Interdisciplinary Neurosurgery 22 (2020) 100809

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery

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

Review Article

The neurological significance of COVID-19: Lesson learn from the pandemic

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ARTICLE INFO

Keywords:
SARS-Cov-2
Neurological significance
COVID-19 complications
Coronavirus

ABSTRACT

Coronavirus Infectious Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019 novel coronavirus) is an emerging and rapidly evolving health issue that has been widespread globally and become a pandemic. The typical symptoms of COVID-19 are: a cough, shortness of breath and a fever; from the initial estimates, about 15% of COVID-19 patients present with severe respiratory symptoms and requires hospitalization and intensive care. Recent accumulated evidences showed that the neurological insults also occurred in patients with COVID-19, ranging from mild headache to severe neurological symptoms. In this review, we summarize the COVID-19 and neurological significance of COVID-19.

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has rapidly spread globally. It is the seventh of human coronaviruses (HCoVs) [1] that could be seized responsible for respiratory disease, besides Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), given some typical symptoms including fever, cough, and breathing difficulties. Despite a similar target in human angiotensin-converting enzyme 2 (ACE2) receptor, the genomic analysis revealed that SARS-CoV-2 has a different spike protein compare to its close relatives and is activated by host-cell enzyme called furin [2–4]. Neurological manifestations has been reported in 30–80% of COVID-19 patients. Nervous system related symptoms may include headache, dizziness, impaired consciousness, agitation, dysexecutive syndrome, acute stroke, seizures, ataxia and peripheral nervous system symptoms such as Guillain–Barre Syndrome, alteration in smell and taste, and painful neuropathy [5–10]. Accumulated reports indicated that this virus attack the nervous system in variety ways, understanding the pathogenesis and neuronal involvement in COVID-19 is needed to manage and prevent long term damage. Herewith, we investigated the activity of SARS-CoV-2 in neurological tissue and determining the possible contribution of neurological tissue damage to the morbidity and mortality in patients with COVID-19 [11,12].

2. COVID-19 caused by SARS-CoV-2

Coronavirus is a large enveloped positive-single-stranded RNA beta coronavirus of the family *Coronaviridae*, which generally cause enteric and respiratory diseases. Previously, six human coronaviruses (HCoVs) had been identified, two of them had caused epidemic in human history, those were severe acute respiratory syndrome (SARS-CoV; emerged in China in 2003) and Middle East respiratory syndrome (MERS-CoV; emerged in Saudi Arabia in 2012) [3,13]. **SARS-CoV-2** appeared in China in late 2019, typically has a genome length of about 26–32 kb [14] with an average diameter more than 100 nm and has large spikes of viral membrane glycoproteins on the cell surface [12,15]. There are 79.5% of genetic similarity between SARS-CoV-2 and SARS-CoV; the seven conserved replicase domains in ORF1ab (used for CoV species classification) of SARS-CoV-2 are 94.6% identical to SARS-CoV, implying those two belong to the same species [16–18]. This novel coronavirus is responsible for causing contagious infection in humans and causing a pandemic (Coronavirus infectious disease 2019, COVID-19).

Abbreviations: COVID-19, Coronavirus Infectious Disease 2019; SARS-CoV-2, Severe acute respiratory coronavirus 2 syndrome; CNS, Central nervous system; SARS-CoV, Severe acute respiratory coronavirus syndrome; ACE2, Angiotensin converting enzyme 2; IL, Interleukin; ADEM, Acute disseminated encephalomyelitis; ANE, Acute necrotizing encephalopathy; MOF, Multiple organs failure; ARDS, Acute respiratory distress syndrome

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https://doi.org/10.1016/j.inat.2020.100809
Received 11 June 2020; Accepted 14 June 2020

The COVID-19 case was first identified in Indonesia in early March 2020, which infected 2 patients, then spread to all provinces in Indonesia [19,20]. The case fatality ratio in Indonesia per May 30th, 2020 reached 9.43, surpassing the Republic of China with 5.87% or even with the world (7.47%). Patients who were confirmed positive, most came from Jakarta Province, which reached 7229 (28%) cases, East Java Province ranks second with 4613 cases, followed by West Java Province with 2231 (8.65%) cases. Among all positive confirmed cases in West Java Province, 640 (28.43%) people were recovered and 146 (6.54%) of case fatality rate (CFR) [21]. Until May 29th, 2020, Dr. Hasan Sadikin Hospital (RSHS), Bandung, West Java, has treated 338 patients in monitoring (PIM) cases, with confirmed COVID-19 positive of 76 cases; there were 59 PIM death cases, with confirmed COVID-19 positive of 23 cases [22]. Based on Indonesian task force for COVID-19, most death cases related to airway problem (cough 17.3% and breathing difficulties 14.7%) [21]. Further, COVID-19 patients rarely developed intracranial signs and symptoms (such as severe headache), whereas about 6.2% of patients with COVID-19 infection in Indonesia had headache [21].

3. Pathogenesis of COVID-19

The entry of SARS-CoV into human host cells is mediated mainly by a cellular receptor of ACE2; which is expressed in human airway epithelial, brain, lung parenchyma, vascular endothelia, skin, lymph node, thymus, bone marrow, spleen, liver, kidney cells, colon and small intestine cells [23–26]. Recent study showed SARS-CoV-2 has at least ten times stronger affinity to this receptor compare to the previous SARS-CoV, hence resulted in more successful infection rate [18,27]. SARS-CoV-2 is transmitted primarily via respiratory droplets of one patient to another [28], with a possible, but unproven, faecal-oral transmission [29]. Once its spike protein S1 attaches to host ACE2 receptor on the cell membrane, the virus strives to take over the cell's machinery, making mass copies of itself and invading new cells.

The pathogenesis of SARS-CoV-2 infection closely resembles that of SARS-CoV infection, with aggressive inflammatory responses strongly implicated in the resulting damage to the tissues [30]. Therefore, disease severity in patients is due to not only the viral infection but also the host response. The pattern of increasing severity with age is also broadly consistent with the epidemiology of SARS-CoV and MERS-CoV [31–33]. SARS-CoV-2 infection and the destruction of lung cells triggers a local immune response, recruiting macrophages and monocytes that respond to the infection, release cytokines and prime adaptive immune responses. In most cases, this process is capable of resolving the infection. However, in some cases, a dysfunctional immune response occurs, which can cause severe lung and even systemic pathology [29].

Cytopathic viruses, including SARS-CoV-2, induce death and injury of infected cells and tissues as part of the virus replicative cycle [34]. Viral infection and replication in airway epithelial cells could cause high levels of virus-linked pyroptosis with associated vascular leakage, as seen in patients with SARS-CoV [35]. Pyroptosis is a highly inflammatory form of programmed cell death that is commonly seen with cytopathic viruses [29]. This may trigger the subsequent inflammatory response [36]. Upon recognition of pathogens, immune system is activated via a wave of local inflammation ensues, involving increased secretion of the pro-inflammatory cytokines and chemokines interleukin (IL)-6, interferon (IFN)-γ, monocyte chemoattractant protein (MCP)-1 and interferon-γ-inducible protein (IP)-10 into the blood of afflicted patients [30]. These cytokines are indicators of a T helper 1 (T_H1) cell-polarized response, which parallels observations made for SARS-CoV and MERS-CoV [37]. Secretion of such cytokines and chemokines attracts immune cells, notably monocytes and T lymphocytes, but not neutrophils, from the blood into the infected site [29]. Pulmonary recruitment of immune cells from the blood and the infiltration of lymphocytes into the airways may explain the lymphopenia and increased neutrophil–lymphocyte ratio seen in around 80% of patients with COVID-19 [37].

The mechanisms by which SARS-CoV-2 subverts the body's innate antiviral remains elusive, but study on SARS-CoV shows that multiple viral structural and non-structural proteins antagonize interferon responses. Antagonism occurs at various stages of the interferon signalling pathway, including by preventing pattern recognition receptor (PRR) recognition of viral RNA [38,39], by preventing PRR signalling through TBK1/inhibitor of nuclear factor-κB kinase subunit-ε (IKKε), TRAF3 and IRF3 [38], by preventing downstream interferon signalling through STAT1 [40] and by promoting host mRNA degradation and inhibiting host protein translation [41]. It is very likely that at least some of these pathways are conserved in SARS-CoV-2. Antagonism of the interferon response aids viral replication, resulting in increased release of pyroptosis products that can further induce aberrant inflammatory responses.

Elevated levels of cytokines such as tumor necrosis factor (TNF) can cause septic shock and multi-organ failure. These may result in myocardial damage and circulatory failure observed in some patients [42]. Older people (those aged over 60 years) and people with co-morbidities are more likely to develop such a dysfunctional immune response that causes pathology and also fails to successfully eradicate the pathogen. The exact reasons for this are unclear, although one reason may be an ageing lung microenvironment causing altered dendritic cell maturation and migration to the lymphoid organs [43] and thereby defective T cell activation. In contrast, children tend not to develop severe disease despite being capable of experiencing high viral titres [44].

It remains debatable whether virus persistence is necessary for ongoing damage. The peak of viral titres in respiratory tract samples might occur even before symptom onset of pneumonia in SARS-CoV and SARS-CoV-2 infections [29]. However, a large retrospective cohort study showed that viral RNA was detectable in non-survivors up until the point of death, suggesting a correlation between virus persistence and poor disease outcome [45]. As viral RNA may linger even after active infection, and is not representative of the infectivity of the virus, whether the poor disease outcome is directly due to large amounts of infectious particles is speculative at this moment. Furthermore, earlier studies of SARS-CoV found that the virus may infect other targets besides lung cells. Notably, virus was found in T cell [46], macrophages [47] and monocyte-derived dendritic cells [48]. Direct virus killing of lymphocytes could contribute to the observed lymphopenia in patients [29,37]. Viral infection in immune cells such as monocytes and macrophages can result in aberrant cytokine production, even if viral infection is not productive [29].

4. Neurological significance

To date, researchers still work toward the pathogenic mechanism behind the neurological disturbance in COVID-19 patients. It is still indefinite if those symptoms are induced by SARS-COV-2 infection or merely a coexisting event in severely ill COVID-19 patients. Some hypothesis arises out of animal models of neurotropic coronavirus infections and neuropathological data from SARS-CoV-1, MERS, HCoV-229E, or HCoV-OC43 patients [49–51]. The upshot of those results is the possibility that the neurological symptoms result from the direct neurotropic effect and indirect virus-induced secondary impact of SARS-CoV-2 infection on the nervous system [50]. SAR-CoV-2 potentially enter the central nervous system (CNS) through direct infection pathways (blood circulation pathways infected vascular endothelium or leukocyte migration across the blood–brain barrier (BBB) and neuronal pathways (including trans-synaptic transfer across infected neurons) causing neuronal death including respiratory centres in the brainstem or direct viral infection of endothelial cells in the brain. ACE2 receptor as the target of SAR-CoV-2 was highly expressed in neurons, astrocytes, and oligodendrocytes, mainly in the substansia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb [23,26,49,51,52]. Another mechanism including a parainfectious

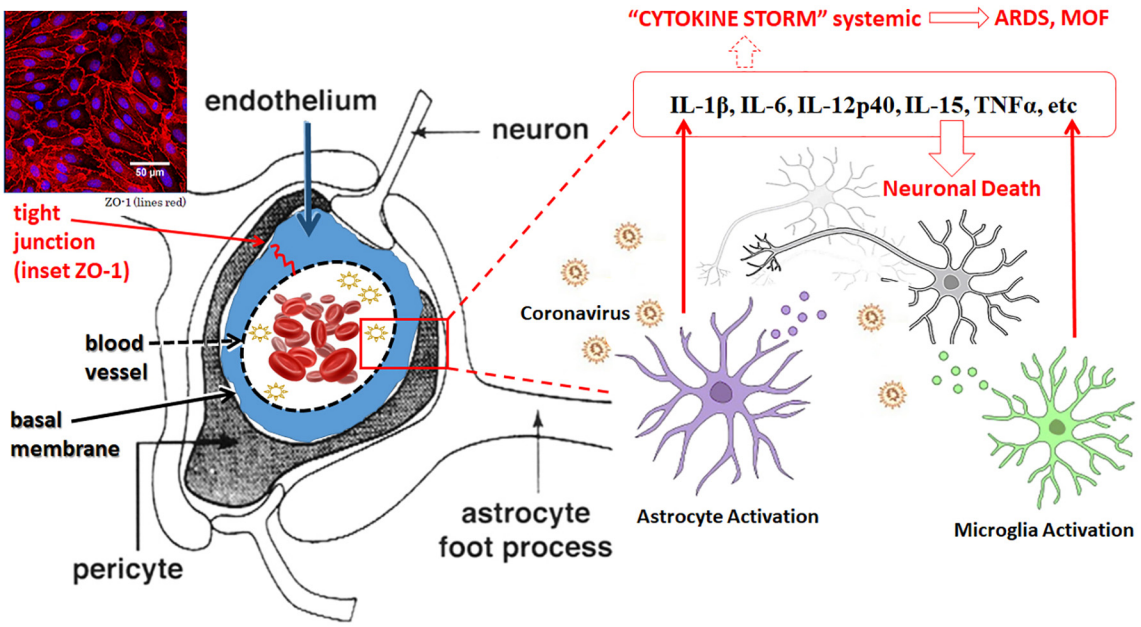

Fig. 1. The coronavirus can cause neuronal damage through direct infectious pathways, *in vitro* blood circulation pathway study have confirmed that primary glial cells (astrocytes and microglial) cultured secrete a large amount of inflammatory factors such as IL-1, IL-6, IL-12p40, IL-15 and TNF-α after being infected with coronavirus [11,47]. Abbreviation: IL, interleukin; TNF-α, tumour necrosis factor alpha; ARDS, acute respiratory distress syndrome; MOF, multiple organ failure.

disease lead to cytokine storm resulting in elevation of proinflammatory cytokines and immune-mediated nerve disturbance such as Guillain-Barre syndrome or Miller-Fisher syndrome, myasthenia gravis, myelitis, or myopathies [5,9,50], Clinical data have revealed that patient with COVID-19 have symptoms related to intracranial infections such as headache, seizures, and consciousness impairment. Several identified risk factors predispose patients with COVID-19 for having neurological complications, such as: (i) Patient age, as the severely ill patients were significantly older (58.2 ± 15 vs. 48.9 ± 14.7 years) with more co-morbid conditions especially hypertension (36.4% vs 15.1%) [5] and (ii) Smokers have a higher risk for neurological complications by SARS-CoV-2 infection, since nicotine stimulation of the nicotinic acetylcholine (nACh) receptor can increase ACE2 expression in neural cells [53].

5. Olfactory dysfunction

Olfactory dysfunction defines as distorted ability to smell (ortho-nasal olfaction) or eating (retro-nasal olfaction) and proposed by American Academy of Otolaryngology-Head and Neck Surgery and Ear-Nose-Throat United Kingdom as the possible marker for COVID-19, in particular among minimally symptomatic or asymptomatic patients [54]. Reports of COVID-19-related olfactory dysfunction (OD) describe a sudden onset of olfactory impairment, which may be in the presence or absence of other symptoms. Among hospitalized patients with COVID-19 in Italy, impaired smell/taste was more frequently seen in younger patients and in women [55]. Unpublished data and anecdotal reports support resolution of olfactory symptoms within approximately 2 weeks. However, because of the lack of long-term follow-up, it is unknown what proportion of patients develop persistent post-infectious OD. One Indonesian COVID-19 patient (confirm positive), male 29 years old, with chief complaint were fever and myalgia back-pain reported develop rhinorrhea and anosmia on day 12, persist until day 14 [56].

Many patients report impairment of smell and taste interchangeably. Although it is possible that SARS-CoV-2 targets both olfactory and gustatory systems, in most cases of dysfunction not related to COVID-19 in which patients describe altered taste, this symptom can be attributed to impaired retro-nasal olfaction (flavour) rather than impaired gustation (sweet, salty, sour, bitter). For this reason, it is thought that chemosensory impairment in COVID-19 is likely olfactory [54]. Magnetic resonance imaging (MRI) shown a signal alteration compatible with viral brain invasion in cortical region associated to olfaction and a subtle hyper-intensity in the olfactory bulbs [57].

Coronaviruses are one of many pathogens known to cause OD and nasal epithelial cells show relatively high expression of the ACE 2 receptor, which is required for SARS-CoV-2 entry [58]. SAR-CoV-2 attach to nasal epithelial cells and then invades olfactory epithelium along the nerve to the olfactory bulb within the central nervous system via transcribial route and spread retrograde along nerve synapse [49]. Disruption of cells in the olfactory neuroepithelium may result in inflammatory changes that impair olfactory receptor neuron function, cause subsequent olfactory receptor neuron damage, and/or impair subsequent neurogenesis. Such changes may cause temporary or longer-lasting OD. Previous work in transgenic animal models showed intracranial entry of SARS-CoV via the olfactory bulb [24]. This has led to speculation that SARS-CoV-2 may penetrate intracranially with possible downstream effects on olfactory and non-olfactory brain regions, which may adversely affect olfactory function.

6. Encephalitis

Beijing Ditan Hospital in China reported for the first time a case of viral encephalitis with confirmation presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) by genome sequencing; adding support to the theory this new virus can also damage the CNS [59]. In the previous SARS-CoV outbreak, autopsy studies discovered signs of cerebral oedema and meningeal vasodilation in the brain of patients with SARS and MERS [60]. Monocytes and lymphocytes infiltration in the vessel wall, ischemic changes of neurons, demyelination of nerve fibers, as well as SARS-CoV genome sequences could be detected in the brain [61,62]. Recent autopsy reports from patients with COVID-19 have revealed brain tissue oedema and partial neuronal degeneration in deceased patients [29]. Those accumulated reports suggesting that CNS damage can be occurred in patients with COVID-19. COVID-19 encephalitis possibly due the presence of SARS-CoV-2 in the CNS and its ability to infect macrophages, microglia, and astrocytes in the CNS, thus

activates glial or immune system to induce a pro-inflammatory state (Fig. 1). The BBB breakdown due to hyper- inflammation state might also play role in viral invasion into the CNS [49]. A 59 years old male was hospitalized in RSHS, Bandung; presenting symptom were multiple seizures, fever, dyspneu, and hemiparesis preceded by two weeks history of headache. Blood analysis showed lymphopenia and CSF features showed a slight elevation of the protein level without pleocytosis or hypo-glycorrhachia. There is cortical dysfunction at bilateral prefrontal, frontal and right temporal upon electroencephalogram (EEG) examination. Chest X-ray showed bilateral bronchopneumonia with ground-glass appearance. Unfortunately, despite the specific clinical and laboratory features, the patient had no chance to perform swab test due to rapid clinical deterioration (unpublished data).

7. Toxic encephalopathy

When a virus proliferates in lung tissue cells, it will lead to alveolar gas exchange disorders and respiratory failure. The accumulation of acid promotes cerebral vasodilation, swelling of brain cells, interstitial oedema, obstruction of cerebral blood flow, and ischemia. Patients with severe COVID-19 often suffer from hypoxia, thus subsequent CNS damage may happen [51]. Infectious toxic encephalopathy refers to a condition of reversible brain dysfunction syndrome affected by systemic toxaemia, metabolic disorders, and hypoxia [63]. This rare condition is seen in patient with cerebral oedema but has no evidence of inflammation on CSF analysis [29,64]. It might also occur as a result of cytokine storm and hyper-inflammation [49]. This condition has diverse symptoms including headache, dysphoria, mental disorder, delirium, disorientation, loss of consciousness, and paralysis. Filatov et al., reported a patient with COVID-19 presented with encephalopathy in the acute setting, the patient experience alteration of mental status with encephalomalacia on CT-Scan and EEG abnormalities, without the evidence of CNS infection [8].

8. Acute necrotizing encephalopathy

Acute necrotizing encephalopathy (ANE) is one of rare complication in viral infection and has been related to intracranial cytokine storms, which result in BBB breakdown, but without direct viral invasion or para-infectious demyelination [49,65]. It has not been reported to have occurred as a result of COVID-19 infection until recently [64]. While predominantly described in the paediatric population, ANE is known to occur in adults as well. The most characteristic imaging feature includes symmetric, multifocal lesions with invariable thalamic involvement [64]. Other commonly involved locations include the brain stem, cerebral white matter, and cerebellum [64]. Lesions appear hypo-attenuating on CT images and MRI demonstrates T2 FLAIR hyper-intense signal with internal haemorrhage. Post-contrast images may demonstrate a ring of contrast enhancement [64].

9. Stroke and vascular events

A numerous reports about COVID-19 showed that the incidence of large vessel stroke or ischemic stroke was approximately 5% among COVID-19 patients [5,10,66,67]. These patients were associated with severe disease and had a higher incidence of risk factors like hypertension, diabetes, coronary artery disease, and previous cerebrovascular disease [67]. However, study from New York suggests that COVID-19 as risk factor for young patients for having ischemic stroke [10]. A case report from Indonesia, a patient with COVID-19 manifested as an ischemic stroke, male 42 years old, with chief complaint were weakness of his right arm along with face drop on the right side, without any respiratory symptoms [68]; with his brain CT scan showed a lacunar infarct in the left lentiform nucleus. The risk factors of these patient were type II diabetes mellitus and hyperthyroid. Coagulopathy and vascular endothelial dysfunction have been proposed as complications of COVID-19 [45]. There were numerous reports that patients with COVID-19 experience elevated CRP and D-dimer, indicating high inflammatory state and abnormalities with coagulation cascade [66].

The pathophysiology behind the stroke in patients with COVID-19 remains elusive. Recent bacterial or viral infections have been known to cause strokes by increasing cardio-embolism as well as arterio-arterial embolism [69]. Another study investigating activated partial thromboplastin time-based clot waveform analysis (CWA) in patients with COVID-19 concluded that CWA parameters demonstrate hypercoagulability that precedes or coincides with severe illness [70]. Other pathophysiology could be directly related to the infection or hypoxia.

10. Perspective

The biological properties of the CNS facilitate exacerbation of the neurological damage caused by Coronavirus infections. The CNS has a dense parenchymal structure and the usual lack of permeability of its blood vessels is a barrier to virus invasion. However, if a virus gains access to the CNS, it is difficult to remove. Due to the lack of major histocompatibility complex antigens in nerve cells, the elimination of viruses in nerve cells depends solely on the role of cytotoxic T cells; however, the apoptosis of mature neurons after SARS-CoV-2 infection also has a relatively protective effect [29,71–73]. Furthermore, the characteristics of the CNS also contribute to the continued existence of the virus. If the SARS-CoV-2 is latent in CNS for a long time, will the recovered patients reappear with neurological diseases because of the latent infection of the SARS-CoV-2 [29,55,73–75], since the late neurological complications maybe reported soon enough.

Early detection of neurological deficits, CSF examination, brain imaging, EEG, and EMG might help to determine any neurological disturbance accordingly to the symptoms therefore the prompt treatment can be taken and improve the outcome. Follow up assessment may also help to figure out the nature of the disease. In patients with neurological-emergencies that need surgical intervention; defined as neurosurgical emergencies for cerebral haemorrhages cases (subarachnoid and intra-parenchymal), any kind of acute hydrocephalus, tumours at risk of intra-cranial hypertension, spinal cord compressions with neurological deficit or at risk of traumatic-brain and -spinal emergencies must perform surgery under personal protection equipment (PPE) as guide lines for it use during the COVID-19 pandemic. Establishing a guideline or protocol for managing neurosurgical emergencies and procedures at region with high incidence of COVID-19 during the pandemic is mandatory to ensure healthcare provider‘s safety and avoid unnecessary decision.

11. Conclusion

In conclusion, SARS-CoV-2 affect the nervous system, and there are growing evidences that multiple cytokine expression profiles are involved in the initial host’s immune response to the infection, which could induce immune impairment in the brain. Patients with COVID-19 should be evaluated for neurological symptoms. Timely analysis of CSF and awareness and management of infection-related neurological complications are key to improving the prognosis of severe patients. This review highlights the importance of the SARS-CoV-2 involvement in the CNS; particularly necessary to make clinicians aware of the various impact of SARS-CoV-2 on the CNS, since our understanding of COVID-19 is still limited. A better understanding of the pathogenesis and therapeutic options will be beneficial for clinicians to ensure optimum management; whether patients in nature needed conservative or more aggressive treatment such as surgery, adapting to new protocol will be needed since the COVID-19 pandemic is **“far from over”**.

Conflict of interest

Authors have declared that no conflict of interest exist.

Acknowledgements

We would like to give special thanks to RSHS-Covid-19 Team, Bandung, for their daily devotions on this pandemic. Also to Universitas Padjadjaran (UNPAD), Bandung, especially Faculty of Medicine, for their technical assistance to publishing this review.

Funding

This review received funding from Universitas Padjadjaran, Bandung, West Java, Indonesia. AF supported by the Grants-in-Aid from Indonesian Ministry of Research and Technology (National Research and Innovation Agency) No. 16/E1/KPT/2020 for Basic Research.

Availability of data and materials section

The datasets gathered and shown in this review is available as an open access data as cited in our references; the corresponding author will make it available on reasonable request.

Authors' contributions

AF, SD, YH, and MZA design the discussion directions. DH and DMAP gathering all the data and drafting manuscript. All authors took part on writing and approved of the final manuscript.

Competing interests

Authors have declared that no competing interests exist.

Consent to publish

Not applicable.

Ethics approval and consent to participate

Not applicable.

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