Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Correlation between viral RNA shedding and serum antibodies in individuals with coronavirus disease 2019

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To the Editor,

To date, an outbreak of an infectious disease—coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)—has caused infection in over 7 million people around the world [1]. A recent report by Fang et al. showed that severe cases of COVID-19 had a prolonged time of viral RNA shedding [2]. Based on currently available information, the relationship between the dynamic of serum antibodies and viral replication is unclear. In this study, we investigated the correlation between serum antibodies and duration of viral RNA shedding.

We retrospectively enrolled 89 hospitalized individuals (admission date from 22 January to 13 February 2020) with laboratory-confirmed SARS-CoV-2 infection in Tongji Hospital of Huazhong University of Science and Technology in Wuhan, China. We enrolled individuals who underwent blood tests intended for antibody detection during hospitalization. All participants had mild to moderate illness, and did not require intubation or admission to the intensive care unit. Throat and/or nasal swabs collected upon admission and during hospitalization were analysed by SARS-CoV-2 real-time RT-PCR according to the manufacturer's protocol (Shanghai Huirui Biotechnology Co., Ltd, Shanghai, China). Specific antibodies IgM and IgG to SARS-CoV-2 were analysed by chemiluminescent immunoassay according to the manufacturer's protocol (Shenzhen Yahuilong Biotechnology Co., Ltd, Shenzhen, China). The kits had two antigens of SARS-CoV-2 (nucleocapsid protein and spike protein) coated on the magnetic beads. An iFlash3000 fully automatic chemiluminescence immunoassay analyser (Shenzhen Yahuilong, Biotechnology Co., Ltd) was used to analyse the samples. Serum IgM and IgG titre (AU/mL) was calculated by the immunoassay analyser. The reference levels of IgM and IgG were 10 AU/mL. Viral RNA shedding was defined as two consecutive negative results. Time to end of viral RNA shedding was considered as the time period between symptom onset and the date of first negative RT-PCR test result. Over 30 days were categorized as prolonged viral RNA shedding. Serial blood samples were collected.

The median age was 62 years (interquartile range (IQR) 52–68), comprising 40 (44.9%) men and 49 (55.1%) women (Table 1). The median period of symptom onset to end of viral RNA shedding was 30 days (IQR 21–44). Individuals with prolonged viral RNA shedding were significantly older (67 years (IQR 63–70) versus 58 years (IQR 44–68); $p < 0.05$) and had more co-morbidities, hypertension being the most significant ($p < 0.001$). Pooled serum IgM was significantly higher in the prolonged shedding groups at weeks 4 and 5 compared with the non-prolonged shedding group (295.0 ± 138.1 AU/mL versus 76.2 ± 42.8 AU/mL; 238.7 ± 96.6 AU/mL versus 77.0 ± 22.8 AU/mL, $p < 0.001$). Serum IgM was similar between two groups from week 6 to week 8 after symptom onset. At week 8, serum IgM in both groups (19.4 ± 8.0 AU/mL and 13.2 ± 4.0 AU/mL) declined almost to the reference level (10 AU/mL). In the prolonged shedding group, serum IgG was slightly higher than that in the other group through week 4 to week 8. However, the difference between the two groups was not significant ($p > 0.05$) (Fig. 1). Both groups' pooled average IgM and IgG values are shown in the Supplementary material (Table S1).

A recent report by Xiao et al. from 34 individuals with COVID-19 found that serum IgM to SARS-CoV-2 can be detected 1 month after symptom onset, revealing that the prolonged IgM response may be common in COVID-19 [3]. Factors associated with viral RNA shedding are not clear based on limited information. We found that those individuals with COVID-19 who had prolonged viral RNA shedding were older ($p < 0.001$) and had more co-morbidities such as hypertension ($p < 0.001$). This finding suggests that dysfunction

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Table 1
The demographic and clinical characteristics of individuals with COVID-19

Variables	All patients (n = 89)	Non-prolonged conversion (n = 43)	Prolonged conversion (n = 46)	p-value
Age (years), median (IQR)	62 (52–68)	58 (44–68)	67 (63–70)	<0.001
Gender, male, n (%)	40 (44.9%)	18 (41.9%)	22 (47.8%)	0.342
Smoking, yes, n (%)	3 (3.4%)	2 (4.7%)	1 (2.2%)	0.595
Exposure to source transmission, yes, n (%)	13 (14.6%)	5 (11.6%)	8 (17.4%)	0.407
Co-morbidities				
Hypertension	36 (40.4%)	10 (23.3%)	26 (56.5%)	<0.001
Diabetes	25 (28.1%)	9 (20.9%)	16 (34.8%)	0.098
Cardiovascular disease	5 (5.6%)	2 (4.7%)	3 (6.5%)	0.935
COPD	2 (2.2%)	2 (4.7%)	0 (0%)	0.255
Malignancy	2 (2.2%)	0 (0%)	2 (4.3%)	0.233
Cerebrovascular diseases	3 (3.4%)	0 (0%)	3 (6.5%)	0.137
Others	5 (5.6%)	3 (7.0%)	2 (4.1%)	0.764
Severity on admission				
Moderate	85 (95.5%)	42 (97.7%)	43 (93.5%)	0.867
Severe	4 (4.5%)	1 (4.8%)	3 (6.1%)	
Onset of symptom to admission (days), median (IQR)	10 (8–14)	10 (7–12)	11 (9–17))	0.186

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IQR, interquartile range.

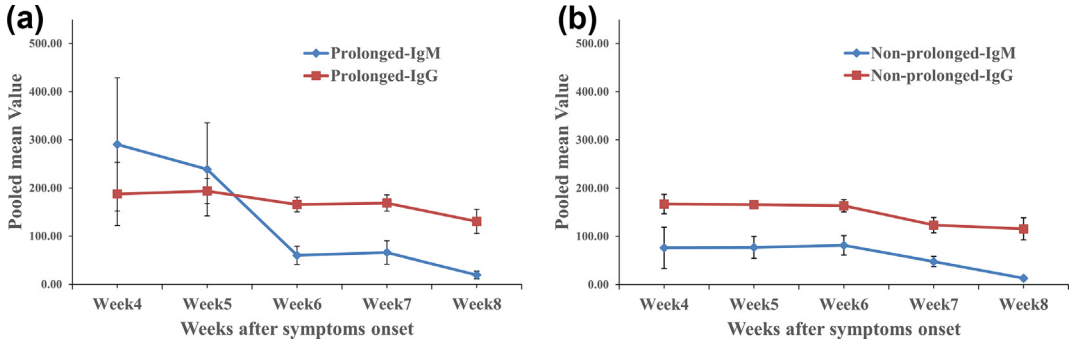

Fig. 1. Dynamic profile of IgM and IgG in prolonged and non-prolonged viral RNA shedding. (a) Dynamic profile of IgM and IgG in prolonged viral RNA shedding. (b) Dynamic profile of IgM and IgG in non-prolonged viral RNA shedding.

of the immune system in older adults may lead to prolonged viral RNA shedding.

The false-negative rate of RT-PCR for SARS-CoV-2 can be relatively high [4]. Our understanding of the dynamics of IgM and IgG can help clinicians to evaluate patient responses and also to rule out false-negative PCR tests. We demonstrated the distinct pattern of serum IgM and IgG between individuals with prolonged and non-prolonged viral RNA shedding. Serum IgM to SARS-CoV-2 persisted at a high level during the acute phase of illness up to week 8. In individuals with prolonged viral RNA shedding, serum IgM was found to be positive (81.3 ± 20.2 AU/mL) at week 6 after symptom onset, which was also consistent with the median time to viral RNA shedding (44 days). Serum IgG persisted at a high level up to 8 weeks in both groups (Fig. 1). Individuals with prolonged viral RNA shedding had a relatively higher IgM level at week 4–5 after symptom onset.

In summary, our study provided a correlation between viral RNA shedding and serum antibodies. Older age and hypertension may lead to prolonged viral RNA shedding. IgM can be reactive up to week 8 after symptom onset and the response may be stronger in individuals with prolonged viral RNA shedding. Larger studies to confirm these findings are needed, but this study might improve our understanding about the dynamics of the serum antibody response and viral shedding in COVID-19.

Author contributions

All authors participated in the study design. CCJ and SZ conceived the study, analysed the data and drafted the manuscript. CG and LZ helped to collect data and designed the study. All authors have agreed on the final version and meet the major criteria recommended by the ICMJE (http://www.icmje.org).

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Ethical approval

This study was approved by the ethics committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. All procedures followed in this study were in accordance with the 1964 Helsinki Declaration and later versions.

Informed consent

Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious disease.

Availability of data and materials

The database used and/or analysed during the current study is not publicly available (to maintain privacy) but can be available from the corresponding author on reasonable request.

Transparency declaration

All authors declare that there are no conflicts of interest.

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We thank Ms Cheng Chen for English grammatical correction of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.05.022.

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