Review

SARS-CoV-2 associated COVID-19 in geriatric population: A brief narrative review

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A R T I C L E   I N F O

A B S T R A C T

Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a fatal pandemic and has crushed even the world's best healthcare systems. Globally, it has affected 40,373,228 individuals and resulted in 1,119,568 deaths as of October 19, 2020. Research studies have demonstrated that geriatric population is vastly vulnerable to COVID-19 morbidity and mortality given their age and preexisting chronic comorbidities such as cardiovascular disease, hypertension, diabetes mellitus, chronic pulmonary and chronic kidney disease The data regarding susceptibility of elderly population to COVID-19 is accruing and suggests that factors like age, gender, chronic comorbidity, inflammaging, immunosenescence and renin angiotensin system may be the contributing risk factors towards COVID-19 and associated mortality in elderly population. Based on updated scientific literature, this narrative review précises the clinical presentations and underlying risk factors that might be associated with COVID-19 morbidity in geriatric population and provides informed insights, and discusses clinical presentation, psychosocial impact, mortality and potential corticosteroid treatment and prevention strategies of COVID-19 in older adults.

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1. Introduction

Coronavirus disease 2019 (COVID-19), a pneumonia-like respiratory pathology, is no more an enigmatic viral infection. Perhaps every individual on earth, in economic, social, physical or psychological way, has been affected since unfolding of the causative

organism; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in late December 2019 in Huanan seafood market Wuhan, China (Shahid et al., 2020). Precisely, 40,373,228 confirmed COVID-19 cases and 1,119,568 deaths have been reported globally (as of October 19, 2020) (Coronavirus disease (COVID-19) (Internet), 2020). Epidemiological studies from China confirmed 96% viral sequence similarity to a bat coronavirus. Originally, it was theorized that the SARS-CoV-2 might spread from bats to humans via an intermediary host (Zhou et al., 2020; Andersen et al., 2020), which was later identified to be pangolins in genomic sequence analysis study from Malaysia (Zhou et al., 2020). The following human-to-human spillover set forth global spread and was declared a pandemic (Cucinotta and Vanelli, 2020). Even the world's best healthcare systems have collapsed.

Despite accumulating evidence, the present body of knowledge epitomizes the tip of the iceberg, given the fact of high rate of worldwide human-to-human transmission, asymptomatic and subclinical infection and most prominently significant differences in susceptibility to COVID-19 morbidity and mortality. The scientific community has united with the uniform undertaking to unearth the pattern of symptoms, underlying mechanistic pathways of infection, heterogeneity in the SARS-CoV-2 virulence, gender and individual differences and the risk factors for morbidity and eventual death. One promising development during the course of understanding the SARS-CoV-2 infection includes inclination of geriatric population to COVID-19 infection and associated mortality. According to recent report of the Centers for Disease Control and Prevention (CDC), individuals 65 years of age or above encompass 31% of COVID-19 infected population in United States (US). In fact, COVID-19 accounts for 31–59% of hospitalizations, 11–31% of intensive care unit (ICU) admissions and 4–11% of deaths in older adults aged between 65 and 84 years (Coronavirus Disease 2019 (COVID-19) Older Adults (Internet), 2020). The outcomes are even dismal in adults aged above 85 years; hospitalizations (31–70%), ICU admissions (6–29%) and deaths (10–27%). This clearly indicates that geriatric population is more prone to get infected with SARS-CoV-2 and have poor prognosis in comparison with general population. This puts an enormous burden on already exhausted healthcare system, irrespective of country groupings of developing and developed nations based on World Bank income, by misbalancing the demand and supply of personal protective equipment (PPE) and mechanical ventilators. Based on updated scientific literature, this narrative review précises the clinical manifestations and underlying risk factors that might be associated with COVID-19 morbidity in geriatric population and provides informed insights, and discusses clinical presentation, psychosocial impact, mortality and potential corticosteroid treatment and prevention strategies of COVID-19 in older adults.

1.1. Clinical presentations of COVID-19 in elderly population

Without a grain of doubt, COVID-19 is no more an infection with just fever, cough and dyspnea. Over a period of last few months, it has presented with multiple clinical manifestations than one would have thought, especially in elderly group. It is highly possible that elderly population may present with atypical signs of COVID-19 infection. This could be due to presence of pre-existing and the severity dynamics of health conditions. A research study from China communicated that 86% of the COVID-19 older adults presented with severe form of coexisting diseases which included congestive heart failure, diabetes, CKD and chronic obstructive pulmonary disease (COPD) (Arentz et al., 2020).

A study by Liu et al. (2020) drew comparison of COVID-19 manifestations between young and old age group (≥60 years) and found fever to be less prevalent in the latter cohort (Liu et al., 2020). Interestingly, Isaia et al. (2020) reported fall as the primary sign of COVID-19 in more than one-fourth of the old age subjects (median age was 86.5 vs 68.0 years). Diarrhea and delirium was also found in their study subjects (Isaia et al., 2020). Ward et al. (2020), in their brief report, documented clinical presenting symptom of altered mental status in elderly COVID-19 cases in the absence of typical manifestations of fever, cough and other respiratory symptoms (Ward et al., 2020). In addition to above, elderly COVID-19 patients may also present with abdominal pain (Ward et al., 2020).

Lately, interest has been shown in the radiological presentation of COVID-19. Characteristic radiological manifestations of COVID-19 in elderly group on computed tomography (CT) chest imaging include ground-glass opacification (bilateral and multilobar), mostly in lower lobes. However, atypical presentations include consolidative opacities overlaid on ground-glass opacification in the geriatric group. A review study emphasized that involvement of multiple lobes was far more prevalent in elderly population than in young and middle aged adults (Perrotta et al., 2020). Besides above, other radiological findings can include bilateral reticular-nodular opacities, peribronchial thickening, pleural effusions and focal consolidations (Shahid et al., 2020).

1.2. Chronic comorbidities in older adults and COVID-19

Chronic nature of disease and comorbidity both adversely impact the risk and development of disease. The globe is experiencing a huge paradigm shift towards older population with chronic diseases. Suggestively, 2 billion individuals will be older than 60 years by 2050 as per recent report (James et al., 2018). Chronic diseases like obesity, diabetes mellitus, cardiovascular disease, chronic kidney disease and cancer trigger systemic inflammation and harmfully influence physiological activity of immune system that promotes immunosenescence (Furman et al., 2019). Increased occurrence of hospital-acquired infection has been reported in chronic comorbidities like obesity (Huttunen et al., 2013). Obesity has been pronounced as a key predictor of increased number of hospitalizations and severe H1N1 influenza and SARS-CoV-2 infection (Luzi and Radaelli, 2020; Simonnet et al., 2020). A nationwide study in China by Guan et al. (2020) documented hypertension and diabetes mellitus as the most frequent comorbidities in COVID-19 subjects. They found that hypertension, diabetes mellitus, COPD, cancer and multicomorbidity were associated with independently associated with poor clinical outcomes after adjustment of covariates (Guan et al., 2020).

It is emphasized that reduced levels of albumin due to chronic disease can enhance SARS-CoV-2 viral shedding and infectivity (Fu et al., 2020). It has been previously shown that despite being vaccinated, adults with chronic disease (obesity) were more likely to get influenza than those without obesity (Green and Beck, 2017). The cytokine surge owing to heightened immune activity has been reported in COVID-19 patients (Ye et al., 2020). Study cites that chronic disease related systemic inflammation provoke immune cells to produce even more stronger cytokine discharge than earlier when infectious disease occurs (Ramos Muniz et al., 2018).

Lately, a systematic review and meta-analysis by Liu et al. (2020) concluded that pre-existing comorbidity is statistically associated with COVID-19 severity and ICU admission, but not with COVID-19 mortality. They further, precisely, shared that, COVID-19 patients with hypertension (Odds Ratio [OR] 2.84 and 95% Confidence Interval [CI] 2.22–3.63), cardiovascular disease (OR 4.18 and 95% CI 2.87–6.09), diabetes (OR 2.61 and 95% CI 1.93–3.52) and chronic respiratory disease (Or 3.83 and 95% CI 2.15–6.80) had significantly increased risk of severe infection (Guan et al., 2020). Above findings indicate that as the global population will grow older with chronicity and comorbidity, more immunocompromised individuals will be susceptible to pandemics

like COVID-19. This will eventually snowball the encumbrance of worldwide morbidity and mortality.

1.3. The duo of inflammation and immunity and COVID-19 in older adults

The geriatric population experience immune senescence; age-driven decline in immune function and equally affect both innate and adaptive immune system (Nikolich-Zugich et al., 2020). In addition, being affected by multiple comorbidities puts elderly population at increased risk of exacerbated immune responses and even chronic inflammation. However, those immune responses, most of the times, are aberrant and thus provide favorable environment for SARS-CoV-2 to invade this vulnerable population. Precise mechanisms through which SARS-CoV-2 evade innate immune system are still mysterious. However, research has demonstrated that structural and non-structural viral protein antigens inhibit interferon counterattack. This allows increased viral proliferation and resultant mounting of pyroptosis which can further potentiate anomalous inflammatory responses (Tay et al., 2020).

Weakened immune system, incessant anomalous immune responses and cellular infiltration of releasates such as proteases and reactive oxygen species (ROS) can directly injure lung parenchyma, besides damage from SARS-CoV-2 itself. Altogether, lung microstructure damage occurs and is evident through diffuse damage of alveoli, including alveolar cells desquamation, formation of hyaline membrane and pulmonary edema (Tian et al., 2020). This impedes alveolar exchange of oxygen, triggering dyspnea (difficulty in breathing) and hypoxemia (reduced oxygen levels in blood) and lung parenchyma befits secondary infections.

Apart from local inflammatory damage, a surge of cytokines (cytokine storm) has domino effect throughout the body. High levels of pro-inflammatory cytokines like interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) has been shown to produce septic shock and multiple organ damage which might cause myocardial and circulatory dysfunction, as evidenced in research (Ruan et al., 2020). The exact etiology of this dysregulated immune response in elderly population is unknown; however, age-related changes in lung microstructure altering physiological function, including movement to lymph nodes, of dendritic cells could be a reason (Zhao et al., 2011), and thus flawed activation of T-lymphocytes. Conversely, children are not prone to severe COVID-19 disease notwithstanding high viral loads (Kam et al., 2020). A report by Tian et al. studied clinical characteristics of COVID-19 positive children under 18 years of age. While over half of the children documented no or mild symptoms, fewer than 6% of the children developed severe COVID-19 clinical manifestations (Tian et al., 2020). Therefore, despite above literature presenting important findings, a clear understanding of role of host immune response, especially in older group, that predisposes to varied degree of COVID-19 symptoms remains inadequately understood.

1.4. Implications of renin angiotensin system (RAS) in COVID-19 for older adults

SARS-CoV-2 shares unique similarity with earlier coronavirus pathogens i.e. SARS-CoV that was accountable for 2002–2004 epidemic in China. Angiotensin converting enzyme 2 (ACE2) receptor provides the passageway to SARS-CoV entry into the host respiratory cells. Notably, SARS-CoV-2 also uses the same ACE2 receptor, as we discussed later (Hoffmann et al., 2020). Research suggests that high levels of angiotensin II might be associated with severity of COVID-19 (increased viral load and lung parenchymal injury) (Liu et al., 2020). These findings implicate RAS in pathogenesis underlying the COVID-19.

Briefly, RAS pathway initiates with release of renin protease from juxtaglomerular cells of kidney. Renin converts angiotensinogen, essentially produced by liver, to angiotensin I. Non-active form of angiotensin I is then converted into biologically active angiotensin II. Angiotensin II promotes vasoconstriction of arterioles, elevates systemic blood pressure and helps in water and sodium reabsorption from kidney. It also plays key role as pro-inflammatory protein via reactive oxygen species, superoxide and nuclear factor-kB (Coronavirus Disease 2019 (COVID-19) Older Adults (Internet), 2020). In fact, it possess chemotactic as well as mitogenic properties (Fisher, 2017). The players of RAS pathway are expressed in lung parenchyma and especially angiotensin II has been reported to be elevated in lung disease (Marshall, 2003).

Hypoxia due to lung pathology is a trigger for increased levels of angiotensin II (Wong, 2016). The SARS-CoV-2 depends on ACE2 protein for entry and infection; however, the virus reduces the expression of ACE2 itself. Thus, SARS-CoV-2 appears to promote the unrestricted angiotensin II levels way more high than any other lung infections and therefore causes severe symptoms owing to overriding RAS in COVID-19 infection (Bahat, 2020). The exacerbated RAS pathway is correlated with overactive inflammation. COVID-19 patients have two-fold increase in angiotensin II levels, as one study reported (Liu et al., 2020). The exaggerated and abnormal immune activity that is specific to old age could result in further dysfunction of angiotensin II. The negative impact of increased RAS activity, specifically angiotensin II would be significantly perilous in elderly population with hyperinflammation feature. In actuality, this could serve as a risk factor for mortality (Saghazadeh, 2020).

1.5. Psychosocial consequences of COVID-19 on elderly population

Being at high risk of SARS-CoV-2 associated complications and mortality, COVID-19 has amplified angst among elderly population. Not only they encounter the shortcoming of chronic comorbidity and aging immune system, but also they are required to tackle the distinct psychosocial needs during this critical time period of their lives. Contrasting with young section of the populace, elderly population is not bombarded with modern gadgets owing to illiteracy or lack of interest and even they do, they are not interested. Despite modern technologies being at the heart of curbing boredom and loneliness, elderly cohort find them less tempting and they utterly require social support which unfortunately remains unfulfilled. Family and social gatherings make them energized, engaged and mentally healthy. In its truest sense, during the last few decades of their life, it is the only and the most important factor determining their mental and physical health. Thus, special attention must be paid for the mental health of this vulnerable population (Mukhtar, 2020).

A study by Meng et al. (2020) assessed the psychosocial health of elderly cohort in China during COVID-19 pandemic. The findings suggested that 37.1% of the elderly subjects were challenged with anxiety and depression due to COVID-19 (Meng et al., 2020). Another study by Qiu et al. (2020) reported that emotional response is more prominent in population aged > 60 years. They further found that women were more prone to experience anxiety and depression as compared to men (Qiu et al., 2020). Armitage et al. (2020) cited that quarantine could have dire consequences on mental health of elderly population as it can increase social detachment and can be a source of significant loneliness, especially in nursing homes and old age homes (Armitage et al., 2020). In fact, this is an independent predictor of anxiety, depression and suicide (Banerjee).

Above findings help us to chalk out following measures that can be taken to maintain the psychosocial health of elderly population: (1) Divert attention towards following elderly group during these trying times including both SARS-CoV-2 infected and non-infected; illiterates, women, divorced, separated and widowed;

(2) Effective psychosocial counseling strategies should be prepared and implemented through consistent telephonic sessions; (3) Healthy family contact should be encouraged; (4) Their personal space must be respected to keep them mentally strong and healthy; and (5) Entertainment strategies should be further improved to increase its acceptability among elderly groups to minimize loneliness.

1.6. Mortality associated with COVID-19 in older adults

While COVID-19 research is gaining momentum, a new clinical phenomenon of *COVID Spiraling Frailty Syndrome* might appear relevant. It is derived from the Frailty Syndrome which include old age, cardiovascular disease and diabetes mellitus and has been merged with the new global infection, COVID-19 (Abbatecola and Antonelli-Incalzi, 2020). Collectively, it worsens the clinical picture for elderly COVID-19 patients and increases the likelihood death.

The COVID-19 associated mortality is very high in older adults. As per the WHO-China joint mission, the overall case fatality rate (CFR) declined from 17.3% (January) to 0.7% (February). On the other hand, CFR in geriatric population above 80 years evidenced exponential increase to 21.9% (Report of the WHO-China Joint Mission on Coronavirus Disease, 2019). A study from China on 72,314 confirmed and suspected COVID-19 cases suggested 2.3% of overall CFR, which interestingly increased to 8% and 14.5% for subjects aged between 70 and 79 years and over 80 years, respectively (Wu and McGoogan, 2020). A research report from Italy enrolled 355 patients and concluded the average age of 79.5 years for patients died due to COVID-19 (Report sulle caratteristiche dei pazienti deceduti positivi a COVID-19 in Italia Il presente report è basato sui dati aggiornati al 17 Marzo, 2020). A study cited below 1% CFR among COVID-19 patients aged <54 years; however, patients aged between 65 and 84 had CFR of 3–11% and >85 years had 10–27%. In fact, over 80% of mortality was reported for patients over 65 years of age (Patients, 2019). Majority of the COVID-19 patients who succumbed to death thus far were older and had multiple comorbidities (Wu and McGoogan, 2020; Liu et al., 2020). A handful of studies have suggested significant burden of chronic non-communicable diseases such as cardiovascular disease, hypertension, diabetes mellitus, COPD (Herzallah et al., 2019; Saquib et al., 2017). According to report by the joint collaboration of WHO and China, patients aged over 60 with comorbidities are at greater risk of COVID-19 severity and mortality. The findings documented 1.4% CFR in COVID-19 subjects without coexisting disease and with cardiovascular comorbidity 13.2%, diabetes mellitus 9.2%, hypertension 8.4%, chronic pulmonary disease 8% and cancer 7.6% (Organization and Organization, 2019). Huang et al. (2020) reported 84% of the fatal cases of COVID-19 with age >80 years and suggested increased odds of death with diabetes mellitus (Huang et al., 2020). Arentz and colleagues (2020), in their study, found that more than three-quarters (86%) of their old and critically ill COVID-19 patients had comorbidities like congestive heart failure, and diabetes mellitus, CKD and COPD (Arentz et al., 2020). As discussed, multicomorbidity increases the propensity of COVID-19 mortality.

1.7. Corticosteroid treatment as a ray of hope

Around 5% of the COVID-19 patients may end up in ICU (Wu and McGoogan, 2020). Most of which are old age severe COVID-19 cases with delayed-onset systemic inflammation triggered by cytokine surge and mentioned as so-called cytokine release syndrome (CRS) (Zhang et al., 2020). Fever, acute respiratory distress syndrome (ARDS), hemodynamic and/or multiorgan failure are some of the manifestations of CRS associated severe COVID-19. In this regard, late-onset cytokine surge in severe COVID-19 patients might respond well to anti-inflammatory drugs such as corticosteroids as shown previously for SARS-CoV infection (Lee et al.,

2004). While corticosteroids have shown promising results in reducing mortality in ARDS patients (Zhao et al., 2019), there is ongoing debate regarding the usefulness, efficacy, timing, dosage and duration of corticosteroids treatment in severe COVID-19 cases.

The major challenge in elderly population with severe COVID-19 is chronic comorbidities with dysfunctional immune response which puts them at increased risk of mortality and therefore, the aim of the COVID-19 therapy should be to minimize the risk of death.

A number of papers have recently been published regarding the possible COVID-19 treatment options; however, corticosteroids have once again garnered the scientific attention in pulmonary and infectious disease medicine with positive findings. A case report of 71-year old woman with severe COVID-19 and chronic comorbidity by Taboada et al. (2020) highlighted initial clinical improvement followed by worsening upon termination of corticosteroids (Taboada et al., 2020). They suggested that COVID-19 appears to have three phases; infection, pulmonary and hyperinflammation phase. It is the final phase during which corticosteroids have its optimum effects. However, it is yet to establish the duration of this final phase, and hypothetically, the long duration could be the reason for rebound inflammation. Another single center case series report from Japan emphasized that short-duration high-dose corticosteroid treatment during early stages of COVID-19 ARDS might offer survival benefit (So et al., 2020). Findings of report by Yang and Lipes (2020) were also in agreement with the former paper. They also showed clinical improvement in severe COVID-19 with administration of corticosteroids (Yang and Lipes, 2020). A recent systematic review and meta-analysis by Ye et al. (2020) found corticosteroids to reduce mortality associated with severe COVID-19 ARDS (Ye et al., 2020).

Besides above evidences, it should be kept in mind that use of corticosteroids has its own shortcomings as well such as hip pain, steroid-induced osteonecrosis of the femoral head (ONFH), claudication, and lower limbs disability (Tang et al., 2020). In the past, a retrospective analysis has shown ONFH in SARS-CoV infected patients treated with corticosteroids (Guo et al., 2014). Advancing age, comorbidity, and above all hyperinflammatory severe COVID-19 can potentiate the effects of aforementioned adverse effects of corticosteroid therapy. Therefore, corticosteroids should be cautiously and only used for severe COVID-19 cases with septic shock or critically ill patients (Shang et al., 2020). Most importantly, corticosteroids should be tapered off gradually and regular follow-ups should be arranged after discharge. In case otherwise, the injudicious administration of corticosteroids to curtail mortality risk in severe COVID-19 infection in old age patients loses its essence.

1.8. COVID-19 prevention in geriatric population

In circumstances of no specific drug therapy and vaccine prevention, there is a dire need of preventive strategies for vulnerable population like older individuals. In this regard, Chhetri et al. (2020) laid out few recommendations for prevention of COVID-19 in older population (Chhetri et al., 2020). Those recommendations were proposed keeping in mind the mass population and burgeoning COVID-19 cases in Asia-Oceania region and were not even part of any specific prevention guideline, but it does hold the importance of breaking the chain of COVID-19 infection and should be implemented as such. Built on numerous preemptive approaches to prevent older population from COVID-19 in the Asia-Oceania, they proposed the following mnemonic of COVID-IAGG-AO; (**C**atnap, **O**ptimistic, **V**igor, **I**ntake, **D**istancing – **I**ncrease social support, **A**dminister routine medicine, **G**et morning sunlight, **G**o to Emergency Room for COVID-19 symptoms – **A**ctively hand washing, **O**rder your food and medicines online or through family and friends).

The basic rationale of COVID-IAGG-AO prevention strategy is that immunity in geriatric population declines with aging and are vulnerable to severe infectious consequences. Adequate sleep, proper diet and physical activity can assist in maintaining and boosting immune activity in this delicate age and avert frailty. Similarly, we cannot underestimate the significance of social distancing to avoid COVID-19 infection as has been stressed since the beginning of COVID-19; however, it can result in poor mental health. Therefore, being hopeful and motivated is sine qua non to successfully combat this global crisis. One good way to stay psychologically healthy is to communicate by means of internet and other mediums alike. Insufficient vitamin D can also expose to risk of infection and therefore getting adequate sunlight to boost vitamin D levels is essential. A study by Grant et al. (2020) also supports this theory and concluded reduced risk of influenza and COVID-19 infection with supplementation of vitamin D (Grant et al., 2020). Due to multiple comorbidities, older individuals have to take medicines on time and thus they should ask family members and their caregivers for support. Most importantly, they must exercise hand hygiene religiously to protect both others and themselves from SARS-CoV-2. Finally, they should seek help in emergency department immediately if they exhibit symptoms such as fever, dry cough, lassitude, chest pain and shortness of breath.

2. Conclusion

In conclusion, the SARS-CoV-2-associated COVID-19 manifests itself severely in elderly population. It can have varied clinical manifestations in elderly cohort and puts them at increased risk of death. Factors such as age, gender, chronic and multicomorbidity, inflammaging, immunosenescence and RAS pathway may be contributing towards COVID-19, psychosocial health and associated mortality in this vulnerable population. Corticosteroids have shown promise and may become part of regimen to treat severe COVID-19 cases in elderly; however, clinical trials and meta-analysis evidence would be worth to look for in coming months. Clinical and basic research is of utmost importance in this regard as some of these factors may vary geographically. By doing so, we might gather new evidence to devise COVID-19 risk, prevention and treatment strategy not only for younger but also for high-risk elderly population as well.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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