Dynamic Antibody Responses in Patients with Different Severity of COVID-19: A Retrospective Study

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic is a serious public health event and poses a global health threat. To study the specific antibody responses would contribute to a better understanding of COVID-19.

Methods: We collected complete follow-up data from 777 patients with pathogen-confirmed COVID-19 with corresponding immunoglobulin G and M (IgG/IgM) testing results.

Results: Overall, the positive rates of IgG and IgM in severe patients were slightly higher than those in non-severe patients. In addition, higher IgG levels were detected in severe patients compared to non-severe patients ($P = 0.026$). Through further analysis, differences in IgG were only significant in serum samples taken in the first 14 days of disease onset ($P < 0.001$). On the basis of analysis of antibody expression levels at different time points in 74 patients who had undergone more than three detection tests, we found that the differences in IgG levels between the severe/non-severe patients were more pronounced than those of IgM. On multivariate logistic regression, after adjusting for cofactors, the higher anti-SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) IgG levels observed in the first 14 days of disease onset were independently associated with severe COVID-19 disease (odds ratio (OR) = 1.368, 95% confidence interval (CI) 1.138–1.645).

Conclusion: We observed differences in antibody responses among patients with different severity of COVID-19. A high IgG level in the first 14 days of disease may be positively associated with disease severity.

Keywords: COVID-19; Immunoglobulin G (IgG); Immunoglobulin M (IgM); SARS-CoV-2
Key Summary Points

Why carry out this study?
To date, there are more than 80,000,000 SARS-CoV-2-infected patients and global health systems face challenges against COVID-19.

We speculate that the level of specific antibodies may be related to the severity of the COVID-19.

What was learned from the study?
The virus-specific IgG against SARS-CoV-2 might be tested seropositive at the same time or earlier than virus-specific IgM.

There were differences in specific antibody immune response in patients with different severity of COVID-19. A strong specific IgG response in the early stage of disease (within 14 days from disease onset) might be associated with severe COVID-19.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14095683.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide, with more than 80 million people infected as of 4 January 2021. At present, virus-specific immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody detection tests are used to predict population immunity against coronavirus disease 2019 (COVID-19) and to screen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected populations. These tests are also critical for patients with undetectable viral loads that are below the lower limit of reverse transcriptase polymerase chain reaction (RT-PCR) assays [1–3].

On the basis of current data, approximately 80% of patients with COVID-19 are considered non-severe. However, for those patients that progress to severe/critical disease, mortality rates increase significantly [4, 5]. As such, potential indicators that can help predict disease progression will have great significance in clinical practice. Previous studies have indicated that the immune response differs between severe and non-severe patients [6, 7]. Therefore, we speculated that differences in immune response may also affect the expression of specific antibodies. At present, however, whether the levels of anti-SARS-CoV-2 antibodies are associated with COVID-19 progression and prognosis remains unclear, and clinical studies remain controversial. For example, Phipps et al. reported that antibody responses were ineffectual at predicting disease progression [8]. In contrast, Liu et al. found that serum IgM titer changes as COVID-19 progresses, and high levels of IgM are associated with acute respiratory distress syndrome (ARDS) in severe/critical patients [9].

In the current study, we aimed to explore the associations between dynamic antibody responses and clinical disease severity in patients with COVID-19. We included 777 patients with pathogen-confirmed COVID-19 and analyzed their SARS-CoV-2 antibody tests. We found that the IgG level in severe patients was significantly higher than that in non-severe patients in the first 14 days after symptom onset; however, this association was not obvious after 14 days. Therefore, our study suggests that early antibody response may be related to COVID-19 prognosis.

METHODS

Study Design and Participants

In total, 777 hospitalized patients with COVID-19 at Tongji Hospital in Wuhan, China, from 18 January to 26 April 2020 were included in this
study. All patients had pathogen-confirmed COVID-19 and consented to serological-specific antibody detection tests. SARS-CoV-2 infection was confirmed by RT-PCR, as previous study [10].

All patients (100%, 777/777) with complete follow-up data reached the endpoints of observation (i.e., discharged or died at hospital). Clinical and demographic data on the confirmed cases were collected from their medical records. Severe COVID-19 cases were defined as those with oxygen saturation of 94% or less while breathing ambient air or needing oxygen support, consistent with Ohmagari et al. [11]. The Ethical Committee of Tongji Hospital approved the study. All procedures were conducted in accordance with ethical standards in the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All data were analyzed anonymously. As a result of the retrospective nature of the study, informed consent was waived.

Detection of Antibodies Against SARS-CoV-2

The SARS-CoV-2 IgM and IgG antibody tests were conducted using YHLO-CLIA-IgM and YHLO-CLIA-IgG kits (YHLO Biotech Co., Ltd., Shenzhen, China) in accordance with the provided instructions, and the samples for IgM/IgG antibody tests were drawn at the same time for each individual patient. Antibody expression was measured in arbitrary units (AU) per milliliter. Positive and negative results for both IgM and IgG were indicated by greater than 10 AU/mL and 10 AU/mL or less, respectively. For each patient, we calculated the interval time between the time from disease onset and date of IgG/IgM tests. The detection method for antibodies against SARS-CoV-2 was consistent with previous research [12]. All serum samples were dated from the day of symptom onset.

Statistical Analysis

All analyses were conducted with SAS v9.4 (SAS Inc.). Measurement data were expressed as the mean and standard deviation (SD) or median and interquartile range (IQR). Comparisons among two or three different groups were performed by t tests or F tests when the measurement data were normally distributed. Otherwise, Mann–Whitney U or Kruskal–Wallis tests were applied. Enumeration data were summarized as frequency rates and percentages. Intergroup comparisons of enumeration data were performed using chi-squared tests. Logistic analysis was used to explore the influence of the log-transformed level of IgG at different sampling times from disease onset on the risk of non-severe or severe. P < 0.05 was considered statistically significant.

RESULTS

We performed a retrospective analysis of 777 patients with SARS-CoV-2 infection. According to disease severity, patients were categorized into severe (417/777, 53.7%) and non-severe groups (360/777, 46.3%). The median (IQR) days from disease onset to IgG/IgM detection for the severe patients, non-severe patients, and total patients were 13.0 (8.0–20.0) days, 25.0 (10.0–38.5) days, and 15.0 (9.0–31.0) days, respectively. Table 1 illustrates the baseline characteristics of the 777 patients with COVID-19. The mean age of the cohort was 58.1 years. The proportions of male to female patients did not differ significantly between the two groups. Patients in the severe group (62.2 ± 13.8 years) were significantly older than those in the non-severe group (53.5 ± 16.7 years). The most common comorbidity was hypertension (31.2%), which was also the only comorbidity that showed significant differences in prevalence between the two groups. Diabetes (15.6%) and coronary heart disease (6.3%) were also common comorbidities in patients. The most common symptoms in more than half of patients were fever (67.8%), cough (54.8%), and expectoration (40.5%). Results indicated that symptoms with significantly different distributions among the (P < 0.05), such as fever, cough, and dyspnea, were more common in severe patients than in non-severe patients. All patients reached the observation endpoints by 26 April 2020, and the clinical outcomes are
Table 1  Baseline characteristics of 777 patients with COVID-19

|                        | Non-severe (<em>n</em> = 360) | Severe (<em>n</em> = 417) | Total (<em>n</em> = 777) | <em>P</em> |
|------------------------|-------------------------------|-----------------------------|---------------------------|--------|
| **Sex (<em>n</em> [%])** |                               |                             |                           | 0.15   |
| Male                   | 168 (46.7)                    | 216 (51.8)                  | 384 (49.4)                |        |
| Female                 | 192 (53.3)                    | 201 (48.2)                  | 393 (50.6)                |        |
| **Age (years, mean [SD])** | 53.5 (16.7)                  | 62.2 (13.8)                 | 58.1 (15.9)               | < 0.0001 |
| **Comorbidities (<em>n</em> [%])** |                       |                             |                           |        |
| Hypertension           | 83 (23.1)                     | 159 (38.1)                  | 242 (31.2)                | < 0.0001 |
| Coronary heart disease | 17 (4.7)                      | 32 (7.7)                    | 49 (6.3)                  | 0.091  |
| Diabetes               | 46 (12.8)                     | 75 (18.0)                   | 121 (15.6)                | 0.046  |
| Chronic obstructive pulmonary disease | 6 (1.7)                  | 6 (1.4)                     | 12 (1.5)                  | 0.80   |
| Chronic kidney disease | 2 (0.6)                       | 4 (1.0)                     | 6 (0.8)                   | 0.69   |
| Cerebrovascular disease| 15 (4.2)                      | 21 (5.0)                    | 36 (4.6)                  | 0.57   |
| Hepatitis              | 5 (1.4)                       | 8 (1.9)                     | 13 (1.7)                  | 0.57   |
| Tuberculosis           | 7 (1.9)                       | 10 (2.4)                    | 17 (2.2)                  | 0.67   |
| Tumor                  | 15 (4.2)                      | 15 (3.6)                    | 30 (3.9)                  | 0.68   |
| **Signs and symptoms (<em>n</em> [%])** |                       |                             |                           |        |
| Fever                  | 222 (61.7)                    | 305 (73.1)                  | 527 (67.8)                | 0.0006 |
| Fatigue                | 47 (13.1)                     | 74 (17.8)                   | 121 (15.6)                | 0.072  |
| Cough                  | 177 (49.2)                    | 249 (59.7)                  | 426 (54.8)                | 0.0032 |
| Expectoration          | 146 (40.6)                    | 169 (40.5)                  | 315 (40.5)                | 0.99   |
| Dyspnea                | 77 (21.4)                     | 167 (40.1)                  | 244 (31.4)                | < 0.0001 |
| Headache               | 6 (1.7)                       | 18 (4.3)                    | 24 (3.1)                  | 0.033  |
| Dizziness              | 21 (5.8)                      | 18 (4.3)                    | 39 (5.0)                  | 0.33   |
| Diarrhea               | 69 (19.2)                     | 78 (18.7)                   | 147 (18.9)                | 0.87   |
| Thoracodynia           | 55 (15.3)                     | 66 (15.8)                   | 121 (15.6)                | 0.83   |
| Nausea                 | 13 (3.6)                      | 26 (6.2)                    | 39 (5.0)                  | 0.095  |
| Myalgia                | 29 (8.1)                      | 38 (9.1)                    | 67 (8.6)                  | 0.60   |
| Chills                 | 29 (8.1)                      | 45 (10.8)                   | 74 (9.5)                  | 0.20   |
| Pharyngalgia           | 20 (5.6)                      | 16 (3.8)                    | 36 (4.6)                  | 0.26   |
| Vomiting               | 7 (1.9)                       | 11 (2.6)                    | 18 (2.3)                  | 0.52   |
| Abdominal pain         | 5 (1.4)                       | 4 (1.0)                     | 9 (1.2)                   | 0.74   |

△ Adis
summarized in Table 1. In total, 5.3% (41/777) of patients died and 94.7% (741/777) of patients were discharged. All deceased patients were severe cases.

As shown in Fig. 1, dynamic changes were found in the positive rates of IgG and IgM in severe/non-severe patients. In the first 14 days from the onset of symptoms, the positive rate of IgG was significantly higher in severe patients (91.8%) than in non-severe patients (74.2%, Fig. 1a), with the same trend observed for IgM (77.6% and 61.7%, respectively, Fig. 1b). In addition, the higher positive rate of IgM in severe patients remained for 15–21 days. After 21 days, the positive rates of IgG and IgM were similar between the two groups. Furthermore, the positive rate of IgG persisted at a relatively high level (greater than 90%) in severe patients for the duration of the study. However, the positive rate of IgG in non-severe patients exhibited an obvious increase, reaching a peak of 93.2% after 21 days.

To further explore the characteristics of patient immune response to SARS-CoV-2 infection, we analyzed the correlations among levels of specific antibodies and clinical progression. The average levels of IgG and IgM in patients with COVID-19 are shown in Fig. 2a, b. The level of IgG was significantly higher in severe patients than in non-severe patients. However, there was no difference in the average level of IgM between the two groups. As a result of the changes in positive antibody rates over time, we suspected that antibody levels may be time dependent. The average levels of IgG and IgM from symptom onset to the first detection of corresponding antibodies are shown in Fig. 2c, d. During the first 2 weeks from disease onset,
we detected increases in the levels of IgG in severe patients, and then a slow decline. In the first 14 days, the IgG level in severe patients was significantly higher than that in non-severe patients. In contrast, the changes in IgM with time were not obvious, and no such time point was found between the severe and non-severe patients. We tested antibody levels in the two groups at up to 14 days and 15 days and later. A significant difference was only observed in the level of IgG within 14 days post disease onset (Fig. 2e, \( P < 0.0001 \)).

To determine the potential impact of laboratory indicators with IgG/IgM differences, we divided patients into different groups according to whether their corresponding laboratory parameters were within the normal range. We then compared the levels of specific antibodies among the distinct groups. In the normal- and abnormal-range groups, most of the 19 laboratory parameters showed no significant differences in IgG, except for IL-10 (\( P = 0.035 \)), procalcitonin (\( P < 0.0001 \)), albumin (\( P = 0.049 \)), and total bilirubin (\( P = 0.0092 \)), which showed significant differences among groups (Table 2). However, significant differences between the normal/abnormal-range groups became more pronounced in IgM. Of note, lymphocyte count (\( P = 0.0010 \)), d-dimer (\( P = 0.019 \)), ferritin (\( P = 0.021 \)), alanine aminotransferase (\( P = 0.036 \)), aspartate aminotransferase (\( P = 0.012 \)), albumin (\( P = 0.0020 \)), high sensitivity C-reactive protein (\( P = 0.0091 \)), and tumor necrosis factor alpha (\( P = 0.0069 \)) differed significantly among the various groups.

To investigate the dynamic changes in IgG and IgM within each individual patient during disease progression, we screened 74 cases where patients underwent serological-specific antibody detection at least three times. T1 represents the first test after admission, T2 represents the test closest to the midpoint of hospitalization, and T3 represents the last test before discharge. We observed that the levels of IgG and IgM showed downward trends. At all three time points, the average levels of IgG and IgM were higher in severe patients than in non-severe patients. In addition, the difference was more pronounced for IgG than for IgM, especially at T1 and T2. The levels of IgM between the
Table 2 Comparison of anti-SARS-CoV-2 IgG and IgM among different laboratory parameter groups

| Laboratory parameters (normal range) | IgG       | \( P^a \) | IgM       | \( P^a \) |
|--------------------------------------|-----------|-----------|-----------|-----------|
| White blood cell count (x 10^9/L, median [IQR]) (3.5–9.5) |           |           |           |           |
| < 3.5                                | 154.9 (93.1–194.3) | 0.50      | 42.0 (13.2–138.9) | 0.23      |
| 3.5–9.5                              | 171.6 (105.9–211.2) |           | 29.3 (8.8–87.5)   |           |
| > 9.5                                | 166.1 (85.8–233.7)  |           | 32.9 (5.8–143.3)  |           |
| Neutrophil count (x 10^9/L, median [IQR]) (1.8–6.3) |           | 0.72      |           | 0.41      |
| < 1.8                                | 167.0 (89.3–221.9)  |           | 25.5 (10.3–109.6) |           |
| 1.8–6.3                              | 170.0 (106.4–207.8) |           | 29.1 (8.6–88.3)   |           |
| > 6.3                                | 172.1 (92.0–232.6)  |           | 36.6 (7.8–136.1)  |           |
| Lymphocyte count (x 10^9/L, median [IQR]) (1.1–3.2) |           | 0.37      |           | 0.0010    |
| < 1.1                                | 171.8 (104.9–215.2) |           | 42.8 (11.1–117.6) |           |
| ≥ 1.1                                | 167.0 (101.4–210.8) |           | 25.0 (7.5–75.7)   |           |
| Monocyte count (x 10^9/L, median [IQR]) (0.1–0.6) |           | 0.12      |           | 0.22      |
| < 0.6                                | 172.4 (107.4–212.6) |           | 33.7 (9.1–94.9)   |           |
| ≥ 0.6                                | 160.8 (90.1–207.0)  |           | 25.5 (5.8–93.7)   |           |
| D-Dimer (µg/ml, median [IQR]) (< 0.5) |           | 0.17      |           | 0.019     |
| < 0.5                                | 163.7 (93.1–203.0)  |           | 24.6 (6.4–72.0)   |           |
| ≥ 0.5                                | 170.0 (104.8–212.6) |           | 35.4 (8.5–107.0)  |           |
| Ferritin (µg/L, median [IQR]) (30–400) |           | 0.69      |           | 0.021     |
| ≤ 400                                | 176.4 (111.9–219.2) |           | 28.3 (9.0–75.4)   |           |
| > 400                                | 171.0 (117.4–210.3) |           | 39.9 (12.6–115.4) |           |
| Alanine aminotransferase (U/L, median [IQR]) (≤ 41) |           | 0.69      |           | 0.036     |
| ≤ 41                                 | 172.3 (104.4–212.5) |           | 28.1 (7.9–90.0)   |           |
| > 41                                 | 171.0 (128.9–204.5) |           | 35.4 (15.9–129.8) |           |
| Aspartate aminotransferase (U/L, median [IQR]) (≤ 40) |           | 0.55      |           | 0.012     |
| ≤ 40                                 | 171.6 (105.5–212.5) |           | 27.3 (7.9–78.9)   |           |
| > 40                                 | 171.5 (125.9–206.0) |           | 43.9 (13.9–132.0) |           |
| Albumin (g/L, median [IQR]) (35–52)   |           | 0.049     |           | 0.0020    |
| < 35                                 | 177.7 (125.0–213.0) |           | 41.6 (13.2–111.9) |           |
| ≥ 35                                 | 168.3 (102.4–211.9) |           | 23.9 (7.8–75.3)   |           |
| Total bilirubin (µmol/L, median [IQR]) (≤ 26) |           | 0.0092    |           | 0.10      |
| ≤ 26                                 | 172.4 (111.2–212.5) |           | 30.8 (9.1–93.7)   |           |
| > 26                                 | 9.9 (2.2–159.1)     |           | 4.1 (0.9–119.7)   |           |
|                              | IgG           | P<sup>a</sup> | IgM           | P<sup>a</sup> |
|------------------------------|---------------|---------------|---------------|---------------|
| High sensitivity C-reactive protein (mg/L, median [IQR]) (< 1) |               | 0.52          | 0.0091        |
| < 1                          | 166.3 (96.2–211.9) |               | 22.3 (4.9–61.1) |               |
| ≥ 1                          | 169.7 (104.0–212.5) |               | 34.6 (9.8–101.0) |               |
| Procalcitonin (ng/mL, median [IQR]) (0.02–0.05) < 0.05          | 182.0 (135.4–222.0) | < 0.0001 | 32.9 (11.6–94.5) |               |
| ≥ 0.05                       | 162.9 (89.3–202.3) |               | 30.8 (6.1–94.5) |               |
| Complement 3 (g/L, median [IQR]) (0.65–1.39)                   | 0.75          | 0.25          |               |
| < 0.65                       | 169.1 (99.2–214.4) |               | 26.7 (7.9–91.3) |               |
| 0.65–1.39                    | 171.0 (108.3–208.0) |               | 36.0 (9.1–96.8) |               |
| > 1.39                       | 189.3 (176.4–202.3) |               | 51.9 (38.1–65.6) |               |
| Complement 4 (g/L, median [IQR]) (0.16–0.38)                   | 0.98          | 0.18          |               |
| < 0.16                       | 169.2 (101.0–214.4) |               | 28.0 (7.9–88.2) |               |
| 0.16–0.38                    | 170.4 (108.3–206.8) |               | 34.8 (9.1–102.5) |               |
| > 0.38                       | 163.5 (122.3–198.9) |               | 67.2 (14.0–334.0) |               |
| Interleukin-2 receptor (U/mL, median [IQR]) (223–710)          | 0.78          | 0.82          |               |
| < 710                        | 171.3 (101.3–215.0) |               | 30.5 (8.9–91.3) |               |
| ≥ 710                        | 170.4 (99.0–207.0) |               | 29.2 (6.3–101.1) |               |
| Interleukin-6 (pg/mL, median [IQR]) (< 7)                       | 0.14          | 0.91          |               |
| < 7                          | 172.5 (110.9–212.6) |               | 30.6 (8.8–91.1) |               |
| ≥ 7                          | 163.6 (88.4–212.6) |               | 30.4 (7.3–99.8) |               |
| Interleukin-8 (pg/mL, median [IQR]) (< 62)                      | 0.44          | 0.17          |               |
| < 62                         | 171.6 (101.3–213.0) |               | 30.3 (8.5–94.0) |               |
| ≥ 62                         | 161.2 (22.2–205.9) |               | 17.7 (2.4–111.2) |               |
| Interleukin-10 (pg/mL, median [IQR]) (< 9.1)                   | 0.035         | 0.63          |               |
| < 9.1                        | 172.5 (101.4–215.2) |               | 28.4 (8.0–91.2) |               |
| ≥ 9.1                        | 151.5 (84.4–192.4) |               | 35.4 (5.1–131.1) |               |
| Tumor necrosis factor alpha (pg/mL, median [IQR]) (< 8.1)      | 0.20          | 0.0069        |               |
| < 8.1                        | 174.8 (108.0–215.3) |               | 35.8 (12.2–98.8) |               |
| ≥ 8.1                        | 169.1 (95.6–212.5) |               | 25.5 (5.2–85.6) |               |

<sup>a</sup> Calculated using the Mann–Whitney U test or Kruskal–Wallis test
severe/non-severe groups were relatively similar at the different time points (Fig. 3).

Logistic regression was conducted to identify the correlation between the log-transformed level of IgG and progression of COVID-19. In the multivariate logistic regression, we included comorbidities, age, sex, interleukin-10, procalcitonin, and total bilirubin as potential cofactors, given that they appear to influence COVID-19 progression and show differential distribution among patients of different severity. After adjustment for cofactors, higher levels of IgG in the first 14 days from disease onset were independently associated with severe illness (odds ratio [OR] = 1.368, 95% confidence interval [CI] 1.138–1.645). However, this significant correlation did not hold after 15 days (OR = 1.050, 95% CI 0.859–1.284) (Table 3).

DISCUSSION

In most viral diseases, virus-specific IgM is usually the first positively identified antibody in the acute stage, followed by an increase in specific IgG at the later stage. However, this may differ in COVID-19. For example, Zhang et al. detected virus-specific IgM and IgG by enzyme-linked immunoassay and identified more patients as IgG positive than IgM positive on the first sampling day and at day 5 [13]. Long et al. also reported the SARS-CoV-2-specific IgM

![Fig. 3 Dynamic changes in antibody responses in selected patients during course of COVID-19. a IgG and b IgM](image)

Table 3 Logistic regression analysis of IgG level\(^{a}\) and disease severity

| Sampling time from disease onset | OR (95% CI) |
|---------------------------------|-------------|
|                                 | Crude\(^{b}\) | Model 1\(^{c}\) |
| ≤ 14 days                       | 1.359 (1.188–1.555)* | 1.368 (1.138–1.645)* |
| ≥ 15 days                       | 0.955 (0.829–1.101) | 1.050 (0.859–1.284) |
| All                             | 1.113 (1.012–1.224)* | 1.194 (1.044–1.365)* |

\(^{a}\)Significant at \(P < 0.05\)
\(^{b}\)log scale (log\(_{10}\))
\(^{c}\)Crude: unadjusted
\(^{c}\)Model 1: adjusted for sex, age, comorbidities, interleukin-10, procalcitonin, and total bilirubin
antibody responses could be observed within 1 week from symptom onset, but high serum levels of IgG can also be detected at the same time or even earlier [14]. Notably, Jin et al. found that the positive rate of specific IgG was significantly higher than that of IgM during COVID-19 [15]. A similar phenomenon was observed in our study, with the positive rate of virus-specific IgG found to be significantly higher than that of virus-specific IgM in the first and second weeks. At present, existing mechanisms cannot explain this result. One possible reason for this phenomenon may be that unlike Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV infections, in which the peak viral load in patients generally occurs 7–10 days after disease onset [16, 17], patients with COVID-19 have higher viral loads at the time of disease onset, similar to that of influenza [2, 18]. Previous research has also shown that levels of specific IgG against SARS-CoV-2 are correlated with virus neutralization titer [2]. In Helicobacter pylori infection, IgG antibodies against H. pylori are positively correlated with colonization density [19]. Although the underlying mechanisms related to strong IgG responses in early-stage COVID-19 are unclear, we suspect it may be related to high viral load.

Whether COVID-19 severity can impact specific antibody detection remains unclear. In a previous 23-case study, serum antibody levels were not correlated with clinical severity of COVID-19 [2]. However, Hou et al. observed that the levels of both specific IgG and IgM against SARS-CoV-2 differed significantly among 338 patients with different illness severity of COVID-19. In our research, we found sampling time from symptom onset to be an important factor when testing specific antibody levels. Previous studies have reported that 14 days after the disease onset might be a meaningful time point for specific antibody response during COVID-19 course, and a similar phenomenon was also observed in our analysis [14, 20, 21]. In the early stage of the disease, severe and non-severe patients may have distinct immune response efficiency. In the first 14 days of symptom onset, patients with severe illness had a significantly higher level of specific IgG against SARS-CoV-2 than non-severe patients. As age, sex, and comorbidities are associated with severe COVID-19 [22–24], we combined these cofactors in a multivariate analysis, which confirmed that a higher level of IgG was significantly associated with severe illness. However, this phenomenon became less obvious at 15 days from disease onset. Previous research has indicated that the detection of specific IgG antibodies against SARS-CoV-2 may play a significant role during the COVID-19 pandemic [25]. For SARS-CoV infected patients, researchers have found that a more robust IgG response is associated with severe illness [26], similar to our results reported here. Furthermore, over 90% of individuals with SARS-CoV-2 infection are IgG seropositive after 14 days of disease onset [14], as confirmed in our study. We found that the level of specific IgM in severe/non-severe patients also differed in the early stages of the disease, but this difference was not as obvious as that of IgG. After examining the serological results of asymptomatic patients, Long et al. found that, in the acute phase, specific IgG levels are significantly lower in asymptomatic than symptomatic patients [27], suggesting that the immune response may be related to disease severity.

The pro-inflammatory cytokines released by various immune cells can contribute to pathogenic inflammation and are related to COVID-19 severity [28, 29]. We also observed differences in the levels of cytokines and other laboratory indicators that may be associated with specific antibodies against SARS-CoV-2.

Several study limitations should be noted. Serological antibody tests can vary in their sensitivity and specificity. Previous infection with other coronaviruses may confound results. In addition, specific antibody production can also be affected in potentially immunodeficient patients.

**CONCLUSIONS**

This study showed a potential positive correlation between a strong specific IgG response in the early stage of disease (within 14 days from disease onset) and COVID-19 severity, although
further studies are needed to validate our conclusions.

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Data Availability. The datasets analyzed in the current study are available from the corresponding author on reasonable request.

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