SARS-CoV-2-specific T cell immunity in mild hypertensive patients with COVID-19 in China

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) pandemic leads to severe illness, life-threatening complications, and death, especially in high-risk groups such as elderly people and individuals with hypertension or diabetes. It has been shown that SARS-CoV-2-specific T cell immunity is important for the patient recovery from COVID-19. However, there are no reports about SARS-CoV-2-specific T cell immunity in hypertensive patients with COVID-19.

Results: In this work, through the study of a cohort of 76 mild cases of hypertensive patients with COVID-19 and 572 hypertensive patients without COVID-19, we discovered that SARS-CoV-2 infection in hypertensive patients is characterized by T lymphopenia during the acute phase and the high frequency of CD4⁺CD25⁺, CD4⁺CD45RO⁺, and CD8⁺CD28⁺ T cells in the recovery phase. We also showed that strong SARS-CoV-2-specific CD4⁺IFNγ⁺ T cell responses are associated with high SARS-CoV-2-specific antibody titers in hypertensive patients with COVID-19.

Conclusions: The subsets of T cells including CD4⁺CD25⁺, CD4⁺CD45RO⁺, and CD8⁺CD28⁺ could be valuable biomarkers for the estimation of the progression of hypertensive patients with COVID-19. The hypertensive patients with COVID-19 exhibits T lymphopenia during the acute phase and have proper immune function during the recovery phase. This study may provide valuable insights for the monitoring and treatment of hypertensive patients with COVID-19.

Keywords: COVID-19, T lymphopenia, CD4⁺CD25⁺ T cells, CD4⁺CD45RO⁺ T cells, CD8⁺CD28⁺ T cells, CD4⁺IFNγ⁺ T cells

Background

In December 2019, a cluster of acute respiratory illness, now known as severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) pneumonia, occurred in Wuhan, China [1-8]. As of February 11, 2020, the Chinese Center for Disease
Control and Prevention has officially reported that there were 2.0% asymptomatic cases, 2.3% death cases, and 80.9% mild cases among 44,672 confirmed SARS-CoV-2 cases; the disease severity was associated with old age [9]. However, the Centers for Disease Control and Prevention (USA) has reported that 38% of the 508 hospitalized SARS-CoV-2 patients were notably young, suggesting that the disease severity may not be mainly related to patient age [10].

According to the World Health Organization (WHO) interim guidance on January 12, 2020, SARS-CoV-2 infection is classified as asymptomatic cases, mild and severe cases of pneumonia, and critical cases of pneumonia (acute respiratory distress syndrome, sepsis, septic shock). Severe cases of pneumonia are defined as patients with respiratory rate of > 30 breaths/min, severe respiratory distress, or peripheral capillary oxygen saturation of < 90% on room air [11]. Hypertension is the most common comorbidities among patients with coronavirus disease 2019 (COVID-19). However, the dynamic changes of immune responses in hypertensive patients with COVID-19 remain elusive [1-8].

In this work, 76 mild hypertensive patients with COVID-19 were admitted and confirmed for SARS-CoV-2 infection with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Enzyme-linked immunosorbent assay (ELISA) was used to detect immunoglobulins in blood samples. Peripheral blood mononuclear cells (PBMC) were analyzed for several subsets of T cells by flow cytometry. The alteration of T cells and SARS-CoV-2 specific antibodies was analyzed during the acute and recovery phases of the virus infection. Our work suggested valuable biomarkers for the progression of mild hypertensive patients with COVID-19.

Results

Mild hypertensive patients with COVID-19 experiences T lymphocyte loss during the acute phase and restoration during the recovery phase after the infection

To study the dynamic regulation of immune response for the mild hypertensive patients with
COVID-19, we analyzed the subsets of T lymphocyte cells (Supplemental Fig. 1). Flow cytometry analyses showed that hypertensive patients with COVID-19 clearly experienced T lymphocyte loss in peripheral blood during the acute phase of infection (Table 1). The mean absolute counts for CD3+, CD4+, and CD8+ T lymphocyte in hypertensive patients without COVID-19 was 1450, 869, and 481 cells/μL, respectively, whereas those in hypertensive patients with COVID-19 were markedly lower, at 641, 265, and 261 cells/μL, respectively ($P < 0.001$). However, EBV infection exhibited proliferative lymphocyte responses (Table 1).

Interestingly, we observed a rapid and significant restoration of CD3+, CD4+, and CD8+ T lymphocyte, B lymphocyte, and natural killer (NK) cells at the third week after the onset of illness in the hypertensive patients with COVID-19 (Table 2).

**Table 1.** Changes in CD3+, CD4+, and CD8+ lymphocyte counts in mild hypertensive patients with COVID-19 or Epstein-Barr virus (EBV) infections and hypertensive patients without COVID-19.

<table>
<thead>
<tr>
<th>Lymphocyte subsets* (cells/μL)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COVID-19</td>
</tr>
<tr>
<td>CD3+ lymphocytes</td>
<td>641 ± 127</td>
</tr>
<tr>
<td>CD4+ lymphocytes, T-h</td>
<td>265 ± 76</td>
</tr>
<tr>
<td>CD8+ lymphocytes, T-s</td>
<td>261 ± 61</td>
</tr>
<tr>
<td>T-h/T-s ratio</td>
<td>1.03 ± 0.48</td>
</tr>
</tbody>
</table>

Abbreviations: T-h, T helper; T-s, T suppressor. *Due to lack of reference ranges for lymphocyte and subset profile of hypertensive patients in Chinese Han population, we systematically analyzed the 572 hypertensive patients of 18-85 years old from hypertension clinic from November 2018 to November 2019. The purpose for the enrollment of hypertensive patients without COVID-19 is to acquire immunological characteristics before the COVID-19 outbreak.
Table 2. Changes in lymphocyte subsets in the acute and recovery phase of mild hypertensive patients with COVID-19 and without COVID-19.

<table>
<thead>
<tr>
<th>Lymphocyte subsets</th>
<th>Acute (n = 76)</th>
<th>Recovery (n = 76)</th>
<th>Controls (n = 572)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3$^+$ lymphocytes</td>
<td>599 ± 161</td>
<td>1,252 ± 291</td>
<td>1,450 ± 450</td>
</tr>
<tr>
<td>CD4$^+$ lymphocytes, T-h cells</td>
<td>260 ± 67</td>
<td>531 ± 110</td>
<td>869 ± 310</td>
</tr>
<tr>
<td>CD8$^+$ lymphocytes, T-s cells</td>
<td>251 ± 71</td>
<td>593 ± 162</td>
<td>481 ± 213</td>
</tr>
<tr>
<td>T-h/T-s ratio</td>
<td>1.04 ± 0.50</td>
<td>0.90 ± 0.68</td>
<td>2.01 ± 0.89</td>
</tr>
<tr>
<td>CD19$^+$ B lymphocytes</td>
<td>135 ± 210</td>
<td>171 ± 228</td>
<td>270 ± 532</td>
</tr>
<tr>
<td>CD16$^+$CD56$^+$ NK cells</td>
<td>161 ± 110</td>
<td>281 ± 112</td>
<td>253 ± 156</td>
</tr>
</tbody>
</table>

The subsets of T cells are reduced during the acute phase and returned during the recovery phase of mild hypertensive patients with COVID-19. We next explored some important CD4$^+$ and CD8$^+$ subset T cells in hypertensive patients with COVID-19. The data showed that CD4$^+$CD25$^+$ T cells were 0.8% and 3.9% in the acute phase and in the recovery phase, respectively (Table 3). CD4$^+$CD25$^+$ T cells in the recovery phase was 4.9-fold higher than those in the acute phase. The frequency of CD4$^+$CD45RO$^+$ T cells (act as memory T helper cells) and CD8$^+$CD28$^-$ T cells (act as cytotoxic suppressor T cells) in the recovery phase were higher than those in the acute phase ($P < 0.05$). Therefore, our data first indicated that the memory T helper and cytotoxic suppressor cells are recovered in hypertensive patients with COVID-19.

Table 3. Changes of immune responses in mild hypertensive patients with COVID-19 during the acute and recovery phase.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Percentage (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD4$^+$CD25$^+$</td>
</tr>
<tr>
<td>Acute (n = 76)</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>Recovery (n = 76)</td>
<td>3.9 ± 3.1</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
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<tr>
<td>( P )</td>
<td>&lt; 0.01</td>
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**SARS-CoV2-specific IgG increases during the recovery phase of hypertensive patients with COVID-19**

In order to understand the dynamic regulation of the immune response of hypertensive patients with COVID-19, we conducted a longitudinal profile analysis of SARS-CoV-2-specific antibodies against the virus infection of available 8 hypertensive patients (Fig. 1A). Among them, 50% (4/8), 25% (2/8) and 0% (0/8) were tested positive for IgG, IgM, and IgA at week 1 after the onset of symptoms, suggesting that IgG responded earlier than IgM and IgA. All eight patients were IgG, IgM, and IgA-positive in week 2 after the onset of symptoms. The IgG, IgM, and IgA mean titers peaked at 1:1040 at week 6, 1:400 at week 4, and 1:320 at week 4, respectively. The IgG titers were maintained at a high level whereas the IgM and IgA titers peaked during the acute or early convalescent phase and then declined at week 5 after the onset of symptoms.

**SARS-CoV2-specific antibody correlates with spike-specific CD4^+^IFN\( \gamma \)^+ T cells**

To investigate their relationship between protective antibody responses and the T cells, we next performed a longitudinal profile analysis of SARS-CoV-2-specific CD4^+^IFN\( \gamma \)^+ T cells against SARS-CoV-2 infection of hypertensive patients (Fig. 1B) since most protective antibody responses are dependent on CD4^+^ T helper cells. The results showed that CD4^+^IFN\( \gamma \)^+ T cells were gradually increased after the onset of COVID-19 in the mild hypotensive patients. Given that spike is the primary target of SARS neutralizing antibodies, we examined spike-specific CD4^+^IFN\( \gamma \)^+ T cells. The data showed that spike-specific CD4^+^IFN\( \gamma \)^+ T cell responses correlated well with the magnitude of the anti-spike RBD IgG titers (\( R = 0.93; P < 0.0001 \); Fig. 2A). Anti-spike IgM titers (\( R = 0.3895; P = 0.013 \); Fig. 2B) and anti-spike IgA titers (\( R = 0.3893; P = 0.013 \); Fig. 2C) also correlated with spike-specific CD4^+^IFN\( \gamma \)^+ T cells
but at a worse degree than that of anti-spike IgG titers. Therefore, the anti-spike RBD antibody response produced by COVID-19 patients is comparable to the spike-specific CD4+IFNγ+ T cell response.

Discussion

Most hypertensive patients with COVID-19 are severe or critical cases of COVID-19 and it is difficult to follow up to the recovery phase of COVID-19 [1-6]. Therefore, we selected mild hypertensive patients with COVID-19 as a model to conduct this study. In this work, we first reported the detection of SARS-CoV-2-specific T cell immunity in mild cases of hypertensive patients with COVID-19 and described the pathogenesis in the recovery phase.

It is intriguing to see the human immune system response in a drastically distinct manner to different viral infections. Whereas EBV infections lead to proliferative lymphocyte responses [12], swine foot-and-mouth disease virus [13] and respiratory syncytial virus [14] are associated with generalized lymphopenia. In swine foot-and-mouth disease virus and respiratory syncytial virus infection, the underlying mechanism is much less clear [13, 14]. It has been reported that antiviral drugs can reduce viral loads and alleviate the severity of disease in patients [15] and corticosteroid therapy can induce lymphopenia on lymphocyte recirculation [16]. To rule out this effect, all patients enrolled in our study had not received any antiviral or corticosteroid therapy.

Chen et al. [17] reported immunological features of 11 severe cases (median age of 61.0 years) and 10 moderate cases (median age of 52.0 years) of COVID-19. Immunological characteristics include a reduction in the number of CD4+ and CD8+ T cells and changes in CD8+CD28+ and CD4+CD45RO+ T cells, etc. However, they did not report the dynamics of cellular immune responses and humoral immunity. Our data may be beneficial to previous study.

Regulatory T cells (Tregs) play key roles in the maintenance of lymphoid homeostasis in a number of immune circumstances. The so-called “natural” CD4+CD25+ Tregs arise as a
distinct lineage from the thymus in human [18]. However, changes of Treg status in hypertensive patients with COVID-19 were not reported previously. Our data showed that the frequency of CD4^+CD25^+CD45RO^+ and CD8^+CD28^+ T cells in the recovery phase was significantly higher than those in the acute phase, indicating that hypertensive patients with COVID-19 have proper immune function in the recovery phase.

Long et al. [19] reported that serological courses could be followed for 26 patients who were initially seronegative and then underwent seroconversion during the observation period. Three types of seroconversion were observed: synchronous seroconversion of IgG and IgM (9/26 patients), IgM seroconversion preceding to IgG seroconversion (7/26 patients), and IgM seroconversion after IgG seroconversion (10/26 patients). Our data showed that 50% (4/8) and 25% (2/8) patients were tested positive for IgG and IgM at week 1 after the onset of symptoms, respectively, suggesting that IgG seroconversion was earlier than that of IgM, which is consistent with the previous report [19].

The profile of antibodies against SARS-CoV-2 was consistent with previous findings [19], which may be helpful in the diagnosis and in epidemiologic survey of COVID-19 patients. The presence of high titers of IgG antibody to SARS-CoV-2 in the patients at the convalescent phase also suggests that a live attenuated or inactivated vaccine for active immunization and a concentrated human anti-SARS-CoV-2 spike RBD antibody for passive immunization could be developed for the treatment of SARS-CoV-2 infection [20, 21].

Grifoni et al. [22] first identified SARS-CoV-2-specific T cells in convalescent patients with COVID-19. They found that the mean percentage of SARS-CoV-2-spike-specific CD4^+ T cells in 10 convalescent patients with COVID-19 is about 0.3% and SARS-CoV-2-specific CD4^+/CD8^+ T cell responses and SARS-CoV-2-specific antibodies are well correlated. Consistent with this, our data showed that the mean percentage of SARS-CoV-2-specific CD4^+IFNγ^+ T cells was 0.15% at week 6 (Fig. 1B), which is consistent with the previous report [22]. Our data further showed that SARS-CoV-2 spike-specific CD4^+IFNγ^+ T cell responses correlated well with the magnitude of the anti-spike RBD immunity in mild
hypertensive patients with COVID-19. The recovery patients exhibited high SARS-CoV-2-specific immunity. Furthermore, 31.6% recovery patients were > 65 years old, which does not completely support the conjecture that old age is associated with disease severity of COVID-19 in our study group. Since 38% of the severe cases were notably young, suggesting that it is critical to further study SARS-CoV-2-specific immunity in severe cases of young group [10].

Conclusions

In summary, to the best of our knowledge, our data first demonstrated that there is SARS-CoV-2-specific T cell immunity in convalescent hypertensive patients with COVID-19. This finding may be benefit to the understanding of the progression and recovery of COVID-19 patients and to the development of vaccine for the prevention of SARS-CoV-2 infection.

Materials and Methods

Patients and diagnosis

Between January and February 2020, we enrolled 76 mild hypertensive patients with COVID-19 (40 male and 36 female, 31.6% > 65 years, with mean age of 51 [standard deviation (SD) = 20]) and mean hypertension history of 19 (SD = 11) years, according to WHO interim guidance [11]. It was confirmed that all patients had come into close contact with people with COVID-19. The patients’ temperatures were between 37.5°C and 39.5°C at the time of diagnosis. The most common respiratory symptoms were cough, productive cough, sore throat, and dyspnea. Chest radiographs demonstrated the air-space consolidation, with bilateral patchy patterns, local patchy and ground glass opacity. Most of the patients had relatively normal liver and renal functions. In addition, all participating patients were antibody- and antigen-negative for Epstein-Barr virus (EBV). None of them received any kind of antiviral or corticosteroid treatment. The 76 mild hypertensive patients with COVID-19
were treated with medications of thiazide diuretics (30.3%) and angiotensin-converting enzyme (ACE) inhibitors (69.7%). All patients were followed up to the recovery phase. Due to lack of reference ranges for lymphocyte and subset profile of hypertensive patients in Chinese Han population, we systematically analyzed the 572 hypertensive patients of 18-85 years old from hypertension clinic from November 2018 to November 2019, before the COVID-19 outbreak. Among them, 315 were male and 257 were female, with a mean age of 49 (SD = 18) and mean hypertension history of 16 (SD = 12) years. Patients were treated with medications of thiazide diuretics (35%) and ACE inhibitors (65%). The purpose for the enrollment of hypertensive patients without COVID-19 is to acquire immunological characteristics before the COVID-19 outbreak. All these confirmed patients were initially admitted to Chinese PLA General Hospital, Peking Union Medical College Hospital, Zhongnan Hospital of Wuhan University, and Shanghai University of Medicine and Health Sciences Hospital. A confirmed case of COVID-19 is defined as a positive result on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of pharyngeal swab specimens [1-4]. The case series was approved by the institutional ethics board of Chinese PLA General Hospital (#2020-111), Peking Union Medical College Hospital (#ZS-1830), and Shanghai University of Medicine and Health Sciences (#2019-LCHZ-18-20190507). Written informed consent was obtained from the controls and waived to COVID-19 patients due to the rapid emergence of this infectious disease, which was approved by the Ethics Commission of Zhongnan Hospital of Wuhan University (#20200020) for emerging infectious diseases. Patients in the acute phase of COVID-19 were defined as those in the first and second week of the illness. Recovered patients were defined as body temperature returning to normal for more than 3 days and respiratory symptoms significantly improved, pulmonary imaging indicating obvious inflammation absorption, and two consecutive negative respiratory tract nucleic acid tests (taken at least 24 h between each sampling).

For comparison, blood samples were also obtained from 12 EBV-positive patients,
confirmed by RT-PCR as described previously [23]. Acute EBV infections were detected by anti-EBV IgM in serum using an EBV IgM detection kit (Beier Biological, China).

SARS-CoV-2 spike glycoprotein peptide pools

SARS-CoV-2 spike glycoprotein peptide pools (SPs, RP30020) were from Genscript Biotech. SPs include 316 peptides (delivered in two subpools, each with 158 peptides) derived from a peptide scan (15 mers with 11 amino acid overlap) through the entire spike glycoprotein (Protein ID: P0DTC2) of SARS-CoV-2.

Cell preparation

Whole blood was centrifuged for 15 min at 1800 rpm to separate the cellular fraction and plasma. The plasma was then carefully removed from the cell pellet and stored at -20°C. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Hypaque density gradient centrifugation (GE Healthcare Life Sciences) according to the manufacturer’s instructions. Isolated PBMCs were cryopreserved in cell recovery media containing 10% DMSO (Gibco), supplemented with 10% heat inactivated fetal bovine serum (Gibco) and stored in liquid nitrogen until further use. Cryopreserved PBMCs were thawed by diluting them in 10 mL complete RPMI 1640 with 5% human AB serum (Gemini Bioproducts) in the presence of benzonase (2 μL/mL) before an experiment.

Intracellular cytokine staining assay

PBMCs were stimulated with or without SPs in the presence of anti-CD28 (1 μg/mL) and anti-CD49d (1 μg/mL) in 15 mL Falcon tubes. After the first 1 h incubation, brefeldin A (10 μg/mL, Sigma-Aldrich) was added to the culture to enable intracellular protein to accumulate in all stimulations. After incubation for a total of 6 h, cells were washed, fixed, permeabilized using saponin (Sigma-Aldrich) and blocked with human IgG (25 μg/mL) for 30 min at 4 °C. Cells were then stained with anti-IFNγ antibodies (Becton Dickinson), washed twice in PBS containing 0.1% saponin, 0.1% BSA and 0.05% NaN₃, resuspended in 300 μL PBS, and
analyzed by FACSVerse™ flow cytometry (Becton Dickinson).

**Enzyme-linked immunosorbent assay (ELISA) for the detection of immunoglobulin**

Specific antibodies (IgA, IgG, and IgM) to SARS-CoV-2 were determined with two different ELISAs: an in-house assay using SARS-CoV-2 receptor binding domain (RBD) protein (Genscript Biotech) as an antigen, or a commercial kit (SARS-CoV-2 spike RBD ELISA Kit, Sino Biological, China). Microtiter plates were coated with 50 ng/well of target protein overnight at 4 °C. Plates were then blocked for 2 h at 37 °C using 200 μL of 5% non-fat milk in phosphate buffered saline (PBS). Serum samples were then diluted into 1:50 using PBS and 100 μL of each sample was applied to the coated ELISA plate and incubated for 2 h at 37 °C. Plates were then washed and incubated with horseradish peroxidase-labeled anti-human IgA, IgG, and IgM (Sigma Aldrich), diluted to 1:2000 in 5% non-fat milk in PBS. After incubation for another 1 h at room temperature, the plates were washed and developed with TMB/E substrate (Merck Millipore). Finally, the reaction was stopped with 1 M H₂SO₄ and the optical density (OD) at 450 nm was measured. Negative serum control was run each time when the assay was performed. A sample is positive if its adjusted OD value (OD\text{test} – OD\text{control}) exceeds the mean plus 3 standard deviations (SDs) of the normal controls.

**Flow cytometry analysis**

Abbott CellDyn 3500 (Mountain View) was used to determine the hematological profile. All antibodies were obtained from BD Biosciences. Two blood samples in two tubes (100 μL each) were stained with antibodies according to the manufacturer’s instruction. Then, red-cell lysis buffer (1 mL) was added to each tube, the samples were incubated for 10 min and washed with Sorvall cell washer (Thermo Fisher Scientific). Cells were then resuspended in 350 μL PBS and analyzed by a flow cytometry. Calibration and quality control for the instrument were carried out daily with the use of eight-color setup beads (BD Biosciences). All specimens were analyzed in duplicates with coefficient of variation (CV) < 5% by two independent technicians under the inter-laboratory quality control. The experiments were
repeated if the results showed CV > 5% according to the manufacturer’s instructions.

Statistical analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described by means. Means for continuous variables were compared using independent group $t$-tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Data (non-normal distribution) from repeated measures were compared using the generalized linear mixed model.

Supplementary information

Additional file 1. Supplemental Fig. 1. A representative gating of flow cytometry.

Abbreviations

COVID-19, coronavirus disease 2019; CV, coefficient of variation; EBV, Epstein-Barr Virus; IFN, interferon; PBMCs, peripheral blood mononuclear cells; PBS, phosphate buffered saline; RBD, receptor binding domain; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus 2; SD, standard deviation; SPs, spike glycoprotein peptide pools.

Author contributions

QZ, GH, YL and YX conceived and designed the experiments; QZ, GH, YL, and SD performed the experiments; QZ, GH, YL, SD, YX, and GX analyzed the data; YX and GX wrote and revised the manuscript.

Funding

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Availability of data and materials

The data supporting the conclusions of this article are included within the article and its additional file.

Ethics approval and consent to participate

The study was approved by the institutional ethics committees. Written informed consent was obtained from controls and waived to COVID-19 patients due to the rapid emergence of this infectious disease.

Competing interests

The authors declare that they have no competing interests.

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Figure legend:

Fig. 1 Longitudinal profile of SARS-CoV-2-specific antibodies (A) and SARS-CoV-2-specific CD4+IFNγ+ T cells (B) against SARS-CoV-2 infection of hypertensive patients in 6 weeks. The plasma samples of eight patients with COVID-19 were subject to the detection of IgG, IgM, and IgA and SARS-CoV-2-specific CD4+IFNγ+ T cells at each week. Means±SDs (standard deviations) were plotted. In (A), the cutoff value for a positive result was 1:10, and patients with negative results were considered to have a titer of 0 for the calculation of the mean titers. In (B), Student’s t-test was used to calculate the P-value. ****: P < 0.0001.

Fig. 2 CD4+IFNγ+ T cells correlated with IgG in SARS-CoV-2 infected patients. Spearman correlation of SARS-CoV-2-specific CD4+IFNγ+ T cells vs. SARS-CoV-2-specific IgG (A), IgM (B), and IgA (C) was calculated. Data were obtained from eight patients and tests were conducted every week.