Response to "Correspondence on "Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician reported registry" by Arnaud and Devilliers". Risk prediction models for risk of COVID-19-related death.

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We thank Arnaud and Devilliers[1] for their correspondence on our article.[2] They raise the important topic of risk prediction models for estimating the risk of Coronavirus Disease 2019 (COVID-19)-related death, and the potential development of a risk prediction tool using data from our article.

We agree with the authors that patients using immunosuppressive/immunomodulatory agents have different risks, depending on factors such as their age, chronic conditions, and specific drug therapies. However, we also recognize that there are significant limitations in using the estimates published in our manuscript to develop a COVID-19-related death risk prediction model to guide vaccination strategies. These limitations include:

1. While robust models that predict the prognosis of COVID-19 are desirable to support decisions about shielding, hospital admission, treatment, and population level interventions such as COVID-19 vaccination, this was not the primary aim of the published study. Importantly, it should be noted that owing to the voluntary nature of the registry there is an inherent selection bias, with an overrepresentation of severe cases, as discussed in our manuscript. Any model developed in a specific dataset will only reflect the risk for a particular patient under similar circumstances and receiving similar care. Therefore, in the same way that the hospitalisation and death rates reported in our article cannot be extrapolated to the entire population of patients with rheumatic diseases, a risk model developed using the reported data may lack generalisability.[3]

2. Given the rapid and dynamic evolution of COVID-19, static risk prediction models are likely to rapidly become obsolete. COVID-19 warrants the need to develop "living" risk prediction models which can be updated regularly as our understanding of COVID-19 increases and more data becomes available. For example, the performance and generalisability of any risk prediction model will depend heavily on contextual and environmental time-dependent factors, such as the underlying burden of infection and immunity levels in the population of interest. Temporal trends can be dictated by improved testing capacity, vaccination efforts, and increased ability to better treat patients with COVID-19 (e.g. pharmacological treatment with glucocorticoids and remdesivir, changes in invasive/non-invasive ventilation strategies, prone positioning, and prophylaxis/prevention of complications such as thromboembolic events). They can also arise from typically unmeasured time-dependent factors such as adherence to shielding and other infection control measures (that can affect the likelihood of exposure to SARS-CoV-2) and health-care resource availability, which has not only varied significantly over time, but also between and within countries and regions at the same point in time.[4]

3. A systematic review of published risk prediction models for COVID-19 found that most models are subject to a high risk of bias with optimistic reported performance, raising concern that these models may be unreliable when applied in practice.[5] Indeed, development of risk prediction models should

follow a robust and standardised approach, as outlined in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[6] This recommended standardised approach includes aspects such as assessment of model performance, calibration and internal/external validation. All these steps are essential to be undertaken before a risk prediction model can be used to support population risk stratification in relation to public health interventions such as vaccine utilisation.

All these elements being clarified, and for reasons of data transparency, we provide here the estimate of the intercept of the model ($\hat{\beta}_0 = -4.059$).

We appreciate the comment from Arnaud and Devilliers,[1] and agree that risk prediction models have the potential to help patients and doctors reach a shared understanding of risk, and help stratify risk in populations for public health purposes. However, developing a risk prediction model for risk of COVID-19-related death in patients with rheumatic diseases should constitute a separate effort, undertaken with a larger sample size, and taking the above considerations into account.

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