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Review Article

# Aging and Immunity in COVID-19

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## ABSTRACT

The COVID-18 pandemic severely affected people older than 65 years, especially those with age-related comorbidities, causing a disproportionate death burden in this age group. The reasons for this difference from other respiratory virus pandemics have been attributed to the aging-induced changes in the immune system, and their effects on the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia. In this brief review, I summarize some of the recent findings throwing light on the relationship between aging, immunity, and the severity of COVID-19.

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## 1. Introduction

The dramatic appearance of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV2]) associated with a febrile illness rapidly leading to acute respiratory distress syndrome (ARDS) and with a high mortality burden, shook the entire world in the first half of 2020. The definition of a new disease, named COVID-19, quickly was followed by the outbreak of a pandemic. Combined efforts from many groups unveiled the transmission routes of the new virus and its genetic and antigenic constitution. Rapid advances were made for diagnosis, using molecular biology techniques, and several types of vaccines were developed, clinically tested, approved, made available in an amazing record time, by the end of the same year. Looking back to the past 34 months, we realize that this success could not have been achieved at such speed without the worldwide cooperation of scientists and institutions, both in the public and private sectors. However, several aspects of this new infection remain obscure and need further investigation.

### Age and COVID-19

In recent months, several studies have focused on why mortality from COVID-19 is so much higher in aged people compared to young subjects, and why, in symptomatic cases, elderly patients show more severe manifestations. This disproportionate distribution was observed since the reports of the first cases from Wuhan (China) and confirmed in all published series [1-11], giving at first sight, the (false) impression that COVID-19 should be regarded as a disease of the elderly [12-14]. This seemed to represent a different feature from the great influenza pandemic of the previous century and other more recent pandemics [15-18].

Several hypotheses raised at the beginning of the pandemic were soon abandoned, but it took another year before a clearer view of this new pathogen and the disease it caused emerged from thousands of studies, the early ones coming from Chinese scientists [1, 4, 9-11, 19] who had the opportunity to gather information on the first cases, while tight measures of public health adopted there brought the pandemic under control. The debate is still open and ongoing on some aspects, and new issues have emerged, such as the multisystem inflammatory syndrome in children (MIS-C), cardiomyopathy, autoimmunity, and long COVID-19 [20-23]; however, the main points have been ascertained. Remarkably, a very early publication from Italian scientists [24] described many characteristics of the pathogenesis of COVID-19 pneumonia, and the role of dysregulated innate immunity in causing hyper response with the following “cytokine storm”. Other studies, some of which were written by Iranian scientists [13], described disease severity, risk factors, laboratory, and immune parameters altered in the various stages of the disease [7, 8, 10, 12, 25-30], although at first, it was difficult to relate all these and build a general picture of the pathogenesis of COVID-19.

As pointed out in a recent Nature Review [31], age is a major determinant of COVID-19 severity, and represents the single crucial risk factor for mortality. Therefore the view has changed, to the point that COVID-19 is not a disease of the elderly, but being older puts the individuals at risk of worse outcomes [32]. The information provided online by the United States centers for disease control and prevention (accessed on Sept.1, 2022) compares rates of COVID-19-associated hospitalizations and deaths in various age groups with 18–29 years old as a reference group because it has accounted for the largest cumulative number of COVID-19 cases compared to other age groups. Although no difference was observed for the prevalence of infected subjects in all age groups, hospitalization rates doubled for those aged 30 and 49 years, to five times the reference for ages 65-74 years, and 8 or more times for those aged 75 years. The increase was more striking and steeper when considering the death rate from COVID-19 compared to the reference group, the rate was already tenfold in people aged 40-49, rising to 25 times for ages 50-64 and 60 times at age 65-74. This rate soared up to 330 times in subjects aged 85 years and above. According to these figures, it is estimated that 80% of all deaths related to SARS-CoV-2 infection occur in individuals older than 65 years, at least in the United States [32]; the same trend is evident also in Europe and other parts of the world. Therefore older age greatly impacts the severity of symptoms and the mortality of COVID-19. While elderly subjects have a higher prevalence of comorbidities independently associated with increased risk of severe COVID-19, including type 2 diabetes, cardiovascular disease, hypertension, chronic pulmonary or kidney disease, tumors, and other ailments causing frailty [33], chronological age is still the single greatest risk factor for COVID-19 mortality [31, 32].

### Immunity and COVID-19

The intricate relationship between an infectious agent and the immune response shows that a delicate balance is needed to overcome aggression and avoid tissue and organ damage. In immunocompromised subjects, the pathogen has an advantage, but many organisms, particularly viruses, have developed sophisticated ways to

disable the defenses also in immunocompetent hosts and evade the immunological counterattack. This seems to be the case for SARS-CoV2, which blocks the early innate immune response, centered on type I and III Interferons, giving time to the virus for massive replication, which in turn it elicits a hyper-reaction with excess inflammation and lung damage, with systemic involvement and dysregulated immunity. In a paper in the second half of 2020, Anka et al. [34] pointed out the similarity with previous coronavirus and wrote "in SARS-CoV and Middle East respiratory syndrome–related coronavirus (MERS-CoV) infection, delayed release of interferons (IFNs) hampers the body's antiviral response in the initial phases of infection", giving way to the higher response later, with the result "type I interferon continuous activation of infiltrating monocytes and monocyte-derived macrophages, oxidative stress, anti-spike protein immunoglobulin G (IgG) immune complexes, and NOD-like receptor pyrin domain containing (NLRP)3 inflammasome activation could explain the pathophysiology of COVID-19 as it does for SARS and MERS". The importance of the delayed IFN response in the early stage of infection has recently been underlined by Sapir et al. [35], who clarify three distinct phases of infection by SARS-CoV2, and also pinpoint the role of the complement system, another key component of the innate immune response, in the hyperinflammatory later stage. They write "this pathway is especially seen in the second week after disease onset, following the decline in IFN seen in the earliest phase of the disease. Regulation of the IFN system is then of great importance to COVID-19 outcomes, underactivation in the early stages, SARS-CoV-2 enters the body undetected, while overactivation in later stages results in serious damage to the host". That is why even fatality cases show signs of a robust immune response to the virus, as well as organ and non-organ-specific autoimmunity.

### Immunosenescence

This is a scenario well known to immunologists in geroscience, who describe immunosenescence as the result of both an inflammatory milieu and an out-of-control immunity [7, 8, 12, 25, 27, 30, 31, 36-42]. The accumulation of senescent cells and the decrease of naïve T lymphocytes lead to the shrinkage of the repertoire and the loss of regulatory signals, with both innate and adaptive immunity skewed toward an inflammatory pattern. In COVID-19, lymphopenia is present in severe cases, and this has been explained as part of the PANoptosis sparked by hyperactivation and inflammation [31]. Recently, the infection of CD4+T cells by the SARS-CoV2 virus has been observed, mediated by non-spike dependent mechanisms, leading to selective depletion of T lymphocytes with subsequent lymphopenia [32, 43]. Among immune cells, the progressive accumulation of exhausted T lymphocytes exists, with impaired regulatory function, promoting the skewing of monocytes towards an inflamed phenotype [12, 36, 38, 39, 41, 42, 44, 45]. This month, the role of a calcium-binding protein secreted by adipocytes in the extracellular matrix, called SPARC, has been revealed in causing features of aging, by inducing tissue macrophages to promote the inflammatory state characteristic of older people [46, 47]. The presence of inflammatory aged or senescent cells with a senescence-associated secretory phenotype (SASP), accumulated through life and persisting, is conspicuous in aging, and they display an abnormal secretory phenotype characterized by the production of cytokines, chemokines, growth factors, matrix metalloproteinases, fibronectin and reactive oxygen species [39, 41, 45]. Senescent cells have a paracrine pro-thrombotic effect, which together with the procoagulant activity of pro-inflammatory cytokines, may explain other aspects of severe COVID-19 and its worse outcomes in aged subjects [8, 12, 26, 36, 37, 48].

Several studies [7, 8, 10, 12, 25, 27, 30, 32, 34-36, 38, 39, 41, 44, 48-52] have highlighted other mechanisms linking immune system aging (immunosenescence) to COVID-19 severity, including e.g. natural killer (NK) cells lower functionality, CD8+T cell dysfunction and B lymphocyte hyporeactivity, which I shall not reiterate here. The mechanism of lymphocyte aging includes multiple changes in the signal transduction from the relevant antigen receptors to the genes involved in different aspects of the immune response, so the discussion would be long and complicated.

## 2. Conclusion

Aging is both a chronological as well as a functional phenomenon. Certain aspects of aging may begin early in life, but at a different rate in different organs and different individuals. Studies on longevity have dissected both genetic and environmental determinants of aging.

The aging of the immune system is a multifaceted process that is thought to be the leading cause of organ and individual aging. Confrontation with the exome shapes immunological responses and our immune repertoire throughout life. Among external cues, infectious agents (especially viral ones) and local microbiota have emerged as major factors affecting both our responses and tissue inflammation. Since low-level inflammatory milieu has been proposed to underlie immunosenescence (inflam m-aging), this mechanism predisposes elderly subjects

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infected with SARS-CoV2 to a more severe course and possibly the development of acute respiratory distress syndrome (ARDS) and death. However, chronological and immune aging does not always overlap, since many factors may contribute to immune aging in an individual including genetics, environmental factors, diet, health behaviors, psycho-affective attitude, and allostatic load, and we still need specific biomarkers to measure their total contribution to immunosenescence.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Conflict of interest

The author declared no conflict of interest.

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## References

[1] Tian R, Wu W, Wang C, Pang H, Zhang Z, Xu H, et al. Clinical characteristics and survival analysis in critical and non-critical patients with COVID-19 in Wuhan, China: A single-center retrospective case control study. Sci Rep. 2020; 10(1):17524. [DOI:10.1038/s41598-020-74465-3] [PMID] [PMCID]

[2] Azwar MK, Setiati S, Rizka A, Fitriana I, Saldi SRF, Safitri ED. Clinical Profile of Elderly Patients with COVID-19 hospitalised in Indonesia's National General Hospital. Acta Med Indones. 2020; 52(3):199-205. [PMID]

[3] Chen T, Dai Z, Mo P, Li X, Ma Z, Song S, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (covid-19) in Wuhan, China: A single-centered, retrospective study. J Gerontol A Biol Sci Med Sci. 2020; 75(9):1788-95. [DOI:10.1093/gerona/glaa089] [PMID] [PMCID]

[4] Gao S, Jiang F, Jin W, Shi Y, Yang L, Xia Y, et al. Risk factors influencing the prognosis of elderly patients infected with COVID-19: A clinical retrospective study in Wuhan, China. Aging (Albany NY). 2020; 12(13):12504-16. [DOI:10.18632/aging.103631] [PMID] [PMCID]

[5] Huang X, Wei F, Hu L, Wen L, Chen K. Epidemiology and Clinical Characteristics of COVID-19. Arch Iran Med. 2020; 23(4):268-71. [DOI:10.34172/aim.2020.09] [PMID]

[6] Kadambari S, Klenerman P, Pollard AJ. Why the elderly appear to be more severely affected by COVID-19: The potential role of immunosenescence and CMV. Rev Med Virol. 2020; 30(5):e2144. [DOI:10.1002/rmv.2144] [PMCID]

[7] Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: Insights into pathogenesis and clinical decision-making. Aging Clin Exp Res. 2020; 32(8):1599-608. [DOI:10.1007/s40520-020-01631-y] [PMID] [PMCID]

[8] Promislow DEL. A geroscience perspective on covid-19 mortality. J Gerontol A Biol Sci Med Sci. 2020; 75(9):e30-3. [DOI:10.1093/gerona/glaa094] [PMID] [PMCID]

[9] Wei C, Liu Y, Liu Y, Zhang K, Su D, Zhong M, et al. Clinical characteristics and manifestations in older patients with COVID-19. BMC Geriatr. 2020; 20(1):395. [DOI:10.1186/s12877-020-01811-5] [PMID] [PMCID]

[10] He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. J Clin Virol. 2020; 127:104361. [DOI:10.1016/j.jcv.2020.104361] [PMID] [PMCID]

[11] Kong FZ, Wang Y, Wang MX, Cheng QZ, Logan R, Wu GH, et al. Clinical characteristics of the first known cases of death caused by COVID-19 pneumonia. Aging (Albany NY). 2020; 12(22):22405-12. [DOI:10.18632/aging.104171] [PMID] [PMCID]

[12] Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, immunity, and covID-19: How age influences the host immune response to coronavirus infections? Front Physiol. 2020; 11:571416. [DOI:10.3389/fphys.2020.571416] [PMID] [PMCID]

[13] Mirbeyk M, Saghazadeh A, Rezaei N. Geriatrics and COVID-19. Adv Exp Med Biol. 2021; 1318:209-22. [DOI:10.1007/978-3-030-63761-3_13] [PMID]

[14] Akbarzadeh MA, Hosseini MS. Is COVID-19 really a geriatric syndrome? Ageing Res Rev. 2022; 79:101657. [DOI:10.1016/j.arr.2022.101657] [PMID] [PMCID]

[15] Yang J, Chen X, Deng X, Chen Z, Gong H, Yan H, et al. Disease burden and clinical severity of the first pandemic wave of COVID-19 in Wuhan, China. Nat Commun. 2020; 11(1):5411. [DOI:10.1038/s41467-020-19238-2] [PMID] [PMCID]

[16] Wu Z, Harrich D, Li Z, Hu D, Li D. The unique features of SARS-CoV-2 transmission: Comparison with SARS-CoV, MERS-CoV and 2009 H1N1 pandemic influenza virus. Rev Med Virol. 2021; 31(2):e2171. [DOI:10.1002/rmv.2171] [PMCID]

[17] Sooksawasdi Na Ayudhya S, Kuiken T. Reverse Zoonosis of COVID-19: Lessons from the 2009 influenza pandemic. Vet Pathol. 2021; 58(2):234-42. [DOI:10.1177/0300985820979843] [PMID] [PMCID]

[18] Cozza A, Maggioni G, Thiene G, Bonati MR. The 1918 Influenza pandemic versus covid-19: A historical perspective from an Italian point of view. Am J Public Health. 2021; 111(10):1815-23. [DOI:10.2105/AJPH.2021.306412] [PMID]

[19] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020; 395(10229):1054-62. [DOI:10.1016/S0140-6736(20)30566-3] [PMID]

[20] Callard F, Perego E. How and why patients made Long Covid. Soc Sci Med. 2021; 268:113426. [DOI:10.1016/j.socscimed.2020.113426] [PMID] [PMCID]

[21] Hoffer EP. Long coviD: Does it exist? What is it? We can we do for sufferers? Am J Med. 2021; 134(11):1310-1. [DOI:10.1016/j.amjmed.2021.05.023] [PMID] [PMCID]

[22] Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021; 27(4):626-31. [DOI:10.1038/s41591-021-01292-y] [PMID] [PMCID]

[23] Munblit D, O'Hara ME, Akrami A, Perego E, Olliaro P, Needham DM. Long COVID: Aiming for a consensus. Lancet Respir Med. 2022; 10(7):632-4. [DOI:10.1016/S2213-2600(22)00135-7] [PMID]

[24] Matricardi PM, Dal Negro RW, Nisini R. The first, holistic immunological model of COVID-19: Implications for prevention, diagnosis, and public health measures. Pediatr Allergy Immunol. 2020; 31(5):454-70. [DOI:10.1111/pai.13271] [PMID] [PMCID]

[25] Akbar AN, Gilroy DW. Aging immunity may exacerbate COVID-19. Science. 2020; 369(6501):256-7. [DOI:10.1126/science.abb0762] [PMID]

[26] Bencivenga L, Rengo G, Varricchi G. Elderly at time of COronaVIrus disease 2019 (COVID-19): Possible role of immunosenescence and malnutrition. Geroscience. 2020; 42(4):1089-92. [DOI:10.1007/s11357-020-00218-9] [PMID] [PMCID]

[27] Cunha LL, Perazzio SF, Azzi J, Cravedi P, Riella LV. Remodeling of the Immune Response With Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. Front Immunol. 2020; 11:1748. [DOI:10.3389/fimmu.2020.01748] [PMID] [PMCID]

[28] Jurado A, Martin MC, Abad-Molina C, Orduna A, Martinez A, Ocana E, et al. COVID-19: Age, Interleukin-6, C-reactive protein, and lymphocytes as key clues from a multicentre retrospective study. Immun Ageing. 2020; 17:22. [DOI:10.1186/s12979-020-00194-w] [PMID] [PMCID]

[29] Salimi S, Hamlyn JM. COVID-19 and crosstalk with the hallmarks of aging. J Gerontol A Biol Sci Med Sci. 2020; 75(9):e34-41. [DOI:10.1093/gerona/glaa149] [PMID] [PMCID]

[30] Vellas C, Delobel P, de Souto Barreto P, Izopet J. COVID-19, virology and geroscience: A perspective. J Nutr Health Aging. 2020; 24(7):685-91. [DOI:10.1007/s12603-020-1416-2] [PMID] [PMCID]

[31] Bartleson JM, Radenkovic D, Covarrubias AJ, Furman D, Winer DA, Verdin E. SARS-CoV-2, COVID-19 and the ageing immune system. Nat Aging. 2021; 1(9):769-82. [DOI:10.1038/s43587-021-00114-7] [PMID] [PMCID]

[32] Witkowski JM, Fulop T, Bryl E. Immunosenescence and COVID-19. Mech Ageing Dev. 2022; 204:111672. [DOI:10.1016/j.mad.2022.111672] [PMID] [PMCID]

[33] Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, Covic A. Different aspects of frailty and COVID-19: Points to consider in the current pandemic and future ones. BMC Geriatr. 2021; 21(1):389. [DOI:10.1186/s12877-021-02316-5] [PMID] [PMCID]

[34] Anka AU, Tahir MI, Abubakar SD, Alsabbagh M, Zian Z, Hamedifar H, et al. Coronavirus disease 2019 (COVID-19): An overview of the immunopathology, serological diagnosis and management. Scand J Immunol. 2021; 93(4):e12998. [DOI:10.1111/sji.12998] [PMCID]

[35] Sapir T, Averch Z, Lerman B, Bodzin A, Fishman Y, Maitra R. COVID-19 and the immune response: A multi-phasic approach to the treatment of covid-19. Int J Mol Sci. 2022; 23(15):8606. [DOI:10.3390/ijms23158606] [PMID] [PMCID]

[36] Banic M, Plesko S, Urek M, Babic Z, Kardum D. Immunosenescence, inflammaging and resilience: An evolutionary perspective of adaptation in the light of covid-19 pandemic. Psychiatr Danub. 2021; 33(Suppl 4):427-31. [PMID]

[37] Chen Y, Klein SL, Garibaldi BT, Li H, Wu C, Osevala NM, et al. Aging in COVID-19: Vulnerability, immunity and intervention. Ageing Res Rev. 2021; 65:101205. [DOI:10.1016/j.arr.2020.101205] [PMID] [PMCID]

[38] Kohli J, Veenstra I, Demaria M. The struggle of a good friend getting old: Cellular senescence in viral responses and therapy. EMBO Rep. 2021; 22(4):e52243. [DOI:10.15252/embr.202052243] [PMID] [PMCID]

[39] Muller L, Di Benedetto S. How immunosenescence and inflammaging may contribute to hyperinflammatory syndrome in covid-19. Int J Mol Sci. 2021; 22(22):12539. [DOI:10.3390/ijms222212539] [PMID] [PMCID]

[40] Witkowski JM. Immune system aging and the aging-related diseases in the COVID-19 era. Immunol Lett. 2022; 243:19-27. [DOI:10.1016/j.imlet.2022.01.005] [PMID] [PMCID]

[41] Evangelou K, Veroutis D, Paschalaki K, Foukas PG, Lagopati N, Dimitriou M, et al. Pulmonary infection by SARS-CoV-2 induces senescence accompanied by an inflammatory phenotype in severe COVID-19: Possible implications for viral mutagenesis. Eur Respir J. 2022; 60(2):2102951. [DOI:10.1183/13993003.02951-2021] [PMID] [PMCID]

[42] Nehme J, Borghesan M, Mackedenski S, Bird TG, Demaria M. Cellular senescence as a potential mediator of COVID-19 severity in the elderly. Aging Cell. 2020; 19(10):e13237. [DOI:10.1111/acel.13237] [PMID] [PMCID]

[43] Shen XR, Geng R, Li Q, Chen Y, Li SF, Wang Q, et al. ACE2-independent infection of T lymphocytes by SARS-CoV-2. Signal Transduct Target Ther. 2022; 7(1):83. [DOI:10.1038/s41392-022-00919-x] [PMID] [PMCID]

[44] Farheen S, Agrawal S, Zubair S, Agrawal A, Jamal F, Altaf I, et al. Patho-physiology of aging and immune-senescence: Possible correlates with comorbidity and mortality in middle-aged and old covid-19 patients. Front Aging. 2021; 2:748591. [DOI:10.3389/fragi.2021.748591] [PMID] [PMCID]

[45] Sabbatinelli J, Matacchione G, Giuliani A, Ramini D, Rippo MR, Procopio AD, et al. Circulating biomarkers of inflammaging as potential predictors of COVID-19 severe outcomes. Mech Ageing Dev. 2022; 204:111667. [DOI:10.1016/j.mad.2022.111667] [PMID] [PMCID]

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Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

[46] Maltzman JS. A SPARC-ling link to inflammaging. Sci Immunol. 2022; 7(75):eade5698. [DOI:10.1126/sciimmunol.ade5698] [PMID]

[47] Ryu S, Sidorov S, Ravussin E, Artyomov M, Iwasaki A, Wang A, et al. The matricellular protein SPARC induces inflammatory interferon-response in macrophages during aging. Immunity. 2022; 55(9):1609-26.e7. [DOI:10.1016/j.immuni.2022.07.007] [PMID]

[48] Gallo A, Pero E, Pellegrino S, Macerola N, Murace CA, Ibba F, et al. How can biology of aging explain the severity of covid-19 in older adults. Clin Geriatr Med. 2022; 38(3):461-72. [DOI:10.1016/j.cger.2022.04.002] [PMID] [PMCID]

[49] Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of immune response during sars-cov-2 infection: Lessons from the past. Front Immunol. 2020; 11:1949. [DOI:10.3389/fimmu.2020.01949] [PMID] [PMCID]

[50] Jergovic M, Coplen CP, Uhrlaub JL, Nikolich-Zugich J. Immune response to COVID-19 in older adults. J Heart Lung Transplant. 2021; 40(10):1082-9. [DOI:10.1016/j.healun.2021.04.017] [PMID] [PMCID]

[51] Ten-Caten F, Gonzalez-Dias P, Castro I, Ogava RLT, Giddaluru J, Silva JCS, et al. In-depth analysis of laboratory parameters reveals the interplay between sex, age, and systemic inflammation in individuals with COVID-19. Int J Infect Dis. 2021; 105:579-87. [DOI:10.1016/j.ijid.2021.03.016] [PMID] [PMCID]

[52] Zazzara MB, Bellieni A, Calvani R, Coelho-Junior HJ, Picca A, Marzetti E. Inflammaging at the time of covid-19. Clin Geriatr Med. 2022; 38(3):473-81. [DOI:10.1016/j.cger.2022.03.003] [PMID] [PMCID]