


LETTER



# Early increases in anti-SARS-CoV-2 antibody isotypes associated with organ dysfunction and mortality in patients hospitalized with COVID-19

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Dear Editor,

The antibody response to SARS-CoV-2 is associated with outpatient outcomes; however, it is unknown whether specific immunoglobulin isotypes, i.e., IgG, IgA and IgM, binding to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein are associated with or alter mortality and use of ventilation or vasopressors in patients hospitalized with acute coronavirus disease 2019 (COVID-19).

This is a sub-study of ARBs CORONA I (NCT04510623), a multi-center observational cohort study of adults ( $n = 137$ ) hospitalized with acute COVID-19. Plasma anti-SARS-CoV2 IgG, IgA, and IgM antibody isotypes were quantified, and changes in their concentrations from day 4 to 7 were investigated for association with mortality and use of ventilation or vasopressors. Antibody isotype concentrations were determined using the immunIQ COVID assay which is a quantitative assay that measures individual anti-SARS-CoV-2 isotypes (i.e., IgG, IgA, IgM, IgD, and IgE) and subtypes in plasma [1].

The ARBs CORONA I study included plasma collections at day 1, 4, 7, and 14 of hospital admission; from these time-points, we chose to analyze samples via the immunIQ assay at day 4 and day 7 only. The rationale

for this selection was twofold: (i) given the likely average time from infection to admission, there were likely to be few measurable antibody responses at day 1, and (ii) we were interested in measurements early enough during admission that they could inform our outcomes of interest. Thus, we examined the association of anti-SARS-CoV-2 antibody isotype absolute concentrations and changes in concentrations in patients who survived to at least day 7 after admission for acute COVID-19.

The primary outcome was 28-day mortality. The secondary outcomes were in-hospital mortality and organ dysfunction, determined as invasion mechanical ventilation, vasopressors, and renal replacement therapy (RRT) that was initiation after day 4 or 7. RRT was not formally analyzed, because too few participants ( $n = 7$ ) received this therapy. The estimated associations between antibody concentrations and binary outcomes were expressed as odds ratio (OR) and 95% confidence intervals (CI) around the estimated OR. As  $\log_2$ -concentrations were entered into these logistical regression models, the OR reflects the change in the odds of a given outcome for a one-unit difference in the  $\log_2$  scale; this is equivalent to a doubling in the concentration in the raw scale.

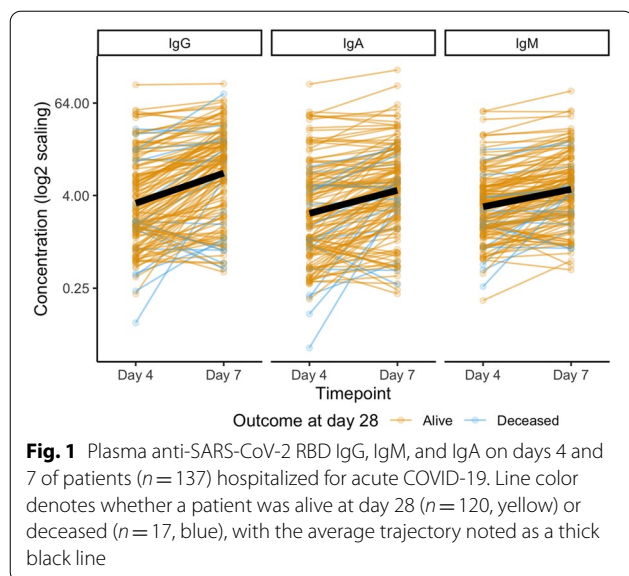
Additional methodological details can be found in the Online Resource.

Figure 1 shows the individual- and group-level change for each of the anti-RBD antibody isotype concentrations from day 4 to day 7. There was a  $2.5 \times$  increase in IgG (95% CI 2.1–2.9),  $2 \times$  increase IgA (95% CI 1.7–2.3), and  $1.7 \times$  increase in IgM (95% CI 1.5–1.9) all  $p < 0.0001$ .

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Anti-RBD IgG, IgA, and IgM were above the lower limit of the measuring interval (LLMI) in 54.7%, 64.2%, and 62% of cases at day 4, respectively, and 80.3%, 83.9%, and 85%, respectively, at day 7.

A doubling in anti-RBD IgG concentration from day 4 to 7 (i.e., a one-unit increase in  $\log_2$  IgG concentration) was associated with a 44% decrease in the likelihood of death by day 28 (OR 0.56, 95% CI 0.32–0.93). A similar, though not statistically significant, association was observed between IgG change and in-hospital death (OR 0.68, 95% CI 0.44–1.03). A doubling in IgM concentration from day 4 to 7 was associated with reduced likelihood of invasive mechanical ventilation after day 7 (OR 0.15, 95% CI 0.02–0.67) and with reduced likelihood of vasopressor use after day 7 (OR 0.17, 95% CI 0.03–0.69). We did not observe an association between IgA change and these clinical outcomes.

Dexamethasone was used in 121 (88.3%) patients and use of dexamethasone soon after admission was associated with a higher antibody response on day 7. The antibody isotype concentrations at day 7 for those who received dexamethasone by day 1 were significantly higher than those who were not on dexamethasone for the first 7 days.

Additional results can be found in the Online Resource.

We believe that there are no prior publications associating anti-SARS-CoV-2-binding antibody isotype concentrations with acute organ dysfunction and need for ventilation or vasopressors in patients hospitalized with acute COVID-19. Ours is the first study, showing that the use of dexamethasone is associated with increased concentration of binding antibodies to SAR-CoV-2. The RBD of the spike protein is the strongest initial (within the first

week) and lasting (more than 6 months) natural antibody epitope and prevents SARS-CoV-2 entry into human cells [2, 3]. Others found that a lack of IgG response 21 days after symptom onset was associated with progression to critical illness [4]. In another study, anti-RBD IgG was associated with survival among ICU-admitted patients [5]. Limitations of our study are that an association study cannot directly determine causation.

In conclusion, in acute COVID-19 hospitalized patients, the concentrations of IgG, IgA, and IgM binding antibodies against SARS-CoV-2 increased significantly from day 4 to day 7. Increases in anti-SARS-CoV-2 IgG and IgM were associated with lower mortality, and less use of ventilation and vasopressors, respectively.

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-022-06662-9>.

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#### Declarations

#### Conflicts of interest

MLD has received grants for COVID-19 research from the Michael Smith Foundation for Health Research and the Canadian Foundation for Innovation. JAR has received grants for COVID-19 research from the Canadian Institutes of Health Research and St. Paul's Foundation. JAR reports patents owned by the University of British Columbia that are related to the use of PCSK9 inhibitor(s) in sepsis, and related to the use of vasopressin in septic shock and a patent owned by Ferring for use of selepressin in septic shock. He is an inventor on these patents, was a founder, Director, and shareholder in Cyon Therapeutics Inc., and is a shareholder in Molecular You Corp. He reports receiving consulting fees in the last 3 years from: Asahi Kasei Pharmaceuticals of America (was developing recombinant thrombomodulin in sepsis), SIB Therapeutics LLC (developing a sepsis drug), and Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin). He is no longer actively consulting for the following: La Jolla Pharmaceuticals (developing angiotensin II; he chaired the DSMB of a trial of angiotensin II from 2015–2017) and PAR Pharma (sells prepared bags of vasopressin). He reports having received an investigator-initiated grant from Grifols (entitled "Is HBP a mechanism of albumin's efficacy in human septic shock?") that was provided to and administered by

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