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Aging and the COVID-19 pandemic: The inter-related roles of biology, physical wellbeing, social norms and global health systems

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Highlights

- Coronavirus disease 2019 (COVID-19) has had a devastating and disproportionate impact on the elderly populations in terms of excess hospitalizations and deaths.
- The detrimental impact goes beyond higher clinical risk, which could be explained by several underlying biological pathways.
- These impacts also include widening of the existing global health disparities, and enhancement of social and economic vulnerabilities among older adults.
- As the global population continues to age, elderly-focused health services should be integrated into the global health systems and global strategies.
- Such reforms are particularly warranted in low- and middle-income settings with historically underfunded public health infrastructure and insufficient elderly care.

Aging and the COVID-19 pandemic: the inter-related roles of biology, physical wellbeing, social norms and global health systems

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating and disproportionate impact on the elderly population. As the virus has swept through the world, already vulnerable elderly populations worldwide have faced a far greater burden of deaths and severe disease, crippling isolation, widespread societal stigma, and wide-ranging practical difficulties in maintaining access to basic health care and social services – all of which has had significant detrimental effects on their mental and physical wellbeing. In this paper, we present an overview of aging and COVID-19 from the interrelated perspectives of underlying biological mechanisms, physical manifestations, societal aspects, and health services related to the excess risk observed among the elderly population. We conclude that to tackle future pandemics in an efficient manner, it is essential to reform national health systems and response strategies from an age perspective. As the global population continues to age, elderly-focused health services should be integrated into the global health systems and global strategies, especially in low- and middle-income countries with historically underfunded public health infrastructure and insufficient gerontological care.

Keywords: COVID-19, healthy aging, global health, health systems, low- and middle-income countries.

INTRODUCTION

Age plays a crucial role in affecting population health and the coronavirus disease 2019 (COVID-19) pandemic was no exception. The pandemic, for instance, had a particularly devastating impact on elderly populations, making them the most vulnerable population group and producing the worst disease outcome estimates compared to any other age group. As the virus swept through the world, elderly populations bore an enormous burden of hospitalizations, severe health complications, and excess deaths[1]. Currently, the COVID-19 infection incidence rates remain fairly similar among all adult age groups worldwide. However, compared to the 18-29 year reference age group, hospitalization rates are 5 and 10 times higher in the 65-74 year and 85+ year age groups, respectively. In similar comparisons of case fatality rates, people in the 65-74 year and 85+ year age groups are 65 and 340 times more likely to die due to COVID-19, respectively [1], highlighting the disproportionately high impact on the elderly populations.

These enormous increases in disease severity, hospitalizations, and an astronomical rise in the mortality rates among elderly populations, observed during the COVID-19 pandemic globally, warrant urgent attention of the scientific community to: 1) better characterize the underlying biological, social, and structural pathways that may have caused this respiratory pathogen to enact such extraordinary adverse clinical impacts on the elderly, and 2) use these insights in informing preventative and healthcare strategies. These assessments are also critical given the increasing trend of life expectancy globally: over 727.6 million people aged over 65 years and almost 146 million over 80 years in 2020, with these numbers expected to double by 2050, and gradually reaching 2.5 billion by 2100 [2]. Such unprecedented and accelerated growth in human population is likely to have tremendous detrimental impacts on the global disease burden and global healthcare systems (some of these phenomena have already been observed during the current pandemic).

In this respect, we present a broad overview of COVID-19 and aging from the interrelated perspectives of underlying biological mechanisms, physical manifestations, societal aspects, and health services with a particular focus on the elderly population.

METHODS

We have conducted a targeted literature review, which is meant to be an informative, rather than all-encompassing, rapid review of the literature on a given topic. Our approach, therefore, involved an in-depth, however, non-systematic literature review of the literature, and followed by an informed selection of relevant, current and high-quality articles on the relevant topics of interest to be cited.

First, we searched PubMed electronic database to systematically identify relevant scientific publications (of interventional and observational studies) and systematic reviews, which had investigated or addressed COVID-19 health outcomes in the specific context of elderly populations globally. We applied no date or language restrictions, and used the *MeSH* terms and free text words (where appropriate) related to 'adult', 'middle aged ''aged', 'coronavirus disease', 'post-acute COVID-19 syndrome', 'immune system', 'sex', 'social isolation', 'social stigma', 'mental health', and 'aging'. Second, To complement our review of the scientific literature, we conducted a supplementary search, based on the same search strategy and by using a benchmark search engine (the Google Search) to identify relevant media reports and regional guidelines on the topic.

We have summarized data from studies reporting biologic, social and healthcare potential determinants of PACS in the elderly in **Table 1** and **Figure 1**.

Possible mechanistic pathways for excess risk among the elderly

Age played a significant role in COVID-19 moderate and severe cases of a complex pulmonary distress syndrome that could evolve into a multi-organ systemic dysfunction [3], and the disproportionally high morbidity and mortality are documented among people aged 65+ years worldwide. The more significant burden of post-COVID condition [4] on survivors was seen among the elderly population.

From a biological perspective, the aging process is marked by a shift in the immune system works, which partly explains the increased morbidity and mortality of the elderly [5]. The immune senescence in older patients with COVID-19 can increase the risk for severe cases by three main mechanisms. First, an increased number of senescent cells at infection leads to a sequence of senescent secretory events [6]. Second, older cells and tissues have a decreased damage repair capacity [7]. These aspects became crucial within the COVID-19 pandemics since SARS-CoV-2 is a virus that triggers an exacerbated innate immune response and depends on the organism's competence in shifting from intrinsic to an adaptive response to be effectively neutralized [8]. Third, the process of so-called "inflammaging" where well-controlled metabolic processes in young individuals progressively and chronically generate detrimental cytokines, oxidative reactive species (ROS) upregulating the innate immune response [9], leading to the attenuated interferon response. In young individuals, the innate immune system maintains the stress generated by the oxidative metabolism, but as aging progresses, the body's ability to sustain this eustress level reduces. Oxidative metabolism starts to chronically trigger inflammatory and innate immune responses activating IL-1β and NF-κB inflammatory pathways, described as inflammaging [10]. COVID-19 promotes age-induced immune cell polarization and gene expression related to inflammation and cellular senescence [11]. Overall, aging appears to significantly influence the biological mechanisms through which SARs-CoV2 affects immune regulation.

Long term consequences of COVID-19 among survivors

There is a scarcity of studies that focus on the potential burden of the post-acute COVID syndrome (PACS) in populations over 65 years of age. In a systematic review that included 45 studies reporting frequency and variety of persistent symptoms after COVID-19 infection [12], only two studies reported a median age above 65 years, representing 1,9% of the included population [13,14]. Both studies looked at the severe form of COVID-19 and reported fatigue, breathlessness,

and psychological distress as the most prevalent persistent symptoms, with significant impacts on functionality, independence, and cognitive function. Recently, extensive American medical databases have been analyzed, and when COVID-19 adult patients were compared to contemporary, historical, and other viral lower respiratory tract illness controls, matched by age and sociodemographic factors, those infected with SARS-CoV-2 presented an excess risk of 11% for one or more persistent symptoms that required medical attention [13]. Moreover, six months following the infection, an excess risk of chronic respiratory failure, cardiac rhythm disorders, acute coronary syndromes, hypercoagulability, encephalopathy, dementia, memory difficulties, stroke, kidney injury, diabetes, and anemia have been reported (potentially increasing the burden on individuals and on the health care with increased outpatient encounters, exams and hospitalizations) [4,15]. A prospective analysis from the REACT-2 program, using linkage data from the National Health Services (NHS) in the United Kingdom showed that being over 65 years was the most significant and independent contributor to persistent symptoms identified [16].

Therefore, taken together, the exact effects of cellular senescence on several physiological systems (such as immune system disbalance), coupled with respiratory system impairment, markedly decreased lung cells regenerative capacity, increased pro-fibrotic mediators, and increased vascular dysfunction, explain a significant part of the risk for developing severe COVID-19 and could also explain longer-lasting symptoms among the elderly.

The roles of sex differential and gender norms on Covid-19

Age and societal inequities (e.g., in healthcare access and socioeconomic circumstances) among populations may influence COVID-19 outcomes [17], and it is possible that gender norms may further widen these disparities among the elderly. Initial reports indicated that 60% of all COVID-19 patients were men, who were also at higher risk of developing systemic inflammation, multi-organ dysfunction, and cardiac injury, with viral shedding longer than women on average [18]. Even though increased mortality rates in men could reflect possible differences in sanitary behavior and unequal access to testing across countries [19], the severity and mortality rates were far worse among men than women in almost all countries globally [20]. Additionally, there may be some mechanistic explanations for the sex differences observed in disease severity and case fatality. For example, while estrogen has been known to trigger an immune response, by contrast, testosterone shows immunosuppressive functions by reducing cytokine production and higher levels of innate immune cytokines associated with acute-phase deterioration in female patients [21]. Furthermore, ACE2 Angiotensin Converting Enzyme 2 (ACE2), a gene coded in the X chromosome, also interferes with interferon regulation by estrogens in different tissues [22,23].

Finally, SARS-CoV-2 entry in cells has shown to be enhanced by cellular transmembrane serine protease 2 (TMPRSS2), which primes the spike protein of the virus and is regulated by androgen receptor signaling [19]. These biological explanations also align well with previous observations that women are less susceptible to severe forms of infection than men due to their somewhat superior immune responses [23].

In addition, studies looking at the post-acute sequelae of COVID-19 have reported a significantly higher sex difference for respiratory failure and acute kidney injury risk [4]. It is unclear to what extent the historical gaps in access to health care and generally higher prevalence of risk factors in postmenopausal women will impact long-term COVID-19 sequelae. One recent study, based on a large prospective cohort of hospitalized COVID-19 patients in Spain [24], showed that female participants reported more post-COVID symptoms, including anxiety, depression, or poor sleep quality, eight months after hospital discharge than males. However, more studies would be needed to replicate these findings since systematic differences in self-reported systems can be distorted by between-individual differences (such as gender norms).

Social stigma, social isolation, and mental health

The sufferings of the older adults started with the start of the endemic, deteriorated with the intensification of the non-pharmacological social distancing measures such as strict generalized lockdowns, and stayed even when the pandemic started to recede. The elderly became victims of infodemic and negative news overdose. A mixed-methods study from Turkey revealed that the average time the elderly spent following news regarding COVID-19 on TV or social media was 2.74 hours/day. It increased the odds of generalized anxiety disorder by a factor of 1.188 [25]. The news of their being at higher risk of getting infected was interpreted differently by their family members. Some thought the elderly were the source of infection or a potential conduit for the virus to enter the household. Such misperceptions caused severe stigma against the elderly worldwide.

For instance, in Bangladesh, some family members deserted their elderly family members in the jungle [26], whereas the elderly suffered domestic violence in parts of South America [27]. For a long time since the onset of the pandemic, however, these issues remained largely ignored in the mainstream academic discussion regarding the impact of the pandemic. Additionally, as the global health systems were almost exclusively unprepared to deal with widespread social stigma [28], or the consequent violence against the elderly, there was hardly any timely remedy to these problems. When the generalized lockdown started, many elderly people suddenly found themselves in a far more isolated circumstance than what they were already experiencing. Overwhelming

evidence soon emerged from numerous studies based on middle and high-income countries worldwide indicating a deterioration of mental health, physical health, quality of life, and general wellbeing among the elderly amidst strict lockdown [25,29]. The inability of the immediate family members to visit led to alienation and psychological breakdown [25,26,29], and in some cases, suicide [30,31].

Physical wellbeing

The isolation that ensued following generalized lockdown also impacted the physical well-being of the elderly. A systematic review of 14 cross-sectional and 11 cohort studies revealed that COVID-19 movement restrictions reduced physical activity due to increased sitting time, increased equivalent metabolic tasks, decreased steps, and reduced exercise frequency and duration [32]; these may eventually result in reduced musculoskeletal strength and endurance and cardiorespiratory capacity. Increased sedentary behavior is also associated with high blood pressure, and cardiovascular and metabolic diseases [33], among others. Several other studies from the Netherlands [34], France [35], Turkey [25], China [36], and Japan [37] also reported a sharp decline in physical activity among the elderly during the COVID-19 confinement. The elderly are prone to developing sarcopenia, cardiometabolic disorders, and other comorbidities [38]. All of these may lead to functional decline, culminating in limitations in daily life and an increased risk of falls [34].

In addition to adverse health consequences of isolation and physical inactivity, an inability to access essential health care owing to service disruption further worsened the overall health condition of the elderly. Community-bound elderly patients suffering from NCDs in China, for example, faced difficulty in collecting medicines essential to control their conditions [39]. Elderly patients from Argentina reported significant schedule difficulties in accessing routine consultations for chronic illnesses, palliative care, and mental health conditions [40]. Similar reports of service disruptions emerged from Asia [41], the Americas, and Europe [42]. Additionally, as the pandemic progressed, many who survived the disease eventually fell victim to PACS [4], creating further challenges for already struggling global health systems, especially in low- and middle-income countries (LMICs) settings.

CONCLUSION AND RECOMMENDATIONS

COVID-19 pandemic has demonstrated that the detrimental impact of a novel virus on elderly populations could go beyond a higher clinical risk of severe disease manifestation and hospitalization. As the world now seeks to return to normalcy, the elderly population, however,

remains the ones left behind, especially in resource-limited LMIC settings where the healthcare services and social safety net are historically poor. COVID-19 pandemic may have significantly worsened the pre-existing health disparities among older adults, including access to essential preventive and curative services, and may further enhance social and economic vulnerabilities. For example, Given the "new norm," many activities have turned online, and such a rapid transition has been difficult for the elderly worldwide, who are often unfamiliar with many emerging technologies. Evidently, such lack of familiarity with the new technologies has discouraged teleconsultation, including a sense of dissatisfaction owing to the virtual nature of clinical consultations. Therefore, besides developing innovative interventions to tackle these issues, further implementation research should be conducted to assess the gaps and challenges in access, adoption, and sustainability of these measures in elderly populations. Furthermore, to tackle future pandemics efficiently, it is essential to reform national health systems with an age perspective. As the global population continues to age, elderly-focused health services should also be integrated into the global health systems and global strategies, especially in the low and middle-income countries with historically underfunded public health infrastructure and insufficient gerontological care.

Contributors

Cristina Baena contributed to conducting the systematic review and manuscript preparation.
Taufique Joarder contributed to conducting the systematic review and manuscript preparation.
Nasar U Ahmed contributed to manuscript preparation.
Rajiv Chowdhury contributed to conceptualization and manuscript preparation.

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Declaration of competing interest

The authors declare that they have no competing interest.

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Tab

Author/Journal	Month/year of publication	Location	Study design	Study population/scope	Analytical strategy	Key findings
Zhou, et al . Lancet.	03/2020	Wuhan, China	Retrospective cohort	191 adult inpatients with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital	Univariable and multivariable logistic regression to explore the risk factors associated with in-hospital death.	Increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03–1·17; p=0·0043)
Cohen et al. BMJ	02/2022	USA	Retrospective cohort	87 337 adults aged ≥65 years after the acute phase of SARS-CoV-2 infection, UnitedHealth Group Clinical Research Database	Propensity score matching with 2019 and 2020 controls	11% excess risk for persistent and new sequelae in adults aged ≥65 years after acute infection with SARS-CoV-2.
Salimi & Hamlin. J Gerontol A Biol Sci Med Sci	06/2020	USA	Narrative review	The potential roles of the hallmarks of aging, coupled with host–coronavirus interactions	Descriptive mechanistic studies	Older adults have developed more severe and critical complications, and therefore are at higher mortality risk. Both the incidence and severity of disease appear to be more prominent in men than women, which can be partially explained by both age-dependent and -independent sex dimorphism in the immune system
Akbar &Gilroy. Science	07/2020	UK	Perspective	Senescent immune system and inflammaging	View point	The effective treatment of COVID-19 patients may require a combination of anti-inflammatory and antiviral regimes to complement vaccination against the virus
Al-Aly et al. Nature	06/2021	USA	Cohort	5,808,018 participants from the US Veterans Affairs electronic Healthcare database	risk of health resource use and death, and the risk of each diagnosis, medication use, and laboratory abnormality	A substantial burden of health loss that spans pulmonary and several extrapulmonary organ systems is experienced by patients who survive after the acute phase of COVID-19
Scully et al. Nat Rev Immunol	06/2020	Spain	Retrospective cohort	1969 individuals (age: 61, SD: 16 years, 46.4% women) were assessed 8.4 months after discharge	Adjusted multivariate logistic regressions	Female sex was a risk factor for the development of some long-term post-COVID symptoms including mood disorders
Sirin et al. Int J Geriatr Psychiatry	11/2021	Turkey		278 participants aged 65 or older.	Quantitative, qualitative mixed-method study using an online questionnaire	During the pandemic, social isolation and lockdown for elderly people make serious risk factor for their mental well-being
Liu et al. J Geriatr Psychiatry Neurol	03/2022	China	Multicenter observational study	1063 inpatients from four major tertiary psychiatric hospitals in China	Multiple logistic regression analysis	Suicidality was common in older patients with clinically stable psychiatric disorders during the COVID-19 pandemic.
Mustaffa et al. J Glob Health	12/2020	Malaysia	Observational data from e the Department of Statistics, Malaysia	National Malaysian COVID-19 statistics	Descriptive cases, deaths and population at risk	The elderly in Malaysia, as in other parts of the world are especially susceptible to the adverse effects of COVID-19; identifying and properly addressing health-related issues are important to ensure optimal outcomes
Fhon et al. Rev Lat Am Enfermagem	11/2020	Brazil and Peru	Documentary, retrospective, descriptive and exploratory research.	4,220 newspaper articles identified	The data were collected from articles published on open-access websites	The health systems need to reorganize for care to the global population, especially the elderly, considering their weaknesses and also the lack of prior professional training to offer care to this population.
Zaman and Rahman.	05/2020	Bangladesh	Editorial	National database	Point-of-view	"It was as if corona patients were personifications of the unknown fear and needed to be punished."

Figure 1. A summary of the inter-related roles of biology, physical wellbeing, social norms and health systems in elderly