Covid-19 and Cognitive Effects: Medical, Neural, and Ethical Implications

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Citation

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Abstract

With the rapidly evolving issues and treatments surrounding the COVID-19 pandemic, cognitive deficits are more progressively being addressed as a frequent complication due to COVID-19, but with very minimal research performed. This paper seeks to take a more in-depth analysis of the various medical, neurological, and ethical implications revolving around COVID-19, specifically in relation to cognitive function. COVID-19 exhibits its effects by causing ischemic, hemorrhagic, systemic inflammatory, and viral encephalitic changes, leading to end-organ dysfunction. Current treatments, such as corticosteroids, remdesivir, and supplemental oxygen, are aimed at combating the respiratory disease and to decrease the symptoms of the infection. However, less is known about the long-term effects of the virus. Understanding the virus' impact on cognitive function could affect treatment of these patients. Research has recently shown that patients infected with COVID-19 have an increased risk for neurologic illness. The virus has also been shown to have both a direct and indirect impact on patients' cognition. This has enhanced the idea that COVID-19 may be more of a 'brain disease' than previously thought. We propose that introduction of formal neuropsychological testing for long-term COVID-19 survivors and patients with pre-existing neurodegenerative diseases be considered to detect long-term neurological and cognitive abnormalities. This approach could potentially help prevent further cognitive deterioration. A series of recommendations are presented guiding clinicians for further steps that should be taken in the care of current patients with cognitive effects of COVID-19, as well as future prevention of neurological complications.

INTRODUCTION

The COVID-19 pandemic continues to be a global public health issue. The infection caused by the SARS-CoV-2 virus has affected individuals spanning every age, sex, and nationality. From late 2019 up until present day, there have been just over 33.5 million cases relating to COVID-19 infection in the U.S. alone, of which close to 612,000 resulted in mortality [1].

SARS-CoV-2 has been classified as a coronavirus, a family of viruses usually associated in causing illnesses ranging from the common cold to more severe cases of Severe Acute Respiratory Syndrome (SARS). Current strains of SARS-CoV-2 have yielded infections that are both symptomatic and asymptomatic, with symptoms taking approximately 2-14 days to manifest [2]. The COVID-19 virus has shown to primarily affect the respiratory system of its infected host, which is highlighted by the notion that approximately 75% of patients with COVID-19 related hospitalizations required an oxygen supplement due to forms of respiratory failures [3]. The general population of patients exhibit symptoms such as fever, chills, shortness of breath, cough, loss in olfactory mechanism functionality, coughing episodes, arthralgias, and myalgias. Other symptoms include pharyngitis, congestion, vomiting, diarrhea, conjunctivitis, and discoloration of extremities [4].

Statistics have shown that individuals aged 65 and older, infants, and those with pre-existing conditions such as asthma, heart disease, or other immunocompromised states are the most susceptible to contracting the COVID-19 virus [5]. However, despite all the knowledge surrounding the COVID-19 virus, there are still avenues that are yet to be explored: To what extent does COVID-19 infection affect other bodily systems? Does the virus have any long-term consequences? How long does immunity last? Given that COVID-19 has only been studied for about 18 months, questions regarding whether or not the virus plays a role in other systemic functionalities have not fully been answered yet. In particular, there is limited research surrounding the

degree to which COVID-19 plays a role in both neurological and cognitive decline. Both the immediate and long-term effects of COVID-19 on cognition have not been fully explored; this paper seeks to take a closer look at which neurocognitive diseases, if any, are attributed to COVID-19 infection.

Due to the fact that there has been increasing research suggesting the potential cognitive impacts of COVID-19 infection, it is crucial to evaluate the ethical issues surrounding treatment, monitoring, and long-term care of these patients. Determining whether or not there are long-term implications on cognitive function is essential for the proposal of future treatment plans. The purpose of this paper is four-fold. First, we discuss several medical complications arising from COVID-19, as well as the known variants of the virus. Second, we present several studies discussing the neurologic findings and cognitive impacts of patients who were infected with the virus. Third, we discuss the ethical aspects centering around COVID-19 highlighting various scenarios and addressing the current landscape of the virus. Fourth, we offer various recommendations regarding how physicians, family members, and caregivers should proceed in monitoring these patients' cognition over time as well as a call for further research in order to prevent these cognitive consequences.

MEDICAL COMPLICATIONS OF COVID-19

The COVID-19 pandemic has gripped the world starting at the end of 2019. As of August 2021, there have been over 200 million reported cases and over 4 million deaths worldwide due to COVID-19. In the United States, there have been over 35 million confirmed cases and over 600,000 deaths [6]. This pandemic was caused by a coronavirus which was termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is now commonly referred to as COVID-19. Coronavirus is an enveloped positive-sense single-stranded RNA virus. This disease can be transmitted either through direct contact with respiratory droplets or through airborne transmission [7].

As discussed above, common symptoms of COVID-19 include fevers, chills, cough, shortness of breath, fatigue, loss of taste or smell, headache, nausea, vomiting or diarrhea. The majority of people infected with COVID-19 will experience mild to moderate symptoms. Severe symptoms of COVID-19 include shortness of breath at rest, chest discomfort and confusion. Some factors that put individuals at increased risk of developing severe disease are older age, underlying medical conditions such as diabetes, cancer, cardiovascular disease and chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Some laboratory abnormalities that are associated with worse outcomes include lymphopenia, thrombocytopenia, elevated liver enzymes, elevated troponin, elevated D-dimer, and elevated creatinine [8].

Several complications have been noted in patients with or recovering from COVID-19. These complications can include permanent damage to the lung parenchyma, heart failure, a hypercoagulable state leading to deep vein thrombosis (DVT) and pulmonary embolism (PE), and neurologic complications such as stroke, movement disorders, seizures, and sensory and motor deficits. Hospitalization is recommended for patients suffering from severe dyspnea which can be defined as shortness of breath at rest or while speaking, oxygen saturation less than 90 percent and changes in mental status [8].

Presently, there are four variants that are currently being monitored in the United States. These variants are B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma) and B.1.617.2 (delta). These variants have been known to spread more easily which can lead to an increase in the number of COVID-19 cases [9]. The delta variant was first originally identified in India in December 2020 but now has spread to over 98 countries. This variant is responsible for 89% of COVID-19 cases in the United States. In addition to being more contagious, it has been shown to have more severe complications including hearing impairment and formation of blood clots that lead to tissue death. Among unvaccinated individuals, which is approximately 52% of Americans, the delta variant is twice as likely to lead to hospitalization when compared to the alpha variant [10].

The mainstay of treatment for patients who require hospital admission is with corticosteroids and remdesivir. Dexamethasone is the recommended corticosteroid and the recommended dosage is 6 mg daily for 10 days or until discharge, whichever is earlier. Remdesivir is a nucleotide analog that has shown to be beneficial in patients that require supplemental oxygen. Barcitinib is a Janus kinase inhibitor and is an immunomodulator that is used for the treatment of rheumatoid arthritis. However, it has been found that baricitinib has some antiviral effects that are beneficial in the treatment of COVID-19. The recommended dosage of baricitinib is 4 mg daily for up to 14 days. In addition, patients are also sometimes given vitamin C, vitamin D and zinc [8].

Antibody based therapies such as monoclonal antibodies and convalescent plasma have been used in hospitalized patients. Monoclonal antibodies work by preventing the entry of virus into the cell. Convalescent plasma is collected from patients who have recovered from COVID-19 and can be given to patients who are immunocompromised. However, many randomized controlled trials did not show a significant survival benefit for either of the above therapies. For patients that do not require hospitalization, symptomatic treatment with antipyretics such as acetaminophen is sufficient [8]. However, treatment options still remain limited and questionable. It is questionable whether these medications are able to treat the neurologic and cognitive consequences of the virus, necessitating further investigation.

Fortunately, vaccines for COVID-19 have become readily available. Limited research has been performed to know if these vaccines fully cover each and every variant, however, there has been some evidence to suggest that vaccinated individuals might have a less severe disease. Vaccines that are widely used in the U.S. are Pfizer, Moderna and Johnson & Johnson. There are also non-mRNA-based vaccines such as Novavax, of which is currently matching the efficacy rates of both Pfizer and Moderna vaccines [45]. These vaccines however have not undergone Phase 3 clinical trials, and are therefore not as 'utilizable' as vaccines from Pfizer and Moderna without further FDA approval. The Pfizer and Moderna vaccines use mRNA to help the immune system recognize a protein, known as the S protein, that is present on the virus. The Johnson & Johnson vaccine uses a genetic material from the virus as a vector. The above vaccines are approved for use in adults and the Pfizer vaccine is currently approved for children 12 years and older in the United States. Even after vaccination, measures such as masking, social distancing and appropriate hand hygiene are recommended to prevent the spread of COVID-19. The Pfizer and Moderna vaccines are given in 2 doses. At this time, a third dose has been approved by the FDA for certain people with weakened immune systems caused either by disease, medical treatments or organ transplants. France and Israel are some of the countries that have recommended a third dose as a booster for immunocompromised patients [11]. All of these vaccines help the immune system to create antibodies to the virus [12].

Most common adverse effects of the above vaccines include local reaction at the injection site including pain and rash. Fever, fatigue and headache have also been commonly reported for all of the above vaccines. Although rare, syncope has been particularly reported in adolescents and young adults immediately following vaccine administration. Therefore, monitoring for 15-30 minutes after vaccine administration is recommended. Thrombosis with thrombocytopenia has been reported in a very small number of recipients of the Johnson and Johnson vaccine. As of May 2021, 28 cases have been reported out of 8.7 million people that received this vaccine. The Advisory Committee on Immunization Practices (ACIP) of the CDC has determined that the benefits of receiving the vaccine outweigh the risks of the rare side effects noted above [11].

Interestingly, one questionnaire-based study reported their findings regarding treatment of COVID-19 with amantadine or memantine, drugs normally used to treat Parkinson's disease, in patients diagnosed with multiple sclerosis, Parkinson's disease, or cognitive impairment. These patients did not report any significant changes in neurological status over the course of their primary neurological disease, suggesting a potential protective effect of adamantanes against COVID-19, particularly in those with nervous system diseases [13].

A phenomenon called "long COVID" has been described in many patients that have recovered from COVID-19 but continue to exhibit symptoms beyond 4 weeks. The most common symptoms that persist include fatigue, shortness of breath, chest pain and cough. Patients can also continue to have anxiety, depression, and PTSD (post-traumatic stress disorder). Cognitive symptoms that can linger include poor memory and decreased concentration, among others [14].

NEUROLOGICAL COMPLICATIONS OF COVID-19

Although COVID-19 is a disease that affects the respiratory system, up to two thirds of patients who are hospitalized exhibit evidence of central nervous system damage. The mechanism of this damage is uncertain, although it is thought to be caused by ischemic, hemorrhagic, systemic inflammatory, and viral encephalitic changes, leading to end-organ dysfunction. There is limited research on the extent to which the inflammatory effects of the virus affect the central nervous system (CNS) vasculature, and how much is due to extracranial cardiac and respiratory manifestations. However, it is thought that the virus may enter the CNS through hematogenous spread or the nasal mucosa and olfactory fibers [15]. While several of the neurologic symptoms present acutely during the course of the infection, very little is known about the long-term

neurologic and cognitive complications that might be caused. Increasing evidence has suggested that patients may have a higher risk of developing cognitive decline after recovering from the infection. A study by Jaywant et al. noted that 81% of patients that underwent inpatient rehabilitation during their recovery from COVID-19 demonstrated cognitive dysfunction, such as deficits in working memory, divided attention and processing speed [16]. Thus, there is a compelling need for particular attention to the neurologic impacts on cognition as a result of COVID-19.

A major study involving over 236,000 patients published by the Lancet found that 34% of COVID-19 survivors were diagnosed with a neurological or psychological condition within 6 months. Effects included anxiety (17% of patients) and mood disorders (14% of patients). These symptoms were more severe in hospitalized patients. Researchers also determined that patients infected with COVID-19 had a 44% increased risk for neurologic and psychiatric illness compared to those who had the flu, and are 16% more likely to exhibit neuropsychological symptoms compared with patients with other respiratory tract infections. This study has intensified the idea that COVID-19 may be more of a 'brain disease' than previously thought [17].

COVID-19 has been shown to have both a direct and indirect impact on patients' cognition. Indirectly, hypercoagulable states with high levels of proinflammatory cytokines have been noted very commonly in patients infected with the virus. This hypercoagulable state often leads to critical illnesses, such as pulmonary emboli, cerebrovascular accidents, or acute cardiac events. As a result, patients often develop profound hypoxia and require intubation and assisted ventilation in severe cases. These patients may require prolonged hospitalization and longer stays in the Intensive Care Unit (ICU). Prolonged hospitalization, in addition to polypharmacy, and severe pain, often leads to delirium. In fact, it has been found that approximately two out of three patients admitted to the ICU experience a condition known as ICU delirium [18]. The metabolic and hypoxic changes may lead to encephalitis, which can ultimately result in additional cognitive deficits. All of these acute effects have been suggested to lead to cognitive decline in infected patients. This may arise either directly from the negative effects of the infection and immune response, accelerated progression or exacerbation of pre-existing neurodegenerative diseases, or inducement of a new cognitive pathology [19]. For example, one observational study found that 33% of patients discharged from the hospital after being admitted for ARDS (acute respiratory distress syndrome) from COVID-19 had cognitive impairments such as inattention and disorientation, and motor impairments such as poorly organized movements in response to commands [20].

Hypoxia and ischemia are two detrimental effects of the virus that commonly occur in infected patients. Cerebral white matter, which is important for cognitive function, is particularly vulnerable to ischemia. The virus has been known to cause a hypercoagulable state, thus potentially leading to cerebral hypoperfusion. The brain damage that is caused could be in the form of a cerebrovascular accident or a silent stroke. There is increasing evidence to suggest that this process accelerates accumulation of amyloid-β and tau pathology, thus potentially increasing the risk for development of Lewy body disease in the brain [15]. Additionally, the hypoxia in ARDS is known to be a common cause of neuropsychological changes; this has been linked to pathological changes in the brain such as cerebral atrophy and ventricular enlargement in a study by Hopkins et al. [21]. A subsequent study also found that the duration of the hypoxia is related to the level of attention, verbal memory, and executive functioning scores in patients at discharge [22]. ARDS may also lead to inflammatory responses, anemia, and ischemia, which may cause end-organ failure. This sequence of neurological and physiological events may aggravate pre-existing neurodegenerative disorders or spark new acute neurological injury, leading to progressive cognitive dysfunction [23].

In a research letter published in JAMA Neurology by Johns Hopkins and Brigham and Women's Hospital, megakaryocytes were discovered on autopsy in the cortical capillaries of 5 patients who died of COVID-19. Megakaryocytes, the cells which are responsible for making platelets, are not usually found in cerebral vasculature. Other studies have also found megakaryocytes in other organs such as the lungs of COVID-19 patients. It is possible that these cells could have entered cerebral circulation and brain tissue during hemorrhage due to endothelial dysfunction from severe COVID-19 infection. This may be from altered signaling and abnormal recruitment of cells, allowing the cells to enter the tissues. The megakaryocytes in the cerebral vasculature could have occluded blood flow, thus causing ischemia, leading to an atypical manifestation of neurologic deterioration [24].

Encephalopathy and encephalitis are also considerable

neurological complications of severe infection with SARS-CoV-2 infection. These may be caused by the systemic inflammatory response and cytokine storm provoked by the virus, as well as hypoxic and metabolic changes, as mentioned above. Encephalopathy tends to be more common in patients who are older, especially over age 50, on mechanical ventilation, critically ill, or with lung abnormalities. Encephalopathy commonly presents as altered consciousness, confusion, delirium, coma, anosmia, and ageusia. Patients are usually already in the ICU, and they frequently exhibit fever, cough, dyspnea, and headache prior to the onset of encephalopathy. Additionally, cortical and subcortical changes are commonly seen on magnetic resonance imaging (MRI) images [25].

There have been several studies regarding the prevalence and causes of encephalopathy in these patients. One study by Chen et al. found that ARDS, sepsis, acute myocardial injury, cardiac failure, electrolyte abnormalities, and acute renal failure were all contributors to the development of metabolic/hypoxic encephalopathy [25, 26]. An observational series of 58 consecutive patients found that delirium was present in 69% of the patients admitted for ARDS due to COVID-19. Additionally, upper motor neuron signs were encountered in 67% of the patients. Imaging of these patients' brains on MRI exhibited leptomeningeal enhancement and cortical signal changes [20, 25].

A Chicago study by Liotta et al., presented by the Harvard Health Blog, compared the severity and outcomes in 509 patients with confirmed COVID-19 with and without neurological symptoms. The study found that 42.2% of patients exhibited neurologic manifestations at onset of the infection, 62.7% at hospitalization, and 82.3% at any point during the course of the disease. The study also showed that of all neurological manifestations of COVID-19, encephalopathy led to the worst functional outcomes. More than 30% of patients showed signs of impaired cognition. Other neurological symptoms exhibited by patients included myalgias, ataxia, seizures, headaches, dizziness, dysgeusia and anosmia. Among the studied symptoms, encephalopathy led to the highest mortality within 30 days of hospitalization, and was more common in older patients. Interestingly, the severity of respiratory disease was not associated with the occurrence of encephalopathy [27, 28].

One theory as to how cognitive decline occurs following COVID-19 infection is from systemic inflammation. The pro-inflammatory state precipitated by SARS-CoV-2 is associated with an increase in levels of cytokine levels. The current understanding is that this may promote cognitive decline and neurodegeneration. Therefore, it is possible that patients who recover from COVID-19 may show signs of neurodegenerative disease in the future. Additionally, in patients with severe sepsis, the incidence of hippocampal atrophy is able to be predicted by the level of cytokines. It is thought that the systemic inflammatory changes lead to damage to the brain; this idea is backed by a study by Helms et al. in which there was an absence of SARS-CoV-2 in all cerebrospinal fluid samples [15, 20]. Moreover, evidence has shown that the coronavirus ORF3a protein induces activity of the NLRP3 inflammasome. This specific type of inflammasome has a role in the unfavorable pathogenesis of ARDS. Experimentally, ventilation-induced hypercapnia has been shown to cause cognitive impairment related to this inflammasome. Therefore, it is very possible that the NLRP3 inflammasome is activated in patients suffering from COVID-19, leading to subsequent activation of proinflammatory pathways. It is possible that this process could adversely influence neurological homeostasis and cognitive function [15].

Just as COVID-19 has been linked to hypercoagulable states, systemic inflammation, and ischemia, it has also been associated with hemorrhagic manifestations. One rare complication of COVID-19 is acute hemorrhagic necrotizing encephalitis (AHNE). This condition generally involves subcortical white matter of the brain and has the potential to alter cortical areas involved in cognition. One case report found this in a previously healthy middle-aged woman without comorbidities who subsequently developed progressive cognitive impairment after infection with SARS-CoV-2. She ultimately developed generalized tonic-clonic seizures, progressed to a comatose state, and subsequently died. In this case, COVID-19 was manifested as a rare, acute, and isolated cognitive impairment in the absence of any respiratory disease [29].

From existing research, it is clear that COVID-19 has the potential to induce brain damage, either directly by encephalitis, or indirectly by ischemia and hemorrhage. It is also certain that damage to brain tissue is more likely to occur in patients in the ICU. However, less is known about the extent of brain damage in less severe and recovered COVID-19 infections. A Chinese study published in the Journal of Psychiatric Research evaluated the cognitive function in 29 patients who were presumed to have fully recovered from COVID-19 infection. The study discovered a significant difference in impaired attention and cognition in

these COVID-19 survivors [28, 30].

Due to the numerous pathophysiologic changes on the central nervous system sparked by SARS-CoV-2, there is a compelling need for long-term neurologic surveillance and care in patients recovering from COVID-19. Patients with pre-existing neurodegenerative or neurologic diseases should be made aware of the potential detrimental effects that the virus could have on their brains, and to take the necessary precautions to avoid becoming infected. Family members, caregivers, and physicians, should also be warned of these effects, as well as the neurologic impacts on cognition caused by COVID-19. There may also be an increase in patients seen by psychiatrists and neurologists in the near future. The long-term neurological complications are not known, so long term cognitive follow up of COVID-19 survivors is especially important in patients who develop cerebrovascular and neurologic complications [15, 19].

Interestingly, a study done by Wang et al. found that patients with dementia, particularly African American patients with dementia, are more likely to contract COVID-19. The study adjusted for common risk factors such as advanced age, living in a nursing home, and comorbid conditions such as asthma, diabetes, and cardiovascular disease. Although the findings in the above study are correlational instead of causational, it is still important to take more precautions to prevent COVID-19 in people with dementia. The precautions can include quarantine of affected family or staff members, vaccination, etc. [31]. Another study from a large academic medical center in Chicago, with a total of 50 patients (48% blacks and 24% Latino) found that the most common neurological manifestations of COVID-19 were encephalopathy, cerebrovascular disease, cognitive impairment, seizures, hypoxic brain injury, dysgeusia, and extraocular movement abnormalities. Of their patient population, a higher percentage of blacks and Latinos developed neurologic symptoms [32].

Recent studies have begun to further confirm the notion that COVID-19 leads to neurological complications related to the CNS. A study done by Mahalakshmi et al. found that activated glial cells expressed by ACE2 receptors, which were triggered by COVID-19 infection resulted in immune mediated neurodegeneration, demyelinating disease, and cerebrovascular damage [33]

In order to better understand the long-term effects of COVID-19, the World Health Organization (WHO) has created a global COVID-19 clinical platform case report form. Clinicians and patients can use this form to report their experiences with COVID-19 [8]. The National Institute of Health (NIH) has also dedicated $1.15 billion to research the long-term consequences of COVID-19 [34].

ETHICAL ANALYSIS OF COVID-19

Since the first outbreak of COVID-19 over a year and a half ago, medical authorities and researchers are still learning a great deal about how this virus works and impacts on human lives. From the various studies listed above, it is now clear that many patients who have recovered or are recovering from COVID-19 or the various variants are experiencing neurological, psychiatric and cognitive issues. According to recent studies, these issues are present in nearly a third of COVID-19 patients who have been hospitalized. New research is suggesting “that there may be long-term neurologic consequences in those who survive COVID infections, including more than seven million Americans and another 27 million people worldwide. Particularly troubling is increasing evidence that there may be mild-but very real-brain damage that occurs in many survivors, causing preventive yet subtle cognitive, behavioral, and psychological problems [28]. These symptoms appear to impact COVID-19 patients and their quality of life long after their recovery [35]. In a study by Jaywant et al., they found that “medically stable inpatients who were recovering from prolonged COVID-19 hospitalizations and required acute inpatient rehabilitation prior to discharge, commonly have impairments in attention and executive functions including working memory, divided attention and set-shifting [16]. With this new medical data, questions are arising not only among medical professionals and researchers but also among the general public. Are there long-term cognitive effects of COVID-19? Does this virus play a role in systemic functionalities? Why are not more clinical studies being done on the short and long-term cognitive effects of COVID-19? Answers to these questions are imperative for patients, their families and society as a whole. It will be argued that—according to the ethical principles of respect for persons, beneficence/nonmaleficence, and justice—action must be taken immediately to address the concerns surrounding cognitive impairment, both short and long-term, in patients due to Covid-19. Such action will not only save lives and improve the quality of life of patients but will also do much to ensure the dignity and respect of our citizens.

RESPECT FOR PERSONS

This principle incorporates two ethical convictions: first, that

persons should be treated as autonomous agents; and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy [36]. Respect for human persons refers to the right of a person to exercise self-determination and to be treated with dignity and respect. All people, no matter their race, creed, color, sexual orientation or health care condition, deserve autonomy and to be treated with dignity and respect. Failure to provide any person with adequate health care violates this basic right of respect for persons. The limited number of studies on the possible cognitive impairments of patients recovering from COVID-19 may lead to future quality of life issues for these patients. There are studies showing that 'post-COVID syndrome', 'long COVID' or 'post-acute COVID-19' patients are showing persistent psychiatric symptoms. “Many COVID-19 survivors experience persistent physical symptoms such as cough, fatigue, dyspnea and pain after recovering from their initial illness. There is a high probability that symptoms of psychiatric, neurological and physical illnesses, as well as inflammatory damage to the brain in individuals with post-COVID syndrome increase suicidal ideation and behavior in this patient population. COVID-19 survivors without post-COVID syndrome may also be at elevated suicide risk. Studies of suicidality in COVID-19 survivors are urgently needed and will be a new area of suicide research. An appropriate management of psychiatric, neurological and medical conditions may reduce suicide risk among COVID-19 survivors with or without post-COVID syndrome [37]. Without clinical data we are failing to provide adequate health care and protection to our most vulnerable citizens. These COVID-19 patients are vulnerable people because they are facing numerous unknown effects of this deadly virus. Failure to provide pertinent data about the effects of COVID-19 is clearly a violation of the principle of respect for persons.

Second, as an autonomous agent an individual has the right of informed consent. The elements of informed consent include professional disclosure, patient comprehension of the information, patient voluntariness and competence to consent. This means that patients and their proxies have the right to know both the short and long-term impacts of COVID-19 especially the neurological complications. Unless this information is provided to patients and their proxies we are not providing these patients and families informed consent. More studies need to be done on the short and long-term cognitive complications of COVID-109. “The U.S. National Institutes of Health has allocated $1.15 billion in funding for research into the prolonged health consequences of SARS-COV-2 infection. Part of this effort will include large studies involving electronic health records, to capture a broad amount of data over time [34]. This is a good start but more money needs to be allocated for large and comprehensive studies on this issue. In addition, these studies must be diverse and inclusive regarding age, race, ethnic backgrounds, etc. Racial and ethnic minorities experience health disparities more than Whites yet they are not included in research studies as often as White people are. This is true even though researchers who get NIH funding have been required since 1993 to report race, ethnicity, and gender of participants in their biomedical research. African Americans and Latinos make up 30% of the U.S. population but account for less than 10% of participants in genetic studies [38]. Studies have shown the impact of COVID-19 on minorities especially African-Americans. One study found that “Black people with dementia were nearly three times as likely as white people with dementia to become infected with the virus, a finding that experts said most likely reflected the fact that people of color generally have been disproportionally harmed during the pandemic [39]. Racial bias is a major factor preventing diversity in clinical research. This must be addressed, especially regarding cognitive issues with COVID-19 patients. In addition, these research studies should also be global in nature. We need to start sharing data internationally, because COVID-19 impacts the entire world. “Researchers in England and Australia created a global registry that will collect information about cases of newly diagnosed diabetes following COVID-19: some have suggested that the infection elevates diabetes risk [34]. This model should be used as a paradigm for international research on the cognitive effects of COVID-19. Unless this research is done comprehensively, globally, and without bias, it will be very difficult to assure that patients are giving informed consent for their treatments.

The failure of state, federal and global authorities to be proactive in addressing the medical needs of this most vulnerable population in regards to short and long-term cognitive effects of COVID-19 is causing needless suffering and possibly even more deaths. To deny patients and their proxies the right to obtain valuable data that may help them and others clearly violates the ethical principle of respect for persons and our responsibility to help others in society and the world at large.

BENEFICENCE/NONMALEFICENCE

The principle of beneficence involves the obligation to prevent, remove, or minimize harm and risk to others and to promote and enhance their good. Beneficence includes nonmaleficence, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim primum non nocere ("Above all, do no harm"). Patients and their proxies have the right to know the cognitive impact of COVID-19. The few research studies that have been done in this area show that COVID-19 has the potential to induce brain damage either directly by encephalitis or indirectly by ischemia and hemorrhage. The problem is that more research needs to be done on a larger scale both nationally and internationally to determine the extent of brain damage in less severe and recovered COVID-19 patients. There is also a great need for long-term neurologic surveillance and care in patients recovering from COVID-19. Unless this data is obtained and analyzed, the health, quality of life and even life of these patients is in jeopardy.

Healthcare professionals have, as moral agents, an ethical responsibility to treat their patients in a way that will maximize benefits and minimize harms. Failure to adequately communicate and educate patients and families about the short and long-term cognitive effects of COVID-19, is not in the best interest of the patient, their families, or the society as a whole. Interventions that address cognition, such as neuropsychiatric testing and cognitive rehabilitative therapy should become an integral part of the rehabilitation process for these patients. Patients have the right to expect the most beneficial treatment. Physicians and other pertinent healthcare professionals such as physical therapists, occupational therapists, etc. should make sure patients, family members and the general public are aware of potential cognitive abnormalities in those individuals who have been infected with COVID-19. Early screening and cognitive behavioral therapy are essential to prevent further cognitive disease progression. This will require more extensive research studies to ascertain the full implications of COVID-19 cognitively. Further research should also be done on the impact of the 4 variants of the virus to determine if they may also cause additional neurologic and cognitive consequences. To do this, a data base should be established nationally to coordinate all the data. It is the responsibility of the federal government and the various health care agencies to coordinate this data collection and the verify that the data is made available to all pertinent researchers. Data sharing benefits the researcher, research sponsors, data repositories, the scientific community, and the public. It encourages more connection and collaboration between scientists, and better science leads to better decision making. "Data sharing can benefit not just the recipients of data, but also the sharers. A 2018 study of such practices in neuroscience revealed that sharers who used data released by others had larger sample sizes in their studies — achieved by using those open data — than did non-sharing scientists [40]. Healthcare professionals and researchers have the responsibility to provide the best standards of care and safety to protect their patients. Failure to recognize this great need is a failure not only of the test of beneficence; it may also be a failure of the test of nonmaleficence.

JUSTICE

This principle recognizes that each person should be treated fairly, equitably, and be given his or her due. The issue of government funding for additional cognitive research for those patients recovering from COVID-19 also focuses on distributive justice: the fair, equitable, and appropriate distribution of medical resources in society. At a time when reforming healthcare in this country has become a high priority, failure to initiate preventative measures that would save medical resources and possibly human lives in the long-run violates the principle of distributive justice.

Besides funding for additional medical research on the cognitive impact of COVID-19 for recovering patients, there needs to be additional funding for formal neuropsychological testing, evaluating both sustained attention and cognition from a laboratory and at-home setting as a viable route that will be essential in monitoring the onset and progression of cognitive deterioration of recovering COVID-19 patients. This type of research is necessary to better understand the nature and progression in cognitive decline in these patients so that effective therapies can be implemented and patient functioning can be maintained [41]. This method would allow for early screening of patients for cerebrovascular complications and cognitive deterioration before they have a chance to further progress. This type of federal funding would verify that all people are being treated with dignity and respect, especially the most vulnerable.

Americans espouse the belief that all men and women are created equal. Equality has also been a basic principle of the medical profession. If we truly believe in equality, we should insist that all men, women and children receive equal

medical treatment and resources. Denying appropriate medical treatment to those recovering patients of COVID-19, because we have failed to fund the appropriate research, violates a basic tenet of justice. To understand the full implications of COVID-19, more long-term research studies must be funded and implemented. Additional research is needed to understand the possible cognitive impairment in COVID-19 survivors, and the widespread effects in the general population. Once data has been obtained, the data must be shared with all researchers both nationally and internationally in order to protect the best interest of all people. Covid-19 is a pandemic that is impacting the entire planet. No country or people are free from the grip of this deadly virus and its numerous variants. The full implications of this virus must be known for the betterment of humanity. Internationally, the World Health Organization needs to design, implement and fund an international data base to help researchers and medical professionals around the world fight against the cognitive implications of COVID-19. Nationally, the Centers for Disease Control and Prevention and other appropriate government health agencies have an ethical obligation to use available resources fairly and to distribute them equitably. Failure to do so is ethically irresponsible and morally objectionable. To compromise the basic ethical foundations upon which medicine stands is destructive not just to the survivors of COVID-19 but to society as a whole and the world community.

RECOMMENDATIONS

Based on the medical, neurological, and cognitive complications of COVID-19 that are becoming increasingly apparent, there is a great need to take the appropriate precautions in order to prevent them. The ethical issues presented earlier suggest that a holistic analysis of COVID-19 is needed. In this section, we present various recommendations for further steps that should be taken in the care of current patients with cognitive effects of COVID-19, as well as future prevention of neurological complications.

- It is important to warn physicians, family members, patients, and caregivers about the potential cognitive decline caused by COVID-19. The long-term consequences of the virus are unknown, therefore primary care physicians should be vigilant for signs of neurological decline in their patients who have recovered. In addition, neurologists and psychiatrists may need to expect an increase in their patient populations in COVID-19 survivors. They should be on alert for changes to their patients' cognition after recovering, as well as future and long-term effects [15].
- There is an increasing need for more prospective studies to be performed in order to investigate the possible correlations between acute COVID-19 infections and the long-term cognitive impacts on COVID-19 survivors, especially in patients who have had neurological or cerebrovascular complications. Additionally, patients with pre-existing neurodegenerative diseases who have recovered from COVID-19 should be evaluated and monitored for cognitive decline [15].
- Funding for formal neuropsychological testing, evaluating both sustained attention and cognition from a laboratory and at-home setting (i.e family, friends, caregivers) is another viable route that will be essential in monitoring the onset and progression of cognitive deterioration in COVID-19 survivors. With this method, patients would be screened for cerebrovascular complications and cognitive deterioration before they have a chance to further progress.
- Interventions that address cognition, such as neuropsychiatric testing and cognitive rehabilitative therapy (CRT), could be an integral part of the rehabilitation process for patients recovering from COVID-19 [42]. Healthcare providers, physical therapists, friends, family members, and the general public should be vigilant of cognitive abnormalities present in those who have been infected with COVID-19 and subsequently have access to certain rehabilitative interventions such as early screening and cognitive behavioral therapy to prevent further cognitive disease progression in conjunction with COVID-19. Those with pre-existing neurodegenerative diseases should be especially monitored carefully.
- Since the central nervous system effects may additionally cause communication impairments, speech-language pathologists may also need to be called to action to become involved in these patients' acute and chronic care. These patients may require their services throughout their disease course and also throughout the recovery process [44].
- Further research should be performed to determine if the other variants of the virus cause the same neurologic and cognitive consequences. Clinicians should continue to report new findings in their patients. Research should also be performed in order to study the severity of the post-infection cognitive effects in vaccinated versus unvaccinated individuals.
- The US National Institute of Health has allocated $1.15 billion in funding for research into the prolonged health consequences of SDARS-COV-2 infections. Part of this effort will be to include large studies involving electronic health records to capture the broad amount of data over time. This funding must be expanded to include cognitive issues as well as neuropsychological testing, evaluating sustained attention and cognition from a lab and at home setting.
- England and Australia have created a global registry that will collect data about the causes of newly diagnosed diabetes from COVID-19. This paradigm should be funded by the WHO to create a

global data base for cognitive impairments for COVID-19 patients and the data must be shared internationally.

CONCLUSIONS

The COVID-19 pandemic continues to be a global issue, affecting all ages, races, and geographies. Available research has shown that patients infected with COVID-19 have an increased risk for neurologic illness, particularly affecting cognition. This is giving credence to the thought that COVID-19 may affect the brain more than previously thought. Current treatment options are limited, as medications such as remdesivir and corticosteroids do not directly treat the nervous system effects. Introduction of formal neuropsychological testing for long-term COVID-19 survivors and patients with pre-existing neurodegenerative diseases should be considered to detect long-term neurological and cognitive abnormalities. The further identification of these cognitive consequences will enable better treatment plans for patients in the future, and could potentially even help prevent further cognitive deterioration. In conclusion, vigilance and further investigation of the short and long term cognitive effects of the virus should be performed in order to combat this ongoing issue.

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