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Review Article

COVID-19 in Geriatric Age Group - A Review

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A B S T R A C T

Coronavirus pandemic is an unprecedented global crisis that has affected the entire mankind. The elderlies are a specific cluster of high-risk patients for developing COVID-19 infection with rapid clinical deterioration. Frailty and comorbid conditions in the geriatric age group may be associated with mortality, considering the diversity of results in the existing literature. The present document has been drafted to review the available literature and evidences on this infection in geriatric age group which is particularly vulnerable to this disease and its fatal manifestations.

Keywords: Geriatric Age, COVID-19, Comorbidity, Therapeutics, ACE2 Receptor, Frailty

Introduction

Coronaviruses (CoVs) represent a heterogeneous cluster of positive stranded RNA viruses, that target the human respiratory system.[1] They belong to the family of Coronaviridae, the alpha and beta-coronavirus being the genera of human interest. Other outbreaks of coronavirus that have been a major threat to public health in the past include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV.[2]

In late December 2019, a group of patients with an initial diagnosis of pneumonia of unknown etiology were admitted to the hospital in Wuhan, Hubei, China. Epidemiologically, these patients were linked to a seafood market in Wuhan.[2,3] Research identified the cause of infection being a novel coronavirus labelled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was referred to as COVID-19 by WHO on Feb 11, 2020.[4] As of September 2, 2020, the World Health Organization has confirmed 25,541,380 cases of COVID-19 in 216 countries worldwide. India has reported 3,794,314 confirmed cases of COVID-19 and 66,678 deaths so far whereas 2,920,122 infected patients have been recovered.

The rate of mortality of COVID-19 increases with advancing age while children are observed to be less susceptible to death.[5,6] Italy and Spain are the world's two worst hit countries by the COVID-19 pandemic. The two Mediterranean countries have large elderly populations, highly social citizens and densely populated cities. Spain and Italy's failure to recognize the magnitude of the pandemic led to around 40% of total global COVID-19 deaths in April 2020.

Infection with this virus causes diverse clinical manifestations which include respiratory symptoms, from the common cold to severe pneumonia with an Acute Respiratory Distress Syndrome (ARDS), septic shock, multi organ failure and death.[7] The present document has been drafted to review the available literature and evidences on this infection in geriatric age group which is particularly vulnerable to this disease and its fatal manifestations.

Pathogenesis of Covid-19

SARS-CoV-2 is a single, positive stranded RNA virus, enveloped in a lipid bilayer. The lipid bilayer fuses with the host cell membrane to release RNA into the cytoplasm

and causes translation of various viral proteins.[1-3] The replicated RNA genome and synthesized viral proteins reassemble into new viruses, which burst out of the cell. Like the other coronaviruses, SARS-CoV-2 uses its Spike (S) protein, main structural component of the viral particle , to attach to human cells.[1,3-5] The viral S - protein binds with the human protein receptor Angiotensin Converting Enzyme (ACE2), that is found in the lungs, endothelium, heart, kidneys, cells of oral mucosa and gastrointestinal system. In the lung cells, ACE2 generates ANG I-VII, which down regulates the inflammatory effects of AngII.[8] Upon viral entry, the spike proteins of both SARS-CoV and SARS-CoV-2 cause the degradation of ACE2 that primarily contributes to lung damage (Figure 1). SARS and SARS-CoV-2 uses the same mechanism for entering the host cell. SARS-CoV-2 accumulates more in the system at a slower speed, thus having a longer intubation period and more transmissibility. While SARS presents with more symptoms and disease severity.[9]

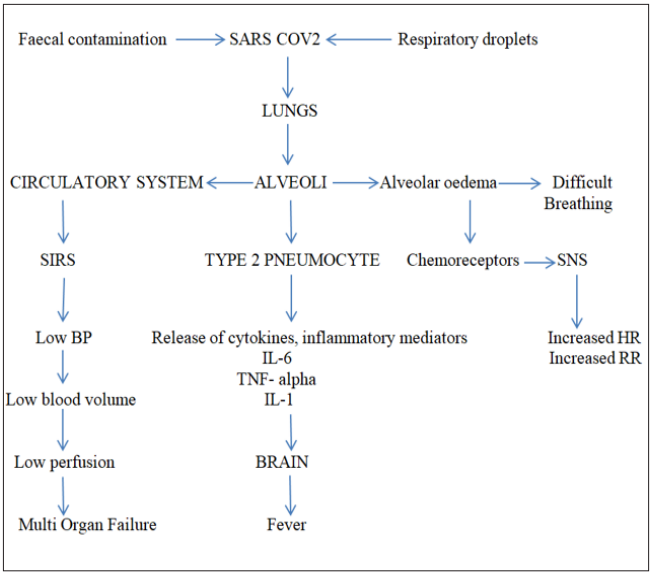

Figure 1.Pathogenesis of SARS-CoV-2

Factors that Make Older People more Susceptible to Infection

The high incidence of comorbid conditions such as hypertension, chronic kidney disease and diabetes in the elderly predisposes them to take ACE inhibitors and Angiotensin- Receptor Blockers (ARBs) that up regulate the ACE2 receptor.[10] The ACE2 (an integral membrane protein with multiple physiological functions) has been identified as the cellular entry point for the virus.[5,8,10] Binding of this virus to the receptor alters protective mechanism of lungs, which contributes to its pathogenicity.

There is an age related decline in the clearance of inhaled particles in a small airway region, suggesting high incidence of respiratory symptoms among the elderly. Martin et al. demonstrated that the size of upper airway decreases with age in both males and females. Ageing related physiologic processes like high prevalence of frailty and comorbidities reduce the functional reserve, thereby undermining the intrinsic capacity and resistance to disease and infection. Disruption of both innate and adaptive arms of the immune system occurs as the age advances. A complex network between innate and adaptive immune effector cells is important for competent response against microbes.

There is a continual production of inflammatory mediators and cytokines, also called 'inflammaging' in the elderly. Viral infections responsible for chronic and latent infections are suspected to influence T-cell function in elderly. A negative correlation between CD4/CD8 T-cell ratio and severity of frailty in the geriatric patients has been reported.[11,12] The number of circulating 'competent' B cells significantly decrease with age, whereas the percentage of terminally differentiated and senescent memory CD27-B cells have been reported to increase in the elderly.[12]

Elderly patients with pre-existing cardiovascular disease have a higher risk of severe symptoms and death. Like the other coronavirus infections, development of myocarditis has been described in patients infected with COVID-19.[6,10] Patients with COVID-19 exhibit changes in coagulation parameters, an elevated concentration of D-dimer particularly, which increases thrombogenic risk and higher mortality.

Nursing homes are frequently being isolated due to COVID-19 outbreak. The group of elderly people residing in such old age homes are more vulnerable to infection for reasons such as close contact with their careers and other residents, cognitive decline & dependency. Such group of patients spend considerable amount of time in enclosed spaces with equally vulnerable population. Another factor that makes geriatric age group more prone to infection is poor access to telemedicine options due to poor knowledge and lesser adaptability to digital technologies.

All these factors contribute to adverse clinical outcomes in SARS CoV-2 infection and assessment and treatment becomes challenging.

Transmission & Infectivity

Several reports have suggested that person to person transmission is the route for spread of COVID-19 infection.[13,14] Person to person transmission primarily occurs by direct close contact or droplets spread by coughing or sneezing from an infected individual. There is limited evidence to suggest its spread via air. Stadnytskyi et al used laser-light scattering to detect droplets emitted by healthy volunteers while speaking and reported that for SARS-CoV-2, one minute of loud speaking generated around 1,000 small, virus-laden aerosols, 4 micrometres in diameter that

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remained airborne for at least 8 minutes. Thus, normal speaking may cause airborne transmission of viral particles in confined environments.[15] No viral RNA is detected in urine or serum samples of infected patients.[16] On the other hand, viral RNA can be detected on fomites like plastic, metal surfaces etc.

The incubation period of COVID-19 is about 3-9 days.[17] An individual may become contagious before presence of any symptoms. The period from the onset of COVID-19 symptoms to death ranges from 1 to 6 weeks. It has been reported that 44% of transmission is estimated to occur before symptoms arise.[18] Certainity of getting infected after being in close contact with an infected patient is still unpredictable. Asymptomatic cases constitute to about 18%.[19,20] Regardless of lab or CT scan findings, the asymptomatic carriers can be contagious. The younger age group generally is found to be asymptomatic whereas the elderly population usually shows symptoms.

Symptoms of COVID-19 tend to resolve after 10 days.[21] COVID-19 RNA viral shedding continues for about 18 to 20 days, uptill 25 days after initial symptoms arise in severe cases.[22] It has been reported that severe cases of COVID-19 have 60 times more viral load than mild cases. However, the potential of spreading infection based on severity has still not been discovered. Considering these findings, the Chinese Municipal Health Commission has recommended to not discharge patients until the patient has remained afebrile for three days and RT-PCR becomes negative.

Clinical Manifestation

The clinical presentation of COVID-19 is variable. In a Chinese study, 72,314 patients were studied out of which 44,672 were laboratory confirmed cases, 16,186 were suspected, 10,567 were clinically diagnosed and 889 were asymptomatic cases. The study reported mild clinical severity in 81.4% of cases, severe in 13.9% cases and critical in 4.7% cases.[23]

Liu K et al.[14] analysed the clinical manifestations of COVID-19 in elderly patients to dissect differences between geriatric and younger age group. The most common symptoms in both age groups include fever, dry cough, fatigue and sputum production; less common symptoms include sore throat, running nose, headache, haemoptysis, dyspnoea and lymphopenia. Some patients developed gastrointestinal symptoms like diarrhoea, small percentage of MERS-CoV or SARS-CoV patients also experienced similar GI symptoms. COVID-19 causes pneumonia like symptoms which may sometimes be complicated in severely ill patients by an acute respiratory distress syndrome with distributive, cardiogenic or mixed shock. Specifically, the geriatric age group with pre-existing comorbidities is most vulnerable and frequently present more severe forms of the disease.[12]

In a study of 56 patients infected with COVID-19, the proportion of patients presenting with fever was smaller for those older than 60 years, percentage difference being small. Thus, due to absence of fever, the suspicion of COVID-19 should never be ruled out in such patients.[14,24]

The Pneumonia Severity Index (PSI) score of the geriatric age group was found to be higher than the young and middle age group. Number of Patients with PSI grade IV and V was significantly higher in elderly age group.[25] Other atypical symptoms specific to the older age group include low grade hyperpyrexia, abdominal pain and delirium , which complicates the diagnostic course.[14]

Laboratory Findings & CT Imaging

Laboratory findings in COVID-19 infection are lymphopenia (<1.5 ×10ˆ9/L), prolonged prothrombin time along with serum urea, creatinine, elevated lactate dehydrogenase, elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated D-dimer, elevated neutrophils, eosinopenia (<0.02×10ˆ9/L), significant elevation of C-reactive protein in the elderly and elevated troponin levels.[7,11,26]

Gold standard for diagnosis of COVID-19 is Reverse Transcription Polymerase Chain Reaction (RT-PCR), its specificity being nearly 100% with no reported false positive cases.[27] RT-PCR presents negative to positive at a mean of 5.1 days and positive to negative at a mean of 6.9 days.28 If the initial RT-PCR is negative, then chest CT scans are recommended.

Chest CT scans of positive COVID-19 patients present with bilateral multilobar ground-glass opacification in early stages and consolidation at later stages. Involvement of multiple lobes was more common in the geriatric age group than in the young and middle age group.[29] Some cases have reported consolidation along with architectural distortion, traction bronchiectasis, lymph node enlargement and pleural effusions. Findings of CT scan show a sensitivity of 84-98% and specificity of 80.5-25% as compared to RT-PCR.[29-31]

Impact of Covid-19 on Mental Health of Elderly People

Pandemics have a significant impact on the mental health of the society. Insomnia, stress, anxiety of wellbeing and panic are the major offshoots. Social isolation of the elderly age group is a serious public health concern due to a greater vulnerability biologically, socially, psychologically and physiologically.[32,33] Particularly in old age homes, social distancing has become a major factor for increased incidences of depression, anxiety disorders and suicide.

Banskota S et al.[34] have suggested 15 mobile applications which are thought to be helpful for the elderly with

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cognitive, visual and hearing impairments. Furthermore, regular telephonic counselling, healthy contact with family and relatives, timely acknowledgement of their medical and psychological needs are important considerations of mental health care in the geriatric age group. The effects of the quarantine can lead to loneliness, physical distance from loved ones, grief, anxiety and chronic stress that affect the older people psychologically. Stress further decreases the immunity adding on to the weakened physiological immune system in the elderly. Due to limited domestic help during the lockdown and lack of travel options, basic living amenities have become a problem for seniors living alone. Furthermore, lack of physical activity and loneliness is a risk factor for cognitive disorders and may cause a state of depression in the elderlies.

Therapeutics, Vaccines and Research

Various medications and vaccines are currently under investigation. The U.S. Food and Drug Administration has not yet approved any certain treatment or vaccine for potential therapy of humans, except Remdisivir. Remdisivir is a nucleoside triphosphate analogue which has anti-viral activity against a broad spectrum of human and zoonotic coronaviruses.[35] Emergency use authorization for Remdisivir for severe cases has been issued by the FDA. A multicentre cohort study suggested that 36 out of 53 patients showed an improvement after first dose administration. About 60% of patients developed certain side effects like hypotension, increased hepatic enzymes, diarrhoea, rashes and renal impairment.[36]

Particularly in the ageing population, Chloroquine-related compounds inhibit beta-galactosidase, a senescence marker has been thought to be beneficial.[37] These agents can develop serious adverse effects like QTc prolongation, neuro-psychiatric effects, retinopathy and hypogycemia.[38] The adverse effects of anti-retroviral drugs get exacerbated by combination therapy and liver injury associated with COVID-19, so they must be avoided in frail, old patients with underlying hepatopathy. Literature on pharmacy practice, clinical treatment and possible new therapeutic options for COVID-19 have been published. Until more specific therapy becomes available, broad spectrum antiviral agents that provide therapeutic options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), RNA synthesis inhibitors.

Sargiacomo C et al.[38] have reported that senolytics and drugs like azithromycin and doxycycline may benefit the older patients by inhibiting viral replication and IL-6 production. In infected patients with severe pneumonia or ARDS, group of drugs like corticosteroids have been used to counteract the inflammatory response of the virus, but the benefits are outweighed by metabolic side effects, precipitating pre-existing comorbidities like diabetes, bone fractures, hypertension and cardiac ailments.

Har-Noy M et al.[39] have proposed an allo-immunization method for the elderly as an adjuvant to vaccination. Intradermal injections of activated, intentionally mismatched, ex vivo differentiated and expanded living Th1-like cells (AlloStim®) was used for allo-priming the elderly. The authors believe that the viral specific Th1/CTL provides immunity and memory to prevent recurrence of the disease. Interferon nebulized inhalation in elderly patients with respiratory symptoms has been reported to produce faster relief. A positive role of ACE-1s and ARBs in inhibiting the ARDS inflammation pathways activated by the virus has been suggested.

Despite appropriate medical treatment, some patients with end stage COVID-19 pneumonia progressed to irreversible loss of lung function. A case report describes successful lung transplantation in 2 critical elderly patients with severe COVID-19 pneumonia. The authors do not recommend lung transplantation in patients with positive retro-viral RNA tests.[40]

Important areas of research have been identified during the pandemic. The unique challenges faced by the elderly and their care takers, strategies for improving health care while maintaining a social distance, identification of clinical and epidemiological factors, understanding the transmission of the disease, assessment of biological emunctory activity and selection of drugs based on the side effects, factors in the geriatric population that affect prognosis are some areas of further research. There is an urgent need to develop a non-human primate model to study COVID-19 infection so as to establish specific novel chemotherapeutic drugs and potential vaccination for human use, along with providing a better understanding of host-viral interactions.

Ayurveda Awareness

India is known for its traditional system of medicine namely Ayurveda, Siddha, and Unani. Moreover, India is a vast repository of medicinal plants that are used in traditional medical treatments, constituting an important component of health care system in the country. About 70% of rural population in India depends on the traditional Ayurvedic system of medicine whereas in western countries, 40% of the population uses herbal medicines for treatment of various diseases.[41] Together with the modern medicinal approach, Traditional Chinese Medicine (TCM) was extensively used to survive the epidemic.[42-44] In India, the Central Government has created an Interdisciplinary AYUSH research Task force for COVID-19 that explores the possibility of integrating Ayurveda with the allopathic medicines to control the pandemic effectively. The Ministry of Ayush has issued

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a set of guidelines to boost immunity and measures for self-care using the Ayurvedic principles.

The 'Rasayana tantra' of Ayurveda and "khameeras" in the Unani medicinal system strengthen immunity, especially among the elderly.[60] Some general measures for respiratory illness such as consumption of warm water, hot food, herbal preparations, steam inhalation, nasal oil application and gargling with medicated water have been proposed in Ayurveda which provide symptomatic relief in mild cases.[45] Cinaltl J et al. have reported that an active component in liquorice named Glycyrrhizin was found to be more effective in inhibition of SARS virus replication, adsorption and penetration than common antiviral agents.[46]

People are more likely to have faith in the deeply rooted traditional practices of medicine, especially the elderly. Ayurvedic medicine appears more feasible for large scale implementation and more promising, simple and affordable. Indeed, this is the time to explore enormous potential of traditional medicine systems and integrate the Ayurvedic science in search for potential treatment for this global health crisis.

Discussion

The emergence of COVID-19 poses a dynamic and real threat to the health and wellbeing of older people. The research field is rapidly evolving as understanding of the clinical manifestations, transmission & infectivity, and necessary public health and interventional measures becomes clearer. As documented by Leung and Zhang,[47,48] advancing age is associated with mortality due to COVID-19. Understanding the mortality was further enhanced by age stratification in the geriatric age group. Wang et al.,[26] in a study of 138 hospitalised patients with COVID-19 aged between 22 to 92 years has reported that dyspnoea was more common in patients admitted to the ICU. Muscle ache in patients infected with COVID-19 was not found to be common in the results of the study.

Another study of 913 patients with bacterial infection by Yamamoto et al., 2006 suggested lower prevalence of fever in deceased patients. Lower body temperature was found to be associated with increased risk of mortality.[49] In a recent study reviewed clinical features of patients infected with COVID-19 in Hainan General Hospital. A significant difference was found in the prevalence of fever between young/middle aged and elderly patients.[24] Several studies have documented lower baseline body temperature in the elderly due to aging, which has been suggested to be a reason for such results.

On the contrary, it is not recommended to lower the threshold temperature in the case definition of COVID-19 in the geriatric age group because an individual's baseline body temperature is also determined by a number of factors like comorbid conditions, physiological measurements and demographic factors.[50] Association between comorbidities and rate of disease mortality in the Chinese COVID-19 infected patients has shown mixed results in several studies. Zhang et al. in a study of 140 patients has reported no significant difference in the proportion of patients with hypertension, diabetes and coronary heart disease between severely ill and non-severe patients.[42]

There is a need for further research to identify the comorbid conditions that may be associated with mortality, considering the diversity of results in the existing literature.

Conclusion

This document presents a brief review of the current literature that has been published about the disease pattern and effects of COVID-19 pandemic in regard to the geriatric age group. Based on the available published literature, there is a need for an individualized approach to elderly patients targeting the beneficial and harmful effects of therapeutic decisions and understanding the association between the comorbidities in old age and rate of mortality due to COVID-19. A fast changing scenario exists where evidences, knowledge and guidelines are changing rapidly, representing an important geriatric emergency of 2020.

Conflict of Interest: None

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