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Letter to the editor

Response to: Letter to the Editor on "Bonafè M, Prattichizzo F, Giuliani A, Storci G, Sabbatinelli J, Olivieri F. Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev" by Eugenia Quiros-Roldan, Giorgio Biasiotto and Isabella Zanella

Dear Editor,

we read with vivid interest the commentary by Quiros-Roldan and colleagues [1], which suggests that the framework we proposed to explain the high rate of mortality of Coronavirus Disease 19 (COVID-19) in elderly and age-related disease (ARD)-affected populations [2] might not apply to HIV-infected patients, despite the pervasive role of inflamm-aging and immune-senescence in this setting of patients.

Preliminary data on an Italian cohort suggest that only a minor portion of HIV-positive patients with probable SARS-CoV-2 infection died, which yields a low case-fatality rate if compared to other high-risk populations [3]. Similarly, data on a large Chinese cohort and another case series both reported a low incidence and a mild severity of SARS-CoV-2 infection in HIV-infected patients [4,5]. Nevertheless, another patient cohort in Spain conveyed a rate of infection in HIV-positive individuals similar or slightly higher (but lower when including suspected cases) compared to the general population [6]. In this study, overall mortality was lower than that reported in the general population, but double in the age range from 50 to 59 years, with a higher age-adjusted mortality. Of note, the mean age of all the four HIV-positive cohorts was lower compared to other reports showing data of SARS-CoV-2 infection in the general population [7]. Finally, the prevalence of patients with a more severe form of COVID-19 was higher in HIV-positive subjects compared to the general population [6].

Accumulating data suggest that the COVID-19 cases suffering the worst outcome are those with reduced count and functional exhaustion of T lymphocytes, as well as those affected by the cytokine release syndrome, i.e. the cytokine storm [8]. Notably, the majority of HIV-positive patients enrolled in the four abovementioned studies had next-to-normal CD4 cell counts, while one of the studies showed that those with low recent CD4 cell counts suffered from increased disease severity than individuals with proper immunity [6]. In addition, also viral load was well controlled in the majority of tested patients (as it is observed in clinical practice), suggesting that the eventual pro-inflammatory drift promoted by HIV might be limited. Of note, no data regarding markers of T cell exhaustion were reported in any of studies conducted thus far, while only one reported circulating levels of interleukin-6 (IL-6) [6]. On the basis of the literature above, we posit that testing for T-cell senescence markers (e.g. PD-1, Tim-3, CTLA-4, and TIGIT) [9] and measuring major inflammatory markers in patients co-infected with SARS-CoV-2 and HIV is mandatory to disentangle the relevance of immune senescence and inflamm-aging in the COVID-19 outcome in this specific population. Nevertheless, a protective role of multiple anti-retroviral drugs cannot be excluded at this stage. Indeed, while preliminary findings suggest a lack of activity of tenofovir or protease inhibitors on SARS-CoV-2 viral lifecycle [3–6], the low number of patients studied so far bars prevents any exhaustive analysis. In regard to this issue, preliminary data from a non-randomized clinical trial suggest a non-significant decrease in mortality in COVID-19 patients treated with the protease inhibitor Lopinavir/Ritonavir [10]. Finally, the peculiar immune make-up of HIV-positive patients is worth to be carefully considered. Indeed, HIV patients have a complex remodelling in interferon (IFN) responses, with an early increase in IFN-α and a delayed, systemic rise of IFN-γ [11]. In turn, these two mediators have been suggested to halt (with a variable degree of success) the infection or the replication of SARS-CoV, the virus responsible for the previous outbreaks of SARS [12–14]. To this respect, it would be interesting to explore if patients with diseases characterized by high levels of type I IFNs, e.g. systemic lupus erythematosus, or treated with recombinant type I IFNs are protected to some extent from SARS-CoV-2 infection. Of note, interferon-α2b improves outcome in rhesus macaques infected with MERS-CoV, another member of the coronavirus family [15]. More recently, it was reported that the detrimental hyper-inflammatory response to SARS-CoV-2 infection is tightly coupled with an impaired capability to trigger type I IFNs [16]. A randomized controlled trial evaluating the efficacy of a triple antiviral therapy with combined interferon beta-1b, ribavirin, and lopinavir-ritonavir on COVID-19 patients proved the superiority of the triple antiviral therapy compared to lopinavir-ritonavir alone in terms of improved clinical recovery and faster rate of viral clearance, with a striking suppression of IL-6 levels in the interferon arm of the study after 48 h of treatment [17]. Similarly, the results of an on-going trial testing the safety and the efficacy of interferon-α2b in patients with COVID-19 may help to clarify the potential beneficial effects of type I interferon on COVID-19 (Clinicaltrials.gov, NCT04293887). In this regard, it is worth remembering that Type I IFNs not only exert anti-viral activity, but inhibit the activation of the inflammatory response, thus preventing destructive local phenomena and systemic life-threatening outcomes [16,18]. Another, alternative hypothesis is that a "mild" state of immunosuppression (but with no overt signs of inflamm-aging) may eventually be helpful to limit the SARS-CoV-2 induced damage, a framework that is currently being explored [19].

More broadly, the development of a signature properly summarizing the inflamm-aging/immune senescence status is being demonstrated hard to develop, given the emerging complexity and heterogeneity of the aging process and in particular of the two abovementioned components [20]. On the other side, this appears the best approach at present to predict which patients will most likely suffer of SARS-CoV-2 consequences, given that aging-related characteristics (*e.g.* age and obesity) or

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surrogate markers of aging (IL-6, lymphocyte count) represent the best tools to foresee mortality in this setting [21–23].

Overall, the interesting observations provided by Quiros-Roldan and colleagues support the notion that much research is needed to better disentangle the underpinning of the diverse outcomes observed among different patients infected with SARS-CoV-2. However, their reasoning also reminds us that, while several features of immune senescence and inflamm-aging are recapitulated in HIV patients, these phenomena are much more complex than that those occurring following a chronic viral infection. In other words, inflamm-aging and immune senescence occur in a complex context, where the aging immune system interacts with an aging body that undergoes complex metabolic reshaping and remodelling. This consideration should prompt further research effort aimed at better characterizing the pillars of aging and, generally, the aging process itself, in order to develop diverse strategies beyond vaccination and anti-viral drugs to protect the most exposed part of the society against the ongoing, but also eventual, future pandemic.

Author contributions

MB, FP, JS, and FO conceived the idea and wrote the manuscript. AG, AC, and GS provided critical advice and reviewed the manuscript. All authors approve the final version of the manuscript.

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Declaration of Competing Interest

All authors: No conflict.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.07.013.

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