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Review Article

How does SARS-CoV-2 targets the elderly patients? A review on potential mechanisms increasing disease severity

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ABSTRACT

Importance: Among COVID-19 cases, especially the (frail) elderly show a high number of severe infections, hospital admissions, complications, and death. The highest mortality is found between 80 and 89 years old. Why do these patients have a higher risk of severe COVID-19? In this narrative review we address potential mechanisms regarding viral transmission, physical reserve and the immune system, increasing the severity of this infection in elderly patients.

Observations: First, the spread of COVID-19 may be enhanced in elderly patients. Viral shedding may be increased, and early identification may be complicated due to atypical disease presentation and limited testing capacity. Applying hygiene and quarantine measures, especially in patients with cognitive disorders including dementia, can be challenging. Additionally, elderly patients have a decreased cardiorespiratory reserve and are more likely to have co-morbidity including atherosclerosis, rendering them more susceptible to complications. The aging innate and adaptive immune system is weakened, while there is a pro-inflammatory tendency. The effects of SARS-CoV-2 on the immune system on cytokine production and T-cells, further seem to aggravate this pro-inflammatory tendency, especially in patients with cardiovascular comorbidity, increasing disease severity.

Conclusions and relevance: The combination of all factors mentioned above contribute to the disease severity of COVID-19 in the older patient. While larger studies of COVID-19 in elderly patients are needed, understanding the factors increasing disease severity may improve care and preventative measures to protect the elderly patient at risk for (severe) COVID-19 in the future.

1. Introduction

On November 18th 2020, there have been over 55 million confirmed cases of SARS-CoV-2 infection causing COVID-19, with up to 1.3 million deaths worldwide. In the Netherlands alone, there are up to 8,600 registered deaths, a number that is still on the rise. The risk of hospitalization and death increases with age,[1-3] illustrated by a case fatality rate increase from a 2.3% in the general population, to 14.8% in patients over 80 years old.[4] A contact survey study from Wuhan and Shanghai found the highest susceptibility to infection in individuals older than 65 year.[5] While patients over 65 years old comprise 17% of the total population in the United States of America, they make up 31% of COVID-19 cases, 45% of the associated hospitalizations, 53% of intensive care unit admissions, and 80% of deaths.[6]

The highest mortality rate in the Netherlands is found in the age group between 80 and 89 years and among frail patients receiving chronic medical care in nursing home facilities through the Dutch long-term-care-act.[1,7] Since polymerase chain reaction (PCR)-testing was limited in the beginning of the pandemic, especially in this patient group, it is likely that the total number of COVID-19-attributable cases and deaths are underestimated. During the (first) outbreak of the pandemic, the mortality rate in this group of patients increased from 1,160 to 2,400 deaths a week with a mortality excess of 53%.[1,7] In Europe, the all-cause excess mortality from week 1 to 18 in 2020 was an

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astonishing 185,287, of which 48% occurred in patients 85 years or older.[8] This may directly be caused by COVID-19, or indirectly from delay in diagnosis and treatment due to decreased accessibility of healthcare. Important reasons for decreased accessibility were downscaling inpatient and outpatient (elective) care to prevent further spread of the infection, strain on the medical capacity due to an increase in COVID-19-related care, and fear of patients to seek medical care during the pandemic.

Compared with younger cases, patients over 65 years old show higher pulmonary severity index scores, multiple lobe involvement on CT-scan and a higher rate of acute respiratory distress syndrome (ARDS).[9] A small study including relatively few deaths (17 patients) shows that the median time from occurrence of the first symptom to death might be shorter in patients aged over 70 years, compared with younger patients (median 12 versus 20 days).[10] Thus, in elderly patients, COVID-19 is associated with more severe (pulmonary) complications and with a higher mortality rate. In this narrative review we address the issue: Why do elderly patients have a higher risk of severe COVID-19?

2. Viral exposure

2.1. Increased viral shedding

One of the mechanisms explaining the large incidence in older COVID-19 patients, especially in nursing homes, might be increased viral shedding. In Influenza A and B infection, viral load is significantly higher in children <1 year and individuals > 65 years old, compared with other age groups.[11] Viral shedding of SARS-CoV (which caused the SARS epidemic) also seems to increase with age.[12] Increased viral shedding has been found for SARS-CoV-2 as well. A small study of 26 cases from Hong Kong detected higher peak viral load in respiratory specimens of older COVID-19 patients.[13] More severe COVID-19 may be associated with higher viral loads, and patients with more severe COVID-19 are older than patients with milder infections (mean age 56 versus 44 years old).[14] Since older patients have higher peak viral loads, they are likely to shed more virus. The cause of increased viral loads in the elderly is not fully clear but may be the result of the effects of aging on both airway clearance and the immune system as described below.

2.2. Atypical presentation

The majority of elderly patients at the emergency department has an atypical presentation of illness including falls and may lack any specific symptoms of the underlying COVID-19.[15] Patients may not develop a fever in the case of infection and may only show cognitive or functional decline, especially patients with pre-existing cognitive disorders. In a case series of 19 patients with COVID-19 admitted to a geriatric unit with a mean age of 84 years, 79% of the patients presented with a delirium and 32% with a fall, while only a minority showed typical symptoms like coughing (26%) and fever (37%).[16] Atypical presentations of SARS-CoV-2 are frequent and may delay diagnosis in elderly patients. In the first weeks of the pandemic, the diagnosis could have been further delayed because PCR-testing for SARS-CoV-2 availability was limited. This was especially the case for patients at home or in nursing homes, further complicating the early identification of infected individuals and thus facilitating viral transmission.

2.3. Difficulty to ensure quarantine

In nursing homes, outbreaks of viral gastrointestinal and respiratory infections occur frequently and may be related to close contact of patients with care providers during care and assistance, and other residents.[17,18] There were multiple outbreaks of COVID-19 reported within nursing homes during the first wave of the pandemic. Both lack of PCR-test possibilities and a shortage in personal protective materials for care providers contributed to these outbreaks. Furthermore, protective measures to prevent infection, e.g., frequent handwashing and coughing/sneezing in the elbow, are difficult to introduce to patients with cognitive impairments such as dementia. Quarantining infected individuals is often challenging, as cognitively impaired patients may have an urge to wander. Furthermore, patients may suffer from anxiety and agitation when applying isolation, especially when they do not have the cognitive capabilities to understand the need for this type of measurements.

Taken together, older patients may have higher viral shedding. Older and frail patients may present with atypical symptoms and may make it difficult to quickly identify infected individuals. Preventing spread of the infection by adequate hygiene measures and applying quarantine when needed may be difficult in patients with cognitive capabilities, especially when there is a shortage in testing and personal protective materials.

3. Co-morbidity

With aging, the prevalence of various diseases increases, e.g., respiratory diseases including chronic obstructive pulmonary disease, diabetes mellitus and cardiovascular disease (CVD). Over half of patients over 75 years old in the Netherlands have multiple chronic diseases.[19] The increase in co-morbidity and the decrease in physiological reserve in the elderly may increase the risk of severe (viral) infections and complications.

3.1. Respiratory co-morbidity

Aging is associated with a decrease in lung volumes, decreased respiratory muscle function (including the diaphragm) and cough strength.[20] Furthermore, protective mechanisms like mucociliary clearance may be diminished.[21] Mucociliary clearance encompasses the action of ciliated cells in the upper and lower airway to clear mucus and particles out of the lungs. A study in 90 healthy adults showed decreased nasal mucociliary clearance time and increased ciliary disarrangement with increasing age.[21] Also, the clearance of radiolabeled particles out of the small airways was negatively associated with age.[22] These age-related changes including decreased pulmonary reserve and airway clearance may partially explain the increased frequency and severity of (any) pulmonary infection.

3.2. Cardiovascular and cerebrovascular co-morbidity

Pre-existing hypertension, diabetes, and cardiovascular disease are all associated with more severe COVID-19.[23,24] The correlation between co-morbidity and disease severity is not yet fully understood, but poor outcome is associated with pre-existing atherosclerosis, down regulation of angiotensin-converting enzyme 2 (ACE2) and local renin-angiotensin-aldosteron system (RAAS) activation (see dysfunctional immune response below). In a study of 138 hospitalized patients, elevated cardiac biomarkers and echocardiography abnormalities were present in 7.2% of all COVID-19 cases and in 22% in severe COVID-19 cases.[25] Respiratory infections in general are associated with an increased risk of cardiac infarction.[26] Myocarditis and stress cardiomyopathy have been proposed as a cause of cardiac injury in COVID-19.[27] Infection induces inflammatory cytokines, such as interleukins 1, 6, and 8, and TNF-alpha, which can activate inflammatory cells in atherosclerotic plaques.[26] Furthermore, COVID-19 is associated with a prothrombogenic state and with an increase in arterial and venous thrombotic complications.[28-30] In a case series of six patients with COVID-19 and acute ischemic stroke, five had a history of cardiovascular disease including hypertension, ischemic heart disease, stroke, and atrial fibrillation.[31] In a retrospective observational study in Wuhan in 214 patients, patients with more severe COVID-19 were older and showed a higher rate of stroke (5.7 versus 0.8%).[32] In the United Kingdom, among 125 patients with neurological complications with

COVID-19, 62% consisted of an cerebrovascular accident (74% ischemic, 12% hemorrhagic).[33] Among these patients, 82% was over the age of 60. Thus, this type of viral pneumonia in an elderly patient, especially with atherosclerosis and a history of cardiovascular disease, seem to increase the risk of developing cardio- and cerebrovascular complications.

3.3. Frailty

Frailty is defined as a geriatric syndrome characterized by an increased risk/vulnerability for developing adverse clinical outcomes like dependency and/or death. Frailty can be caused by and influenced by factors like comorbidity, decreased functional reserve, nutritional status, muscle weakness, physical activity, and mental state. Higher frailty scores, including in sepsis, are associated with worse patient outcomes like mortality and morbidity.[34-37] The COPE study included 772 (49.4%) frail patients with COVID-19 with a median age of 74 year.[38] Higher clinical frailty scale (CFS) was associated with both higher mortality and longer time from hospital admission to discharge compared to patients with low CFS. The pulmonary, cardiac, and/or neurologic co-morbidity mentioned above may cause or worsen the frailty 'status' of an elderly patient. Interestingly, frailty is correlated with higher levels of IL-6, CRP and TNF-α.[39,40] Frailty in the elderly appears to be in close association with chronic inflammation, where chronic inflammation may contribute to worsen physical reserve and limit resilience in the elderly patient. In several countries, nationwide intensive care protocols included high age and CFS as a relative contra-indication for intubation in COVID-19, due to scarcity of intensive care beds during the first peak of the pandemic combined with the high mortality and high risk of further increasing frailty and dependence in activities of daily living in this patient group.[41,42]

4. Dysfunctional immune response

4.1. Reduced ACE2

In viral infections, viral and host membranes fuse after binding with a receptor, viral genetic material enters the cell and the virus multiplies itself in the host cell. The spike protein receptor-binding domain of SARS-CoV-2 is a ligand of the receptor of ACE2.[43] ACE2 is expressed in the lung, heart, kidney, blood vessels, brain, intestine and in fat tissue. SARS-CoV-2 may directly infect endothelial cells via ACE2. Since these endothelial cells and the glycocalyx regulate vessel wall integrity, coagulation and vascular tone, infection may induce inflammatory cell infiltration and microvascular prothrombotic effects.[44] The D-dimer, an acute phase reactant and marker of activated coagulation, has been found to be frequently elevated in patients with COVID-19 and predictive of adverse outcomes.[3] A study regarding autopsy of 21 patients with COVID-19 showed that organs were mainly affected by an inflammatory response.[45] In the majority of patients (83%), endotheliitis and microthrombi were present in the lungs, next to neutrophilic infiltrates in the lungs and other organs.[45] ACE2 is down-regulated on cell surfaces after binding with the SARS-CoV-2 spike protein.[46,47] ACE2 has an anti-inflammatory effect by converting angiotensin II to angiotensin-(1–7). Angiotensin II has pro-inflammatory properties and may mediate acute lung injury through vasoconstriction and increased vascular permeability. Down-regulation of ACE2 may result in angiotensin II accumulation and local RAAS activation and vascular permeability, which might contribute to the lung damage.[47] Additionally, ACE2 expression may decrease with increasing age and in persons with CVD.[48-50] The use of ACE inhibitors and angiotensin-receptor blockers, which may upregulate ACE2 expression, has not been shown to affect the risk of severe COVID19.[51,52] Thus, reduced ACE2 may exaggerate pulmonary inflammation in the elderly, especially those with CVD.

4.2. Immunaging

After infection with a virus, infected cells produce type I interferons (e.g., IFN-α and IFN-β), by transcription of the interferon genes induced by phosphorylation of interferon regulatory transcription factor (IRF) 3 and 7. These type I interferons lower the susceptibility of neighboring cells to viral infection and activate natural killer cells and Th1-lymphocytes, amplifying the anti-viral response. In human monocytes of older donors infected with influenza A, type 1 interferon production seems impaired with diminished IRF-3 and -7 phosphorylation, but pro-inflammatory TNF-α production was preserved.[53] Interestingly, 10.2% of the patients with severe COVID-19 showed presence of neutralizing auto-antibodies against type I interferons and 3.5% had genetic mutations in loci regarding type I interferon immunity.[54,55] The presence of auto-antibodies was more prevalent in patients over 65 years old, implying an effect of age.[54]

Severe cases of COVID-19 including patients requiring intensive care admission showed higher levels of TNF-α, among other pro-inflammatory cytokines like interleukin-6 (IL-6).[56,57] This over-expression, in early research in the pandemic referred to as a '*cytokine-storm*', is a feature of severe COVID-19, and might contribute to the development of ARDS and multi-organ failure.[58] In a study in 48 patients in Wuhan, detectable serum viral RNA was associated with higher levels of IL-6 and increased severity of COVID-19 in critically ill patients. The group of critically ill patients seemed older, though not statistically significant, than the patients with moderate to severe disease (80 years vs 53 and 64 years old).[59] Aging is characterized by chronic, low-grade inflammation, also referred to as *inflammaging*.[60,61] In a prospective population-based study of 1155 patients age 65-102 years, a stratified inflammatory index using IL-6 and TNF-α-receptor 1 levels could predict 10-year mortality.[62] It remains to be determined whether this cytokine storm is the cause of or a symptom of severe COVID-19, or maybe even of aging. Taken together, diminished type I interferons production and pre-existing low-grade inflammation with pro-inflammatory cytokines might tilt the immune status of the elderly patient to a more pro-inflammatory status.

4.3. Immunosenescence

With aging, migration, chemotaxis and phagocytosis of the innate immune system including neutrophils, macrophages, and dendritic cells, decreases.[60,61,63] While the number of circulating T-cells of the adaptive cellular immune system remains relatively constant with age, there is a shift in T-cell subpopulations leading to a decrease in naïve T-cells and increase in memory T-cells, which limits the response against novel infectious agents.[63,64] Expression of CD28, a costimulatory receptor in T-cells, decreases with age, what is associated with a weakened immune responses.[63,64] Higher TNF-α with aging inhibits CD28 expression, contributing to further T-cell dysregulation.[65] Further suppression of the adaptive immunity, is caused by lymphopenia, a hallmark phenomenon seen in COVID-19, reducing the number of total, $CD4^+$, and $CD8^+$ T cells.[66] In conclusion, both the innate and the adaptive cellular immune system of the older patient is weakened (*immunosenescence*), with a pro-inflammatory tendency (*inflammaging*), which seems to be intensified during COVID-19, increasing disease severity.[61,66-68]

5. Conclusion

In this narrative review, we discuss several features of COVID-19 and aging to clarify the increased mortality in older patients, summarized in Figure 1. This review does not cover all of the aspects of COVID-19 and those of the aging immune system. There are still aspects unknown, and while it is theoretically plausible that changes seen in the aging immune system are causatively related to disease severity, further studies are required. Also, many of the studies on comorbidity and complications encompass relatively small numbers of elderly patients and need to be

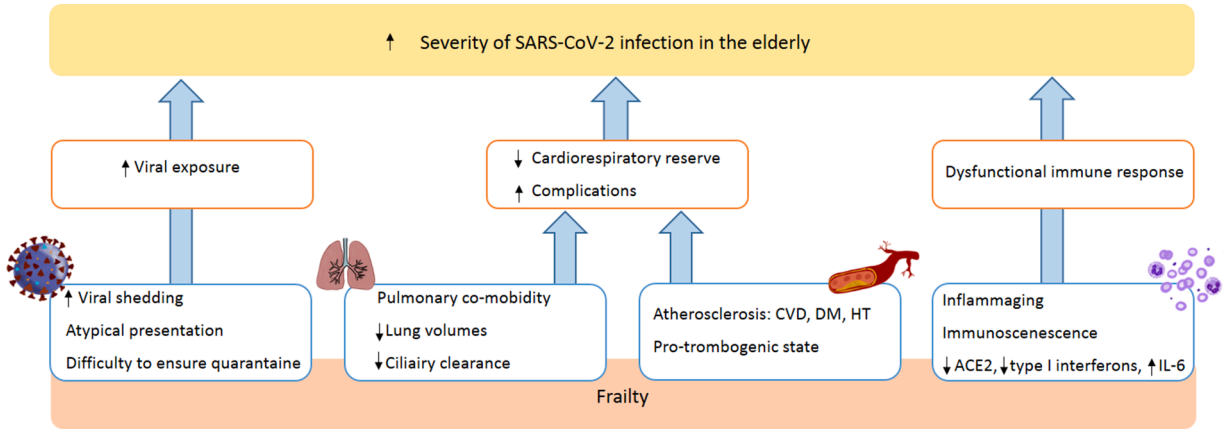

Figure 1. Factors contributing to disease severity of SARS-CoV-2 infection in the elderly. Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; HT, hypertension; ACE-2, angiotensin converting enzyme 2; IL-6, interleukin 6.

confirmed in prospective observational studies. Especially the frail elderly show a higher number of severe infections, requiring hospital admission, and leading to death. Elderly patients may show high viral shedding. Furthermore, ways to limit spread of the infection by early identification may be complicated due to atypical disease presentation and has been limited by lack of testing capacity in the recent past. Opportunities to apply quarantine measures in patients with cognitive disorders can be limited. Elderly patients have a decreased cardiorespiratory reserve and are more likely to have co-morbidity including atherosclerosis, rendering them more susceptible to complications. The aging innate and adaptive immune system is weakened, while there is a pro-inflammatory tendency. The combination of these factors contributes to the disease severity of COVID-19 in the older patient. Understanding these aspects may help to improve preventive measures and care of the older patient at risk for (severe) COVID-19 in the future.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Acknowledgements

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