Determinants of SARS-COV-2 seroconversion in a cohort of recovered patients

Arturo Ciccullo[1], Matteo Tosato[2], Alberto Borghetti[1], Davide Moschese[1], Massimo Fantoni[1], Simona Di Giambenedetto[1], Francesco Landi[2] on behalf of the Gemelli Against COVID-19 Post-Acute Care Study Group

[1]U.O.C. Malattie Infettive, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [2]Geriatrics Department, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Dear Editor,

Despite the high burden of mortality of the ongoing SARS-CoV-2 pandemic, with an estimated 1,700,000 deaths worldwide (as of December 22nd 2020), the majority of patients eventually recover and are discharged. Reports regarding recurrent positivity for SARS-CoV-2 after recovery have meanwhile emerged, as well as concerns about the lack of seroconversion, which could lead to a lack of protection against re-infection [1, 2]. In April, we started a post-acute, outpatient service for discharged patients who recovered from COVID-19 and had at least two consecutive negative SARS-COV-2 RNA tests [3]. Overall, we analyzed 243 patients: 142 were males (58.4%), with a median age of 56 years (IQR 47-67). A total of 193 (79.4%) patients required hospital admission: among those, 133 required oxygen supplementation, 28 required transfer to an Intensive Care Unit (ICU) and 11 required mechanical ventilation. Median time between symptoms onset and clinical evaluation at our post-acute clinic was 67 days (IQR 52-85). At the time of the visit, a molecular assay through nasopharyngeal swab was performed: 29 patients (11.9%) had a positive result. Among them, 3 (10.3%) had negative IgG titer. At our post-acute evaluation, 13 patients (6.4% of the 202 patients who performed a serologic assay) had negative IgG titer. In a multivariate analysis, seroconversion was predicted by a higher C-Reactive Protein (CRP) value at admission (aHR 1.39, 95%CI 1.05-1.84, p=0.022) and by the use of hydroxychloroquine as part of the treatment strategy (aHR 13.57, 95%CI 1.17-157.03, p=0.037). None of the patients who had a recurrent positive molecular assay needed hospital re-admission, but only 5 of them (17.2%) were asymptomatic at the time of the evaluation. Given patients' overall stable clinical conditions, we concluded that these recurrent positivities were viral relapses and not re-infections. Regarding IgG response, in contrast with other works, we did not observe a correlation between disease severity and IgG seroconversion [4]. In our cohort, mechanical ventilation or ICU hospitalization were not predictors of seroconversion, while CRP value at admission was, highlighting a probable correlation between the inflammatory cascade and the intensity of the immune response. Interestingly, the use of hydroxychloroquine was positively associated with IgG seroconversion. Hydroxychloroquine has a known immunomodulatory effect both on innate and cellular immune responses and has been used for decades in the treatment of autoimmune diseases [5]. Further studies are needed to shed a light on the association between seroconversion and COVID-19 treatment strategies. In conclusion, our results, in line with the findings from Petersen *et al.*, show that over 90% of patients developed IgG antibodies to SARS-CoV-2 [2]. However, giving the increasing pandemic numbers, this would mean leaving a significant proportion of individuals at risk of re-infection while

Corresponding author
Arturo Ciccullo
E-mail: arturo.ciccullo@gmail.com

also casting several doubts about the possibility of obtaining a sustained immune response when the long-awaited vaccines arrive.

Conflict of interest
Authors report no conflict of interest related to this study.

Funding
This study was performed as part of our routine clinical activity.

Authors contribution
AC, MT and FL conceived the work. AC and MT wrote the manuscript. AB, DM and MF managed patients and collected data. SDG and FL critically revised the manuscript. All authors approved the final version of the manuscript.

Acknowledgments
We would like to thank the other members of the Gemelli Against COVID-19 Post-Acute Care Study Group: Gremese E, Bernabei R, Gasbarrini A, Settanni CR, Benvenuto F, Bramato G, Carfì A, Ciciarello F, Lo Monaco MR, Martone AM, Marzetti E, Napolitano C, Pagano F, Rocchi S, Rota E, Salerno A, Tritto M, Calvani R, Catalano L, Picca A, Savera G, Cauda R, Tamburrini E, Borghetti A, Murri R, Cingolani A, Ventura G, Taddei E, Stella L, Addolorato G, Franceschi F, Mingrone G, Zocco MA, Sanguinetti M, Cattani P, Marchetti S, Posteraro B, Sali M, Bizzarro A, Lauria A, Rizzo S, Savastano MC, Gambini G, Cozzupoli GM, Culiersi C, Passali GC, Paludetti G, Galli J, Crudo F, Di Cintio G, Longobardi Y, Tricarico L, Santantonio M, Buonsenso D, Valentini P, Pata D, Sinatti D, De Rose C, Richeldi L, Lombardi F, Calabrese A, Leone PM, Montemurro G, Calvello MR, Intini E, Mazzarella A, Varone F, Pasciuto G, Porro LM, Sani G, Janiri D, Giuseppin G, Molinaro M, Modica M, Natale L, Larici AR, Marano R, Paglionico A, Petricca L, Gigante L, Natalello G, Fedele AL, Lizzio MM, Tolusso B, Alivernini S, Santoliquido A, Santoro L, Nesci A, Popolla V.

REFERENCES

[1] Mei Q, Li J, Du R, Yuan X, Li M, Li J. Assessment of patients who tested positive for COVID-19 after recovery. *Lancet Infect Dis.* 2020; 20 (9), 1004-5.
[2] Petersen LR, Sami S, Vuong N, et al. Lack of antibodies to SARS-CoV-2 in a large cohort of previously infected persons. *Clin Infect Dis*. 2020 Nov 4: ciaa1685.
[3] Gemelli Against COVID-19 Post-Acute Care Study Group. Post-COVID-19 global health strategies: the need for an interdisciplinary approach. *Aging Clin Exp Res*. 2020; 11, 1-8.
[4] Lynch KL, Whitman JD, Lacanienta NP, et al. Magnitude and kinetics of anti-SARS-CoV-2 antibody responses and their relationship to disease severity. *Clin Infect Dis*. 2020; Jul 14: ciaa979
[5] Chandler LC, Yusuf IH, McClements ME, Barnard AR, MacLaren RE, Xue K. Immunomodulatory effects of hydroxychloroquine and chloroquine in viral infections and their potential application in retinal gene therapy. *Int J Mol Sci*. 2020; 21 (14), 4972.