



Is COVID-19 really a geriatric syndrome?

Mohammad Amin Akbarzadeh^{a, b, c}, Mohammad-Salar Hosseini^{b, c, d, *}

^a Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

^b Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

^c Iranian Evidence-Based Medicine (EBM) Centre, Joanna Briggs Institute Affiliated Group, Tabriz, Iran

^d Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Keywords:

COVID-19
Geriatric syndrome
Immunosenescence
Older adults
Vaccination

ABSTRACT

Geriatric syndromes are a group of medical conditions, such as cognitive impairment, delirium, frailty, dizziness, syncope, and incontinence, associated with age increase. Many studies have reported a higher mortality rate for older COVID-19 patients, which could be explained by the complications of COVID-19, including the components of geriatric syndromes. We read with great interest the paper “Prevalence of unwillingness and uncertainty to vaccinate against COVID-19 in older people: A systematic review and meta-analysis” by Nicola Veronese et al. Their valuable work determines how uncertainty and unwillingness towards receiving the COVID-19 vaccine are more prevalent among older adults and how this hesitancy could affect vaccine uptake, and ultimately, the mortality rate. Regarding this paper, we wish to address some points.

Dear Editor,

We read with great interest the paper “Prevalence of unwillingness and uncertainty to vaccinate against COVID-19 in older people: A systematic review and meta-analysis” by Nicola Veronese et al. (2021). Their valuable work determines how uncertainty and unwillingness towards receiving the COVID-19 vaccine are more prevalent among older adults and how this hesitancy could affect vaccine uptake. Regarding this paper, we wish to address some points.

First, the authors have described COVID-19 as a geriatric syndrome, both in the manuscript (“It could be hypothesized that COVID-19 is a geriatric syndrome since epidemiological data have clearly indicated that the mortality rates are extremely high in older persons and that the prevalence of COVID-19 is more elevated in older compared to younger persons. Moreover, in settings dedicated to the older people, such as nursing homes, the highest mortality rate has been observed”), and among the highlights (“COVID-19 is considered a geriatric syndrome people”). However, according to the definition, COVID-19 cannot be considered a geriatric syndrome.

Geriatric syndromes (GSs) refer to a group of medical conditions primarily associated with increased age (Inouye et al., 2007). Although a definite age range has not been established for this term, most studies

consider the age over 65 for definition (Sanford et al., 2020). The primary conditions are cognitive impairment, delirium, falls, frailty, dizziness, syncope, and urinary incontinence — although due to poor definition of the term, other age-related conditions can also be considered (Díaz et al., 2020; Inouye et al., 2007). In simpler words, GSs are health-related conditions associated with the increase in age, as a risk factor of occurrence.

Although studies have reported a higher COVID-19 mortality rate for groups of older adults (Docherty et al., 2020), COVID-19 cannot be considered a GS. Age is considered a risk factor for case fatality, and the aged population is at an increased risk of severe COVID-19 disease (Arahamian and Cesari, 2020). In better words, almost all of the GSs become inevitable by age, while COVID-19 infection is an external factor – regardless of age – which might affect older adults or not. The key point is that older adults possibly have more unfavorable results due to the delay in diagnosis, weakened immune system, neglect and lack of attention, underlying conditions and comorbidities, and concurrent GSs (Arahamian and Cesari, 2020; Kuper and Shakespeare, 2021; Mueller et al., 2020; Wanhella and Fernandez-Patron, 2022). As a matter of fact, COVID-19 infection is not a component of GSs; nevertheless, the GSs could contribute as risk factors for severe COVID-19 and/or post-COVID

Abbreviations: ARDS, Acute respiratory distress syndrome; COVID-19, Coronavirus disease 2019; CRS, Cytokine release syndrome; GS, Geriatric syndrome; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

* Correspondence to: Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Golgasht Street, Tabriz, Postal code 5166/15731, EA, Iran.

E-mail addresses: hosseini.msalar@gmail.com, hoseinim@tbzmed.ac.ir (M.-S. Hosseini).

<https://doi.org/10.1016/j.arr.2022.101657>

Received 31 March 2022; Received in revised form 23 April 2022; Accepted 27 May 2022

Available online 29 May 2022

1568-1637/© 2022 Elsevier B.V. All rights reserved.

complications, not the occurrence of the disease. In more details, the emerging evidence has highlighted possible correlations between the two phenomena. Almost all body systems go through significant changes through aging (Oh et al., 2019), consequent of various immunologic, genetic, and lifestyle factors, including:

- Inability to regulate the pro- and anti-inflammatory settings: Inflammaging is the chronic activation of the innate system and accumulation of inflammatory markers, such as interleukins, due to the persistent tendency of cells to secrete pro-inflammatory agents (Franceschi et al., 2018). This phenomenon can gravely affect the prognosis of the aged patients affected by SARS-CoV-2 (Padilha de Lima et al., 2022).
- Weak immune responses: Immunosenescence – the decline in the immune system’s efficiency secondary to aging – makes the immune system more susceptible to malignancies, autoimmune diseases, and, prominently, infections (Bartleson et al., 2021). The remodeling of different immune system parts could contribute to worse outcomes of the COVID-19 infection (Bajaj et al., 2020).
- Delay in identifying viral pathogens: This delay worsens the patients’ prognosis by leading to critical conditions such as acute respiratory distress syndrome (ARDS) (Bhatnagar et al., 2021; Liu et al., 2019).
- Altered production of defensive barriers: Lack of mucins and glycoproteins contributes to an unchallenging entrance of viral pathogens (Chatterjee et al., 2021; Xu et al., 2019).
- Intrathymic infiltration of adipose tissue: By affecting the production of T cells and memory lymphocytes, this could result in a compromised function of the adaptive immune system against SARS-CoV-2 (Ongrádi and Kövesdi, 2010).
- Hypercoagulable state: The available molecular data support that the increase in cytokine production and activation of cytokine release pathways results in a hypercoagulable state, resulting in coagulopathy and significant end-organ damage and failure (Mueller et al., 2020). The current molecular data suggest that the older people, male patients, and the Caucasian and African-American ethnicities might be more susceptible to hypercoagulability (Abou-Ismael et al., 2020; Fogarty et al., 2020). Aging, epigenetic dysregulation, and immune defects are cited as the underlying roots of the increase in cytokine release syndrome (CRS) and the consequent COVID-19 fatality (Mueller et al., 2020).

Second, it is stated in the manuscript that “This systematic review adhered to the PRISMA statement and followed a pre-planned, but unpublished protocol that can be requested by contacting the corresponding author.” However, as PRISMA states, systematic reviews should be registered at inception (i.e., at the protocol stage) to help avoid unplanned duplication and enable the comparison of reported review methods with what was planned in the protocol. Moreover, “a review protocol should be a public document in order to facilitate future purposeful replications or updates of the review and to help future users evaluate whether selective reporting and potential bias were present in the review process” (Page et al., 2021a, 2021b). Therefore, a systematic review protocol should be registered/published in advance and made publicly available to prevent accidental duplications and parallel projects.

Third, this study lacks the risk of bias assessment. According to the PRISMA statement and checklist, authors should “specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process” (Item #11). Please note that this stage of study is apart from the assessment of the reporting bias (Item #14). As a result, Item #18 (presentation of risk of bias assessment in each of the included studies) has also been neglected.

We applaud the authors for their novel and insightful work. However, scientific accuracy and transparency should not be sacrificed, even

at the time of facing a public health crisis.

Funding

None.

CRediT authorship contribution statement

MAA: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. MSH: Conceptualization, Data curation, Writing - original draft, Writing - review & editing.

Declarations of interest

None.

References

- Abou-Ismael, M.Y., Diamond, A., Kapoor, S., Arafah, Y., Nayak, L., 2020. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb. Res.* 194, 101–115.
- Aprahamian, I., Cesari, M., 2020. Geriatric syndromes and SARS-Cov-2: more than just being old. *J. Frailty Aging* 9, 127–129.
- Bajaj, V., Gadi, N., Spihlman, A.P., Wu, S.C., Choi, C.H., Moulton, V.R., 2020. Aging, immunity, and COVID-19: how age influences the host immune response to coronavirus infections. *Front. Physiol.* 11, 571416.
- Bartleson, J.M., Radenkovic, D., Covarrubias, A.J., Furman, D., Winer, D.A., Verdin, E., 2021. SARS-CoV-2, COVID-19 and the ageing immune system. *Nat. Aging* 1, 769–782.
- Bhatnagar, J., Gary, J., Reagan-Steiner, S., Estetter, L.B., Tong, S., Tao, Y., Denison, A.M., Lee, E., DeLeon-Carnes, M., Li, Y., Uehara, A., Paden, C.R., Leitgeb, B., Ueyeki, T.M., Martines, R.B., Ritter, J.M., Paddock, C.D., Shieh, W.J., Zaki, S.R., 2021. Evidence of severe acute respiratory syndrome coronavirus 2 replication and tropism in the lungs, airways, and vascular endothelium of patients with fatal coronavirus disease 2019: an autopsy case series. *J. Infect. Dis.* 223, 752–764.
- Chatterjee, S.K., Saha, S., Munoz, M.N.M., 2021. Activation of mucosal immunity and novel prophylactic and therapeutic strategy in combating COVID-19. *Explor. Immunol.* 1, 374–397.
- Díaz, L.B., Casuso-Holgado, M.J., Labajos-Manzanares, M.T., Barón-López, F.J., Pinero-Pinto, E., Romero-Galisteo, R.P., Moreno-Morales, N., 2020. Analysis of fall risk factors in an aging population living in long-term care institutions in Spain: a retrospective cohort study. *Int. J. Environ. Res. Public Health* 17, 7234.
- Docherty, A.B., Harrison, E.M., Green, C.A., Hardwick, H.E., Pius, R., Norman, L., Holden, K.A., Read, J.M., Dondelinger, F., Carson, G., 2020. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *bmj* 369.
- Fogarty, H., Townsend, L., Ni Cheallaigh, C., Bergin, C., Martin-Loeches, I., Browne, P., Bacon, C.L., Gaule, R., Gillett, A., Byrne, M., Ryan, K., O’Connell, N., O’Sullivan, J. M., Conlon, N., O’Donnell, J.S., 2020. COVID19 coagulopathy in Caucasian patients. *Br. J. Haematol.* 189, 1044–1049.
- Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* 14, 576–590.
- Inouye, S.K., Studenski, S., Tinetti, M.E., Kuchel, G.A., 2007. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J. Am. Geriatr. Soc.* 55, 780–791 (See Editorial Comments by Dr. William Hazzard on pp 794–796).
- Kuper, H., Shakespeare, T., 2021. Are older people with disabilities neglected in the COVID-19 pandemic? *Lancet Public Health* 6, e347–e348.
- Liu, L., Wei, Q., Lin, Q., Fang, J., Wang, H., Kwok, H., Tang, H., Nishiura, K., Peng, J., Tan, Z., Wu, T., Cheung, K.W., Chan, K.H., Alvarez, X., Qin, C., Lackner, A., Perlman, S., Yuen, K.Y., Chen, Z., 2019. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 4.
- Mueller, A.L., McNamara, M.S., Sinclair, D.A., 2020. Why does COVID-19 disproportionately affect older people? *Aging* 12, 9959.
- Oh, S.J., Lee, J.K., Shin, O.S., 2019. Aging and the immune system: the impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. *Immune Netw.* 19, e37.
- Ongrádi, J., Kövesdi, V., 2010. Factors that may impact on immunosenescence: an appraisal. *Immun. Ageing* 1 A 7, 7.
- Padilha de Lima, A., Macedo Rogero, M., Araujo Viel, T., Garay-Malpartida, H.M., Aprahamian, I., Lima Ribeiro, S.M., 2022. Interplay between inflammaging, frailty and nutrition in covid-19: preventive and adjuvant treatment perspectives. *J. Nutr., Health Aging* 26, 67–76.
- Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021a. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71.

- Page, M.J., Moher, D., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., McKenzie, J.E., 2021b. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 372, n160.
- Sanford, A.M., Morley, J.E., Berg-Weger, M., Lundy, J., Little, M.O., Leonard, K., Malmstrom, T.K., 2020. High prevalence of geriatric syndromes in older adults. *PLoS One* 15, e0233857.
- Veronese, N., Saccaro, C., Demurtas, J., Smith, L., Dominguez, L.J., Maggi, S., Barbagallo, M., 2021. Prevalence of unwillingness and uncertainty to vaccinate against COVID-19 in older people: a systematic review and meta-analysis. *Ageing Res. Rev.* 72, 101489.
- Wanhella, K.J., Fernandez-Patron, C., 2022. Biomarkers of ageing and frailty may predict COVID-19 severity. *Ageing Res. Rev.* 73, 101513.
- Xu, F., Laguna, L., Sarkar, A., 2019. Aging-related changes in quantity and quality of saliva: where do we stand in our understanding? *J. Texture Stud.* 50, 27–35.