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## Serum IgG4 elevation in hyper-inflamed COVID-19 patients. Author's reply

## ARTICLE INFO

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Dear Editor, we thank Dulak and Trzciński for their insightful and pertinent comments on our observation about serum IgG4 levels predicting mortality in hospitalized patients affected by Coronavirus Disease 2019 (COVID-19) [1,2]. In particular, we agree that serum IgG4 levels may vary significantly in healthy individuals and in various inflammatory and allergic diseases [3,4]. We also recognize, as acknowledged in the discussion, that the limited number of patients included in the study does not allow definitive conclusions about the practical utility of our findings. Yet, collecting informative blood samples was quite challenging because most patients referred to our hospital during the second pandemic wave of COVID-19 were already on medium/high dose glucocorticoids as part of their domiciliary therapy, a treatment regimen that typically rapidly affects serum IgG subclasses concentration [5]. Despite these limitations, we were able to assemble an informative cohort of COVID-19 patients and to return statistically significant results according to which also Dulak and Trzciński do not completely exclude the possibility that patients with elevated baseline IgG4 are more susceptible to a severe course of COVID-19.

This is, indeed, the most relevant pathogenic implication of our results whereby, regardless of the underlying condition responsible for baseline serum IgG4 elevation, hosts with physiological or pathological propensity to develop IgG4 skewed immune responses might be more permissive to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. On the other hand, since we also found a positive correlation between the concentration of serum IgG4 and IL-6 - a pleiotropic cytokine implicated in IgG class-switch during viral infections - it is possible that hyper-inflammation in COVID-19 patients is physiologically associated with a prominent production of IgG4 antibodies [6-8]. Indeed, IgG4 elevation in the context of high IL-6 levels has been already reported in other inflammatory disorders such as Castelman's disease, suggesting that the increase of serum IgG4 observed in hyper-inflamed COVID-19 patients more likely represents an intrinsic disease feature rather than an occasional finding related to other causes [3]. Still, due to the lack of additional mechanistic studies, our preliminary and correlative observations clearly deserve further investigation.

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## Ethical approval information

This study was approved by the San Raffaele Hospital Ethical Committee (no. 34/int/2020).

## Data sharing statement

The authors agree to share the data generated by the present research and to make them openly and publicly available upon publication.

## CRediT authorship contribution statement

**Emanuel Della-Torre:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Marco Lanzillotta:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Giuseppe Alvise Ramirez:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Lorenzo Dagna:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Moreno Tresoldi:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing.

## Declaration of Competing Interest

The authors have not received any financial support or other benefits from commercial sources for the work reported in the manuscript, or any other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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