



## Early View

Research letter

### **Distinct features of SARS-CoV-2-specific IgA response in COVID-19 patients**

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## **Distinct features of SARS-CoV-2-specific IgA response in COVID-19 patients**

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To the Editor:

In comparison to severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 appears to be more contagious[1], and Coronavirus Disease 2019 (COVID-19) patients demonstrate varied clinical manifestations distinct from those seen in patients with SARS-CoV and middle east respiratory syndrome coronavirus (MERS-CoV) infections[2]. Collective results from the clinical and epidemiological observations suggest a distinct viral-host interaction in COVID-19 patients. Profiling of the antibody response during SARS-CoV-2 infection may help improve our understanding of the viral-host interaction and the immunopathological mechanisms of the disease.

Studies on humoral responses to infections have been mainly geared toward the production of high-affinity IgG antibodies that efficiently resolve an infection. It has been well recognized, however, that humoral immune response to infection can be a double-edged sword that either serves as a protective mechanism to resolve the infection or aggravates the tissue injury, e.g. IgG response causes fatal acute lung injury by skewing inflammation-resolving response in SARS[3]. In the case of respiratory infection, while IgM and IgG isotypes have been the primary emphasis in characterizing immunity, mucosal and systemic IgA responses that may play a critical role in the disease pathogenesis, have received much less attention.

This study was designed to better understand the timing and patterns of humoral immune responses to SARS-CoV-2 in a cohort of COVID-19 patients and evaluate their relationship with the disease course and severity. 37 patients with COVID-19, average age of  $52.3 \pm 16.3$  years old, were enrolled in this study. The enrolled COVID-19 patients consisted of 25 males (67.6%) and 12 females (32.4%). All patients had positive testing for viral nucleic acid of SARS-CoV-2 (Real-Time Fluorescent RT-PCR Kit, BGI, Shenzhen). According to the Guidelines of the Diagnosis and Treatment of New Coronavirus Pneumonia (Edition 7) published by the National Health Commission of China[4], the enrolled COVID-19 patients were categorized into 2 groups: 20 severe cases (54.1%) and 17 non-severe cases (46.0%). The non-severe group included patients with mild and moderate symptoms who were also required to be admitted to hospital by the COVID-19 control policy in China. The severe group included severe and critically ill patients. Mild patients did not show abnormal CT imaging. Moderate patients included had fever and/or classical respiratory symptoms, and typical CT images of viral pneumonia. Severe patients met at least one of following

additional conditions: (1) Shortness of breath with respiratory rate (RR)  $\geq 30$  times/min, (2) Oxygen saturation (SpO<sub>2</sub>, Resting state)  $\leq 93\%$ ; or (3) PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq 300$  mmHg. Critically ill patients met at least one of the extra following conditions in addition to the COVID-19 diagnosis: (1) Respiratory failure that required mechanical ventilation; (2) Shock; or (3) Multiple organ failure that required intensive care unit (ICU). All clinical diagnosis were confirmed by a team of trained physicians. All the blood samples were collected within a timeframe of 0-8 weeks after admission. A total of 183 serum samples collected during the hospitalization period of the 37 patients were tested for SARS-CoV-2 spike (S) protein specific antibodies. The levels of SARS-CoV-2 S protein-specific IgA, IgM and IgG antibodies were assayed by chemiluminescent immunoassay. The S-protein peptide was acquired from University of Science and Technology of China.

Our study shows the first seroconversion day of IgA was 2 days after onset of initial symptoms, and the first seroconversion day of IgM and IgG was 5 days after onset. The positive rate of antibodies in the 183 samples was 98.9%, 93.4% and 95.1%, for IgA, IgM and IgG, respectively. The seroconversion rate for IgA, IgM or IgG was 100% 32 days after symptom onset. According to the cumulative seroconversion curve, the median conversion time for IgA, IgM and IgG was 13, 14 and 14 days, respectively. The levels of both Ag-specific IgA and IgG were markedly increased around 2 weeks after the symptom onset and remained continuously elevated for the following 2 weeks. In contrast, the levels and time dependent changes of IgM were minimal. The relative levels of IgA and IgG were markedly higher in severe patients compared to non-severe patients (**Figure 1**). There were significant differences in the relative levels of IgA ( $P < 0.001$ ) and IgG ( $P < 0.001$ ) between the severe and non-severe groups. In contrast, no statistically significant changes occurred in the levels of IgM between severe and non-severe patients after the disease onset. In further subgroup analysis, we found a significant positive association of SARS-CoV-2 specific IgA level and the APACHE-II score in critically ill patients with COVID-19 ( $r = 0.72$ ,  $P = 0.01$ ), while the level of SARS-CoV-2 specific IgG and IgM did not show correlations with disease severity.

The present study showed that the levels of specific IgM antibody were significantly lower than those of IgA in both severe and non-severe patients. This pattern of humoral immune response is different in case of SARS-CoV infection, in which IgM and IgA showed similar chronological profiles in terms of both seroconversion time and antibody titres[5], in line with the knowledge that viremia is common in SARS.

As a mucosal targeted virus, SARS-CoV-2 would be expected to generate secretory IgA (sIgA) and induce strong mucosal immunity. Indeed, the mucosal anti-viral immunity has been shown to result in part from the IgA-mediated interactions with the pathogenic microorganisms to prevent pathogens from adhering to the cell surface[6]. However, recent studies also found that sIgA is able to induce interleukin (IL)-6, IL-8, monocyte chemoattractant protein (MCP)-1 and granulocyte–macrophage colony stimulating factor (GM-CSF) production by normal human lung fibroblasts (NHLFs)[7]. It is also proposed that sIgA may have synergistic effects with IgG in promoting antibody-dependent cellular cytotoxicity (ADCC) [8]. In contrast to mucosal IgA, the role of serum IgA have been relatively unexplored. Previous studies have shown that IgA mediates either pro- or anti-inflammatory effects in innate immune cells and suggested a plausible role of IgA as a driver of autoimmune diseases and regulator of immune hyperactivation[9]. Monomeric binding of serum IgA to the Fc alpha receptor (Fc $\alpha$ RI) has been suggested to mediate inhibitory function via the receptor inhibitory signals in a variety of myeloid cells[10]. In contrast, crosslinking of the Fc $\alpha$ RI by IgA and pathogen is able to transmit activating signals leading to phagocytosis, respiratory burst, ADCC, increased antigen presentation, degranulation, and cytokine release[11]. Cytokines including transforming growth factor beta (TGF- $\beta$ ) and IL-10 can induce antibody isotype switching[12]. Upregulated IgA production may be the result of increased levels of TGF- $\beta$  and IL-10 that promote antibody switching in SARS-CoV-2 infection.

Considering the roles of mucosal and systemic IgA in COVID-19, inducing IgA production, e.g. using Lactoferrin to activate canonical TGF- $\beta$  signaling[13], or retinoic acid to enhance lactoferrin-induced IgA responses[14], has been proposed as novel therapies for severe COVID-19. However, as highlighted by our study, enhanced IgA responses observed in severe COVID-19 might confer damaging effects in severe COVID-19. As a result, we hypothesize that severe COVID-19 might be at least in part an IgA-mediated disease (related to IgA deposition and vasculitis), which helps to explain common organ injuries in COVID-19, e.g. acute pulmonary embolism, kidney injury, etc.[15] We acknowledge the limitations of this study, including no measurement of local IgA, and limited number of patients. Future investigative efforts are certainly needed to explore the functional significance of mucosal and systemic IgA in COVID-19 and if local interventions at the mucosal level at the nasopharynx/ oropharynx could reduce viral load and symptoms.

## **Figure legends**

Figure 1. Chronological profiles of antibodies in COVID-19 patients. Patient's samples collected from week 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8 since illness onset were pooled for analysis. (A-B) The medians of antibody detection value (luminescent value) of samples at the same time point since onset was used to plot the graph. A: all patients; B: patients with severe illness. (C-E) Time-serial changes of the level of different antibody comparing in severe and non-severe groups. The medians of antibody detection value (luminescent value) of samples at the same time point since onset was used to plot the graph. C: IgA; D: IgG; E: IgM.

**Author Contributions:** HY, BS, ZF, JZ, XL, YL, XS, ZL and NZ participated in the study design. HL, BZ, ZH, PZ, LT, HQ, DL, EW, XX, SL, FY, LG and DH contributed to patient recruitment, data collection, data analysis, and literature search. ZF, ZH and PZ conducted the experiments on antibodies detection. HY, BS, ZF, LT, HQ and HH drafted the manuscript. NZ and ZL critically reviewed and revised the manuscript. All authors read the manuscript and approved the final version.

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