Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Aging & COVID-19 susceptibility, disease severity, and clinical outcomes: The role of entangled risk factors

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ABSTRACT

The emergence of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) in late 2019 has been associated with a high rate of mortality and morbidity. It has been determined that the old population are not only at an increased risk for affliction with COVID-19 infection, but also atypical presentations, severe forms of the disease, and mortality are more common in this population. A plethora of mechanisms and risk factors contribute to the higher risk of infection in the old population. For instance, aging is associated with an increment in the expression of Angiotensin-Converting Enzyme-2 (ACE-2), the receptor for SARS-CoV-2 spike protein, which precipitates replication of the virus in the old population. On the other hand, immune dysregulation and changes in gut microbiota as a result of aging can contribute to the cytokine storm, one of the main indicators of disease severity. Decrement in sex steroids, especially in women, as well as growth hormone, both of which have crucial roles in immune regulation, is a key contributor to disease severity in old age. Senescence-associated oxidative stress and mitochondrial dysfunction in both pneumocytes and immune cells contribute to the severity of infection in an exacerbative manner. In addition, lifestyle-associated factors such as nutrition and physical activity, which are compromised in old age, are known as important factors in COVID-19 infection. Aging-associated comorbidities, especially cardiovascular diseases and diabetes mellitus, also put older adults at an increased risk of complications, and disease severity.

1. Introduction

In late 2019, a new virus called Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) emerged bringing about a global concern. The exact origin of the novel coronavirus is yet to be discovered. However, it has been suggested that SARS-CoV-2 has originated from bat coronavirus (Deshmukh et al., 2020). This virus typically develops a respiratory infection resulting in pneumonia-like illness, although a plethora of other symptoms has been recognized for this infection (Basu, 2020). As of today, there is no cure for Coronavirus Disease 2019 (COVID-19) and treatment options are limited. Nevertheless, people are being vaccinated globally and several clinical trials have shown promising results.

Data accumulated from patients suggests that older adults have higher mortality rates and constitute a larger proportion of the patients (Martín-Sánchez et al., 2020). Therefore, it is important to understand the underlying mechanisms that make older adults more susceptible to SARS-CoV-2. Furthermore, a lesser percentage of elderly patients manifest the classical triad of the disease (fever, cough, and dyspnea) compared with the younger patients (Azwar et al., 2020; Guo et al., 2020; Wang et al., 2020b). This can prevent old patients from being diagnosed in the early stages of the disease, which can lead to more fatality. Importantly, underlying diseases increase the morbidity and mortality of COVID-19. Cardiovascular diseases (Fan et al., 2020), diabetes, chronic kidney diseases, cancer, and respiratory diseases, which are linked to higher severity of the disease (da Silva Figueiredo et al.,

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2020; Deshmukh et al., 2020; Escalera-Antezana et al., 2020), are more prevalent in elderly people (Abduljalil and Abduljalil, 2020). Reduced T cell and B cell counts can be observed in older men which conforms to lower CD4+ and CD8+ levels in severe cases of COVID-19 (Azwar et al., 2020; Guo et al., 2020; Song et al., 2020).

Nutritional status can also alter the immune responses and may be a contributory factor in disease susceptibility among older adults (Bencivenga et al., 2020) . For instance, vitamin D deficiency is associated with increased severity of COVID-19 symptoms, which is in accordance with a higher susceptibility of men and older adults (Benskin, 2020).

In this paper, we aimed to review variable clinical manifestations in older patients compared with other age groups. Further, aging-related risk factors and mechanisms associated with the affliction with COVID-19 and its prognosis in older adults are reviewed. For this aim, keywords such as "aging, elderly, old" and "COVID-19, SARS-CoV-2" were used for searching Medline and Scopus to find the relevant articles in April 2021. The search was done without any time and language limitation for the included studies. We reviewed reference lists of included articles for additional relevant articles.

2. SARS-COV-2 clinical manifestation in older adults

It was observed that the emergent SARS-CoV-2 virus spreads more quickly in countries with higher rates of elderly (Hilton and Keeling, 2020) and among older adults who get afflicted, death is more probable (Petretto and Pili, 2020). Moreover, higher rates of both mortality and morbidity are observed in older adults, which is dissimilar from other pandemics where older adults had more mortality but less morbidity (Cortis, 2020). Approximately 50% of the patients older than 60 demonstrate the triad of fever, cough, and dyspnea which are classically associated with SARS-CoV-2; however, fever and cough are still the most common symptoms in the senile population (Azwar et al., 2020; Guo et al., 2020; Niu et al., 2020; Wang et al., 2020b), while in young people with a healthy immune system, COVID-19 more commonly presents with this triad, or is otherwise asymptomatic (da Silva Figueiredo et al., 2020). The lack of high temperature in some patients may have several reasons including low basal temperature, distortion of heat regulation, and certain medications in older adults (Guo et al., 2020). Moreover, expectoration and difficulty in breathing have a higher frequency in older adults compared with other age groups (Chen et al., 2020a; Zhang et al., 2020b). Older patients less frequently present with classic COVID-19 symptoms (Martín-Sánchez et al., 2020; Medetalibeyoglu et al., 2020) and are more susceptible to uncommon symptoms of SARS-CoV-2 such as confusion, fall, and significant gastrointestinal (GI) symptoms (Vrillon et al., 2020). In a recent study, delirium was the first clinical manifestation of COVID-19 in 36.8% of the aged patients and it was significantly linked to death (Poloni et al., 2020).

Furthermore, imaging findings in older adults may differ from other age groups; For instance, chest computed tomography (CT) images of roughly 50% of the patients under 70 and 33% of patients above 70 showed bilateral pneumonia. About one in three patients had normal CT images in both age groups (Kerr and Stacpoole, 2020). In another study, CT images in SARS-CoV-2 patients aging above 60 showed involvement of one or both of the lungs in 5.8% and 94.2% of the patients respectively, most of whom (74%) needed oxygen therapy (Li et al., 2020a). In another survey, it was reported that 64% of older patients showed involvement in both lungs (Song et al., 2020). Elderly patients (above 60) tend to have more severe pneumonia with the involvement of more lobes compared with young patients (Liu et al., 2020a). Surprisingly, in another essay, the risk of lung involvement was not associated with age. In two other studies, CT imaging of elderlies demonstrated more affected lobes, more subpleural lesions and pleural thickening, in addition to crazy paving sign and bronchodilation in comparison with younger counterparts (Wang et al., 2020a; Zhu et al., 2020). As mentioned previously, dyspnea, chest distress, and shortness of breath are more common among older patients, which could be correlated well with chest CT findings (Chen et al., 2020a; Zhang et al., 2020b).

Both men and women diagnosed with SARS-CoV-2 who are older than 50 years old are generally at increased risk of disease severity and death, and have longer hospital stays compared with their younger counterparts (Islam et al., 2020; Zhou et al., 2020). Among patients older than 60 years old, those who were older than 75 years old experienced more complications in comparison to those younger than 75 years old (Guo et al., 2020). Based on the American College of Cardiology Clinical Bulletin "COVID-19 Clinical Guidance for the cardiovascular Care Team", the fatality rates of 70-79 year-olds and $\geq$80 year-olds were 8.0% and 14.8%, respectively (Mullen, 2020).

Old patients with SARS-CoV-2 tend to show increased levels of D-dimer, urea, and lactate dehydrogenase (LDH) compared with younger patients (Chen et al., 2020a; Zhang et al., 2020b). In a study performed on 1096 definite COVID-19 patients, the risk factors associated with the higher probability of admission to intensive care unit were smoking, age above 50 years old, elevated C-Reactive protein (CRP), a quick sequential organ failure assessment (qSOFA) score above 0, and elevated procalcitonin levels (Almazeedi et al., 2020). Furthermore, the rate of death was higher among patients who had experienced ARDS, a sign of fast disease advancement (Vrillon et al., 2020; Wang et al., 2020b). Decreased kidney function and low blood pressure are also linked to higher fatality. Laboratory findings such as low blood lymphocyte count, increased CRP, D-dimer, creatinine, aspartate aminotransferase, procalcitonin, blood urea nitrogen (BUN), LDH, troponin, and decreased albumin level were also correlated with death (Chen et al., 2020a; Covino et al., 2020; Guo et al., 2020; Vrillon et al., 2020; Wang et al., 2020b). Interestingly, a study indicated that age, on its own, is not a risk factor and decreased blood partial pressure of oxygen, increased CRP, and elevated LDH, which are correlated with age, increase the risk for death (Covino et al., 2020). Tables 1 and 2 summarize clinical findings, complications and severity in the old COVID-19 patients (Fig. 1).

3. Angiotensin converting Enzyme-2 (ACE-2)

SARS-CoV-2 virus uses a spike glycoprotein trimmer for detecting and binding to Angiotensin Converting Enzyme-2 (ACE-2) receptors in the lungs, which are mostly expressed by type II pneumocytes leading to higher vulnerability of the lower respiratory tract to the virus (Ziegler et al., 2020). However, the lung is not the only organ having ACE2 receptors. ACE2 is expressed in many tissues of the human body and is responsible for regulating blood pressure and electrolyte and liquid homeostasis (Viana et al., 2020). For instance, epithelial cells of the GI tract, liver, kidney, pancreas, olfactory epithelium, cardiomyocytes, pericytes, and fibroblasts of the heart are sites where ACE2 can also be found, affecting various organs and thereby leading to heterogeneous clinical manifestation of the disease (Gadi et al., 2020).

Upon SARS-CoV-2 spike protein binding to ACE-2 receptor, the membrane-bound ACE2 (mACE2) domain, becomes soluble (shortly, sACE2) through ADAM-17 action (Song et al., 2020; Swärd et al., 2020; Zhao et al., 2020). It has been hypothesized that the higher prevalence of severe types of COVID-19 in older patients may stem from the differential mACE2 and sACE2 expression and function of renin-angiotensin-system (RAS) in old age. For instance, from 12 years of age, as children get older, the sACE2 expression increases with a higher rate of increase in males, leaving male elderly with the highest levels of sACE-2 (Swärd et al., 2020). Increased sACE-2 levels in old age have been attributed to an increment in ADAM17-sheddase activity, which is responsible for removing the ectodomains of membrane proteins such as ACE-2 and can facilitate virus entry to the cells (Zipeto et al., 2020). Growth differentiation factor-15 (GDF-15), N-terminal pro hormone BNP (NT-proBNP), and high-sensitive cardiac troponin T (hs-cTnT) levels are correlated with the level of sACE2, and thus it can be used as an indicator of a severe disease and as mentioned earlier, the level of sACE2 increases with aging, male gender, along with some underlying diseases including cardiovascular diseases and diabetes (Wallentin et al., 2020).

Table 1
Characteristics and severity of COVID-19 infection in the elderly in comparison with non-elderly and survivors compared to non-survivors.

Study, year	Group	Severity			
		Mild	Moderate	Severe	Critical
Guo et al., 2020 (Guo and others 2020)	All patients (Age ≥ 60)	4.8%	61.9%	22.9%	10.5%
	Age 60-75	5.9%	61.2%	22.4%	10.6%
	Age ≥ 75	0%	65%	25%	10%
Wang et al., 2020 (Wang and others 2020b)	All patients (Age ≥ 71)	–	29.5%	46.9%	23.6%
	Survivors	–	36.1%	56.6%	7.3%
	Non-survivors	–	1.5%	6.2%	92.3%
Niu et al., 2020 (Niu and others 2020)	Age 50–64	80.2%	–	19.8%	
	Age 65–79	56.8%	–	43.2%	–
	Age ≥ 80	18.8%	–	81.3%	–
Lian et al., 2020 (Lian and others 2020)	Age ≥ 60	75%*	–	16.18%*	8.82%*
	Age < 60	93.25%*	–	5.98%*	0.77%*
Covino et al., 2020 (Covino and others 2020)	All patients (Age ≥ 80)	20.3%	–	43.5%*	36.2%
	Survivors	28.3%	–	47.8%*	23.9%
	Non-survivors	4.3%	–	23.9%*	60.9%
Cheng et al., 2020 (Cheng and others 2020)	All patients (Age ≥ 65)	–	35.5%	56.4%	8.1%
	Survivors	–	42.3%	54.5%	3.2%
	Non-survivors	–	0%	66.7%	33.3%
Chen et al., 2020 (Chen and others 2020a)	Age ≥ 65	12.7% (Stable)*	–	43.6% (Serious)	43.6%*
	Age < 65	60.1% (Stable)*	–	33.1% (Serious)	6.8%*
	Survivors (Age ≥ 65)	19.4% (Stable)	–	58.3%* (Serious)	22.2%*
	Non-survivors (Age ≥ 65)	0% (Stable)	–	15.8%* (Serious)	84.2%*
Vrillon et al., 2020 (Vrillon and others 2020)	All patients (Age: 86–92)	15.8%*	32.9%*	51.3%*	–
	Survivors	22.2%*	44.5%*	33.3%*	–
	Non-survivors	0%*	4.5%*	95.5%*	–

* indicates significant differences between groups.

In addition, it has been determined that in several tissues, ACE-2 expression increases with advancing age. For instance, analysis of duodenal biopsies also confirmed an increment in ACE2 expression with age (Vuille-dit-Bille et al., 2020) and nasal expression of ACE-2 shows a linear pattern of increase with age (Bunyavanich et al., 2020). More importantly, it has been shown that in the patients with mechanical ventilation and alveolar damage, ACE-2 expression increases along with aging, providing an explanation for higher mortality in older adults (Baker et al., 2021). Overexpression of ACE2 may precipitate virus replication in the lung and enhance vascular permeability and thereby result in increased severity of infection (Peron and Nakaya, 2020). It was also suggested that as a result of prevalent usage of ACE inhibitors (ACEIs) and Angiotensin II receptor type 1 (AT1R) blockers (ARBs) in older adults, the overexpression of ACE-2 is more frequent and thus, the rate of mortality is higher in older adults (Peron and Nakaya, 2020). Moreover, usage of these medications can result in low cytosolic pH which expedites the entry of virus via ACE2 receptors and the increased ACE2 level results in decreased angiotensin, cardiac complications, and this triggers the defective cycle of letting more virus enter the cells (Cure and Cumhur Cure, 2020; Filardi and Morano, 2020). However, based on a systematic review of animal studies, ACE-2 overexpression, is a rare consequence of ACEIs and ARBs consumption and further studies are needed to provide a more clear evidence in this regard (Kai et al., 2021).

On the other hand, high viral load and occupation of ACE-2 receptors with the virus, leads to down-regulation of ACE2 receptors and thereby provokes inflammation in the respiratory tract, further leading to Acute Respiratory Distress Syndrome (ARDS), which is associated with disease severity and worse prognosis. These effects may be lethal in patients with underlying low levels of ACE2, e.g., in patients with heart failure (Verdecchia et al., 2020). Importantly, ACE2 converts the noxious angiotensin II into Angiotensin 1-7 (Ang 1-7) heptapeptide which, by binding to G-protein-coupled receptor Mas, has vasoprotective effects, as well as contributing to cardiac and renal protection (Tetzner et al., 2016). In addition, this heptapeptide has shown potential for protection against lung injury. During SARS-CoV-2 infection, the virus occupies the ACE2 receptor, thereby due to low levels of Ang 1-7, its protective effects are withdrawn from these systems (Verdecchia et al., 2020). Furthermore, high levels of Angiotensin II, due to down-regulation of ACE-2 receptors, contribute to thrombosis and vasoconstriction, which are known to be responsible for mortality, especially in older adults (Dolatshahi et al., 2021; Yuan et al., 2020). Such effects are amplified in older adults with age-associated comorbidities which are linked to higher severity of the disease (Viana et al., 2020).

4. Immune alteration in elderly and SARS-COV-2

Aging is associated with a progressive dysregulation in immune function and leads to a systemic, chronic, and low-grade proinflammatory response called inflammaging, in an attempt to promote clearance of senescent cells (Franceschi, 2007). Along with aging, telomeric disruption, oxidative stress, accumulation of cellular debris, microbiota changes, and several other mechanisms lead to activation of immune cells such as microglia and macrophages, as well as dendritic cells (DCs) (Pietrobon et al., 2020), and thereby increase the activity of nuclear factor kappa light chain enhancer of activated B-cells (NF-κB), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), resulting in the release of proinflammatory cytokines such as interleukin-6 (IL-6), IL-1 and tumor necrosis factor alpha (TNF-α) (Agostinho et al., 2010; Dantzer et al., 2008). On the whole, aging shifts immune cell response toward inflammatory states and up-regulates the inflammatory gene expression in these cells. It is also associated with diminished antigen-presenting capacity and reduced heterogeneity of the effector, cytotoxic, and exhausted CD28+ T cells as well as age-associated B cells, thereby compromising the functionality of the adaptive immune system in restricting infections and inflammation (Baruch et al., 2013; de Candia et al., 2020; Sabahi et al., 2021; Salam et al., 2013). RNA sequencing and mass cytometry analyses have shown that in the old population, T cell polarization and immune cell gene expression signature shifts toward an inflammatory type, and the expression of genes making the individuals more susceptible to SARS-CoV-2 is up-regulated (Zheng et al., 2020). On the other hand, SARS-CoV-2 can further enhance the age-associated escalation of inflammation, called cytokine storm, and in a feed-forward loop, inflammation and severity of symptoms are escalated (Zheng et al., 2020). In addition, increased IL-18 levels and inflammasome activation are associated with disease severity and poor clinical outcome in COVID-19 (Pietrobon et al., 2020), and similarly, an increment in IL-18 levels are observed with advanced age, consistent with inflammaging (Youm et al., 2013).

Reduced lymphocyte count is a common observation in afflicted

Table 2
Characteristics and complications in the elderlies compared to non-elderlies, and survivors compared to non-survivors.

Study, year	Group	Complications				Findings
		ARDS	Acute cardiac injury	Acute kidney injury	Acute hepatic injury	
Guo et al., 2020 (Guo and others 2020)	All patients Age ≥ 60	10.5%	4.8%	4.8%	1%	ARDS, Acute cardiac injury, Acute kidney injury, and Acute hepatic injury are significantly higher among older patients
	75 > Age ≥60	5.9%	1.2%	2.4%	1.2%	
	Age ≥ 75	30%	20%	15%	0%	
Liu et al., 2020 (Liu and others 2020a)	Elderly (Age ≥ 60)	22.22%	16.67%	38.89% (acute kidney and liver injury)	38.89% (acute kidney and liver injury)	There were no significant difference in complications between the two groups.
	Non-elderly (Age < 60)	5.26%	10.53%	7.89% (acute kidney and liver injury)	7.89% (acute kidney and liver injury)	
Song et al., 2020 (Song and others 2020)	All patients	20.3%	11.6%	8.7%	–	ARDS and Acute cardiac injury are more significant in older patients.
	Non-elderly (Age < 60)	11.4%	2.3%	4.5%	–	
	Elderly (Age ≥ 60)	36%	28%	16%	–	
Wang et al., 2020 (Wang and others 2020b)	All patients (Age ≥ 71)	21%	21% 10.4% (Arrhythmia) 17.4% (Cardiac insufficiency)	–	28.7% (liver enzyme abnormalities)	ARDS, acute cardiac injury, arrhythmia, cardiac insufficiency, Acute kidney injury, and acute hepatic injury are more common among non-survivors compared with survivors.
	Survivors	5.5%	11.4% 8.1% (Arrhythmia) 12.1% (Cardiac insufficiency)	–	27.1% (liver enzyme abnormalities)	
	Non-survivors	87.5%	65% 20.6% (Arrhythmia) 42.4% (Cardiac insufficiency)	–	36.7% (liver enzyme abnormalities)	
Zhang et al., 2020 (Zhang and others 2020b)	All patients	4.39%	7.69% 5.49% (Arrhythmia)	13.18%	7.69%	Arrhythmia, acute cardiac injury, kidney injury, and liver injury are more common in older patients.
	Elderly (Age ≥ 65)	11.11%	22.22% 14.81% (Arrhythmia)	25.92%	18.51%	
	Non-elderly (Age < 65)	1.56%	1.56% 1.56% (Arrhythmia)	7.81%	3.12%	
Wei et al., 2020 (Wei and others 2020)	Age ≥ 60	28.7%	21.6%	4.2%	11.4%	ARDS, acute cardiac injury, and heart failure are more significant in older patients
	59 ≥ Age > 45	22.3%	3.2%	0.6%	7%	
	Age ≤ 45	14.7%	4.4%	2%	8.8%	
Lian et al., 2020 (Lian and others 2020)	Age ≥ 60	16.91%	–	2.21%	7.35%	ARDS is more significant in older patients
	Age < 60	5.37%	–	1.53%	11.04%	
Godaert et al., 2020 (Godaert and others 2020)	All patients (Age ≥ 60)	–	–	58.8%	47.1%	No comparison
Gao et al., 2020 (Gao and others 2020)	All patients (Age ≥ 60)	13%	–	2%	–	ARDS and acute kidney injury are more common among non-survivors
	Survivors	1%	–	0%	–	
	Non-survivors Age ≥ 60	71%	–	11%	–	

Abbreviations: ARDS: Acute respiratory distress syndrome.

patients and may be because of lymphocytes being eliminated by the virus as a result of impairment of cytoplasmic constituents, mitochondrial malfunction or apoptosis. Importantly, lymphocyte count can reflect the extent of viral invasion and thus is considered an important prognostic factor (Wang et al., 2020b). Increased neutrophil count, in exchange for decreased lymphocyte count, has been shown to be associated with a higher death rate (Li et al., 2020a) and decrement in levels of CD4+ and CD8+ T cells is a more common phenomenon in severe cases of COVID-19 compared with non-severe cases (Song et al., 2020; Wang et al., 2020b). Moreover, men tend to show a more prominent age-associated activation of pro-inflammatory pathways, as is also the case in COVID-19 (Domingues et al., 2020). For instance, older men tend to have a higher decrease in T cell and B cell counts compared with their female counterparts (Azwar et al., 2020). In male patients, T cell response is associated with better outcomes and negatively correlates with the patient's age (Jin et al., 2020; Takahashi et al., 2020).

Overall, these findings imply that repressed cellular immunity and increased inflammatory reactions in the older population is correspondent with findings in patients with severe forms of COVID-19 (Wang et al., 2020b). Thus, severe COVID-19 in the old population can be, at least partly, attributed to the age-associated changes in the immune system.

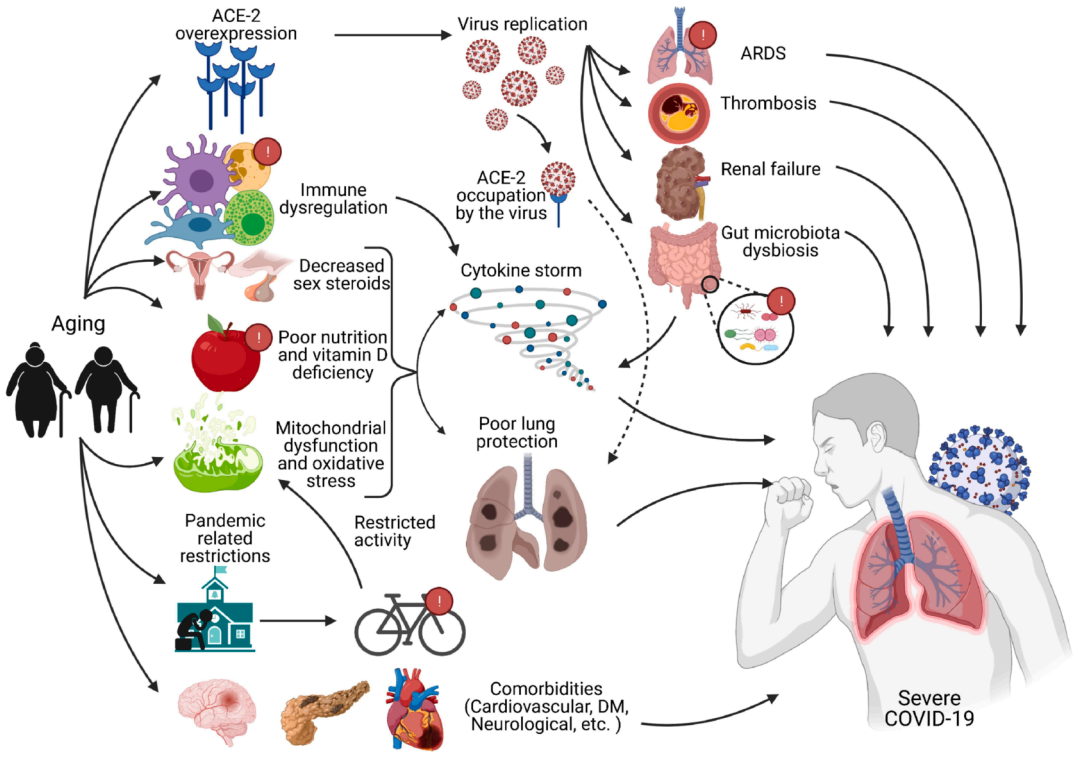

Fig. 1. Mechanisms and risk factors associated with disease severity in the elderly with COVID-19. Aging is associated with ACE-2 overexpression, immune dysregulation, decreased sex steroids, poor nutrition and vitamin D deficiency, mitochondrial dysfunction and oxidative stress, co-morbidities, and lower physical activity, which is exacerbated by pandemic-related restrictions. These effects result in increased virus replication, cytokine storm, and poor lung protection against virus. Also, complications of COVID-19 infection such as ARDS, thrombosis, and renal failure occur more prevalently in the elderly and will ultimately cause severe COVID-19 infection.

5. Mitochondrial dysfunction

Mitochondria have various functions in cells, such as immune cells, and mitochondrial impairment tends to correlate with increased age and obesity (Ayala et al., 2020; Tavernarakis, 2020). Mitochondrial dysfunction leads to oxidative stress, which thereby contributes to the appearance of inflammaging (Franceschi and Campisi, 2014). Accordingly, old COVID-19 patients tend to demonstrate scarce degrees of chronic inflammation, linked to mitochondrial malfunction (Moreno Fernández-Ayala et al., 2020), which leads to the explosive release of inflammatory cytokines and cytokine storm causing severe pneumonia, multi-organ failure, and eventually death in COVID-19 patients (Ayala et al., 2020). Mitochondrial dysfunction also leads to dysregulation of T-cell activity, which, in a vicious cycle, intensifies COVID-19 infection (Desdín-Micó et al., 2020). In addition, COVID-19 infection by hijacking mitochondria of immune cells, for the aim of replication within these structures, impairs mitochondrial function, which is more prominent in older adults. This will further perpetuate age-associated mild mitochondrial dysfunction in immune cells (Ganji and Reddy, 2021).

Furthermore, it has been observed that superoxide dismutase 3 (SOD3) gene is down-regulated in type II alveolar cells of older adults compared with younger adults (Starr et al., 2011). This effect was also observed in other genes involved in redox homeostasis. Oxidative stress can be detrimental to survival of type II alveolar cells in the presence of external assaults such as SARS-CoV-2 infection. This may be an underlying mechanism explaining the higher severity of SARS-CoV-2 in older adults, although more research is required for validation of this hypothesis (Abouhashem et al., 2020).

In this regard, modification of mitochondrial function has been suggested as a protective measure against COVID-19. Irisin, a mitochondrial protector, can preserve the lungs from ischemia and reperfusion injury (Chen et al., 2017). Irisin has also been discovered to favorably modify genes in SARS-CoV-2-affected adipocytes (de Oliveira et al., 2020) and to modulate reactive oxygen species (ROS) production in macrophages, exhibiting antioxidant and anti-inflammatory properties (Korta et al., 2019). Also, antioxidant supplementation therapy might be used as a preventative measure in healthy older people. The ketone body beta-hydroxybutyrate, in particular, decreases mitochondrial ROS generation and inhibits histone deacetylases, upregulating the transcription of certain anti-oxidant genes (Shimazu et al. 2013). Additionally, ketone bodies reduce ROS generation by increasing the expression of mitochondrial uncoupling protein (UCP), which reduces mitochondrial membrane potential (Sullivan et al. 2004).

Thus, mitochondrial dysfunction in the old age through up-regulating inflammation and oxidative stress could play a key role in higher susceptibility to COVID-19 infection and its severity. Importantly, therapies and life-style modifications that enhance mitochondrial function may be critical to long-term recovery for the old population who are not in optimum health.

6. Physical activity

Along with aging, physical activity and exercise are prone to a decline, which is intensified due to the restrictions in the pandemics. On the other hand, consistent physical activity is associated with less severe outcomes in COVID-19 afflicted patients (Sallis et al., 2021). A variety of cellular mechanisms entangling redox-sensitive transcription factors, cytokines (pro-inflammatory/anti-inflammatory), and other stress-associated molecules are involved in the beneficial effects of exercise, in particular its anti-oxidant and anti-inflammatory effects. The mitochondrion is an important player in this adaptation, as such stressors improve mitochondrial activity in a variety of tissues, including muscle (Sallam and Laher, 2016). Exercise also can up-regulate fatty acid oxidation and improve mitochondrial function in peripheral blood

mononuclear cells (PBMCs) and enhance their survival (Liepinsh et al., 2020). Thus, maintaining routine physical activity and exercise may attenuate mitochondrial dysfunction, oxidative stress, and the resultant inflammatory milieu in aging and aging-associated co-morbidities, and thereby less severe COVID-19 infection.

7. Hormonal changes & sex differences

Generally, it is supported that older age and male gender increase predisposition to SARS-COV-2 infection (Abraham et al., 2020; Bwire, 2020; Giesen et al., 2020; Kalantari et al., 2020; Khan et al., 2020; Niquini et al., 2020). In addition, Borghesi et al. demonstrated that older SARS-CoV-2 patients' lungs are more involved with infection compared to that of younger patients and this involvement is higher in males compared with females (Borghesi et al., 2020). Nevertheless, one survey showed that the at-risk population for affliction with virus entail children, old people, females, and family members (Liu et al., 2020b). Another study suggested that age and co-morbidities were associated with higher mortality rates while sex and occupation were not (Asfahan et al., 2020).

Such differences in susceptibility to SARS-CoV-2 infection in males and females can be attributed to genes as well as hormones, while co-morbidities, behavioral, and social factors may play a role (Gadi et al., 2020). Due to the location of ACE2 gene which is on X chromosome, women can be heterozygous for this gene in contrast to men who are homozygous (Gemmati et al., 2020). Accordingly, most of the studies have shown that the expression of the ACE-2 is higher in men than women (Bwire, 2020). However, estrogen up-regulates the expression of ACE-2 gene and in human atrial tissue, a positive correlation between ERα and ACE2 mRNA has been observed (Stilhano et al., 2020; Wang et al., 2021). Similarly, ERα and GPER expression levels in human atrial tissue are associated with ADAM-17 and TMPRSS-2 gene transcriptions, which regulate ACE-2 shedding (Wang et al., 2021). Nevertheless, it has been shown that in spontaneously hypertensive rats, sex hormones promote opposite effects on ACE and ACE2 activity, cardiac hypertrophy, and contractility (Dalpiaz et al. 2015). Females had higher ACE2 activity after ovariectomy, whereas men had lower ACE2 activity after orchiectomy. Consistent with these findings, estradiol replacement decreased ACE2 expression (Fischer et al. 2002). Overall, based on these findings, testosterone maintained high ACE2 levels in the heart and kidney, while estrogen seemed to decrease ACE2 expression in both organs (Gebhard et al. 2020).

Despite the fact that most of the studies show that the expression of ACE2 gene, as well as ADAM-17 and TMPRSS-2, is enhanced under the influence of estrogen, the mortality is lower in female adults (Stilhano et al., 2020). This observation can be attributed to a myriad of factors:

First of all, ACE-2 expression levels are not necessarily associated with severe forms of COVID-19, as ACE-2 can have protective effects via other pathways (Li et al., 2020c). For instance, estrogen modifies the local RAAS in human atrial myocardium by downregulation of ACE and concomitant elevation of ACE2, angiotensin II receptor type 2 (AT2R), and Mas expression levels (Bukowska et al., 2017). Therefore, in women, the ACE2/Ang1-7/Mas receptor axis, which has protective effects against virus, plays a more prominent role than in males (Chappell et al., 2014).

Secondly, the response to pathogens in men can differ from women. For instance, ACE2 is generally expressed higher in males than in females, primarily under pathological circumstances (Chappell et al., 2014; Liu et al., 2010; White et al., 2019).

Third, sex differences are shown to play a role in immune system function against pathogens. For instance, stronger humoral and cell-mediated immune responses to antigenic stimulation, immunization, and infection in women is observed compared to men (Klein et al., 2010), as well as substantially greater baseline immunoglobulin levels (Butterworth et al., 1967) and antibody responses (Cook, 2008). In addition, females show greater cytotoxic T cell activity, as well as higher expression of antiviral and proinflammatory genes, many of which contain estrogen response elements in their promoters (Hewagama et al., 2009). Innate and adaptive immune responses are weaker in men compared with women, as the cytokine response is inhibited by the androgenic inflow. This is supported by the increase in IL-1β and TNFα levels in men with androgen deficiency (Ilardi et al., 2020). Although gonadal hormones induce numerous sex variations in immunological function, the inherent imbalance in the expression of genes encoded on the X and Y chromosomes may also contribute to some of these disparities (Arnold and Chen, 2009). Polymorphisms or variability in sex chromosomal genes, as well as autosomal genes that code for immunological proteins, can play a role in immune response variations between men and women (Poland et al., 2008).

Importantly, it has been shown that sex hormones have an impact on the immune responses as well (Gadi et al., 2020). For instance, estrogen has regulatory effects on T cells, neutrophils, DCs, and pro-inflammatory cytokine production (IL-6, IL-1β, and TNF-α) (Pinna, 2021). In addition, the binding of sex steroids to their corresponding steroid receptors has a direct impact on cell signaling pathways such as NF-κB, cJun, and IFN regulatory factor (IRF) 1, leading to cytokine and chemokine production differences in men and women (Kovats et al., 2010). Higher levels of these cytokines, particularly IL-6, are associated with poor prognosis in COVID-19 patients (Zhang et al. 2020a).

Also, progesterone has immunomodulatory effects, by modulating T cell differentiation and attenuating its cytotoxic effects (Pinna, 2021). In Influenza A infection, for example, progesterone administration by up-regulating regulatory Th17 cytokine production (IL-22 and TGF-β), promoted damaged epithelium proliferation and thereby enhanced pulmonary resistance against secondary bacterial infections (Hall and Klein, 2017). Additionally, it is suggested that estrogen has a protective effect against ARDS, which is considered as a complication of COVID-19 (Stilhano et al., 2020).

Changes in sex hormone concentrations normally observed during the menstrual cycle, following contraception, after menopause, and during hormone replacement therapy, as well as during pregnancy, might affect immune responses to viruses (Klein, 2013). Also, it was supported that menopause-associated hormonal, and especially estrogen changes played a major role in the declined ability of old females in fighting against infections (Gubbels Bupp et al., 2018). Importantly, sex differences in the risk of affliction with COVID-19 alter along with aging as menopause occurs in women. Along with menopause in women, the protective effects of estrogen are withheld, thus making post-menopausal women prone to infections like COVID-19 (Al-Lami et al., 2020). For instance, it has been demonstrated that during the menopausal transition, serum estradiol concentrations negatively correlated with serum IL-6, IL-2, IL-8, and GM-CSF (Gubbels Bupp et al., 2018). Accordingly, exogenous estrogen has been suggested for prevention from COVID-19 infection, as well as treatment of non-severe COVID-19, especially post-menopausal women (Seeland et al., 2020; Suba, 2020).

8. Growth hormone

A progressive reduction in the secretion of growth hormone (GH) is observable after the third decade of life, which is roughly 15% for every decade. This age-associated decline can be attributed to the decrease in upstream signals from growth hormone-releasing hormone (GHRH) and somatostatin (SS), as well as changes in body composition, diet, daily activity, energy expenditure, sleep, and some comorbidities associated with aging (Elkarow and Hamdy, 2020; Sherlock and Toogood, 2007). Growth hormone has key roles in immunity through enhancing T and B cell proliferation, immunoglobulin production, and maturation of myeloid progenitor cells. It also modifies cytokine production and plays an important role in immune regulation (Meazza et al., 2004). Even more, lower levels of IGF-1 which have been recognized in patients with ARDS, are shown to be associated with higher mortality rates from ARDS (Ahasic et al., 2012). Such factors make it understandable how aging-

associated GH deficiency can at least partly explain the increased risk and severity of COVID-19 in older adults (Elkarow and Hamdy, 2020). It is suggested that recombinant treatment with GH might be beneficial due to the relationship between GH deficiency and COVID-19 (Lubrano et al., 2020).

9. Nutrition

Nutritional status can be another explanation of the more susceptibility to infection with COVID-19 in older adults and maintaining optimal consumption of various micronutrients can be beneficial in lowering the risk for affliction with the virus in the highly susceptible population, e.g. older adults (Richardson and Lovegrove, 2020). Poor nutrition leads to alterations in the innate and adaptive immune systems resulting in increased susceptibility to COVID-19 infection and worse outcomes in older adults suffering from COVID-19 (Bencivenga et al., 2020). Micronutrient and/or macronutrient deficits are common in older individuals (De Morais et al., 2013). Older patients tend to have lower albumin rates which may be linked to malnutrition and disease advancement (Lian et al., 2020). Although there are limited data on malnutrition in SARS-CoV-2 patients, given the high frequency of severe illness among the elderly, it is likely that a large number of these patients were malnourished at the time of their hospitalization (Mehta, 2020). In a cross-sectional analysis of patients with COVID-19, the risk of malnutrition and malnutrition in persons >65 years old was 27.5% and 52.7%, respectively, supporting this theory (Li et al., 2020b). The increased frequency of poor nutritional status in older COVID-19 patients might be due to a variety of factors. First, skeletal muscle loss may be caused by a catabolic condition generated by the inflammatory response to SARS-CoV-2 infection. Pro-inflammatory indicators such as C-reactive protein, TNF-α, and ferritin are commonly elevated in ma individuals (Jia, 2016). Second, gastrointestinal symptoms have been observed to be the most common in the aged COVID-19 patients, after respiratory symptoms (Guan et al., 2020). As a result, digestive system disturbances in older COVID-19 patients might aggravate their poor nutritional condition. Finally, immunosenescence may play a role in exaggeration of all COVID-19 associated changes (Barazzoni et al., 2020). Therefore, maintaining nutrition, especially in the phase of the disease can be beneficial in restricting the complications of COVID-19 infection and its severity.

From another aspect, the production of energy in mitochondria through respiratory chain decreases as people get older (Singh, 2006). As a result, in aerobic animals, mitochondrial integrity is critical for efficient energy supply from consumed nutrients. In most organisms, life spans are generally proportional to their metabolic rate, and therefore to the rate at which ROS are produced (Vitetta and Anton, 2007). On the other hand, diet has been shown to have a pivotal role in the mitochondrial autophagy and therefore, cellular health (Varghese et al., 2020). Higher consumption of macronutrients, by increasing ROS production, is known to contribute to premature mitochondrial dysfunction, and promote apoptotic pathways. Therefore, it can negatively affect cell survival, and leading to severe respiratory distress and organ failure, as well as immune cell dysfunction (inflammaging). In this regard, it is suggested that calorie restriction, through a myriad of mechanisms including modulating mitochondrial function, can potentially decelerate aging process and increase the resistance against systemic diseases in old age (Ruetenik and Barrientos, 2015).

10. Vitamin D

Vitamin D acts as an immunomodulatory molecule that can prevent cytokine storm and there is evidence that vitamin D deficiency, which is more common in older adults, is linked to higher severity of COVID-19 symptoms, which can be a contributory factor to the higher vulnerability of men and elderly to infection (Benskin, 2020). Additionally, appropriate serum 25-hydroxy vitamin D 25(OH)-D levels are essential for effective function of the respiratory system (Tramontana et al., 2020) and older adults often suffer from vitamin D deficiency since they are more often at home and less exposed to sunlight (Boucher, 2012).

11. Comorbidities associated with Old Age

Aging is associated with several co-morbidities. Underlying illnesses are the main predictors of mortality in COVID-19 infection. The most common underlying diseases are hypertension, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), malignant tumors, cerebrovascular diseases, and renal diseases, all of which are more common in older adults (Li et al., 2020a; Niu et al., 2020; Wang et al., 2020b; Zhang et al., 2020b). In one study, it was indicated that 60-90% of the COVID-19 patients who passed away, suffered from one or more of the non-communicable diseases (NCD) including respiratory diseases, hypertension, diabetes mellitus, and heart diseases (Basu, 2020). In another study, it was demonstrated that 6.0% percent of the fatality was associated with hypertension, 7.3% was related to diabetes, and 10.5% was due to cardiovascular disease (CVD) (Mullen, 2020). Hence, macrovascular and microvascular diseases can impose a risk for increased mortality in patients with COVID-19 infection (Mullen, 2020) . Moreover, in a survey including seven studies, it was suggested that COPD, cardiovascular diseases, and hypertension are the most common causes of severe disease or admission to intensive care unit (ICU), respectively (Jain and Yuan, 2020).

Some factors that menace the individuals are the low densities of arachidonic acid (AA) and lipoxin A4 (LXA4), which is observed in older adults, and people suffering from insulin resistance, obesity, type 2 diabetes mellitus, hypertension, and coronary heart disease (Das, 2018).

11.1. Cardiovascular diseases

In a study aimed at comparing the mortality risk between patients suffering from COVID-19 with different pre-existing morbidities, it was suggested that the patients with pre-existing coronary heart disease (CHD) were more susceptible to death and had a lower probability of estimated 30-day survival (Gu et al., 2020). Also, higher rates of disability, incidence, and fatality were observed in patients suffering from cerebrovascular diseases (Gu et al., 2020). In addition, COVID-19 may result in myocardial injury and acute decompensation in patients with pre-existing chronic heart failure (Niquini et al., 2020). Cardiac complications are more frequent in older patients in comparison to their younger counterparts (Lian et al., 2020). Elevated ultrasensitive cardiac troponin I (ultra-Tnl), which could be a marker of cardiac dysfunction, was also shown to be linked to higher fatality in another study (Li et al., 2020a).

11.2. Diabetes

Diabetes and obesity are considered threatening risk factors for people who get afflicted with COVID-19, which necessitate major protective steps in such patients (de Siqueira et al., 2020). In addition, SARS-CoV-2 generally increases blood glucose which hinders infection control. In another study investigating the characteristics of COVID-19 patients with or without type 2 diabetes, it was found that the prevalence of hypertension, coronary heart disease, and chronic kidney diseases was higher in them, which might further add to the increased risk of such patients for affliction with COVID-19 infection (Chen et al., 2020c). Moreover, in a study that aimed to investigate the prevalence of diabetes among people suffering from COVID-19 it was demonstrated that diabetes was more prevalent among older adults (Desai et al., 2020). Furthermore, it was supported that measures like CRP, LDH, the need for renal replacement therapy/hemodialysis (RRT/HD), and the need for vasopressors were higher among diabetics with COVID-19 and the risk of developing a severe form of the disease was higher among them (Fox et al., 2021). Table 3 summarizes clinical findings in COVID-

Table 3
Characteristics and clinical findings in patients with Diabetes Mellitus (DM).

Study, year	Subjects	Patients with DM	HbA1c	Mean age	Clinical finding (comorbidities)	Manifestations	Measures
Alessi et al., 2020 (Alessi and others 2020)	120	120	75 mmol/mol	54.8	Psychological distress	–	–
Chen et al., 2020 (Chen and others 2020c)	208	96 (46.2%) (type 2)	–	≥45	1) HTN: (DM+: 58.3%, DM-: 31.2%), 2) CAD: (DM+: 17.1%, DM-: 8.0%) 3) CKD: (DM+: 62%, DM-: 0%)	1) Ground-glass opacity: (DM+: 85.6%, DM-: 64.9%) 2) Bilateral patchy shadowing (DM+: 76.7, DM-: 37.8%)	1) BS (mmol/L): (DM+: 7.2, DM-:5.46) 2) LDL (mmol/L): (DM+: 2.2, DM-: 1.75) 3) SBP (mmHg): (DM+: 130, DM-:122)
Chung et al., 2020 (Chung and others 2020)	110	29	–	DM+: 66.3 ± 8.9, DM-: 53.5 ± 17.9 ($p < 0.001$)	Higher rates of HTN, severity score, and highly progressed to SCO	–	Higher levels of inflammation-related biomarkers, SBP, and DBP
Fisher et al., 2020 (Fisher and others 2020)	1382	763 T1Ds and 619 T2Ds	T1D: 6.9 ± 1.0, T2D: 7.1 ± 1.1.	T1D: 53.3 ± 15.3, T2D: 64.9 ± 10.3	Increased diabetes-related stress	–	–
Kim et al., 2020 (Kim and others 2020)	1082	235	–	–	Patients with DM, especially with age ≥ 70 years exhibited higher mortality	–	–
Fox et al., 2021 (Fox and others 2021)	355	47%	–	>18	Diabetes lead to severe disease, only age was an independent index for death rate The need for RRT/HD (DM+: 21%, DM-: 11%), The need for vasopressors: (DM+: 28%, DM-: 18%)	–	1) Peak inflammatory markers like CRP: (DM+: 184, DM-: 142) 2) Peak LDH: (DM+: 560, DM-: 499)

Abbreviations: HTN: Hypertension; DM: Diabetes mellitus; T1D: type 1 Diabetes; T2D: type 2 Diabetes; CAD: Coronary artery disease; SCO: severe and critical outcome; BS: Blood sugar; LDH: Lactate Dehydrogenase; SBP: systolic blood pressure; CKD: Chronic kidney disease; CRP: C-reactive protein; RRT/HD: renal replacement therapy/hemodialysis.

19 patients with diabetes. Additionally, it was concluded that the diabetic patients which were 70 years or older had higher mortality rates, and the use of dipeptidyl peptidase-4 inhibitor or a renin-angiotensin system inhibitor was of no benefit (Kim et al., 2020). Some variants of the TMPRSS2 and CD26 genes, especially rs13015258 a 50 UTR variant of CD26, which makes it easier for the virus to enter the cells can be the reason why patients suffering from type 2 diabetes are more prone to this virus and demonstrate worse outcomes (Senapati et al., 2020).

11.3. Obesity

Obesity is another risk factor for severe COVID-19 infection and it threatens life significantly when the BMI is equal to or higher than 35 kg/m2 (Rottoli et al., 2020). It has been shown that obese patients more commonly require mechanical ventilation and have a more severe disease (Muscogiuri et al., 2020; Simonnet et al., 2020). Since the expression of ACE-2 is higher in adipose tissue than in lung tissue, it comes to mind that adipose tissue may be susceptible to SARS-CoV-2 (Kassir, 2020), thereby adipose tissue contributes to viral shedding, resulting in a more severe infection (Sattar et al., 2020). Importantly, adipose tissue produces many pro-inflammatory adipokines and cytokines, which leads to low-grade inflammation and recruitment of immune cells and may clarify the connection between obesity and COVID-19 severity (Muscogiuri et al., 2020; Simonnet et al., 2020). Moreover, obesity and the Western diet can change the microbiota in the intestine and escalate intestinal permeability. This is linked to the translocation of bacteria and lipopolysaccharide from the intestine to the blood and adipose tissue, resulting in metabolic endotoxemia, which fuels meta-inflammation (Amar et al., 2011). This meta-inflammation caused by IL-6 and other proinflammatory factors can cause the immune system to become skewed, allowing SARS-CoV-2 to unleash its lethal inflammatory complications (Winer et al., 2017). Furthermore, some adipokines secreted by adipose tissue are linked to pulmonary dysfunction and may exacerbate ARDS (Melo et al., 2014; Oh et al., 2015).

11.4. Renal & genitourinary diseases

It is supported that urological diseases like benign prostatic hyperplasia which are common among older adults are usually accompanied by other co-morbidities or immunological insufficiencies, which might increase the risk for COVID-19 infection (Chen et al., 2020b). In a retrospective cohort study analyzing the data of 740 subjects, it was found that chronic kidney disease can be a risk factor for developing severe disease. Moreover, the mean mortality rate is higher in patients which are under routine dialysis when compared to the general population, which can be attributed to their older age (70-90 vs. 20-60) (Kikuchi et al., 2020).

11.5. Cancer

It is observed that patients undergoing anti-cancer therapy are more prone to the infection regardless of the type of the cancer (Asokan et al., 2020). However, there is controversy in this regard and some studies have shown that cytotoxic medications do not increase mortality (Duarte et al., 2020). Another study showed that the probability of developing pulmonary complications was higher in the patients suffering from lung cancer and chemotherapy might worsen the situation (Banna et al., 2020).

11.6. Neurological diseases

In a cohort study aimed at establishing the correlation between disease susceptibility and different comorbidities, it was found that neurological and cognitive diseases in individuals older than 65 years and depression in males older than 65 years are considered as risk factors (Yanover et al., 2020). It was suggested that special attention should be drawn to Alzheimer's disease (AD) patients who were suffering from COVID-19, as these patients tended to have symptoms of delirium, which increases the need for treatment of AD patients (Balli et al., 2020).

In a study investigating the characteristics of multiple sclerosis (MS) patients during the pandemic, it was found that the MS patients with more severe forms of COVID-19 tended to be older (Chaudhry et al., 2020). In addition, behavioral problems were aggravated in elderly people suffering from dementia as a result of increased stress during pandemic (Hilton and Keeling, 2020). In another study investigating the relationship between different variables in Parkinson's disease (PD), it was observed that living in nursing homes or hospitals and oncologic comorbidities had a more dominant role than other PD-related variables in imposing COVID-19 complications to the patients (Sainz-Amo et al., 2020). Because people with more advanced dementia are not able to understand, recognize, or recall any of the COVID-19 related recommendations, individuals with AD and underlying dementia are at high risk for COVID-19 and its associated morbidity and mortality. Moreover, individuals with AD and dementia live in various conditions and rely on the availability and accessibility of a variety of services, due to the nature of their disease. In the case of the COVID-19 pandemic, these factors may have an effect on the probability and the severity of the disease in both the individual and the community (Brown et al., 2020).

12. Treatment and prevention in older adults

There is currently no treatment known to be fully effective for COVID-19. In one cohort study, most elderly patients were administered antivirals, the most common being lopinavir and ritonavir, combined with inhaled human IFN-α2b. Antibiotics were used for more than 50% of the patients (Guo et al., 2020). Inhalation of human IFN-α2b was helpful in alleviating cough in the patients and this was shown to be more effective in senile patients compared with their younger counterparts (Liu et al., 2020a). Interferons are the key mediators of the innate immune response toward viral infection and this interferon-mediated immune response is compromised in patients who are more susceptible to COVID-19 (Monk et al., 2021). Several clinical trials are testing the effectiveness of vaccination to decrease the possibility of more people suffering from the COVID-19 disease. Many Countries have started vaccination of their population. Sputnik V, a heterologous recombinant adenovirus (rAd)-based vaccine, was more than 87% effective in all age and sex subgroups and 91.8% effective in people older than 60 years (Logunov et al., 2021). Moderna and Pfizer, mRNA vaccines, were also 94.1% and 95% effective respectively (Polack et al., 2020). BNT162b2 or the BioNTech, Pfizer vaccine, is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine which encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. A recent clinical trial demonstrated that this vaccine is 95% effective in preventing Covid-19 (Polack et al., 2020). Moderna vaccine or mRNA-1273 SARS-CoV-2 is a mRNA vaccine that uses the same method as the Pfizer vaccine. In a recent clinical trial, it was demonstrated that this vaccine is 94.1% effective and no prominent safety concern was noted (Baden et al., 2020). Similar vaccine efficacy among different age groups was observed in both of the mRNA vaccines. Several other vaccines against COVID-19 were also developed in the past months. These findings, along with public vaccination increase the hope for a significant decline in mortality, especially older population who are generally more susceptible to severe forms of COVID-19.

13. Conclusion

Patients who have underlying diseases are at more risk for developing severe forms of COVID-19. It is important to handle chronic illnesses in senile patients with an emphasis on screening and regulating blood pressure and glucose as well as quickly identifying old people who have COVID-19 in order to take appropriate measures. However, as some elderlies do not present with the classical symptoms of the disease and have atypical presentations, this may be a challenge. Thus, older adults should be informed of atypical symptoms of the disease so that they can be diagnosed and treated on time and it is vital for elderly patients to receive careful monitoring and seek medical advice, in order to receive timely medical care especially for those with co-morbidities which put them at higher risks. Several factors such as alterations in ACE-2 expression levels, immunologic profile, sex hormone and growth hormone secretions associated with old age, as well as oxidative stress and mitochondrial dysfunction, play a prominent role in higher susceptibility of old population. Vitamin D deficiency and low albumin levels are linked to higher mortality in older adults, which emphasizes the importance of proper nutrition and in case of vitamin D deficiency, receiving supplementation. The older population should be advised to maintain exercise, physical activity, and healthy nutrition on a daily basis. Several laboratory and clinical findings are predictive of the disease state and future mortality, which may be beneficial for classifying patients and planning the required interventions, accordingly. Along with community-based vaccinations, especially with a priority for old population for receiving vaccines, there is a hope for reduced complications in this population.

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