Response to "Immunoglobulin G glycome and severity of COVID-19: more likely a quantification of bias than a true association."

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We thank Dr Trkulja and his colleagues for their efforts in preparing the Letter to Glyco Forum commenting on our recent study (Petrović et al., 2020). We agree that there are multiple limitations in the study design, primarily regarding the number of patients involved in the study and the detailed information about all comorbidities. Nevertheless, since the changes we report were replicated in three independent cohorts we believe that they represent the real biological association and not a "quantified bias". In our manuscript we clearly acknowledged study limitations (in particular potential confounding) and conclude that the results "suggests the need for further research in this direction". We are currently conducting several large studies that will take into an account known potential confounders and provide more detailed insight into the role of IgG glycosylation in COVID-19.

We would also like to refer to three main objections regarding the data analysis: univariate analysis, fixed effects meta-analysis and false discovery rate (FDR) control. We believe that a univariate approach is perfectly adequate for answering the question "Does any individual glycan trait provide relevant information on the phenomenon studied?". Univariate methods, which include t test, linear regression, ANOVA and logistic regression, do not represent some obscure choice for doing analysis in omics studies. Instead, they constitute a standard set of statistical methods of the vast majority of genomic, epigenomic, proteomic, metabolomic and glycomic studies, including some of our own studies that were published in leading journals (Krištić et al., 2018; Peng et al., 2019; Šimurina et al., 2018)

Regarding the objection that is inappropriate to use fixed effects meta-analysis approach in our case due to assumed medical heterogeneity we would like to mention that the paper Trkulja et al. cited in their comment to support this objection actually concludes: "*Therefore, contrary to what is often stated in the literature, it is important to realize that the fixed-effects model does not assume that the true effects are homogeneous. In other words, fixed-effects models provide perfectly valid inferences under heterogeneity, as long as one is restricting these inferences (i.e., the conclusions about the size of the average effect) to the set of studies included in the meta-analysis."* (Viechtbauer, 2010)

Finally, in our study we clearly stated that FDR, and not FWER, was controlled using the Benjamini-Hochberg approach. For FDR control we used R programming language function p.adjust(method = "BH") in which the author re-interpreted original BH procedures in terms of adjusted p-values.

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