

COMMENTARY

Significant reduction of humoral response to SARS-CoV-2 4 months after the diagnosis of COVID-19

Kang Zhang^{1,*}, Zhen-Guo Ma^{2,3,*}, Lei Yang⁴, Wei Kang¹, Yun Yin⁵ and Johnson Yiu-Nam Lau⁶

¹University Hospital and Faculty of Medicine, Macau University of Science and Technology, Macau SAR, China

²Department of Cardiology Renmin Hospital of Wuhan University, Wuhan 430060, China

³Hubei Key Laboratory of Metabolic and Chronic Diseases, Wuhan 430060, China

⁴The First affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, China

⁵School of Business, Macau University of Science and Technology, Macau SAR, China

⁶Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, Hong Kong SAR, China

*Correspondence: Kang Zhang, E-mail: kang.zhang@gmail.com; Zhen-Guo Ma, E-mail: zhengma@whu.edu.cn

Editor's note

A commentary on “Humoral immune response to SARS-CoV-2 in Iceland”.

Key words: humoral response; antibodies; COVID-19; SARS-CoV-2

Humoral response to COVID-19 disease, including IgM and IgG antibodies against SARS-CoV-2 virus, is well documented.^{1,2} Neutralizing activities against SARS-CoV-2 virus have also been confirmed in patients who have recovered from COVID-19.² These observations form the basis for the assumption that SARS-CoV-2 vaccines can be developed through stimulation of the host immune system to generate neutralizing antibodies to SARS-CoV-2 virus. Certainly, if the vaccine can also induce a T-cell response, it may have an ideal profile in terms of B-cells and T-cells creating synergy in their responses and the potential of T-cells to eliminate the infected cells while the neutralizing antibodies are neutralizing the virus.³

However, the recent observation of re-infection in patients who have recovered from COVID-19 is disturbing. First, it was reported that patients who had

recovered from the SARS-CoV-2 infection could get re-infected a few months after the first infection.⁴ Second, as a continuation of the first point, there were concerns with regards to how long the humoral response against SARS-CoV-2 infection will last in convalescent patients. For the second point, Ibarro et al. reported a significant drop of antibodies against SARS-CoV-2 in patients with mild COVID-19.⁵ They also estimated that the half-life was around 36 days based on data from 31 patients.⁵ However, in a cohort in Iceland, Gudbjartsson et al. recently reported that the humoral immune response to SARS-CoV-2 did not decline within 4 months after diagnosis.⁶

Here, we share our experience derived from a prospectively collected dataset from patients from the Wuhan epidemic who showed a significant reduction in antiviral

Received: 6 October 2020; Revised: 14 October 2020; Accepted: 15 October 2020

© The Author(s) 2020. Published by Oxford University Press on behalf of the West China School of Medicine & West China Hospital of Sichuan University. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

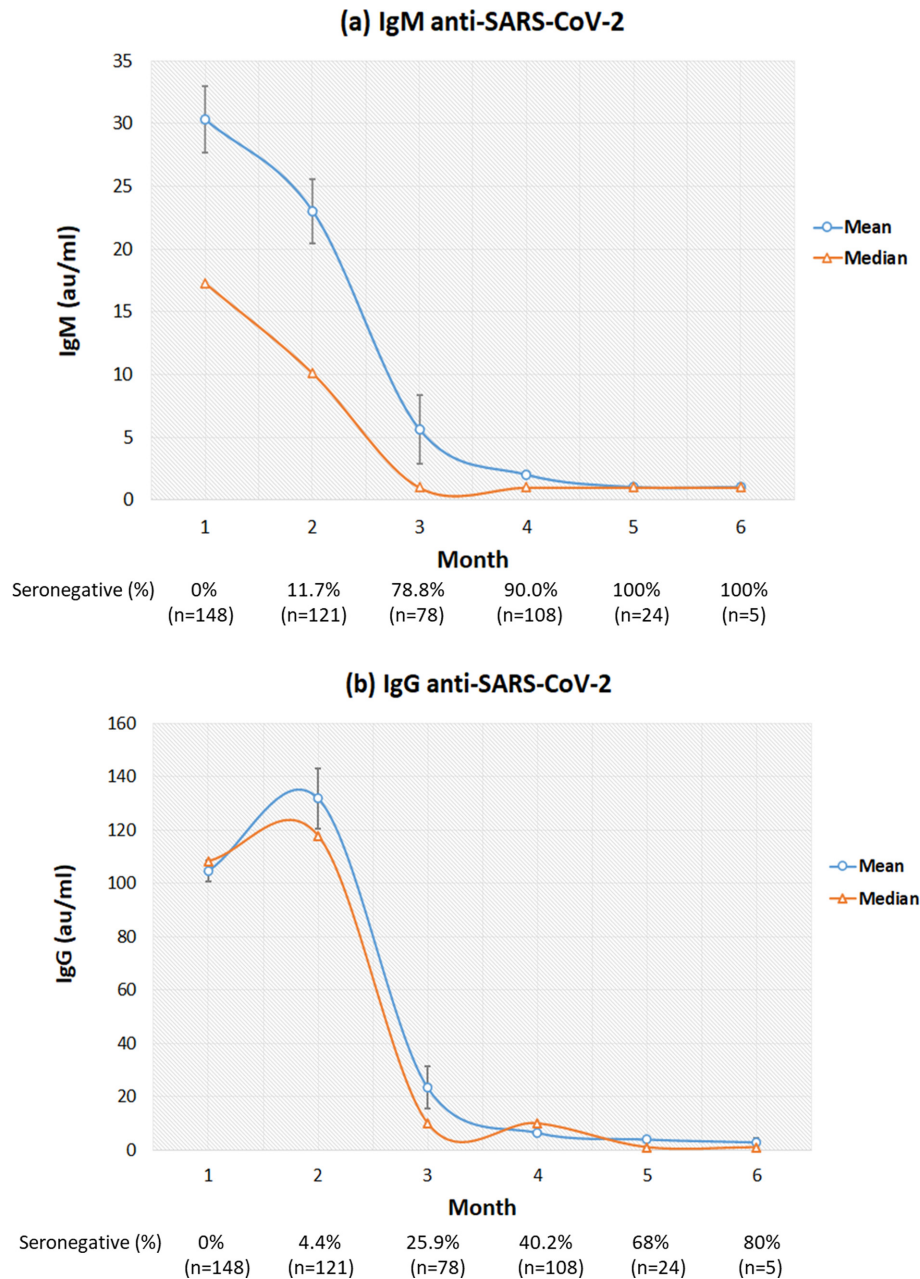


Figure 1. Average (a) IgM and (b) IgG titers (error bars represented standard errors of the mean, SEM) in follow-up of patients in the first 6 months after diagnosis with COVID-19 based on RT-PCR. The antibody titers are represented as arbitrary units per ml (au/ml). As a proportion of samples were seronegative for antibodies when they were first positive by RT-PCT, the antibody titer on the day of diagnosis is not presented here.

antibody titer 4 months after the diagnosis of COVID-19. We also estimated the half-life of the antibodies in these recovered patients and determined its correlation with the demographic and clinical parameters.

A cohort of 148 patients [M:F 51:97, mean age 43.7 ± 14.9 (range 23–84), average hospital stay 24.1 ± 16.1 days (range: 2–144 days)] with COVID-19 diagnosed by reverse transcription polymerase chain reaction (RT-PCR) based on SARS-CoV-2 sequence between January and February 2020 was respectively followed in the Remin Hospital of Wuhan University. The patients selected for this analysis included those with at least two serial positive tests for antibodies to SARS-CoV-2. The assay

was as described previously, consisting of capture antigens from nucleoprotein and a peptide from the spike protein containing the receptor binding domain (RBD).² COVID-19 disease severity was assessed based on the classification³ recommended by the Chinese Health Authority (7th edition) into mild 11, moderate 108, and severe 29 [the Chinese Health Authority 7th edition; mild cases as asymptomatic/relatively asymptomatic without CXR/chest CT changes; moderate cases as fever and/or respiratory symptoms and/or with radiological result of pneumonia (can be relatively asymptomatic but have positive radiologic changes); severe cases as severe respiratory symptoms with oxygen saturation of

Table 1. Half-lives of the IgM and IgG antibodies and correlation with age (≤ 50 and > 50) and gender. No correlation was identified with the other demographic and clinical parameters.

IgM	Group	Half-life (\pm SD) in days	P-value
Age	≤ 50	25.5 \pm 14.6	P < 0.001
	> 50	16.8 \pm 15.8	
Gender	Female	25.5 \pm 14.6	P < 0.001
	Male	17.2 \pm 15.2	
IgG	Group	Half-life (\pm SD) in days	P-value
Age	≤ 50	26.5 \pm 16.3	P < 0.001
	> 50	18.1 \pm 19.5	
Gender	Female	27.4 \pm 17.1	P = 0.006
	Male	17.0 \pm 17.1	

<93%, decreased arterial oxygen tension, or CXR/chest CT showing more than 50% pulmonary involved; and ICU admission is defined as patients requiring ICU care and mechanical ventilation because of respiratory distress or organ failures].

Figure 1a and b shows the average IgM and IgG antibody titers during the first 6 months after the patients were diagnosed with COVID-19 based on RT-PCR. The IgM antiviral antibodies dropped rapidly after the diagnosis (Fig. 1a) with 11.7% (n = 121), 78.8% (n = 78), 90.0% (n = 108), 100% (n = 24) and 100% (n = 5) converted to seronegative from month 2 to month 6, respectively, after the diagnosis. For the IgG antibodies, there was an increase in IgG titer in month 2 but this dropped rapidly from month 3, with 4.4% (n = 121), 25.9% (n = 78), 40.2% (n = 108), 68% (n = 24), and 80% (n = 5) samples converted to seronegative from month 2 to month 6, respectively.

The half-lives of serum IgM and IgG in these patients were estimated to be 22.7 ± 15.3 days and 23.9 ± 17.7 days, respectively. Correlation with demographic and clinical/laboratory parameters showed that only two factors were significant, gender and young age, in that female gender and younger age group (age ≤ 50) correlated with significantly longer half-lives of both serum IgM and IgG (Table 1).

Our data show that a large proportion (40.2% in month 4 to 80% in month 6) of patients with COVID-19 in Wuhan had no detectable antiviral antibodies 4–6 months after the diagnosis of COVID-19, which is consistent with the report from Ibarrodo *et al.* but different from the impression derived from the study by Gudbjartsson *et al.*^{5,6} Longer term follow-up of the cohort in Iceland to determine whether there is a significant drop later, from month 4 onwards, will be critical. Data from other centers on their experiences will also be critical for a more global perspective on the humoral response to SARS-CoV-2 in patients of different ethnic origins during recovery.

Whether this rapid drop is related to host or viral factors is also not known. The half-life of antibodies in our study is lower than that reported by Ibarrodo *et al.*,⁵ being in the order of around 22 days. This may

suggest that when patients recovered from the SARS-CoV-2 infection, the RNA virus did not persist and, therefore, there was no continuous stimulation of the humoral response to the viral antigens.

Another key question is whether this rapid decline in antiviral antibody titer will protect the convalescent patients from re-infection. We have recently reported two patients diagnosed to have SARS-CoV-2 re-infection within 58 days and 43 days, respectively, based on clinical and laboratory testing results in Wuhan.⁴

The relative contributions of B-cell and T-cell responses in protection of the convalescent subjects will also need to be established. Needless to say, this observation may have important implication in vaccine development. If the same pattern of rapid antibody drop is observed in recipients of the vaccine, there may be a need for regular booster doses.³

Our finding also poses a challenge to the use of seroprevalence in determination of past SAR-CoV-2 infection to estimate the cumulative attack rate. Certainly, infected subjects who are studied 4–6 months after the infection may have no detectable antibodies and therefore may not be identified.^{1,8} If so, the assumption used for the mathematical models for COVID-19 infection that convalescent patients are immune to the virus will also need to be adjusted.^{7,8}

Conflict of interest

As a Co-EIC of *Precision Clinical Medicine*, the first author Dr Kang Zhang was blinded from reviewing or making decisions on this manuscript.

References

- Xu X, Sun J, Nie S, *et al.* Seroprevalence of immunoglobulin M and G antibody against SARS-CoV-2 in China. *Nat Med* 2020;**26**:1193–5. doi:10.1038/s41591-020-0949-6.
- Chowdhury MA, Hossain N, Kashem MA, *et al.* Immune response in COVID-19. A review. *J Infect Public Health* 2020;**13**:1619–29. doi:10.1016/j.jiph.2020.07.001.
- Yang J, Wang W, Chen Z, *et al.* A vaccine targeting the RBD of the S protein of ASRS-CoV-2 induces protective immunity. *Nature* 2020;**586**:572–7. doi:10/1038/s41586-020-2599-8.

4. Zhang K, Lau JYN, Yang L, et al. SARS-CoV-2 reinfection in two patients who have recovered from COVID-19. *Precis Clin Med* 2020. doi:10.1093/pcmedi/pbaa031.
5. Ibarondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild COVID-19. *New Engl J Med* 2020;383:1085–7. doi:10.1056/NEJMc2025179.
6. Gudbjartsson GF, Norddahl GL, Melsted P, et al. Humoral immune response to SARS-CoV-2 in Iceland. *New Engl J Med* 2020;383:1724–34. doi:10.1056/NEJMoa2026116.
7. Wang T, Wu Y, Lau JYN, et al. A four-compartment model for the COVID-19 infection—implications on infection kinetics, control measures, and lockdown exit strategies. *Precis Clin Med* 2020;3(2):104–12. doi:10.1093/pcmedi/pbaa018.
8. Zhang K, Tong W, Wang X, et al. Estimated prevalence and viral transmissibility in subjects with asymptomatic SARS-CoV-2 infections in Wuhan, China. *Precis Clin Med* 2020. doi:10.1093/pcmedi/pbaa032.