# COVID-19 and Dementia; Hard to Forget Yet Haunting Forgetfulness!

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## Abstract

The current pandemic has affected almost everyone worldwide. Although the majority of people survive the illness, bad cognitive repercussions might last a long time, resulting in a lower quality of life and disability, particularly in severe cases. We tried to understand and bring together the various possible mechanisms leading to dementia in COVID-19. The link between COVID-19 and dementia will help public health workers plan and allocate resources to provide better care for a community suffering from sickness and improve quality of life. A conceptual framework for care of infected people in the older age group and care of dementia people is proposed.

**Keywords:** COVID-19, dementia, neuro-inflammation, neuro-invasion

## Introduction

COVID-19 caused by the SARS-CoV 2 virus has quickly spread to become a worldwide pandemic. COVID-19 related severe sickness primarily affects the elderly and persons with underlying medical conditions.[1] A larger proportion of proven cases, according to the US Centers for Disease Control and Prevention (CDC), are observed in people aged 18–64 years.[2] Though the majority of people survive the illness, poor cognitive consequences can be long-term, resulting in a reduced quality of life and disability, especially in severe instances.[3]

Dementia is characterized by a gradual loss of cognitive ability that interferes with daily tasks. It is debilitating not just to the individual suffering from it, but also to the caretakers. Dementia incidence has grown dramatically during the last few decades. According to recent research, dementia is the most prevalent co-morbidity in COVID-19-related fatalities.[4] Cardiovascular illness, obesity, diabetes, and hypertension are all significant risk factors for cognitive deterioration and dementia.[5] Many of these frequent co-morbidities in dementia patients are potential risk factors for COVID-19 and are linked with poor clinical outcomes. Understanding the relationship between COVID-19 and dementia will assist public health professionals in planning and allocating resources to better care for a community struggling from illness and improve quality of life.

## Methodology

This article is a narrative review focusing on the neurological manifestations and consequences of SARS CoV 2 infection. We searched four databases – PubMed, Scopus, Embase, and Google Scholar with keywords – COVID-19, dementia, neurological manifestations, neuropsychiatric symptoms, delirium, and dementia management. We selected relevant 84 articles out of 120 and narrated the possible mechanism of dementia in SARS CoV 2 infection, its clinical manifestations, and its management.

### The link Between COVID-19 and dementia

It is well known that COVID-19 individuals have a history of pulmonary complications. Furthermore, these individuals' senses of smell and taste have been frequently observed to be impaired which could be attributed to the viral entry through the nasal epithelium. In a study done in Strasbourg, France, 58 out of 64 COVID-19 positive patients who presented with the symptoms of Acute Respiratory Distress Syndrome (ARDS) were also reported to have neurological manifestations. They had associated encephalopathy, restlessness, and disorientation, as well as corticospinal tract symptoms.[6]

Previous studies have reported that nearly one-third of critically ill patients usually develop delirium but a recent study showed that in the case of COVID-19, out of 2000 affected critically ill patients, 55% developed delirium.[7] A single instance of delirium can raise the chance of getting dementia years down

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the lane, as well as expedite the rate of cognitive deterioration in individuals who have had the illness.[8] Already existing dementia also increases one's chances of developing delirium. In a retrospective study done by Wang *et al.*, 5.14% of the senior adult patients affected with COVID-19 were also diagnosed with dementia.[4]

Studies have shown that people with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease are at a higher risk of COVID 19 infection and this correlation was independent of confounding variables, such as age and other physiological comorbidities and did not vary considerably between primary neurodegenerative disorders and neurodegenerative diseases with a primary vascular component.[9] The possible mechanism is the increased vulnerability to infection, which might be caused by a dysregulated immune system, further implicated in the development of neurodegenerative illnesses, including changes in peripheral immunological responses.[10] A UK based cohort study documented a clear correlation between various neurodegenerative diseases and increased risk of COVID 19, especially the most severe and fatal form[11] In another study, it was proved that SARS-CoV-2 infection enhanced Alzheimer's markers associated with brain inflammatory response, and some viral invasion factors are found in blood-brain barrier cells. Another observational study which was aimed to interpret the neurological and psychiatric complications following COVID-19 reported that the incidence of neuropsychiatric complications following 6 months post COVID-19 infection is 33.62%; of which 0.67% is attributed to dementia. Patients with severe COVID-19 were at the highest risk, although this was not restricted to them.[12] Another study reported the prevalence of dementia in COVID-19 affected patients to be 13.1%. The mortality rate is 62.2% for COVID-19 patients with dementia when compared to 26.2% in patients without dementia. Among dementia patients, the most common signs of onset were delirium, particularly in the hypoactive type, and deterioration of functional outcome.[13]

The demographic disparity is also observed in COVID-19 infected patients with dementia. A study has reported that COVID-19 infection was more common in Blacks with dementia when compared to Whites with dementia.[4] This is similar to the previous findings which showed COVID-19 affects the Black population in general at a higher proportion.[14]

Elderly patients with COVID-19 have a higher risk of death, and men have a mortality rate that is double that of women. This is in line with the fact that COVID-19 mortality is disproportionately influenced by old age and because of the impacts of potentially unhealthy habits, cardiovascular health, and other variables, men's mortality risk is generally higher than women's.[15]

## Plausible mechanisms of dementia in COVID-19

### *Neuroinflammation*

It is postulated that viruses can reach the brain via affected immune cells, which can also act as storage for the virus. The blood vessels, meninges, and choroid plexus are all entrance routes for monocytes, neutrophils, and T cells into the brain, and these locations might be points of entry for pathogenic immune cells.[16] Immune cells move into the brain parenchyma during encephalitis. T-lymphocytes, macrophages, and, to a lesser extent, PMN are recruited as part of the viral CNS infection cascade. In the context of viral meningitis, an increase in CD4+ T-cells, CD8+ T-cells, and NK cells has been seen.[17] The inflammatory mediators such as IL-1β, IL-6, IL-8, IL-33, tumor necrosis factor-alpha (TNF-α), are released by activated microglia, astrocytes, neurons, T-cells, and mast cells. These mediators will ultimately lead to the destructive cycle of neurodegeneration and dementia.

### *Direct neuroinvasion*

A systematic review documented that only 14 out of 733 patients with SARS -CoV-2 had the virus in the CSF[18] indicating that direct neural invasion by SARS -Co V- 2 is rare. The low incidence of CSF positive SARS-CoV-2 results can be related to various reasons. CSF testing was originally low as it's performed only in instances with severe CNS signs; if patients did not have severe CNS signs, they wouldn't have been examined. Also, due to quick CSF clearance, low titers, or delayed collection, isolation of SARS-CoV-2 in CSF may be difficult.[19] Even though CNS is not the major organ infected by SARS-CoV-2, viruses can directly attack the CNS and cause damage to nerves and neurons that have been identified as potential targets of the virus. The recruitment of CD4+ and CD8+ T cells, as well as the subsequent generation of neutralizing antibodies, is an important part of any immune reaction including SARS-CoV-2. Intriguingly, the anti-SARS-CoV-2 antibody profile in plasma and CSF varies amongst the same COVID-19 patient, implying a compartmentalized immune response inside the brain. In acute infection, this differential humoral response indirectly favors SARS-CoV-2 neuroinvasion. SARS-CoV-2 can infect motor or sensory nerve terminals and move in retrograde or anterograde fashion via motor proteins.[20]

### Intracranial extension of nasal infection

A murine study revealed that on intranasal inoculation of the SARS-CoV-2 virus, 68% of the mice brains were tested positive for COVID-19.[21] Evidence also suggests that when the olfactory sensory neurons are degenerated by zinc sulfate, it completely denied access to the virus.[22] These studies suggest that olfactory epithelium can pave a way for the intracranial invasion of the virus and subsequent neurological complications. The ACE2 receptor is more concentrated in the nasal lining than in the lower airways, resulting in a gradient of infection susceptibility from the nasal cavity to lower regions of the lung's deep areas.[23] The concept of SARS-CoV-2 infecting the olfactory nerve is feasible, given numerous patients have been reported to suffer increasing ageusia and anosmia.[24] After the virus infects the CNS via the olfactory nerve, it spreads to various parts of the brain, including the basal ganglia, dorsal raphae nuclei, and piriform and infralimbic cortices, but the thalamus and hypothalamus

are less usually reported as positive.[25] Despite this evidence, the neuro-invasive capacity of SARS-CoV-2 remains unknown, as some study suggests that only epithelial (sustentacular) cells of the nasal mucosa, not olfactory neurons, can be infected.[26]

### Viral invasion through choroid plexus

It has been found that certain choroid plexus cells have been shown to exhibit the ACE2 and other SARS-CoV-2 entrance proteins such as the TMPRSS2. In a study, in iPSC-derived brain organoids, SARS-CoV-2 infection of choroid plexus cells produced significant epithelial degradation and subsequent leakage over this crucial blood-CSF barrier. However, infection of the neuron was not observed. This implies that the infection of supporting CNS cells, rather than the direct infection of neuronal cells, may be the cause of neurological symptoms in COVID-19 individuals.[27]

### Viral invasion through the blood-brain barrier (BBB)

There has been evidence of direct viral infections caused by Human Immuno deficiency virus (HIV), Herpes simplex virus (HSV), Japanese encephalitis, and Human herpes virus (HHV) involved in the etiology of neurodegenerative diseases. Influenza viruses and coronaviruses have been involved in the etiology of neurodegenerative diseases.[28] Generally, the brain is immunoprivileged from any peripheral inflammation because of its blood-brain barrier (BBB). Once this barrier is disrupted, it is no longer protected from the immune cytokines. The primary binding receptor for SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE2) which is expressed in neurons and cerebral blood vessels. ACE2 protein, which when activated results in the release of cytokines.[29] Interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), and IL-17 are SARS-CoV-2-associated cytokines that disrupt the BBB and may promote viral entry. These cytokines are the predominant mediators of neuroinflammation. The virus then infiltrates neurons and causes neuroinflammation in an ACE2-dependent manner, ultimately resulting in impaired cerebral blood flow, vascular endothelial damage, and cell death leading to cognitive dysfunction[30] Co-morbidities are observed often in COVID-19, such as cardiovascular risk factors or pre-existing neurodegenerative problems, may enhance BBB permeability alone or in conjunction with cytokines.[31]

### *Genetic predisposition*

The researchers also investigated the genetic variables that allow the SARS-CoV-2 virus to infiltrate brain cells and tissue. SARS-CoV-2 has a tight network connection with genes/proteins linked with Alzheimer's disease, resulting in COVID-19 causing Alzheimer-like dementia.[32] The key genetic risk factor for Alzheimer's disease is APOE4 (AD).[33] Persons who were homozygous for APOE4 had a more than twice greater risk of COVID-19-related hospital admissions than those who had the most common APOE 3/3 genotype. One possible mechanism for this link is that APOE 4 drives up blood-brain barrier permeability, which results in wide-ranging CNS inflammation in responding to COVID infection — APOE 4 is known to intensify microglia-mediated neuro-inflammation and resulting neurodegeneration. Furthermore, higher cytokine production in response to inflammatory stimuli is linked to APOE 4, which might exacerbate the already strong inflammatory response linked to COVID-19, culminating in the so-called cytokine storm.[34]

### *Hypoxia*

SARS-CoV-2 stimulates the cytokines and hypercoagulation pathways in the blood by attaching to respiratory epithelial cells, raising levels of inflammatory markers such as C-reactive protein, ferritin, IL-1, IL-6, TNF-, and D-dimer. This hypercoagulable state can cause blood clots in both the cerebral arteries and veins, resulting in stroke and cerebral venous thrombosis.[35] In a study done at Columbia University, where an autopsy was performed on 41 patients who died of COVID, it was found that there was no evidence of viral RNA or protein in the brain cells but there were evident signs of hypoxic brain death. The authors contradict the direct neuroinvasion by SARS-CoV-2 and postulated that these hypoxic lesions are a consequence of thromboembolic events that are secondary to COVID infection and it is hypoxia responsible for the neurological signs of COVID. They also noticed a large number of activated microglial cells in the brains of these patients. The microglia may have been activated by inflammatory cytokines, such as Interleukin-6, associated with SARS-CoV-2 infection. Hypoxia can cause the surface of neurons to produce 'attack me' messages, rendering hypoxic neurons more sensitive to activated microglia. So, COVID-19 can harm the brain even if it does not directly infect brain cells.[36] In a similar study, where an autopsy was done on the brains of 18 patients who died of COVID-19, histopathological examination showed only hypoxic changes. The cytoplasmic viral staining was negative on immunohistochemical analysis suggesting hypoxia to mediate neurological manifestation of COVID-19.[37]

In extreme cases, thromboembolic events can result from the rupture of susceptible atherosclerotic plaques in the context of a significant pro-inflammatory condition following COVID-19 infection, ultimately resulting in hypoxic brain damage[38]

### *Electrolytic disturbance leading to dementia*

Hypokalemia and hyponatremia are prevalent in COVID-19 patients, and they are linked to the severity of renal damage. Hypokalemia is a common abnormality in COVID-19 patients. It could be attributed to respiratory alkalosis due to hypoxia-driven hyperventilation, anorexia as a result of wearing a face mask or a ventilation helmet for an extended period, or as a result of a serious sickness or the cytopathic effects of viruses on gastrointestinal cells may contribute to potassium losses from the digestive tract.[39] Alfano *et al*.[40] reported hypokalemia in 41% of hospitalized patients with COVID-19. Booth *et al*.[41] reported hypokalemia in 43% of the patients infected with SARS-CoV-2. Hypokalemia causes a broad spectrum of clinical manifestations, ranging from muscle weakness, and areflexic paralysis to cardiac arrhythmia. Neurological complications include disorientation, confusion, memory impairment, lethargy, fatigue, apathy,

and depressed mood. It also can mimic anxiety reactions, such as irritability, headache, paresthesias, nervousness, muscle discomfort, and visual disturbances.[42] The exact mechanism of hypokalemia causing cognitive disturbances and psychiatric manifestations is not well known. However, studies have revealed that improved potassium, magnesium, and calcium consumption in the diet lowered the incidence of all-cause dementia.[43] Cisternas *et al*.[44] discovered that increasing the potassium intake lowered oxidative stress and inflammation while also improving cognition in an animal model of Alzheimer's disease. This implies that hypokalemia secondary to COVID-19 could attribute to the development of cognitive impairment.

Hyponatremia occurred in nearly a third of coronavirus diseases and was associated with an increased risk of encephalopathy. Frontera *et al*. reported hyponatremia in 30% of the hospitalized patients with COVID-19. When compared to individuals with elevated sodium levels, people with severe hyponatremia (Na 120 mmol/L) seemed to have eight times increased chance of encephalopathy.[45] The exact mechanism of hyponatremia in patients with COVID-19 is not clearly understood. It is potentially caused by systemic inflammation associated with non-osmotic stimuli for vasopressin production. Interferon-6 has been linked to the cytokine storm involved in the development of severe COVID-19 complications and may contribute to excessive, unwanted production of antidiuretic hormone resulting in hyponatremia.[46] Quick reversal of hyponatremia is associated with demyelination, whereas hyponatremia induces widespread cerebral edema.[47] Current studies have proven that hyponatremia could result in attention deficits and cognitive disturbances.[48] As an initial adaptation to hyponatremia, there is an increase in the concentration of the brain's extracellular glutamate. To achieve a steady signal-to-noise ratio in extrasynaptic and synaptic transmissions and to avoid glutamate neurotoxicity caused by massive glutamate receptor activation, the extracellular glutamate concentration must be ideally kept low. The low extracellular glutamate concentration is maintained by astrocyte glutamate uptake which is mediated by sodium dependant glial glutamate transporters. Glial glutamate uptake and metabolism are affected by hyponatremia. Increased extracellular concentration of glutamate ultimately results in synaptic dysfunction and affects neuron survival resulting in neurodegeneration.[49]

### *Stress and fear*

While emphasizing social distancing during preventive measures, the social interaction of people was lost. Which itself led to depression and a sense of despair and anxiety adding further to the misery of dementia people. Loneliness, anxiety, economic instability, and the daily avalanche of negative news brought on by the coronavirus pandemic were affecting mood. The link between negative symptoms and dementia's functional impairment is still being researched. Negative symptoms may add to the functional impairment produced by cognitive degeneration, according to certain theories.[50] The fear of getting infected and the social stigma of the disease itself and further its consequences eventually reach a threshold, leading to the onset of dementia.

## Effect of dementia on COVID-19

People with dementia are the most susceptible group to infectious diseases, such as respiratory syncytial virus disease, severe acute respiratory syndrome coronavirus, and influenza A due to age, fraility, lack of autonomy, chronic immunological disorders, and other chronic illnesses, particularly co-morbidities of vascular diseases. Their post-infection clinical result is poorer than that of the normal community. People with dementia have been hit worse than the other majority of people by the COVID-19 pandemic.[51] Research combining data on dementia and COVID-19 cases from 185 countries discovered a substantial link between dementia and COVID-19 occurrences.[33] Patients with dementia had a greater death rate than individuals with other psychological conditions, according to retrospective cohort research.[52]

COVID-19 has a greater occurrence and death rate in dementia patients due to the following factors. The most significant determinants for a bad outcome have often been age and associated co-morbidities.[53] Second, the "cytokine storm" is thought to be a factor in the poor prognosis after SARS-CoV-2 infection. People with dementia could be at increased risk of cytokine storm because of the existence of elevated baseline inflammation.[54] People with dementia are not able to adhere to COVID-19 preventive measures such as following coughing etiquette, tracking and reviewing COVID-19 symptoms, and maintaining a reasonable distance from everyone else to prevent the spread of COVID-19.[55] Due to depression, patients with moderate memory loss or minimal dementia may be hesitant or otherwise unable to cooperate. Patients with dementia, including those in residential facilities or care facilities, require constant supervision. Medical assistance, in conjunction with stringent supervision, should be provided to these patients because of their susceptibility [Figure 1].

## Impact of COVID-19 on dementia

Individuals with dementias have been particularly affected by the COVID-19 pandemic. Neurologists believe that the inflammatory cascade induced by the cytokine storm during NeuroCovid Stage II and III may lead to new ischemic stroke, intracranial bleeding, and aggravation of pre-existing cerebrovascular illness, including vascular dementia.[56] Patients with dementia's living settings can have a significant influence on their vulnerability to severe infection. As the condition worsens, they will need a lot of help to get around regularly. Their state support and healthcare systems have been rendered inaccessible due to lockdowns and social distancing efforts which aggravate the dementia individuals' pre-existing neuropsychiatric problems.[56] Dementia patients may experience disruptions in their daily routines, a loss of cognitive stimulation, feelings of loneliness and anxiety, fear of abandonment, and sadness. They may endure a worsening

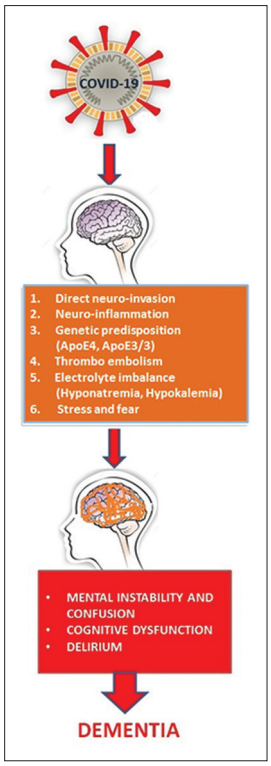


**Figure 1:** Pathogenesis of dementia in COVID-19. COVID-19 induced neuro-invasion, neuro-inflammation, thrombo-embolism, electrolyte imbalance, stress, and fear cause mental instability, cognitive dysfunction, and delirium leading to dementia in a genetically susceptible individual

of their disease, sleep difficulties, behavioral changes, self-neglect, and early hospitalization. The requirements of persons with dementia are at risk of going away or unmet when daycare facilities close and home care services and visits from friends and family are curtailed or halted. During this COVID-19 pandemic, the health and rights of people with dementia, as well as their caretakers, have been put in jeopardy. People with dementia require extra care during the COVID-19 pandemic because they may find it much harder to adhere to the preventive measures needed to keep the virus from spreading. It has also imposed the risk of discontinuation of the ongoing treatment, especially for those who depend on external help for reminders or assistance and closure of memory clinics. Memory clinics worldwide have closed their face-to-face consultations and non-pharmacological interventions for dementia, such as cognitive therapy, exercise, and socialization, have been suddenly stopped during lockdown.[57]

## Clinical features

The clinical presentation of COVID-19 varies widely ranging from simple rhinorrhoea mimicking the seasonal flu to life-threatening pneumonia. Studies have also reported olfactory disturbances as the only presenting symptom in some cases of COVID-19.[58,59] A recent study suggests that dementia is the most prevalent co-morbidity in COVID-19-related fatalities.[4] COVID-19 infection in people with dementia is linked to a poor outcome, and it has its own set of clinical characteristics. People with dementia could present differently or have a higher chance of mortality from COVID-19. The most common biochemical abnormality observed was lymphopenia (84.8%).[60] Delirium in COVID-19 has indeed been linked to urinary retention, associated comorbidities, polypharmacy, cytochrome interactions, insomnia, tissue hypoxia, and desaturation. It has been noted that in individuals with severe COVID-19 infection irrespective of the status of dementia, there is elevated neurofilaments and glial fibrillary acid protein, which suggest activation of astrocytes and neuronal damage.[61] Another commonly reported symptom is fall; falls and gait impairment are more frequently seen in COVID-19 patients with dementia than the individuals with normal aging.[62] Male sex, multiple co-morbidities, lymphopenia, and elevated C-Reactive Protein (CRP) were independent factors for poor outcomes.[60,63] [Table 1].

Because individuals with dementia display very different COVID-19 signs and symptoms, delayed detection of COVID-19 might result in these patients' adverse consequences. As a result, better detection of COVID-19 and methods to prevent SARS-CoV-2 infection in this sensitive population are required, as well as meticulous evaluation of relevant mental health issues and psychological support while executing these interventions.

## Management

Dementia is one of the most debilitating age-related illnesses, having serious consequences for one's health and social well-being. COVID-19 is known to increase the risk of severity and fatality in older persons with pre-existing medical conditions. Integrated dementia care, which includes adequate safety and psychological concerns, is an essential component of public health.

### *Non –pharmacological interventions*

Physical protection goes hand in hand with psychological well-being, and preventive actions against a pandemic must be well-guided and overseen by care providers and matched to the cognitive demands of persons living with dementia.

### Promote social interaction

Where social isolation and loneliness tend to aggravate the cognitive symptoms in persons with dementia, digital interaction and stimulation could be used as an alternative. The delivery of content to people with dementia should be done slowly, with numerous breaks, in brief, and clear words, and with the use of audio-visual aids. The patient should be taught how to telecommunicate using a cell phone or computer. Simple infographic visual charts can serve as triggers to assist in reinforcing information. Material for people with dementia is better presented in their own language, with socio-cultural surroundings adapted to them. Frequent and regular telecommunication promotes for the patients a sense of compassion and bonding. All information on COVID – symptoms, when to seek medical help, appropriate preventive measures to be taken should be provided to the persons suffering from dementia in a manner that could be understood by them and the caregivers at home should ensure the preventive measures are properly adopted by the patients.[74]

**Table 1: Spectrum of clinical presentation of COVID-19**

| Authors | Number of cases | Median age | Clinical features |
|---|---|---|---|
| Chen *et al*.[64] | 99 | 55.5 years | fever (83%), followed by cough (82%), shortness of breath (31%), muscle ache (11%), confusion (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%) |
| Guan *et al*.[65] | 1099 | 47 years | Fever (88.7%), cough (67.8%), vomiting (5%), diarrhea (3.8%) |
| Wang *et al*.[66] | 138 | 56 years | fever (98.6%), fatigue (69.6%), and dry cough (59.4%) |
| Huang *et al*.[67] | 41 | 49 years | fever (98%), cough (76%), and myalgia (44%); sputum production (28%), headache (8%), haemoptysis (5%), and diarrhoea (3%). |
| Moein *et al*.[68] | 60 | 46.5 years | 25% anosmic, 33% severely microsmic, 27% moderately microsmic, 13% mild microsmic |
| Spinato *et al*.[58] | 374 | 56 years | 64.4% anosmia, 68.3% fatigue, 55.5% fever, 60.4% cough |
| Vrillon *et al*.[60] | 125 | 86 years | delirium (82.4%), asthenia (76.8%), fever (72.8%). |
| Butt *et al*.[69] | Case report | 77 year | Acute confusion |
| Tay *et al*.[70] | Case report | 94 year | delirium |
| Harb Amro *et al*.[71] | 531 | 65 years | 36.2% delirium, 45.7% dyspnoea, 8.6% diarrhoea, 8.6% myalgia, 4.3% chills, 6.9% nausea, vomiting, 0.9% headache |
| Kennedy *et al*.[72] | 817 | 77.7 years | 28% delirium, 56% fever, 51% dyspnoea, 50% cough, 30% fatigue |
| Poloni *et al*.[73] | 59 | 82.8 years | 36.8% delirium, 14% no typical symptoms |

## Caregiver education

When family caregivers live with a person who has dementia, the increased time spent together, the lack of assistance, and worries about managing can lead to stress, fatigue, and even violence. Because of their own urge to isolate and the restricted resources available during the pandemic, caregivers who are older and living with health concerns may find it extremely difficult to discharge their caregiving obligations. Caregivers should be tele-counseled from time to time about how to support people with dementia both practically and emotionally how to structure the day and keep the patient active and engaged, ensure a good diet, manage medication, access to fresh air, and also how to take care of their own needs. National mental health counseling helplines should be used and connected with elder service helplines. There are many online home-based exercise and cognition training programs. Caretakers help the patients familiarize themselves with these web-based programs.[75] Caretakers can place signboards in the rooms of dementia persons, which will frequently remind them of hand washing, wearing masks, and maintaining social distancing. They should ensure the patients are completely vaccinated against COVID-19.

## Conceptual framework of home-based care strategies amid the COVID-19 pandemic

It will be ideal if a case manager can help coordinate care across the continuum of community-based services and partner with persons from the social support network, with a special focus on managing the following key areas: implementing infection control measures at home, care for basic needs, tackling behavioral problems, maintaining brain-healthy lifestyle activities, managing medical/cognitive problems, showing concern for and appreciation to caregivers. Although user-friendly telehealth technologies can facilitate better care delivery in many ways, making simple phone calls may sometimes serve a similar purpose.[74]

### *Pharmacological interventions*

Memantine is a potential drug of choice for the management of dementia in COVID-19 as it inhibits surplus glutamate release in the medulla, which would be a potential neurotoxic consequence of ACE2 depletion following the binding of SARS-CoV-2 to ACE receptors.[76] In a recent study, 22 patients with neurological disorders following RT-PCR confirmed SARS-CoV-2 infection was successfully treated with memantine.[77] Studies have shown that 10%-30% of the patients experience symptoms that persist for more than three months and probable nerve damage has been postulated for the same and it has been found treating some of these patients with immunotherapies that are used to target inflammatory neuropathy led to improvements in symptoms.[78]

Knowledge about drug interaction is essential for the management of COVID-19 in patients with dementia. Treatment with Chloroquine, hydroxychloroquine, and lopinavir/ritonavir increases the drugs levels of cholinesterase inhibitors like donepezil, galantamine, and rivastigmine by the interaction via cytochrome P450. These drugs also interact with antipsychotics and antidepressants used in the management of AD. Arrhythmia and other cardiac events are commonly seen in the treatment with azithromycin, chloroquine, hydroxychloroquine, and Cholinesterase inhibitors; making frequent electrocardiographic monitoring necessary. Memantine and haloperidol are the preferred drugs for the management of AD and agitation in patients with COVID-19 due to the low risk for drug interactions. Drugs that are used in the treatment of COVID-19 such as tocilizumab, ribavirin, favipravir, and remdesivir have no potential interaction with AD treatments.[79]

### *Palliative care*

Wherever possible and with adequate precautions, health care providers can be encouraged to give focused care to people

with dementia. To get through the barrier created by masks and face shields, voice modulation and nonverbal interaction may be necessary. Health care personnel's should put in all possible effort to enable interaction with families and close friends of the person with dementia via mobile and internet in residential care facilities. They should ensure particular attention is being paid to maintaining routines, providing information whilst not causing distress, and providing emotional support to people with dementia. Some remuneration for informal caregivers can be recommended. It is advised that helplines, legal aid, and social services be established to safeguard vulnerable people against abuse and exploitation and to give corrective assistance. This might be paired with caregiver and community education.[80]

Dyspnea, agitation, drowsiness, and depression are the most common symptoms for the referral to palliative team care. Dyspnea is common management with opioids and oxygen supplementation. Benzodiazepines along with opioids can be useful in patients with agitation and anxiety. Haloperidol is the safest antipsychotic for the palliative management of delirium in patients with COVID-19 and dementia.[81]

## Conclusion

COVID-19-related severe sickness primarily affects the elderly and persons associated with co-morbidities, especially with dementia. There is a bi-directional association between COVID-19 and dementia. Caretakers of persons living with dementia must be psychologically prepared to provide continuity of care. Most essential, it is a collaborative obligation of all stakeholders to recognize the requirements of persons with dementia and their caretakers, as well as to develop prepared measures for their help that may be utilized long after the pandemic has passed.

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### Conflicts of interest

There are no conflicts of interest.

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