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.

Post-recovery enhancement of anti-variant neutralisation after severe COVID-19

Improving the durability and breadth of vaccine-induced neutralising antibodies against immune-evasive SARS-CoV-2 variants is a pressing need when cases of the heavily mutated omicron variant are surging at an unprecedented rate (appendix pp 8–9). In view of the broadly reactive neutralising antibodies identified in vaccine-boosted individuals with previous SARS-CoV-2 infection,[1] researchers have found that prolonged or repeated SARS-CoV-2 antigen exposure, such as those seen in repeated or breakthrough infections, could improve antibody affinity to emerging variants via enhancing affinity maturation.[2,3] Given that convalescent sera from standard COVID-19 cohorts has performed poorly in neutralising omicron,[4,5] we wonder whether more severe disease courses could induce durable and effective neutralising antibodies against omicron and other immune-evasive variants by affinity maturation.

We studied two prospective cohorts of patients recovered from severe COVID-19 (n=18) and vaccinated health-care workers without a history of COVID-19 (n=24) in Xiangyang, China (appendix p 2). Recovered patients had contracted SARS-CoV-2 during the first outbreak and were not vaccinated before the study. The health-care workers had been vaccinated with CoronaVac (Sinovac Biotech, Beijing, China; n=12) or BBIBP-CorV (Sinopharm, Beijing, China; n=12), both of which are two-dose inactivated vaccines. In serum samples we analysed total antibody concentrations against SARS-CoV-2 receptor-binding domain (RBD) and pseudovirus neutralisation titres (pNT_{50}; calculated as the half-maximal effective concentration) of circulating variants and the ancestral Wuhan-Hu-1 strain. Covalescent sera of recovered patients was collected at 1 month and 12 months after recovery, and compared with the sera of the health-care worker group who were followed-up at 1 month and 6 months after full vaccination (appendix p 7). All samples in the present study were randomly chosen from seropositive cohorts. Further details on the study protocol are provided in the appendix (pp 2–6).

As expected, convalescent sera showed a 2·7-times decrease in geometric mean signal or positive cutoff ratios of anti-RBD antibodies and a 9·0-times decrease in geometric mean pNT_{50} (GMT) of Wuhan-Hu-1 from 1 month to 12 months after recovery, sharing a similar (normal) decay pattern with that of vaccinated sera from 1 month to 6 months after vaccination (appendix p 10). Between 1 month and 12 months, convalescent sera showed similar GMTs of immune-evasive variants omicron (p=0·35), mu (p=1·0), and gamma (p=0·65); whereas, neutralisation of the less evasive delta (p=0·0016) and lambda (p<0·0001) variants was less durable and decreased in parallel with Wuhan-Hu-1 neutralisation (p<0·0001; appendix pp 11–12). Thus, severe infection might induce an enhancement of antibody affinity to immune-evasive variants between 1 month and 12 months after recovery. By contrast, GMTs of both CoronaVac and BBIBP-CorV sera showed consistently decreasing trends across tested variants over time, although the decrease in some longitudinal pairs did not reach statistical significance due to sample size or the limit of detection (appendix p 11). When comparing late versus early GMT ratios (month 12 *vs* month 1 ratio, or month 6 *vs* month 1 ratio) across variants, we observed that 16 (89%) of 18 samples of 12-month convalescent sera had omicron ratios consistent with (within a 2-fold range) or higher (>2 fold) than each corresponding 1-month ratio, which was distinct to BBIBP-CorV sera (one [17%] of six, p=0·0027 *vs* convalescent) and CoronaVac sera (two [20%] of ten, p=0·0005 *vs* convalescent) after excluding 1-month samples with a GMT less than 1·0 (appendix pp 13–14). This enhanced neutralisation at 12-month convalescence was also observed for gamma and mu, while vaccinated sera showed no such enhancement at 6 months (appendix pp 13–14).

These data provide evidence of long-term enhancement of antibody affinity to immune-evasive SARS-CoV-2 variants, which might be unique to survivors of severe COVID-19. The underlying mechanism could be utilised to improve vaccine efficacy against emerging variants.

We declare no competing interests.

YL and YZ contributed equally. YL and PH conceived and designed the study, conducted neutralisation assays and statistical analyses, and wrote this piece. YZ and ZC recruited participants, collected specimens, conducted clinical laboratory tests, and interpreted findings. MC assisted with statistical analyses and conducted data quality checks. YL, YZ, and PH accessed and verified the data. All authors had full access to all the data, read and approved the final version, and accept responsibility to submit for publication. This study was supported by the National Key Research & Development Program of China (grant number 2017YFC1105000), the National Natural Science Foundation of China (grant number 31501116), and the US Department of Veterans Affairs (grant number 5I01BX001353). The funding sources had no role in the study or preparation of this work. No authors were precluded from accessing data in the study. We thank the nurses and technicians at the Department of Laboratory Medicine of Xiangyang Central Hospital for their assistance in participant enrolment, blood collection, and sample preparation.

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See **Online** appendix

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