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How can Biology of Aging Explain the Severity of COVID-19 in Older Adults

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KEYWORDS

• Aging • Comorbidities • COVID-19 • Immunosenescence • Inflammaging • Sarcopenia • Malnutrition

KEY POINTS

- Aging has been identified as one of the most relevant risk factors for poor outcomes in COVID-19 infection, representing an important predictor both for higher mortality and disease severity.
- Different mechanisms have been proposed to explain the worse outcomes in the elderly, including the remodeling of immune system, the higher prevalence of malnutrition and sarcopenia, the increased burden of multimorbidity, and, to a lesser extent, the direct effects of age on the respiratory system and hormonal profile.
- The interplay between all these causes, rather than the individual pathophysiological mechanism, explains the increased severity of the disease with age.

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INTRODUCTION

In December 2019 a cluster of pneumonia caused by a previous unknown coronavirus, SARS-CoV-2, was identified in Wuhan, China.[1] SARS-CoV-2 belongs to the subgenus of beta-coronavirus,[2] as SARS-CoV and MERS-CoV, respectively emerged as epidemic in 2003 and 2012. The person-to-person transmission occurring via respiratory droplets or aerosols[3] led to a rapid spreading of COVID-19 infection,[4] firstly through China and then through all the other countries of the world, thus becoming a pandemic.[4] COVID-19 shows a high variability of clinical pictures, ranging from mild or no pneumonia (81% of cases) to severe pneumonia (14% of cases) and critical pneumonia (5% of cases).[5,6]

Aging has been identified as one of the most relevant risk factors for poor outcomes in COVID-19 disease, independently from the presence of preexisting diseases.[7,8] The COVID-19 mortality risk sharply increases for elderly subjects, as showed by the reports of China, Italy, and the United States.[7] In particular, in Italy, case fatality rate for patient aged 40 to 49 years or younger was reported of about 0.4% or lower, 1% among those aged 50 to 59 years, 3.5% in those aged 60 to 69 years, 12.8% in those aged 70 to 79 years, to 20.2% from 80 years and older.[8]

Age is not only an important predictor for mortality, but it is also associated with higher disease severity, in terms of increased hospitalization rates, length of hospital stay, need for intensive care, and invasive mechanical ventilation.[8–11] Since now, different mechanisms responsible for worse outcomes in the elderly have been suggested,[12–14] which include the remodeling of immune system, the higher prevalence of malnutrition and sarcopenia, the increased burden of multimorbidity, and, to a lesser extent, the direct effects of age on the respiratory system and hormonal profile. The interplay between all these causes, rather than the individual pathophysiological mechanism, explains the increased severity of the disease with age.[8–14]

REMODELING OF IMMUNE SYSTEM

The terms “immunosenescence” and “inflammaging” refer to age-related physiologic changes in both innate and adaptive immune system, which lead to a higher incidence of infection, cancer, and autoimmune disease in the elderly population.[15]

The decline of the immune system with age, consisting of inappropriately amplified and dysregulated immune responses,[15] leads not only to a greater susceptibility to bacterial and viral infections but also to more severe consequences of infectious disease, such as severe respiratory failure in COVID-19 infection and lowered responses to vaccination.[15,16] Interestingly, age-related remodeling of the immune system is associated with a sort of paradox: a state of increased autoimmunity and inflammation coexistent with a state of immunodeficiency.[16]

“Immunosenescence” represents the gradual deterioration of the host’s ability to mount an effective immune response against new antigens, whereas “inflammaging” identifies a state of chronic, sterile low-grade inflammation resulting from the long-term physiologic stimulation of an overactive, yet ineffective, immune system. Together, these 2 mechanisms might facilitate the development of cytokine storm in elderly.[16]

Immunosenescence and COVID-19 Infection

Aging strongly affects the immune system, influencing both the humoral and cellular arm of immunity, from hematopoietic stem cells to mature lymphocytes in secondary lymphoid organs.

Since now, several hallmarks of immunosenescence have been identified. One of the salient features of this mechanism is the decrease in peripheral naïve T cell,[17,18]

as a result of the fibroadipose involution of the thymus and the reduced ability of lymph nodes to store, maintain, and support naïve T cells with age. Although there is a 95% reduction in the number of naive T lymphocytes in the elderly compared with young people,[19] there is only a slight reduction in the total number of T lymphocytes in advanced age[19,20] due to the compensatory accumulation of memory T cells.[19] These senescent cells are mainly characterized by a decrease in T-cell receptor (TCR) repertoire[21] and by a reduction in the expression of the costimulatory surface protein CD28+, which is the signature of replicative senescence.[22] Indeed, CD28 is not only important in lymphocyte activation but also plays a role in telomere homeostasis.[23] Memory cells are characterized by low telomerase activity, high production of reactive oxygen species and constitutive activation of p38 mitogen-activated protein kinase, which once activated, blocks signaling via TCRs.[24] All these changes contribute to the decreased ability of the aging immune system to mount an adaptive response against new antigens.

"Immunosenescence" is also characterized by the imbalance of the Th1/Th2 ratio.[25] The host's ability to balance the differentiation of CD4 lymphocytes into Th1 phenotypes, which has a proinflammatory role, and Th2, which has an antiinflammatory function, is vital for the neutralization of pathogens without inducing damages to host tissues.[25,26] It seems that in elderly patient there is an impairment in this mechanism that would favor the development of more severe forms of COVID-19 disease.[25] Indeed, in early stage of the infection there is a predominant Th2 response that would aid viral replication, followed by a rapid upregulation of Th1 response that would lead to cytokine storm and development of critical illness.[25,27] On the same note, in the elderly population there is an upregulation of the proinflammatory pathways mediated by Th17 cells and a loss of the antiinflammatory response mediated by regulatory T cell lymphocytes.[28]

Moreover, a reduction in CD8+ T cells has also been described in severe cases of COVID-19,[29] suggesting an impairment of the host's ability to fight viruses. The functional exhaustion of the cytotoxic function of CD8+ due to the reduction of the coexpression of perforin and granzyme B,[30] has already been associated not only with an increased risk of contracting influenza infection but also with increased disease severity in elderly.[31,32]

As regarding humoral immunity, older people showed both a decrease in bone marrow output of naïve B-lymphocytes[33] and the accumulation of the double-negative B cells subtype, which are exhausted cells with functional impairment.[34,35] The accumulation of these dysfunctional B cells has been reported in healthy elderly subjects and recently in severe cases of COVID-19 disease.[36]

As a result of the decline of both T and B lymphocytes, aged individuals are characterized by an ineffective antibody response, in terms of decreased affinity, poor neutralization of antigens, and production of antibodies more prone to autoreactivity.[35] Moreover, for the same reasons, the duration of protection of immunity following vaccination is usually shortened in this population.[37]

Finally, the mechanism related to the "antibody-dependent enhancement (ADE)" has also been associated with severity of COVID-19 infection.[38] ADE is a phenomenon whereby the binding of virus to nonneutralizing antibodies, produced during other infections, promotes its internalization into host cells and facilitates the downstream inflammatory responses.[39] This mechanism has been described for other coronavirus infections, such as SARS-CoV-1 and MERS,[40,41] as well as for other viral infections (ie, dengue fever and human immunodeficiency virus).[39] It has been suggested that elderly might be more prone to these mechanism because of the exposition of a lifetime to circulating virus.[13]

Inflammaging and COVID-19 Infection

Older patients may show a baseline low-grade inflammation in the absence of infectious processes.[42] This condition, called "inflammaging", is characterized by high baseline serum concentration of C-reactive protein and cytokines (interleukin-6 [IL-6] and IL-8) and is associated with increased fragility and morbidity.[42] Inflammaging may be the result of multiple mechanisms, including the accumulation of misfolded proteins, the gut barrier leaking, and obesity.[43] Moreover, elderly may be characterized by an impaired clearance of dead and dying cells from sites of immune activity,[42] leading to persistent inflammation, and by the presence of senescent cells, which do not proliferate but secrete inflammatory molecules (process known as the senescence-associated secretory phenotype).[22] This excessive inflammation can negatively affect some functions of the immune system.[42] It has been suggested that in COVID-19 lung infections, the presence of a preexisting inflammatory condition and senescent cells can lead to the development of an exacerbated cytokine storm, with recruitment of other inflammatory cells.[42] Molecules such as tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, and monocyte chemoattractant protein-1 determine the expression of natural killer cell receptor (NKR) ligand by nonlymphoid cells of the respiratory tract and lungs, which can be targeted and killed by infiltrating aged T cells expressing NKRs, causing tissue and organ damage.[42]

Severity of COVID-19 disease has also been correlated to the neutrophil-lymphocyte ratio, which usually indicates low-grade inflammation in elderly, as in obesity, metabolic syndrome, and diabetes.[44]

COMORBIDITIES

Several epidemiologic studies reported that the presence of preexisting comorbidities represents a relevant risk factor in patients with COVID-19 for a more severe disease in terms of increased and prolonged hospitalizations and mortality.[45–51]

The most common comorbidities found in cohorts of patients with COVID-19 were diabetes, hypertension, obesity, chronic cardiovascular, pulmonary, and kidney diseases.[45–52] These are all medical conditions characterized by a state of chronic inflammation associated with a weakened immune response that could explain the predisposition to infections and disease complications.

Although there are many studies investigating the role of comorbidities in COVID-19 disease in the general population, there are not many data addressing the association between comorbidities and aging. A Spanish retrospective study including 834 patients aged 60 years and older, hospitalized for COVID-19, showed that patients with heart failure and chronic kidney disease had an increased risk of hospital mortality.[52] A retrospective study conducted on 889 patients showed that the presence of multimorbidity, identified by an increased Charlson Comorbidity Index, together with the presence of symptoms and advanced age (>60 years), was associated with an increase in hospitalization, severity, and fatality in patients with COVID-19.[53]

When stratifying impact of comorbidities in different age subgroups (<50 years, 50–69 years, and 70–90 years), Harrison and colleagues showed that in a total of 31,461 patients with COVID-19, history of myocardial infarction or chronic kidney disease was associated with higher risk of mortality for all groups.[54] Instead, significant differences were found across age subgroups for other chronic conditions and their association with mortality. In particular, in subjects aged 70 to 90 years, congestive heart failure and dementia were significantly associated with higher risk of mortality.[54]

Relevant data on impact of comorbidities in older patients with COVID-19 are also derived from studies on skilled nursing facilities where, mainly during the first

outbreak, a rapid virus transmission between residents was reported.[55] In a context of a US nursing facility, during the rapidly escalating COVID-19 outbreak in March 2020, McMichael and colleagues found a death percentage of 33.7% for residents, in respect to 6.2% for visitors and 0% for staff. Residents showed a medium age of 83 years, most of them having one or more comorbidities, such as hypertension (67%), chronic cardiac disease (60%), kidney disease (41%), diabetes (32%).[55]

The postulated mechanisms for a worse prognosis in these comorbid and older patients mainly include the dysregulation of the immune system associated with chronic low-grade inflammation favoring cytokine storm, the prothrombotic state and endothelial dysfunction with consequent increased risk of thromboembolic events, and the dysregulated and widespread angiotensin enzyme 2 (ACE2) activity promoting viral uptake, as better described in the following paragraphs.

Diabetes represents one of the commonest comorbidities, whose prevalence in patients with COVID-19 ranges from 7.3% in China[5] to more than 30% in Europe.[56] Diabetes does not seem to increase the incidence of SARS-CoV-2 infection,[57,58] but it can unfavorably modify the course of the disease, with an increased risk of disease progression, with development of acute respiratory distress syndrome and multiorgan failure and higher mortality rate.[59] Moreover, retrospective studies showed that patients with COVID-19 diabetes had higher levels of inflammatory biomarkers (such as neutrophil-to-lymphocyte ratio, high-sensitivity C-reactive protein, and procalcitonin) when compared with nondiabetes patients.[60–62] Therefore, diabetes has been recognized as an independent risk factor for poor prognosis in patients with COVID-19. However, when stratifying diabetic subjects to identify those at higher risk of death, Schlesinger and colleagues showed in their meta-analysis that older age (>65 years) was significantly associated with higher risk of COVID-19–associated death and with COVID-19 severity.[63] Reasons for higher COVID-19 complications in this subgroup of diabetics were mainly related to glycemic instability and association with preexiting comorbidities, such as hypertension, cardiovascular, and kidney disease, together with the suggested influence of a chronic low-grade inflammation and factors associated with viral entry (such as ACE2 expression).[60–63]

SARCOPENIA AND MALNUTRITION IN COVID-19 INFECTION

A sufficient protein intake and a good nutritional status are required for an optimal antibody production and for the synthesis of acute-phase proteins (C-reactive protein, ferritin, interleukins, TNF-α).[64] Therefore, an inadequate protein intake or vitamin and trace element deficiencies can lead to weakened immune responses. The risk of malnutrition in geriatric patients is increased compared with the general population. “Anorexia of aging” is a disorder characterized by a reduction of food intake and/or loss of appetite in elderly patients, and it is an independent predictor of worse prognosis.[65] Some physiologic age-related factors are involved in the development of anorexia in elderly patients (reduction of smell and taste, changes among hunger and satiety hormones, chronic low-grade inflammation, abnormality in gastric motility), as well as social (eg, poverty, isolation), psychological (eg, depression, dementia), medical (eg, edentulism, dysphagia, malignancy), and pharmacologic factors.[65]

COVID-19 itself can be a cause of malnutrition, due to the infectious involvement of the gastrointestinal tract with consequent malabsorption.[6,64] It can be also responsible for sarcopenia, due to the acute inflammatory response or as a consequence of the treatment with glucocorticoids.[64] Damayanthi and colleagues conducted a systematic review on correlation between nutritional status of older patient and COVID-19 outcome, highlighting that the prevalence of malnutrition in these patients is high and

negatively influences their prognosis.[64] In particular, Recinella and colleagues, in a cross-sectional study on 109 patients, showed that a moderate/severe geriatric nutritional risk index (GNRI) represented a risk factor for in-hospital death, whereas body mass index represented a protective factor.[66] Two other studies found that either albumin levels (by an observational longitudinal study on 114 patients)[67] or prealbumin levels (by a retrospective cohort study on 446 patients)[68] were associated with a higher risk of transfer to intensive care unit (ICU) and all cause of death, ICU admission, and mechanical ventilation, respectively.

Sarcopenia also affects the respiratory and swallowing muscles. A reduction in the respiratory muscle strength hinders effective coughing.[69] Okazaki and colleagues reported that malnutrition, lower body trunk muscle mass, and respiratory muscle weakness represent risk factors for pneumonia in elderly, and malnutrition represents a risk factor for pneumonia relapse.[69]

Considering that underweight has been correlated with a higher probability of hospitalization in adult patients with viral respiratory infections from coronavirus, metapneumovirus, parainfluenza, and rhinovirus[70] and that malnutrition in the elderly can significantly influence regulatory T cells and senescent natural killer cells, increasing the risk of infections, Lidoriki and colleagues speculated about a possible association between malnutrition in elderly people and COVID-19 prognosis.[70] In particular, they suggested that a combination of a respiratory infection severity score such as CURB-65, malnutrition (GNRI), and performance status (The Eastern Cooperative Oncology Group, Barthel) scores could represent a quick and low-cost prognostic tool for COVID-19 in the elderly.[70]

ULTRASTRUCTURAL CHANGES AND COVID-19 INFECTION

Aging is also associated with ultrastructural changes in the respiratory system, including decline in the clearance of inhaled particles at the level of small airways,[71] gradual reduction in the number of cilia and ciliated cells in the airways, impairment in nasal mucociliary clearance with a slower ciliary beat frequency,[72] and increase in nasal cavity with a decrease in nasal resistance.[73] All the aforementioned changes may contribute to the higher prevalence of respiratory infection and COVID-19 in the elderly.

ACE2 receptor represents the human door for SARS-CoV and SARS-CoV-2 entry into cells and plays a pivotal role in the pathogenesis of COVID-19 disease.[74] ACE2 receptor, a transmembrane type I glycoprotein, is not only expressed by nasal epithelium and type II alveolar cells but also in other tissues (myocardium, kidney, urothelial, ileum, colon, esophagus, and oral mucosa cells), thus explaining the systemic presentation of COVID-19 disease.[75] In human physiology, soluble ACE2 cleaves angiotensin II to angiotensin, limiting the detrimental effects of angiotensin II receptor type I receptors, including vasoconstriction, inflammation, and thrombosis.[76,77] After the binding of SARS-CoV-2 to ACE2 receptors, the spike proteins of both SARS- CoV and SARS-CoV-2 by priming a transmembrane serine protease (TMPRSS2) causes the internalization and degradation of ACE2, with downregulation of these receptors.[77,78] By this way, the decrease of ACE2 activity exacerbates the severity of lung injuries and inflammatory pulmonary diseases, mediated by angiotensin II.[78]

Several factors have been shown to affect the expression of ACE2 and consequently cause the shift of ACE/ACE2 balance toward proinflammatory and profibrotic effects mediated by ACE and the ACE-angiotensin II-AT1 receptor axis.[76,77] Aging is one of these factors. Recent evidence suggests that a decrease in the expression of ACE2 with age could lead to exaggerated inflammatory responses and cytokine

storm.[79] Moreover, genomics and transcriptomics studies have shown an age-related reduction in the expression of ACE2 receptors in many tissues.[80]

Interestingly, different chronic diseases associated with COVID-19 infection and typical of older age, such as hypertension, diabetes, and cardiac disease, share a variable degree of ACE2 deficiency.[75–77] In these conditions, the consequent angiotensin II effects may result in exacerbation of hypertension, cardiac hypertrophy, and maladaptive left ventricular remodeling after a myocardial infarction.[75]

Therefore, ACE2 deficiency seems to play a key role in the pathogenesis but also in the prognosis of COVID-19 infection, mainly in those subjects (ie, elderly and with comorbidities) with baseline ACE2 deficiency.

HORMONAL CHANGES

Among the elderly population, men have a higher risk of death from COVID-19 than women.[81] The reasons for this difference are still under investigation. One of the hypotheses concerns the reduced testosterone levels in elderly men and the related consequences on general health and the immune system.[81]

In men, testosterone levels progressively decline from the age of 30 years.[81] In the elderly men, low testosterone levels can be associated with various symptoms, including loss of libido, erectile dysfunction, and loss of muscle mass, among other symptoms, as well as a greater likelihood of both metabolic syndrome and cardiovascular disease. Reduced testosterone levels and the presence of such symptoms is referred to as late-onset hypogonadism[82] and have also been associated with increased frailty[83] and mortality.[84]

In women there is a progressive reduction of testosterone levels between 20 and 40 years,[85,86] whereas between 60 and 80 years they can increase in varying degrees.[86,87] Testosterone levels in older women do not seem to play a significant role in increasing the risk of frailty.[83]

Papadopoulos and colleagues hypothesized that reduced testosterone levels in elderly men could be associated with increased COVID-19 mortality.[81] One of the reasons may be the inhibitory role of testosterone on the immune system, by reducing the expression of inflammatory mediators (eg, IL-6) and promoting antiinflammatory responses. High levels of IL-6 have been linked to the development of the acute respiratory distress syndrome (ARDS) in COVID-19 infections, and elderly male patients showed a higher risk to develop ARDS and death.[81]

It is also possible that SARS-Cov-2 can act directly on testicular function and testosterone levels. It has been shown in fact that Leydig cells express ACE2 and also TMPRSS2, leading testis to represent another potential target of SARS-CoV2.

SUMMARY

In conclusion, increasing age represents an unquestionable risk factor for poor outcomes in COVID-19 infection. Common features of older people, such as increased incidence of comorbidities, dysregulation of immune system, and malnutrition, interplay with ultrastructural changes of aged systems (mainly the respiratory one) in exacerbating inflammatory deleterious pathways triggered by SARS-CoV-2 virus. In this context, ACE2 role is deserving a lot of interest as key mechanism involved in pathogenesis and evolution of disease, although data on the older subgroups are scarce and mostly theoretic. Further and more specific studies should be encouraged to better understand all these mechanisms, in order to achieve targeted approaches and, hopefully, preventive strategies in frail subjects, such as the elderly.

CLINICS CARE POINTS

- Age represents one of the most relevant risk factor for poor outcome in the majority of diseases.
- The terms "immunosenescence" and "inflammaging" are deserving increased attention.
- However, machanisms involved in age-related more severe course of common disease are not fully understood.

CONFLICT OF INTERESTS

All authors declare that they have no conflict of interest.

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