



Letter to the Editor

COVID-19 mortality amongst the immunosuppressed



Dear Editor,

We read with great interest the article by Leston *et al.*¹ This systematic review and meta-analysis incorporated data from more than one and a half million immunosuppressed (IS) patients with COVID-19 and compared their mortality to immunocompetent people equally suffering COVID-19. As novelty, distinct causes of immunosuppression were considered separately. The study identified solid organ transplantation (SOT), malignancy and use of immunosuppressive agents, such as systemic steroids or biologics, as significant determinants of greater risk than HIV infection or rheumatological conditions.

Our group has had the opportunity to extensively analyse the impact of distinct immunosuppression conditions on COVID-19 mortality in large and multicenter studies.^{2–6} Although our findings tend to support many of the Leston's conclusions, a few points are worth to be discussed. Specifically, we want to highlight four aspects.

First, immunosuppressed patients are a very heterogeneous population. Immunosuppressive drugs, as well as doses, and toxicities, are of utmost importance. With respect to chronic steroid therapy, there is agreement about its influence reducing COVID-19 survival rates.⁴ In contrast, we noticed that the use of biologics should not be considered as a whole. Whilst rituximab therapy prior to SARS-CoV-2 infection has shown a huge impact on COVID-19 outcome and prognosis, other therapies such as belimumab or anti-TNF agents, have shown no effect on COVID-19 mortality.^{7,8}

Second, geographical differences regarding antiretroviral drug access, prices and coverage are of utmost importance when considering the potential impact of HIV infection on COVID-19 prognosis. In a nationwide study we conducted in Spain, where the healthcare system provides free antiretroviral treatment to all HIV-infected individuals, HIV itself did not entail a higher mortality risk from SARS-CoV-2 infection.³

Third, in Leston's study the worst prognosis among SOT was seen in kidney recipients. No increased COVID-19 mortality was noticed among lung, heart or liver SOT. This is somewhat surprising and in contrast with findings from others.^{9,10} In our study, we found that kidney SOT had improved prognosis with respect to other SOT, mostly lung transplanted patients.⁶

Fourth, the impact of baseline comorbidities, frequently related to secondary chronic organ damage because of baseline disease, such as lupus nephropathy, chronic obstructive pulmonary disease leading to lung transplant, or chronic hypertension and diabetes in patients under calcineurin inhibitors drugs, for example, are essential to understand and define COVID-19 mortality among IS patients. For instance, it could help to clarify the discrepancies in SOT

patients' outcomes. In our study, we considered chronic conditions and comorbidities to determine COVID-19 mortality in patients with systemic autoimmune diseases, SOT and HIV.^{2,3,6} We demonstrated that the different rate of certain baseline conditions was the major driver of a worse prognosis of SARS-CoV-2 infection.

In summary, whereas we acknowledge the effort of Leston *et al.* to uniformly classify immunosuppression according to the *UK immunisation against infectious diseases criteria*, we consider that criteria to define the immunosuppressed are still inadequate and COVID-19 prognosis should be properly evaluated for distinct conditions.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Leston M, Elson W, Ordóñez-Mena JM, Kar D, Whitaker H, Joy M, *et al.* Disparities in COVID-19 mortality amongst the immunosuppressed: a systematic review and meta-analysis for enhanced disease surveillance. *J Infect* 2024;**88**(3):106110. <https://doi.org/10.1016/j.jinf.2024.01.009>
2. Moreno-Torres V, de Mendoza C, Mellor-Pita S, Martínez-Urbistondo M, Durán-del Campo P, Tutor-Ureta P, *et al.* Systemic autoimmune diseases in patients hospitalized with COVID-19 in Spain: a nation-wide registry study. *Viruses* 2022;**14**(8):1631. <https://doi.org/10.3390/v14081631>
3. Moreno-Torres V, de Mendoza C, Martínez-Urbistondo M, Mills P, Treviño A, de la Fuente S, *et al.* Predictors of in-hospital mortality in HIV-infected patients with COVID-19. *QJM: Int J Med* 2023;**116**(1):57–62. <https://doi.org/10.1093/qjmed/hcac215>
4. Calderón-Parra J, Cuervas-Mons V, Moreno-Torres V, Rubio-Rivas M, de Blas PA, Pinilla-Llorente B, *et al.* Influence of chronic use of corticosteroids and calcineurin inhibitors on COVID-19 clinical outcomes: analysis of a nationwide registry. *Int J Infect Dis* 2022;**116**:51–8. <https://doi.org/10.1016/j.ijid.2021.12.327>
5. Martínez-Urbistondo M, Gutiérrez-Rojas Á, Andrés A, Gutiérrez I, Escudero G, García S, *et al.* Severe lymphopenia as a predictor of COVID-19 mortality in immunosuppressed patients. *J Clin Med* 2021;**10**(16):3595. <https://doi.org/10.3390/jcm10163595>
6. Moreno-Torres V, Martínez-Urbistondo M, Calderón-Parra J, Mills P, Muñoz-Serrano A, Arias-Milla A, *et al.* COVID-19 in hospitalized solid organ transplant recipients in a nationwide registry study. *Int J Infect Dis* 2023;**134**:154–9. <https://doi.org/10.1016/j.ijid.2023.06.007>
7. Calderón-Parra J, Muñoz-Rubio E, Fernández-Cruz A, García-Sánchez MC, Maderuelo-González E, López-Dosil M, *et al.* Incidence, clinical presentation, relapses and outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients treated with anti-CD20 monoclonal antibodies. *Clin Infect Dis* 2022;**74**(10):1786–94. <https://doi.org/10.1093/cid/ciab700>
8. Marozoff S, Tan J, Lu N, Kirmani A, Loree JM, Xie H, *et al.* Effect of immunosuppressive or immunomodulatory agents on severe COVID-19 outcomes: a population-based cohort study. *ACR Open Rheuma* 2023;**5**(12):685–93. <https://doi.org/10.1002/acr.2.11620>

9. Schaenman J, Byford H, Grogan T, Motwani Y, Beaird OE, Kamath M, et al. *Impact of solid organ transplant status on outcomes of hospitalized patients with COVID-19 infection*. *Transpl Infect Dis* 2022;**24**(4). <https://doi.org/10.1111/tid.13853>
10. Heldman MR, Kates OS, Safa K, Kotton CN, Georgia SJ, Steinbrink JM, et al. *COVID-19 in hospitalized lung and non-lung solid organ transplant recipients: a comparative analysis from a multicenter study*. *Am J Transplant* 2021;**21**(8):2774–84. <https://doi.org/10.1111/ajt.16692>

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