for COVID-19, but whether it complicates into post-viral olfactory disorders (PVOD) remains unknown.[30]

It was initially thought that SARS-CoV-2 had a lesser propensity to cross the Blood-Brain Barrier (BBB), but this is not the case. Three important interpretations found on the basis of post-mortem studies on the cerebral pathology of COVID-19 patients and the use of an advanced 3D microfluid model of the human BBB are: first, the SARS-CoV-2 spike (S) protein-binding receptor, ACE2 is widely expressed in brain microvascular endothelial cells; second, the BBB is directly damaged by S protein to varying degrees; and third, the S protein can induce the inflammatory response of microvascular endothelial cells that change the function of the BBB.[31] These findings revealed that SARS-CoV-2 can alter the BBB and enter the brain, and lead to the appearance of neurological symptoms, the formation of fatal microthrombi, encephalitis, and long-term neurological sequelae associated with COVID-19. In addition, SARS-CoV-2 may enter the brain by trans-synaptic transfer, optic and olfactory nerve channels, and vascular endothelial cells, considering the fact that the olfactory nerve is a potential pathway for entry of SARS-CoV-2 into the brain, as sustentacular cells that maintain the integrity of the sense of smell and stem cells in the olfactory epithelium highly express ACE2 and transmembrane serine protease 2 (TMPRSS2).[32-34]

Recently published studies have focused on the potential causal relationship between viral infections and Alzheimer's Disease (AD).[35] Given the identification of damage to the CNS by SARS-CoV-2, there is concern regarding its long-term effects on cognitive function. Further, long-term studies will be required to identify the relationships among SARS-CoV-2 infection, AD, and other neurodegenerative sequelae. Neuroinflammatory responses, synaptic pruning, and neuronal loss are the structural basis of AD, and SARS-CoV-2 infection most likely accelerates these processes.[36]

In parkinson disease (PD), different CNS sites are damaged with particular types of neurons being more severely affected. However, currently, there is no direct evidence that SARS-CoV-2 causes or accelerates PD. It should be noted that the wide expression of ACE2 in different areas of CNS provides the molecular basis for SARS-CoV-2 to mediate or accelerate the occurrence of PD.[37] Current pieces of evidence of neurological changes caused by SARS-CoV-2 show some similarities with those found in MS. First, the pro-inflammatory 'cytokine storm' caused by SARS-CoV-2 infection is the initiating factor of CNS neuroinflammatory damage.[38] Second, SARS-CoV-2 causes demyelination in the brain and spinal cord. A recently published case report showed that SARS-CoV-2 infection was associated with signs and symptoms similar to those of MS.[39] Previous studies observed the association between coronavirus infection and the onset of MS.[40]

A case series of 901 COVID-19 infected patients from China and France described the neurological manifestations of the disease. Encephalopathy has been reported in 93 patients and Guillain-Barré syndrome in 19 patients. SARS-CoV-2 has also been detected in CSF of some patients. Anosmia and ageusia were common and may occur in absence of other clinical features. Stroke was also reported in 96 patients who frequently had a hypercoagulable state with elevated C-reactive protein, D-dimer, and ferritin due to

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

ongoing inflammation.[41] The neurological manifestations which may produce long-term complications, like stroke and encephalitis can seriously affect the patient's quality of life later. More studies on the risk factors of such complications with larger sample size and longer follow-up are required.

Psychological Complications

The COVID-19 pandemic had a profound effect on the psychological state of COVID-19 survivors across the world. The virus may infect the brain or trigger an immune reaction that causes additional adverse effects on brain functions and psychological state. Mental disorders could be the sequelae of brain damage that are either triggered directly from cerebral hypoxia caused by the viral infection or indirectly from the immunological response.[42] The adverse psychological effects like post-traumatic stress, confusion, depressed mood, insomnia, and anger during the quarantine period, are well documented.[43] The diagnosis of COVID-19 and subsequent need for physical distancing, have been associated with anxiety, feelings of isolation, and loneliness.[44]

Increasing reports of lingering malaise and exhaustion like chronic fatigue syndrome may leave patients with physical debility and affective disorders. Fears of illness, death, and uncertainty of the future are significant stress factors for the mental health of the population, and social isolation resulting from loss of work activities also threatens to worsen the public mental health.[45]

Endocrine Complications

Metabolic Aspect: Pancreatic cells also express ACE-2 receptors. Viral spike protein binds this enzyme receptor and down-regulates its expression causing virus-mediated pancreatic damage.[46] However, long-term observations are needed to know if diabetes will be permanent or SARS-CoV-2 caused a transitory period of hyperglycaemia which will resolve with recovery from the infection.

An observational study analysing the lipid metabolism parameters in SARS recovered patients after 12 years of acute disease showed an increase in triglycerides and very-low-density lipoproteins (VLDL) levels. Dyslipidaemia was noted in 68% of the survivors as compared to 40% of the healthy volunteers.[28]

Hypothalamus-Pituitary-Adrenal Axis: HPA axis plays a fundamental role in the stress response. Studies on SARS found that SARS-CoV could impair this hormonal axis by different mechanisms. In 2004, a Wheatland study showed that among the strategy employed by SARS-CoV to avoid the host's immune reaction, there was expression of an amino acid sequence that mimicked human adrenocorticotrophic hormone (ACTH). This strategy induced the production of autoantibodies against ACTH, preventing the suitable adrenal response to stress.[47] Another study conducted by Leow et al found that adrenal insufficiency might occur as a late consequence of SARS and it was mostly secondary to hypophysitis or direct hypothalamic damage.[48] To date, insufficient data are available on the possible effect of SARS-CoV-2 on the HPA axis function. The use of high doses of corticosteroids during the acute phase of SARS can cause subsequent hypocortisolism. However, assessment of endocrinological parameters of SARS survivors at one year has revealed the presence of hypocortisolism in around 39% of the individuals even in the absence of steroid use in around two-thirds of the studied population. This response has been attributed to the delayed pathological complication of SARS.[49] The hypocortisolism could explain the persistence of symptoms seen in post-SARS patients like apathy, lethargy, malaise, fatigue, weakness, orthostatic dizziness, and anorexia.[48]

Hypothalamus-Thyroid Axis: Hypophysitis causing central hypothyroidism has also been postulated as a possible pathogenic mechanism. Subacute thyroiditis is additionally a condition that must be kept in mind given its close association with viral infections. Patients who are on levothyroxine therapy may experience an increase in TSH levels when given lopinavir/ritonavir (used as a part of research treatment protocols).[50] Keeping the unknown impact of the COVID-19 virus on thyroid function, all survivors of moderate to severe COVID-19 infection should be clinically and biochemically evaluated for potential thyroid dysfunction during the follow-up visit.

Hypothalamus-Gonadal Axis: No data has been reported about SARS and ovarian function. The sole evidence available showed the rise in serum levels of prolactin (PRL), FSH, and LH and reduction of 17ß-estradiol (E2) and progesterone levels in SARS patients compared with healthy controls.[51] As for the male reproductive axis, it should be noted that ACE2 is highly expressed by the human testis, which might be infected by SARS-CoV and, probably, by SARS-CoV-2.[52] A study by Xu et al. found tissue damage indicative of orchitis in autopsy from testicular tissue obtained from six patients who died of SARS. Viral orchitis can severely damage testicular spermatogenic function, causing oligo-zoospermia and even azoospermia resulting in infertility.[53] An Italian study found that male erectile dysfunction may occur as the long-term consequence of COVID-19 especially among elderly patients due to changes in vasculature and mental instability.[5]

Immunological & Hematological Complications

Disseminated Intravascular Coagulation (DIC) may be a manifestation of coagulation failure, and an intermediate link in the development of multi-organ failure. Coagulopathy manifests as increased fibrinogen level, elevated D-dimer, and minimal change in prothrombin time, partial thromboplastin time, and platelet count in the early stages of infection.

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

Several studies have found a high incidence of thrombotic complications (pulmonary embolism, deep vein thrombosis) in patients with COVID-19, even when thromboprophylaxis had been given. Thrombotic events could also be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.[55] Cases of arterial thrombosis, cerebral phlebothrombosis, and acute limb ischemia secondary to thrombosis have been reported.[56,57,58,59] Acute limb ischemia could lead to dry gangrene and subsequent limb amputation resulting in physical disability.

A study conducted by Zheng et al. described haemophagocytosis in a severe COVID -19 patient (without any pre-existing hematological diseases) with worsening respiratory symptoms.[60] In this case report, bone marrow aspiration showed cellular bone marrow with features of haemophagocytosis which may be characteristic of secondary haemophagocytic lymphohistiocytosis, which is, an acute condition typically characterised by poor prognosis that is often caused by severe viral infections. This report implied a possible association between the SARS-CoV-2 infection and the presence of myelosuppressive effects

Post-Acute COVID (Long COVID)

Long COVID is defined as a condition where symptoms persist for more than 3 weeks. Most patients recover within 2 weeks, approximately 10% of the patients still have symptoms after 3 weeks, and few may have symptoms for months, as seen with data from the UK COVID Symptom Study.[61] Nearly 90% of the hospitalized patients who recovered from COVID-19 reported persistence of a minimum of one symptom for 2 months after discharge. Symptoms may relapse and remit and may occur in those with the mild disease only.[62] Common long-term symptoms include persistent cough, low-grade fever, breathlessness, and fatigue. Chest pain, palpitations, myalgia, arthralgia, headaches, vision changes, deafness, and loss of taste/smell, have also been reported.[63]

In one Italian study where 143 COVID-19 patients were followed up for a period of two months after the primary symptom, only 18 (12.6%) patients were symptom-free while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any symptom or signs of acute infection. A high proportion of people still reported fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%).[64]

Post Intensive Care Syndrome

The SARS-CoV-2 infection causes severe lung injury leading to prolonged stay in ICU on ventilators for some patients. Early reports suggest that these patients can present with post-intensive care syndrome, a spectrum of psychiatric, cognitive, and/or physical disability (e.g., muscle weakness, cognitive dysfunction, insomnia, depression, anxiety, post-traumatic stress disorder, delirium, encephalopathy) that affects survivors of critical illness, and persists after the patient has been discharged from the intensive care unit.[65]

Discussion

Our review has found that COVID-19 has been reported with various adverse outcomes in several systems within the body. Most of the adverse health effects were mediated by the hyperimmune response to the virus. Adverse respiratory outcomes which may be due to immune-mediated or direct virus attack, including lung fibrosis and functional impairment has been found to persist beyond recovery from COVID-19 in a few patients. Based on the available data on SARS and MERS, an impaired pulmonary function can persist for years even after recovery from infection, resulting in reduced exercise capacity and quality of life. In the acute phase of the infection, we also found reports on adverse cardiovascular outcomes including myocardial damage, heart failure, arrhythmia, and adverse neurological outcome including olfactory and gustatory dysfunction. Adverse psychological state outcomes were also reported during the pandemics including insomnia, anxiety, and depressed mood. An increase in the risk of some adverse psychological state outcomes, like chronic fatigue, Post Traumatic Stress Disorder (PTSD), depression, anxiety disorder, panic disorder, etc, could persist for years after recovery from the infection. Post-infection care for COVID-19 survivors is probably going to add a burden to the existing healthcare system. Given the increasing numbers of recovered COVID-19 patients compared to the time of the SARS outbreak, it is likely that the extent to which follow-up healthcare services are adopted for COVID-19 survivors are going to be much greater than for SARS globally. With the extensive use of mechanical ventilation in severe COVID-19 patients, post-infection healthcare utilization is projected to be important in these survivors.

A large clinical and administrative records database is the most appropriate choice to evaluate the long-term health outcomes of COVID-19. This may enable us to have a more comprehensive understanding of the immediate impact of COVID-19 on individual patients. Such an analysis could also identify the risk factors of poor outcomes, which in turn, would enable us to devise a strategy to effectively safeguard the patients who are more susceptible to severe illness.

Conclusion

Most of the subjects who recovered from COVID-19 experienced several manifestations ranging from mild symptoms like fatigue, headache to more critical manifestations like pulmonary fibrosis, stroke, and myocarditis. The foremost reported symptoms were fatigue,

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

anxiety, joint pain, and headache. The post-COVID-19 manifestation is essentially like the post-SARS syndrome. All subjects recovered from COVID-19 should undergo long-term monitoring for evaluation and treatment of symptoms and conditions which are persistent or precipitated after recovery from the coronavirus infection. epidemiological studies are needed to investigate further the risk factors related to the adverse outcomes in these patients.

Conflict of Interest: None

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470-3. [PubMed] [Google Scholar]
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. [PubMed] [Google Scholar]
3. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Tao H, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74. [Google Scholar]
4. Calabrese F, Pezzuto F, Fortarezza F, Hofman P, Kern I, Panizo A, Thusen J, Timofeev S, Gorkiewicz G, Lunardi F. Pulmonary pathology and COVID-19: Lessons from autopsy. The experience of European Pulmonary Pathologists. Virchows Arch. 2020 Sep;477(3):359-72. [PubMed] [Google Scholar]
5. Tian S, Xiong Y, Liu H, Niu Li, Guo J, Liao M, Xiao S. Pathological study of the 2019 novel coronavirus disease (COVID-19) through post-mortem core biopsies. Mod Pathol. 2020;33(6):1007-14. [PubMed] [Google Scholar]
6. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2. [PubMed] [Google Scholar]
7. NHS England [Internet]. Aftercare needs of inpatients recovering from COVID-19. Jun 2020. Available from: https://www.cambscommunityservices.nhs.uk/docs/default-source/luton-adults-general/c0388_after_care_needs_of_inpatients_recovering_from_covid-19_5_june_2020.pdf.
8. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020;25:100463. [PubMed] [Google Scholar]
9. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, Zhou X, Liu X, Huang X, Yuan S, Chen C, Gao F, Huang J, Shan H, Liu J. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020;21(1):163. [PubMed] [Google Scholar]
10. Liu X, Zhou H, Zhou Y, Wu X, Zhao Y, Lu Y, Tan W, Yuan M, Ding X, Zou J, Li R, Liu H, Ewing RM, Hu Y, Nie H, Wang Y. Risk factors associated with disease severity and length of hospital stay in COVID-19 patients. J Infect. 2020;81(1):95-7. [PubMed] [Google Scholar]
11. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. [PubMed] [Google Scholar]
12. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-21. [PubMed] [Google Scholar]
13. Liu C, Ye L, Xia R, Zheng X, Yuan C, Wang Z, Lin R, Shi D, Gao Y, Yao J, Sun Q, Wang X, Jin M. Chest Computed Tomography and clinical follow-up of discharged patients with COVID-19 in Wenzhou City, Zhejiang, China. Ann Am Thorac Soc. 2020;17(10):1231-7. [PubMed] [Google Scholar]
14. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med. 2020;5:1-10. [PubMed] [Google Scholar]
15. Zuo W, Zhao X, Chen YG. SARS coronavirus and lung fibrosis. In: Lal SK, editor. Molecular biology of the SARS-coronavirus. Berlin and Heidelberg: Springer; 2010. p. 247-58. [Google Scholar].
16. Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. Eur Respir Rev. 2019;28(153):19-23. [PubMed] [Google Scholar]
17. Li Y, Li H, Liu S, Pan P, Su X, Tan H, Wu D, Zhang L, Song C, Dai M, Li Q, Mao Z, Long Y, Hu Y, Hu C. Pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. Mol Immunol. 2018;99:134-44. [PubMed] [Google Scholar]

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

18. Chen JY, Qiao K, Liu F, Wu B, Xu X, Jiao GQ, Lu RG, Li HX, Zhao J, Huang J, Yang Y, Lu XJ, Li JS, Jiang SY, Wang DP, Hu CX, Wang GL, Huang DX, Jiao GH, Wei D, Ye SG, Huang JA, Zhou L, Zhang XQ, He JX. Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis. Chin Med J (Engl). 2020 Jun 20;133(12):1390-6. [PubMed] [Google Scholar]
19. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10. [PubMed] [Google Scholar]
20. Wilson JG, Liu KD, Zhuo H, Caballero L, McMilan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, Lee JW, Rogers AJ, Levitt J, Wiener-Kronish J, Bajwa EK, Leavitt A, McKenna D, Thompson BT, Matthay MA. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med.2015;3(1):24-32. [PubMed] [Google Scholar]
21. Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. Lancet Respir Med. 2021 Jan;9(1):e8. [PubMed] [Google Scholar]
22. Arastehfar A, Carvalho A, van de Veerdonk FL, Jenks JD, Koehler P, Krause R, Cornely OA, Perlin DS, Lass-Florl C, Hoenigl M. COVID-19 associated pulmonary aspergillosis (CAPA)-from immunology to treatment. J Fungi (Basel). 2020;6(2):91. [PubMed] [Google Scholar]
23. Chennamchetty VK, Adimulapu S, Kola BP, Padua MD, Ambika C, Verma MK, Rao MVR. Post-COVID pulmonary mucormycosis- A case report. IP Indian J Immunol Respir Med. 2021;6(1):62-6. [Google Scholar]
24. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus. 2020;12(9):10726. [Google Scholar]
25. Kumar N, Kumar S, Vardhan H, Lakhtakia L, Daga MK. Cardiovascular Manifestations of SARS CoV-2: A Review. J Adv Res Med. 2020;7(2):1-10. [Google Scholar]
26. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):819-24. [PubMed] [Google Scholar]
27. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, Xu L, Li X, Liu H, Yin P, Li K, Zhao J, Li Y, Wang X, Li Y, Zhang Q, Xu G, Chen H. Altered lipid metabolism in recovered SARS patients twelve years after infection. Sci Rep. 2017;7(1):9110. [PubMed] [Google Scholar]
28. Yu CM, Wong RS, Wu EB, Kong SL, Wong J, Yip GWK, Soo YOY, Chiu MLS, Chan YS, Hui D, Lee N, Wu A, Leung CB, Sung JJY. Cardiovascular complications of severe acute respiratory syndrome. Postgrad Med J. 2006;82(964):140-4. [PubMed] [Google Scholar]
29. Vaira LA, Salzano G, Deiana G, Salzano FA, Riu GD. In Response to: In Reference to Anosmia and Ageusia: Common Findings in COVID-19 Patients. Laryngoscope. 2020;30(10):1002. [Google Scholar]
30. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767-83. [PubMed] [Google Scholar]
31. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol. 2020;16(11):636-44. [PubMed] [Google Scholar]
32. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan. 2005;14(3):113-9. [PubMed] [Google Scholar]
33. Barrantes FJ. Central nervous system targets and routes for SARS-CoV-2: Current views and new hypotheses. ACS Chem Neurosci. 2020;11(18):2793-803. [PubMed] [Google Scholar]
34. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: Identification of cell types and trends with age. ACS Chem Neurosci. 2020;11(11):1555-62. [PubMed] [Google Scholar]
35. Calderón-Garciduenas L, Torres-Jardon R, Franco-Lira M, Kulesza R, Gonzalez-Maciel A, Reynoso-Robles R, Brito-Aguilar R, Garcia-Arreola B, Revueltas-Ficachi P, Barrera-Velazquez JA, Gracia-Alonso G, Garcia-Rojas E, Mukherjee PS, Delgado-Chavez R. Environmental nanoparticles, SARS-CoV-2 brain involvement, and potential acceleration of Alzheimer's and Parkinson's diseases in young urbanites exposed to air pollution. J Alzheimers Dis. 2020;78(2):479-503. [PubMed] [Google Scholar]
36. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brossewon F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405. [PubMed] [Google Scholar]
37. Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, Al-Dalahmah O, Zecca L, Sette A, Bubacco L, Meucci O, Moro E, Harms AS, Xu Y, Fahn S, Chaudhuri KR. COVID-19 and possible links with Parkinson's disease and parkinsonism: From bench to bedside. NPJ Parkinsons Dis. 2020;6:18. [PubMed] [Google Scholar]

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

38. Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, Zaheer SA, Iyer SS, Burton C, James D, Zaheer A. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. Neuroscientist. 2020;26(5-6):402-14. [PubMed] [Google Scholar]
39. Palao M, Fernández-Díaz E, Gracia-Gil J, Romero-Sanchez CM, Diaz-Maroto I, Segura T. Multiple sclerosis following SARS-CoV-2 infection. Mult Scler Relat Disord. 2020;45:102377. [PubMed] [Google Scholar]
40. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. J Virol. 2000;74(19):8913-21. [PubMed] [Google Scholar]
41. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, Zandi MS, Lewis G, David AS. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611-27. [PubMed] [Google Scholar]
42. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, Rubin GJ. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020;395(10227):912-20. [PubMed] [Google Scholar]
43. Galea S, Merchant RM, Lurie N. The mental health consequences of COVID-19 and physical distancing: the need for prevention and early intervention. JAMA Intern Med. 2020;180(6):817-18. [PubMed] [Google Scholar]
44. Carvalho PMM, Moreira MM, Oliveira MNA, Landim JMM, Neto MLR. The psychiatric impact of the novel coronavirus outbreak. Psychiatry Res. 2020;286:112902. [PubMed] [Google Scholar]
45. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47(3):193-9. [PubMed] [Google Scholar]
46. Wheatland R. Molecular mimicry of ACTH in SARS—implications for corticosteroid treatment and prophylaxis. Med Hypotheses. 2004;63(5):855-62. [PubMed] [Google Scholar]
47. Leow MKS, Kwek DSK, Ng AWK, Ong KC, Kaw GJL, Lee LSU. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol. 2005;63(2):197-202. [Google Scholar]
48. Chrousos GP, Kaltsas G. Post-SARS sickness syndrome manifestations and endocrinopathy: how, why, and so what? Clin Endocrinol (Oxf). 2005;63(4):363-5. [PubMed] [Google Scholar]
49. Touzot M, Beller CL, Touzot F, Louet AL, Piketty C. Dramatic interaction between levothyroxine and lopinavir/ritonavir in a HIV-infected patient. AIDS. 2006;20(8):1210-2. [PubMed] [Google Scholar]
50. Wei L, Sun S, Zhang J, Hong Z, Xu Y, Ma Q, McNutt MA, Korteweg C, Gu J. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). Biochem Cell Biol. 2010;88(4):723-30. [PubMed] [Google Scholar]
51. Vignera SL, Cannarella R, Condorelli RA, Torre F, Aversa A, Calogero AE. Sex-specific SARS-CoV-2 mortality: among hormone-modulated ACE2 expression, risk of venous thromboembolism and hypovitaminosis D. Int J Mol Sci. 2020;21(8):2948. [PubMed] [Google Scholar]
52. Xu J, Qi L, Chi X, Yang J, Wei X, Gong E, Peh S, Gu J. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod. 2006;74(2):410-16. [PubMed] [Google Scholar]
53. Sansone A, Mollaioli D, Ciocca G, Limoncin E, Colonnello E, Vena W, Jannini EA. Addressing male sexual and reproductive health in wake of COVID-19 outbreak. J Endocrinological Invest. 2021;44(2):223-31. [Google Scholar]
54. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients With COVID-19 in a New York City health system. JAMA. 2020;324(8):799-801. [PubMed] [Google Scholar]
55. Perini P, Nabulsi B, Massoni CB, Azzarone M, Freyrie A. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19. Lancet. 2020;395(10236):1546. [PubMed] [Google Scholar]
56. Griffin DO, Jensen A, Khan M, Chin J, Chin K, Parnell R, Awwad C, Patel D. Arterial thromboembolic complications in COVID-19 in low-risk patients despite prophylaxis. Br J Haematol. 2020;190(1):11-13. [Google Scholar]
57. Hemasian H, Ansari B. First case of Covid-19 presented with cerebral venous thrombosis: a rare and dreaded case. Rev Neurol (Paris). 2020 Jun;176(6):521-3. [PubMed] [Google Scholar]
58. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT, Barco S, Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14. [PubMed] [Google Scholar]
59. Zheng KI, Wang XB, Jin XH, Liu WY, Gao F, Chen YP, Zheng MH. A case series of recurrent viral RNA positivity in recovered COVID-19 Chinese patients. J Gen Intern Med. 2020;35(7):2205-6. [PubMed] [Google Scholar]
60. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11. [PubMed] [Google Scholar]

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102

61. Carfì A, Bernabei R, Landi F, Gemelli against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-5. [PubMed] [Google Scholar]
62. Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, Leung JW, Belay ED. Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2: a systematic review. J Pediatr. 2020;226:45-54. [Google Scholar]
63. Machhi J, Herskovitz J, Senan AM, Dutta D, Nath B, Oleynikov MD, Blomberg WR, Meigs DD, Hasan M, Patel M, Kline P, Chang RCC, Chang L, Gendelman HE, Kevadiya BD. The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections. J Neuroimmune Pharmacol. 2020;15(3):359-86. [PubMed] [Google Scholar]
64. Rawal G, Yadav S, Kumar R. Post-intensive Care Syndrome: an Overview. J Transl Int Med. 2017;5(2):90-92. [PubMed] [Google Scholar]
65. Harvey MA, Davidson JE. Postintensive Care Syndrome Right Care, Right Now…and Later. Crit Care Med. 2016;44(2):381-5. [PubMed] [Google Scholar]

ISSN: 2349-7181
DOI: https://doi.org/10.24321/2349.7181.202102