

Review of Neurological and Renal Manifestations of COVID 19 and its Management: A Narrative View

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Abstract: *A global public health threat causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the result of the coronavirus disease (COVID-19) pandemic. Patients have been experiencing pneumonia and acute respiratory distress syndrome among others as distinctive severe manifestations of the disease. Furthermore, other articles have stated that aside from respiratory symptoms, neurological damage, acute kidney failure, skin manifestations, renal damage, endocrine organ manifestations and the eyes are also affected by the systemic COVID-19 disease as part of its complications. However, the spectrum of neurological and renal involvement in COVID-19 has not been elucidated yet. Herein, we provide information and data taken from other references as we discussed the complications and potential mechanisms of COVID-19 in the nervous and renal system and the possible optimal therapeutic and non-therapeutic strategies in this review.*

Keywords: SARS-CoV-2 infection; acute respiratory distress syndrome; acute kidney injury; end-stage kidney disease

Objective: To review the pathophysiology and clinical manifestations of the neurologic and renal sequelae of COVID-19 along with corresponding management of the disease condition.

1. Introduction

Coronavirus disease 2019 (COVID-19) has caused a worldwide pandemic viral disease with a major impact on health care systems and economies. Elderly adults are the primary target of the disease; however, younger patients without comorbidities can also be diagnosed with severe disease. SARS-CoV-2 infection presents primarily as a lower tract respiratory infection transmitted via air droplets, but the multisystemic nature of the disease is becoming increasingly apparent as more data are emerging. Indeed, the scope of coronavirus infection and damage has gone beyond pulmonary involvement considering a significant subset of patients experiences various secondary conditions [1, 2].

Respiratory failure, the lethal manifestation of COVID-19, is in most cases responsible for the 5, 213, 720 deaths worldwide [3, 4]. Although the upper and lower respiratory tracts are the main sites of entry of SARS-CoV-2 into the body, resulting in COVID-19 pneumonia as the most common presentation, acute lung damage has usually been followed by pulmonary fibrosis and chronic impairment of lung function, with impaired quality of life. Aside from affecting the respiratory system causing pneumonia, multiorgan dysfunction and failure are likely to occur in severe cases [5]. Growing evidence revealed that coronaviruses can even invade the nervous tissue [6], [7] which results in numerous neurological manifestations (NM) and neurological complications (NC) [8] Upon direct

autopsy examination of these patients, it has been shown that complications have reached beyond the lungs. According to studies, this condition is probably neurogenic in origin and may result from the viral invasion of cranial nerve I, progressing into rhinencephalon and brainstem respiratory centers. The increasing reports of involvement in the central nervous system (CNS) and the peripheral nervous system (PNS) which present damages of the neurons directly or indirectly, lead to long-term neurological sequelae. Mao L, Jin H, Wang M, et al., 2019 reported that a large retrospective observational study from China showed that among 214 hospitalized patients with confirmed SARS-CoV-2 infection, 36.4% had neurological manifestations [14]. Most NM occurred during the early admissions in the hospital for severe cases of infection.

In addition, covid-19 infection causes acute kidney injury and is an independent risk factor for mortality. The proportion of patients developing AKI is significantly higher when they develop severe disease. Patients who die from the severe disease most notably show diffuse acute tubular injury on postmortem examination with a possible contribution of focal macro- and microvascular thrombi. Although a recent autopsy series of patients who died with severe COVID-19 in China found acute tubular necrosis in the kidney, a few patient reports have also described collapsing glomerulopathy in COVID-19 and this can be seen from the renal biopsies of patients with proteinuria and hematuria [9], [12], [13].

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2. Pathophysiology of RENAL-CNS manifestations of COVID-19 Infection

2.1 Pathogenesis in General

SARS-CoV-2 is an enveloped β -coronavirus, with a genetic sequence very similar to SARS-CoV-1 (80%) and bat coronavirus RaTG13 (96.2%) [14]. The viral envelope is coated by spike (S) glycoprotein, envelope (E), and membrane (M) proteins (fig 1). After the SARS-CoV2 spike (S) protein attaches to angiotensin-converting enzyme 2 (ACE2) receptors, the S protein is cleaved and activated by transmembrane serine proteases family (TMPRSS), which allows the virus to release fusion peptide that aids in the membrane fusion [15]. The virus structure and replication cycle are described in figure 1.

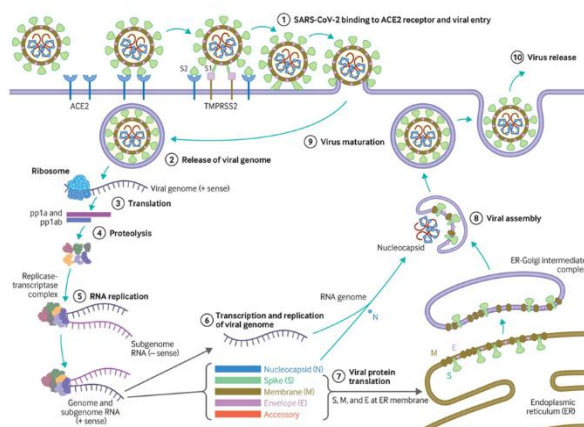


Figure 1: Virus structure and replication cycle [16]

(1) The virus binds to ACE 2 as the host target cell receptor in synergy with the host's transmembrane serine protease 2 (cell surface protein), which is principally expressed in the airway epithelial cells and vascular endothelial cells. This leads to membrane fusion and releases the viral genome into the host cytoplasm (2). Stages (3-7) show the remaining steps of viral replication, leading to viral assembly, maturation, and virus release.

2.2 Mechanism of AKI

COVID-19 infection could be from the synergistic effect of virus-induced direct cytotoxic effect and cytokine-induced systemic inflammatory response. AKI is more pronounced in patients with severe disease, acute respiratory distress syndrome (ARDS), and those needing ICU admission. Other possible mechanisms of AKI could be acute tubular necrosis (ATN) due to multiorgan failure and shock, and possible prerenal etiology from volume depletion secondary to decreased oral intake and high fever. Drug toxicity, hemodynamic insult, and contrast exposure can also play a role. The workup for AKI in COVID-19 infection should be similar to the other causes of AKI. Mohamed et al [17] discussed different etiologies of AKI in their study which include ischemic acute tubular injury, toxic acute tubular injury or combination of both, acute interstitial nephritis, de novo glomerular disease, prerenal azotemia, and unspecified reasons. The contributing factors to different etiologies

include hypotension, shock, rapid atrial fibrillation, prolonged volume depletion, rhabdomyolysis, toxic agents such as vancomycin, and iodinated contrast, overt proteinuria [17].

2.3 CNS Manifestations

COVID-19 mainly manifests with fever, dry cough, and fatigue. Other patients have symptoms of a stuffy or runny nose, headache, myalgia, and diarrhea. But most critically ill patients develop dyspnea or hypoxia 1 week after the onset of illness. In addition to the lung, other organs such as the spleen, liver, heart, kidney, and brain are also affected [18], [19]. Recently, Zhang et al. were the first to prove that SARS-CoV-2 could directly infect induced pluripotent stem cells-derived human neural progenitor cells, and extensive viral replication and viral particles were detected in the neurospheres and brain organoids with SARS-CoV-2 infection. Additionally, they showed that SARS-CoV-2 could productively infect the human brain [20].

A retrospective case series demonstrated that the neurological symptoms include central nervous system (CNS) symptoms or diseases (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy), peripheral nervous system (PNS) symptoms (hyposmia, hypogeusia, hypoplasia, and neuralgia), and skeletal muscle symptoms [21].

Furthermore, according to the report of Wu Y, Xu X, Chen Z, et al, 2020, direct invasion of the nervous system by viruses can be possibly verified by the presence of RNA and protein particles of viruses in the CNS specimens including fluid or parenchyma [22]. In another study by Dos Santos MF, et al, 2020 they stated that clinical and laboratory findings revealed a characteristic of SARS-CoV-2 (COVID-19) as a neurotropic virus that can invade the nervous tissues. Theories on viral entry into the CNS, particularly the brain and its pathophysiology have been proposed by certain literature. The coated-mediating endocytosis /exocytosis served as a possible route of entry to enter and transmit within the cells [23]. CNS manifestations of COVID-19 have been reported to include encephalopathy, encephalitis, loss of consciousness, stroke, headache, dizziness, and epilepsy [24]-[31]. PNS symptoms include Guillain Barré syndrome (GBS), anosmia, ageusia, and skeletal muscle damage, among others [26]. Although the neurologic manifestations are not fully elucidated, these sequelae are important to understand, as they can have a lasting impact on patients [27].

Jasti M, Nalleballe K., et al, 2020 also reported the possible potential mechanisms that include 1) viral entry via ACE2 receptors into the endothelium lining the blood capillaries and subsequent neuro-invasion, 2) neurological edema and brain stem compression as a result of breached blood-brain barrier, 3) neurological edema and hypercoagulability as a result of cytokine storm syndrome, and 4) propagation via mechanoreceptors and chemoreceptors in the lung and lower respiratory airways [28].

Furthermore, it was reported that neurological manifestations of COVID-19 could be a result of hypoxia, respiratory, and/or metabolic acidosis at end-stage disease [29].

3. Possible Link between Sars-Cov-2 Infection and the Nervous System

Although the most established manifestation of SARS-CoV-2 infection is pneumonia, there has been convincing evidence that SARS-CoV-2 can go beyond the pulmonary system and reach up to the nervous system. This can be proven from the numerous neurological clinical manifestations linked with SARS-CoV-2 during the disease process [32] like headache, confusion, and dizziness which are observed in the infected individuals [33], [34]. SARS-CoV-2 has been seen in the brain tissue during autopsy examination of a 56-year-old male patient in China [35]. These findings are further substantiated by Moriguchi et al., who reported first the existence of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF) of an infected patient diagnosed with encephalopathy using the real-time reverse transcription PCR [36].

There can be three possible explanations for this finding, first, the SARS-CoV-2 for the most part is bound to the cell and possibly increase without penetrating the CSF through the cell-to-cell transfer. Second, virus concentration in the CSF did not meet the minimum limit of detection though it is present. And lastly, the CSF itself contains hem products that could possibly interfere in the polymerase for detection of SARS-CoV-2 [34]. With the presented facts available in the literature, it can be safely concluded that most of the severe Covid-19 cases usually develop more elaborate neurological complications compared to those with light infection [37].

In the systematic review conducted by Guerrero et al., various neurological disorders were established as outlined here: 119 showed neurological symptoms, 62 showed neuroimaging findings, 60 studies showed cerebrospinal fluid results, 51 showed CNS and PNS involvement by COVID-19, 28 reported electrophysiological findings, and four described neuropathology findings. With all the studies reviewed, they have established a total of 10, 723 Covid-19 patients who manifested neurological symptoms. Of the total 10, 723 cases, they found 1633 and 43 patients with conditions affecting the central nervous system and peripheral nervous system, respectively. With this data, there are still 9047 patients remaining who presented with neurological symptoms not attributed to any nosological activity. A summary is presented in Table 1. [38]

Moriguchi et al., 2020; Solomon et al., 2020 in their studies reported that clinical-pathological studies have been conducted to test for the presence of the virus in the brain or the cerebrospinal fluid (CSF) and it resulted in mixed results. Some studies have shown SARS-CoV-2 RNA in the brain post-mortem or in the CSF in patients with encephalopathy or encephalitis, but at very low levels [39, 40]. Other studies could not detect viral invasion, even though there was evidence of CSF inflammation [41]. Considering the inconsistent data and the low levels of viral RNA, when

detected, the possibility of artifact or contamination has been raised in the process of conducting the studies [41]. SARS-CoV-2 could pass the blood-brain barrier (BBB) because inflammatory cytokines induce BBB instability or via monocytes [42]. It could reach brain tissue via circumventricular organs (CVOs), midline structures around the third and fourth ventricles, that monitor blood and cerebrospinal fluid content via fenestrated capillaries lacking the junctional proteins expressed in the BBB [43].

Table 1: Clinical Conditions associated with CNS and PNS SARS-CoV-2-infection

Clinical conditions associated with Covid-19 affecting the Central Nervous System	No. of Patients per Proportion
Encephalopathy	990 (60.7%)
Unspecified Stroke Type	416 (225.5%)
Ischemic Stroke	159 (9.7%)
Hemorrhagic Stroke	40 (2.4%)
Encephalitis and Meningoencephalitis	19 (1.2%)
Acute disseminated encephalomyelitis	4 (0.2%)
Venous Sinus Thrombosis	3 (0.2%)
Multiple Sclerosis Exacerbation	2 (0.1%)
TOTAL	1633 (100%)
Clinical Conditions Associated with Covid-19 Affecting the Peripheral Nervous System	No. of Patients per Proportion
Guillain-Barré Syndrome	22 (51.2%)
Other cranial nerve disorders	12 (27.9%)
Facial Palsy	5 (11.6%)
Miller Fisher Syndrome & Polyneuritis Cranialis	4 (9.3%)
TOTAL	43 (100%)

Source: Central and peripheral nervous system involvement by COVID-19: a systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. Adapted from Guerrero. *JBMC infectious diseases* (2021) 21:5115

The researchers begin with the virus' entry into the body, thought frequently to occur at cellular docking ports called ACE2 receptors found in cells of the lungs and arteries (as well as in the heart, kidneys, brain, and intestines). The virus can damage endothelial cells that line blood vessels and arteries. This, the researchers note, can cause inflammation, the formation of blood clots (thrombi), and lead to brain damage [44]. When inflammation becomes systematic in the body, it can have many effects. The result of this systemic inflammation can lead to multi-organ damage that includes the CNS as well as the Kidney. Although many studies reported that the mechanism of renal involvement in COVID-19 is unknown and may be multifactorial, adding that infection by the virus may indirectly injure the kidneys via systemic inflammation, hypoxemia (low blood oxygen), shock, hypotension, and renin-angiotensin system imbalance [45].

Several mechanisms that may overlap have been proposed to explain the link between SARS-CoV-2 infection and nervous

system injury and other organs [46]. Clinical manifestations of COVID-19 might be a consequence of the viral infection per se and/ or the adverse insult of the hyperinflammatory status and dysregulated metabolic function, in combination with the multiple organ damage observed in patients after COVID-19 infection [47], [48]. Direct viral damage of nervous tissue might be possible in different ways. Infection of olfactory neurons in the nose may enable the virus to enter the brain trans neuronal and spread directly from the respiratory tract to the brain and other organs including the heart, kidneys, and gastrointestinal tract [48]. The excessive immune response which results in a hyperinflammatory status and cytokine storm may represent another alternative mechanism. Cytokines can directly pass through the blood-brain barrier causing considerable damage such as acute necrotizing encephalopathy [49].

A possible link of the relation of the neurologic damage with the renal is the direct viral damage in the cellular docking ports called ACE2 receptors found in cells of the lungs and arteries as well as in the kidneys, and brain, causing hyperinflammatory reactions injuring the said organs. The most frequent abnormality in patients with COVID-19 is mild-to-moderate proteinuria which is mediated via several mechanisms [50]. It has been reported that patients in the ICU have higher levels of IL-1 β , IL-8, IFN- γ , and TNF- α [51]. This suggests a potential role of cytokine release syndrome (CRS), also known as “cytokine storm” comparable with sepsis-associated AKI (SA-AKI), where the uncontrolled systemic inflammatory response leads to kidney injury and possible injury to the brain [51]. Other studies have confirmed tropism to monocytes as well as lymphocytes, where the virus induces proinflammatory responses and cell death [52]. Systemic inflammatory response triggers autoimmune mechanisms, leading to dysregulation of the coagulation cascade as reflected by elevated D-dimers, prolonged prothrombin time, high fibrinogen levels, low antithrombin levels, thrombocytopenia and diffuse intravascular coagulation in severely ill patients with COVID-19 [53, 54].

4. Pharmacological Management of COVID-19 Infection

At present, there is no single drug therapeutically used and approved by the US Food and Drug Administration (FDA) for the therapeutic management of SARS-CoV-2 Infection. Normally, to discover a drug for treatment requires one to two decades. But with the advent of the pandemic situation, we are in right now, it is not practical to wait for any drug to be discovered in order to mitigate the pandemic situation immediately. It is therefore necessary to think of a more rational approach to addressing the situation in order to control the spread of the infection [55]. This efficient and economical approach is called Drug Repurposing also known as repositioning, re-profiling, re-tasking, and rescue of drugs. This approach has been shown effective since 75% of known drugs could be possibly repositioned for its application on several diseases [56-58]. Furthermore, repurposed drugs are safer to use because their pharmacokinetics, toxicology, and safety data are already

established. Hence, utilizing repurposing as a primary strategy is highly applicable to the pandemic situation we are facing right now. And currently, this is an ongoing approach used in Covid-19 patients. [59]– [61]. Presently, physicians and scientists are investigating more than 350 COVID-19 therapeutic drugs (mostly repurposed) of which 75% of them has entered human clinical trials, and more than 150 repurposed [62].

4.1 Antiviral Drugs

Since SARS-CoV-2 replication will enable several clinical manifestations of COVID-19, it is, therefore, necessary to give an antiviral drug on the onset of Covid-19 infection because these drugs inhibit viral entry, viral membrane fusion and endocytosis [9]. Moreover, antiviral therapy may create the most impact before the progression of the disease condition to hyperinflammatory state, which is the characteristic of a late stage of the disease [63].

4.2 Treatment Mechanisms

For the mechanism of treatment, there are two postulated approaches that are being used in the repositioning of conventional drugs and the development of novel drug treatment (a) prevention of virus entry into the host cells and (b) suppression of various steps in virus replication inside the cells (Fig.2).

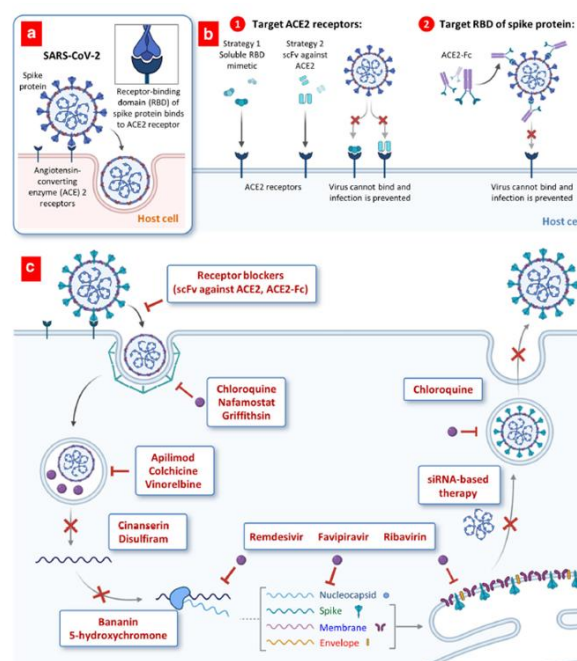


Figure 2: Treatment Mechanisms

a) Prevention of Viral Entry into the Host Cell

The best way to prevent infection is to block the entry of SARS-CoV-2 via the ACE2 receptors so they cannot enter and replicate inside the cell (fig.2c). Since most of the ACE2 receptors are found on the surface of the cells, the spike protein of the SARS-CoV-2 virus attaches to the ACE2 receptor on the cell membrane and receptor-mediated endocytosis [64].

b) Targeting the Coronavirus Replication

Unlike ACE2 receptor blockers, most repurposed drugs do not interact with the viral entry to the host cells. Instead, these drugs perform to hinder viral replication inside the cell. (Fig.2c). Among the drugs used for the treatment are the following: are the following: (a) Chloroquine, Nafamostat, and Griffithsin – these drugs prevent endocytosis; (b) Hydroxychloroquine, Apilimod, Colchicine, Vinorelbine-

these drugs perform to prevent maturation of the endosome; (c) Cinanserin, Disulfiram – these drugs releases viral genome and (d) Bananin, 5-hydroxychromone, Remdesivir, Favipiravir, Ribavirin – these drugs prevent viral replication, transcription, and translation of viral proteins.

See Table 2 for the summary of various repurposed and original antiviral drugs [65]

Table 2: Summary of various repurposed and original antiviral drugs

Drugs	Applications	Targets	Mechanism of action against life cycle of SARS-CoV-2 virus
Favipiravir	Viral diseases	RNA-dependent RNA polymerase (RdRp)	Inhibits viral RNA polymerase and RNA replicase activity
Remdesivir	Ebola virus diseases (EVD)	Viral proteases, RdRp	Interferes with viral RNA polymerase activity and reduces viral RNA synthesis to arrest viral replication
Lopinavir	HIV infections	Viral proteases	Inhibits the viral proteases activity
Ritonavir	HIV infections	Viral proteases	Inhibits the viral proteases activity
Chloroquine	Malarial	Angiotensin Converting Enzyme-2 (ACE2)	Interferes with glycosylation of ACE2
Ribavirin	Respiratory syncytial virus (RSV) infection	RdRp	Inhibits viral RNA polymerase activity
Umifenovir (Arbidol)	Influenza	S-spike glycoprotein	Inhibits membrane fusion and prevent viral entry into the host cells

Source: Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19 by Majumder J and Minko T.

Available from: <https://doi.org/10.1208/s12248-020-00532-2>

4.3 Monoclonal Antibodies

Monoclonal antibodies are made in the laboratory that imitates the ability of the immune system to fight against dangerous pathogens like viruses [66]. These antibodies are specific to a viral protein. CR3014 and CR3022 are two SARS-CoV neutralizing monoclonal antibodies that bind to the receptor-binding domain (RBD) of the SARS-CoV spike protein in order to deactivate the virus [67]. But CR3022 has shown possible therapeutic options for the treatment of Covid-19 infection. Recently, researchers have used a cloning method in the experiment of monoclonal antibodies on recovered Covid-19 patients. They have successfully cloned two anti-SARSCoV-2 RBD-hACE2 blocking monoclonal antibodies (mAbs) from SARS-CoV-2 RBD-specific memory B cells [68]. These two cloned monoclonal antibodies have the ability to block the interaction between the ACE2 receptor and SARS-CoV-2 RBD leading to the neutralization of the SARS-CoV-2 spike protein [69].

Currently, the Food and Drug Administration (FDA) has granted the three monoclonal antibodies for Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). These monoclonal antibodies are for mild to moderate COVID-19 cases only who are not confined in the hospital and have a confirmed positive result based on the laboratory tests. These three mAbs include: Bamlanivimab plus etesevimab: These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.

Casirivimab plus imdevimab: These are recombinant human mAbs that bind to non-overlapping epitopes of the spike protein RBD of SARS-CoV-2.

Sotrovimab: This mAb targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2.

According to the SARS-Cov-2 Treatment Guidelines Panel, the dosing recommendations of the three monoclonal antibodies are the following, (a) Bamlanivimab 700 mg plus etesevimab 1, 400 mg and this can be administered as an intravenous infusion, (b) Casirivimab 600 mg plus imdevimab 600 mg administered as an IV infusion or as subcutaneous (SQ) injections, (c) Sotrovimab 500 mg administered as an IV infusion.

When using casirivimab plus imdevimab, the Panel recommends Casirivimab 600 mg plus imdevimab 600 mg administered as an IV infusion. If an IV infusion is not feasible or would cause a delay in treatment, casirivimab 600 mg plus imdevimab 600 mg can be administered as four SQ injections (2.5 mL per injection).

A further recommendation of the panel includes the following:

When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.

The use of anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the EUA criteria for outpatient treatment.

Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access

programs for patients who either have not developed an antibody response to SARS-CoV-2 infection or are not expected to mount an effective immune response to infection [70].

5. Conclusion

The more than two years of battling with the pandemic brought about by COVID-19 has become a global concern. Several studies and reviews have written a lot about this Sars-Cov 19 virus and found out that the respiratory system is not the only system involved in this disease. In this review, we discussed the possible link of different complications but focused on the correlation of the neurologic (CNS) manifestations with the renal injuries that might be the result of hyper-inflammatory effect resulting to hypoxemia (low blood oxygen), shock, hypotension, and renin-angiotensin system imbalance. The potential role of cytokine release syndrome (CRS), also known as “cytokine storm” was also considered.

The involvement of vital organs such as the lungs, the heart, the gastrointestinal tract, the liver, the central nervous system (brain), the blood, and the kidneys is part of the broad spectrum of clinical signs and symptoms. Multisystemic involvement is commonly associated with severe disease and might predict worse clinical outcomes and increased mortality. The high binding affinity of the virus with the ACE2 receptors that are widely expressed in most human cells are said to be the main mechanism described by most studies and reviews. Still, up to the present, the exact role of ACE2 receptors in COVID-19 pathophysiology is part of the ongoing investigations. Furthermore, the systematic management of treatment for these complications of Covid 19 is currently at the frontline of clinical research, organ-specific treatment strategies for renal and CNS manifestations should also be evaluated in order to optimize the management of patients with severe organ dysfunction. Possible non-pharmacologic treatment could also be considered as there is still no specific treatment approved for patients with COVID-19.

Currently, several pharmacological treatments for COVID-19 are being proposed; these include antivirals previously used for other diseases (Liu et al.2020), corticosteroids, besides generic viral treatments such as vitamin C, zinc, and selenium (Juul et al.2020; Singh et al.2020). However, some non-pharmacological interventions are also being proposed in the world, mainly in order to prevent the contamination and spread of COVID-19. These measures include social distance, washing hands with soap and water, using masks, cleaning with 70% alcohol, closing schools and banning crowds, among others. In addition, non-pharmacological treatments, related to supportive therapies, such as oxygenation, have been used.

In addition to preventive interventions and supportive therapies for COVID-19, there are other types of non-pharmacological interventions being proposed worldwide. Thus, it is important to know the current status of non-pharmacological treatments; these treatments must be

synthesized based on evidence, to guide health managers, mainly for the creation of recommendations for the population. Considering the presented data, this narrative review aims to present some treatment used for therapy of patients with COVID-19, including supportive treatments, and through these studies, to show the current status, as well as the consensus among researchers and to disseminate knowledge of the techniques used as more effective responses to the health emergency caused by the SARS-CoV-2 pandemic.

6. Acknowledgments

We gratefully acknowledge the great minds who put out pioneer research on various topics that led us to reference them. Their proficiency in their respective fields not only helped us put this paper together but also gave us new insight on how SARS-Cov-2 mutates and eventually affects the degeneration of the body and thus appropriate medical and pharmaceutical care should be administered for proper management.

We would also like to thank our professor Dr. Donabelle Dean for her patience and guidance, and for lending us her expertise in pharmacotherapeutics that likewise helped us formulate this particular topic for our research. And most of all, we thank our Lord God and Savior for the wisdom and knowledge He has given to us.

References

- [1] C. Ronco, R. Thiago, S. Faeq Husain. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med.*2020 Jul; 8 (7): 738-742. Available from: DOI: [https://dx.doi.org/10.1016/S2213-2600\(20\)30229-0](https://dx.doi.org/10.1016/S2213-2600(20)30229-0)
- [2] G. Romána, P. Spencer, J. Reisd, et al. The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. *Journal of the Neurological Sciences* 414 Nov 2020; 116884. Available from: <https://doi.org/10.1016/j.jns.2020.116884>
- [3] World meter Available from: https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1
- [4] F. Wang, R. M. Kream, G. B. Stefano. Long-Term Respiratory and Neurological Sequelae of Covid-19. *Med Sci Monit.*2020 Nov; 26: e928996-1–e928996-10. Available from: <https://doi.org/10.12659/MSM.928996>
- [5] W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.*2020; 382 (18): 170820. <https://doi.org/10.1056/NEJMoa2002032>.
- [6] Y-C. Li, W-Z. Bai, T. Hashikawa. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.*2020; 92 (6): 552–5. <https://doi.org/10.1002/jmv.25728>.
- [7] M. Desforges, A. Le Coupancec, P. Dubeau, A. Bourgouin, L. Lajoie, M. Dubé, et al. Human

- coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*.2020; 12 (1): 14.
- [8] SJ. Pleasure, AJ. Green, SA. Josephson. The spectrum of neurologic disease in the severe acute respiratory syndrome coronavirus 2 pandemic infection: neurologists move to the frontlines: neurologists move to the frontlines. *JAMA Neurol*.2020; 77 (6): 679–80. <https://doi.org/10.1001/jamaneurol.2020.1065>.
- [9] CMS Singal, P. Jaiswal, P. Seth. SARS-CoV-2, more than a respiratory virus: Its potential role in neuropathogenesis. *ACS Chem Neurosci*.2020; 11 (13): 1887–99. Available from: <https://doi.org/10.1021/acscchemneuro.0c00251>
- [10] P. Sharma, N. N. Uppal, R. Wanchoo, et al. Covid-19-Associated Kidney Injury: A Case Series of Kidney Biopsy Findings. *J Am Soc Nephrol*.2020 Sep; 31 (9): 1948-1958. Available from: <https://doi.org/10.1681/ASN.2020050699>.
- [11] M. Kapp, A. Fogo, C. Roufouse, et al. Renal Considerations in COVID-19: Biology, Pathology, and Pathophysiology. *ASAIO J*.2021 Oct; 67 (10): 1087–1096. Available from: <https://doi.org/10.1097/MAT.0000000000001530>
- [12] S. Sreedhar Adapa, A. Chenna, M. Balla, et al. COVID-19 Pandemic Causing Acute Kidney Injury and Impact on Patients with Chronic Kidney Disease and Renal Transplantation. *J Clin Med Res* 2020 Jun; 12 (6): 352-361. Available from: <https://doi.org/10.14740/jocmr4200>.
- [13] Y. Cheng, et al. kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*.97, 829–838 (2020).
- [14] AS. Nordvig, KT. Rimmer, JZ. Willey, et al. Potential neurological manifestations of COVID-19. *Neurol Clin Pract*.2020 Jun 30: Epub.
- [15] M. Jasti, K. Nalleballe, V. Dandu, S. Onteddu (2020). A review of pathophysiology and neuropsychiatric manifestations of COVID-19. *J Neurol*. In press. doi: 10.1007/s00415-020-09950-w.
- [16] M. Cevik, K. Kuppalli, J. Kindrachuk, M. Peiris. Virology, transmission, and pathogenesis of SARS-CoV-2 *BMJ* 2020; 371: m3862 doi: 10.1136/bmj.m3862
- [17] MMB. Mohamed, I. Lukitsch, AE. Torres-Ortiz, JB. Walker, V. Varghese, CF. Hernandez-Arroyo, et al. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans. *Kidney360*.2020; 1 (July): 614–22.
- [18] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. (2020) 8: 420–2. doi: 10.1016/S2213-2600 (20) 30076-X
- [19] VG. Puelles, M. Lütgehetmann, MT. Lindenmeyer, JP. Sperhake, MN. Wong, L. Allweiss, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med*. (2020) 383: 590–2. doi: 10.1056/NEJMc2011400
- [20] BZ Zhang, H. Chu, S. Han, H. Shuai, J. Deng, YF. Hu, et al. SARS-CoV-2 infects human neural progenitor cells and brain organoids. *Cell Res*. (2020) 30: 928–31. doi: 10.1038/s41422-020-0390-x
- [21] L. Mao, M. Wang, S. Chen, Q. He, J. Chang, C. Hong, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *JAMA Neurol*. (2020) 77: 683–90. doi: 10.1001/jamaneurol.2020.1127
- [22] Y. Wu, X. Xu, Z. Chen, J. Duan, K. Hashimoto, L. Yang, C. Liu, C. Yang (2020) Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun* 87: 18–22. <https://doi.org/10.1016/j.bbi.2020.03.031>
- [23] MF. DosSantos, S. Devalle, V. Aran, D. Capra, NR. Roque, JM. Coelho-Aguiar, T. Spohr, JG. Subilhaga et al (2020) Neuromechanisms of SARS-CoV-2: a review. *Front Neuroanat* 14: 37. <https://doi.org/10.3389/fnana.2020.00037>
- [24] AS. Zubair, LS. McAlpine, T. Gardin, et al. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol*.2020; 77 (8): 1018-1027.
- [25] A. Whittaker, M. Anson, A. Harky. Neurological manifestations of COVID-19: a systematic review and current update. *Acta Neurol Scand*.2020; 142 (1): 14-22.
- [26] L. Mao, H. Jin, M. Wang, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*.2020; 77 (6): 683-690.
- [27] F. Khatoon, K. Prasad, V. Kumar. Neurological manifestations of COVID-19: available evidences and new paradigm. *J Neurovirol*.2020; 26 (5): 619-630.
- [28] V. Montalvan, J. Lee, T. Bueso, et al. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg*.2020; 194: 105921.
- [29] G. Nepal, JH. Rehrig, GS. Shrestha, et al. Neurological manifestations of COVID-19: a systematic review. *Crit Care*.2020; 24 (1): 421.
- [30] C. Ladecola, J. Anrather, H. Kamel. Effects of COVID-19 on the nervous system. *Cell*.2020; 183 (1): 16-27. e1.
- [31] MA. Ellul, L. Benjamin, B. Singh, et al. Neurological associations of COVID-19. *Lancet Neurol*.2020; 19 (9): 767-783.
- [32] G. Tsivgoulis, L. Palaiodimou, AH. Katsanos, et al. Neurological manifestations and implications of COVID-19 pandemic. *Ther Adv Neurol Disord*. Available from: <https://doi.org/10.1177/1756286420932036>
- [33] N. Chen, M. Zhou, X. Dong, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395 (10223): 507–513. Available from: [https://doi.org/10.1016/s0140-6736 \(20\) 30211-7](https://doi.org/10.1016/s0140-6736 (20) 30211-7)
- [34] BN Harapan and HJ. Yoo. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) and coronavirus disease 19 (COVID 19). *J Neurol* 268, 3059-3071 (2021). <https://doi.org/10.1007/s00415-021-10406-y>
- [35] A. Paniz-Mondolfi, C. Bryce, Z. Grimes, et al. Central nervous system involvement by severe acute

- respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol.*2020 Apr. Available from: <https://doi.org/10.1002/jmv.25915>
- [36] T. Moriguchi, N. Harii, J. Goto, et al., A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis.*2020 May; 94: 55–58. Available from: <https://doi.org/10.1016/j.ijid.2020.03.062>
- [37] L. Mao, H. Jin, M. Wang, Y. Hu, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.*2020 Apr; 77 (6): 683-690. Available from: <https://doi.org/10.1001/jaman.neurol.2020.1127>
- [38] J. Guerrero, L. Barragán, J. Martínez. Central and peripheral nervous system involvement by COVID-19: a systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. *BMC Infectious Diseases* (2021) 21: 515. Available from: <https://doi.org/10.1186/s12879-021-06185-6>
- [39] T. Moriguchi, N. Harii, J. Goto, D. Harada, H. Sugawara, J. Takamino, M. Ueno, H. Sakata, K. Kondo, N. Myose, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2 *Int. J. Infect. Dis.*, 94 (2020), pp.55-58
- [40] I. H. Solomon, E. Normandin, S. Bhattacharyya, S. S. Mukerji, K. Keller, A. S. Ali, G. Adams, J. L. Hornick, R. F. Padera Jr., P. Sabeti Neuropathological Features of Covid-19 *N. Engl. J. Med.* (2020), 10.1056/NEJMc2019373 Published online June 12, 2020
- [41] R. Bernard-Valnet, B. Pizzarotti, A. Anichini, Y. Demars, E. Russo, M. Schmidhauser, J. Cerutti-Sola, A. O. Rossetti, R. Du Pasquier Two patients with acute meningoencephalitis concomitant with SARS-CoV-2 infection *Eur. J. Neurol.* (2020), 10.1111/ene.14298. Published online May 30, 2020. Google Scholar
- [42] BP. Daniels, DW. Holman, L. Cruz-Orengo, H. Jujavarapu, DM. Durrant, RS Klein. Viral pathogen-associated molecular patterns regulate blood-brain barrier integrity via competing innate cytokine signals. *mBio.*2014; 5 (5): e01476-e14. doi: 10.1128/mBio.01476-14 PubMed Google ScholarCrossref
- [43] M. Boldrini, PD. Canoll, RS. Klein. How COVID-19 Affects the Brain. *JAMA Psychiatry.*2021; 78 (6): 682–683. doi: 10.1001/jamapsychiatry.2021.0500
- [44] M. Boldrini, M. D., A Close Look at How COVID-19 Infection Can Damage the Brain.2021 International Mental Health Research VirtualSymposium<https://www.bbrfoundation.org/content/close-look-how-covid-19-infection-can-damage-brain>
- [45] N. A. N. Cruz, et al. (2021) Angiotensin-Converting Enzyme 2 in the Pathogenesis of Renal Abnormalities Observed in COVID-19 Patients. *Frontiers in Physiology.* doi.org/10.3389/fphys.2021.700220.
- [46] AS. Zubair, LS. McAlpine, T. Gardin et al. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A Review. *JAMA Neurol* 2020.
- [47] EJ. Needham, SH. Chou, AJ. Coles, DK. Menon. Neurological implications of COVID-19 infections. *Neurocrit Care.*2020; 32: 667–671.
- [48] A. Nath. Neurologic complications of coronavirus infections. *Neurology.*2020; 94: 809–10.
- [49] N. Poyiadji, G. Shahin, D. Noujaim et al. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology* 2020; 201187.
- [50] Y. Cheng, R. Luo, K. Wang, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.*2020; 97: 829–38.
- [51] C. Huang, Y. Wang, X. Li, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.*2020; 395: 497–506.
- [52] J. Gu, E. Gong, B. Zhang, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med.*2005; 202: 415–24.
- [53] X. Jin, JS. Lian, JH. Hu, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut.*2020; 69: 1002–9.
- [54] N. Tang, D. Li, X. Wang, Z. Sun. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.*2020; 18: 844–7.
- [55] J. Majumder and T. Minko. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. *AAPS J.*2021 Jan 5; 23 (1): 14. Available from: <https://doi.org/10.1208/s12248-020-00532-2>.
- [56] TU. Singh, S. Parida, MC. Lingaraju, et al. Drug repurposing approach to fight COVID-19. *Pharmacol. Rep* 72, 1479–1508 (2020). Available from: <https://doi.org/10.1007/s43440-020-00155-6>
- [57] F. Huang, C. Zhang, Q. Liu, Y. Zhao, Y. Zhang, Y. Qin, et al. Identification of amitriptyline HCl, flavin adenine dinucleotide, azacitidine and calcitriol as repurposing drugs for influenza A H5N1 virus-induced lung injury. *PLoS Pathog.*2020; 16 (3): e1008341. Available from: <https://doi.org/10.1371/journal.ppat.1008341>.
- [58] D. Scherman, C. Fetro. Drug repositioning for rare diseases: Knowledge-based success stories. *Therapie.*2020; 75: 161–7. Available from: <https://doi.org/10.1016/j.therap.2020.02.007>.
- [59] H. Bauchner, PB. Fontanarosa. Randomized clinical trials and COVID-19: Managing expectations. *JAMA.*2020 May; 323 (22): 2262–2263. Available from: <https://doi.org/10.1001/jama.2020.8115>.
- [60] BA. Ahidjo, MWC. Loe, YL. Ng, CK. Mok, JJH. Chu. Current perspective of antiviral strategies against COVID-19. *ACS Infect Dis.*2020 Jun; 6: 1624–1634. Available from: <https://doi.org/10.1021/acsinfectdis.0c00236>.
- [61] S. Malik, A. Gupta, X. Zhong, TP. Rasmussen, JE Manautou, R. Bahal. Emerging therapeutic modalities against COVID-19. *Pharmaceuticals (Basel)* 2020 Aug; 13 (8): 188. Available from: <https://doi.org/10.3390/ph13080188>
- [62] COVID-19 Vaccine tracker.2020 [cited 2020 08/08/2020]; Available from: <https://biorender.com/covid-vaccine-tracker>.

- [63] JM. Sanders, ML. Monogue, TZ. Jodlowski, JB. Cutrell. Pharmacologic treatments for Coronavirus Disease 2019 (COVID-19): a review. JAMA.2020; 323 (18): 1824-1836. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32282022>.
- [64] HK. Siddiqi, MR. Mehra. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant.2020; 39 (5): 405-407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32362390>.
- [65] Coronavirus disease (COVID-19) pandemic. World Health Organization; 2020 [cited 2020 10/31/2020]; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=Cj0KCQjwlvT8BRDeARIsAACRFiW_AoKe8cr7J7MyGq460jb4LEDnznIAUBkEXISSPxIfKCLbfmxjYgUaAriBEALw_wcB.
- [66] Coronavirus (Covid-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of Covid-19. Available from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19>
- [67] J. Ter Meulen, EN. Van den Brink, LL. Poon, WE. Marissen, CS. Leung, F. Cox, et al. Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. PLoS Med.2006; 3 (7): e237. Available from: <https://doi.org/10.1371/journal.pmed.0030237>.
- [68] XW Xu, XX Wu, XG Jiang, KJ Xu, LJ. Ying, CL. Ma, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ.2020; 368: m606. Available from: <https://doi.org/10.1136/bmj.m606>.
- [69] F. Puoci. "Monoclonal-type" plastic antibodies for COVID-19 treatment: what is the idea? J Funct Biomater.2020; 11 (2): 43. Available from: <https://doi.org/10.3390/jfb11020043>.
- [70] Anti-SARS-CoV-2 Monoclonal Antibodies. Available from: <https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/>



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