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Original Article

Clinical significance of serum IgM and IgG levels in COVID-19 patients in Hubei Province, China☆

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ABSTRACT

Background: There have been many studies about coronavirus disease 2019 (COVID-19), but the clinical significance of quantitative serum severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-specific IgM and IgG levels of COVID-19 patients have not been exhaustively analyzed. We aimed to investigate the time profiles of these IgM/IgG levels in COVID-19 patients and their correlations with clinical features.

Methods: A multicenter clinical study was conducted from February 20 to March 5 2020. It involved 179 COVID-19 patients (108 males and 71 females) from five hospitals in Huangshi in Hubei Province, China. To detect SARS-CoV-2-specific IgM/IgG, quantitative antibody assays (two-step indirect immunoassays with direct chemiluminescence technology) based on the nucleocapsid protein (NP) and spike protein 1 (S1) were used. For normally distributed data, means were compared using the *t*-test, χ^2-test, or exact probability method. For categorical data, medians were compared using Mann–Whitney *U* test.

Results: The median age was 57 (44–69) years (58 [38–69] for males and 57 [49–68] for females). The median duration of positive nucleic acid test was 22.32 (17.34–27.43) days. The mortality rate was relatively low (3/179, 1.68%). Serum SARS-CoV-2-specific IgG was detected around week 1 after illness onset, gradually increased until peaking in weeks 4 and 5, and then declined. Serum IgM peaked in weeks 2 and 3, then gradually declined and

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returned to its normal range by week 7 in all patients. Notably, children had milder respiratory symptoms with lower SARS-CoV-2-specific IgM/IgG levels. The duration of positive nucleic acid test in the chronic obstructive pulmonary disease (COPD) group was 30.36 (18.99–34.76) days, which was significantly longer than that in the non-COPD group (21.52 [16.75–26.51] days; $P = 0.025$). The peak serum SARS-CoV-2-specific IgG was significantly positively correlated with the duration of positive nucleic acid test. The incidence rate of severe and critical cases in the IgM^{hi} group (using the median IgM level of 29.95 AU/mL as the cutoff for grouping) was about 38.0% (19/50), which was twice as much as that in the IgM^{lo} group (18.4%; 9/49). The patients with positive chest imaging and lymphocytopenia ($<1 \times 10^9$/L) had a higher SARS-CoV-2-specific IgM level.

Conclusions: Quantitative SARS-CoV-2-specific IgM and IgG levels are helpful for the diagnosis, severity classification, and management of COVID-19 patients, and they should be monitored in each stage of this disease.

Introduction

The coronavirus disease 2019 (COVID-19) outbreak, which was first observed in Wuhan, China, and reported to the World Health Organization (WHO) in December 2019, was characterized as a pandemic by the WHO on March 11, 2020.[1] Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a completely novel threat to human health.[2] There are still many questions about COVID-19 that need to be urgently addressed. For example, unpredicted sudden deterioration and death can occur in patients who were formerly in a stable condition, and some convalescent patients who had two or more negative nucleic acid tests subsequently exhibited positive results. There is currently no reasonable explanation for these phenomena from the immunological point of view, and it is urgent to improve our understanding of human immune response in different stages of the disease.

Detection of virus-specific antibody is effective for the diagnosis of SARS-CoV and middle east respiratory syndrome-coronavirus (MERS-CoV) infection.[3–5] Currently, according to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7),"[6] SARS-CoV-2 antibody assays are extensively carried out for COVID-19 diagnosis.[3] Using bat SARS-CoV Rp3 nucleocapsid protein (NP) as the antigen, Zhou et al.[7] identified dynamic changes in antibodies in the peripheral blood of COVID-19 patients. However, several studies raised concern over the method accuracy, as research revealed that using intact NP as the antigen for serological detection may affect the assay specificity.[3,8] Here, we used quantitative antibody assays based on the NP antigen and the spike protein 1 (S1) antigen to obtain a better understanding of the human humoral immune response to SARS-CoV-2 infection. This may improve future clinical diagnosis, severity classification, and management of COVID-19. We present this article in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist.

Methods

Study design and ethics

This study was a multicenter descriptive study with a duration of 7 weeks. It was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Clinical Research Ethical Committee of Zhongda Hospital, Affiliated with Southeast University (approval number: 2020ZDSYLL018-P01). Written informed consent was provided by the patients or their family members.

Patients

The study included 179 patients (108 males and 71 females) who were admitted to Huangshi Central Hospital, Huangshi Maternity and Child Health Care Hospital, Huangshi Traditional Chinese Medicine Hospital, Huangshi Non-Ferrous Hospital, and Huangshi Mining Bureau Hospital from February 20, 2020 to March 5, 2020. All patients had confirmed COVID-19 based on the "Diagnosis and Treatment Plan of Coronavirus Disease 2019 (Tentative 7th Revised Edition)." Suspected cases with one of the following etiological factors can be diagnosed as confirmed cases: positive real-time fluorescence polymerase chain reaction (PCR) assay for the SARS-CoV-2 nucleic acid; virus genome sequence highly homologous to the known SARS-CoV-2 sequence; or positive IgM and IgG antibodies specific for coronavirus.

Samples

Peripheral blood samples (2 mL) were collected from each patient, weekly from the day of admission to discharge, using a serum separator transport tube (SST; Becton, Dickinson and Company, Franklin Lakes, NJ, USA). SST tubes contain a polymer separation gel that separates the cellular clotted material from the serum, so the serum is located above the polymer barrier after centrifugation. The upper layer (serum) was used for further analysis.

Detection of SARS-CoV-2-specific IgM/IgG

We used quantitative antibody assays based on the NP plus S1 antigens to gain a better understanding of the human humoral immune response to SARS-CoV-2 infection. A two-step indirect immunoassay with direct chemiluminescence technology (Shenzhen Yahuilong Biotechnology Co., Ltd., China) was used, according to the kit specification. The cutoff was 10 AU/mL, so the result was deemed to be non-reactive if the antibody level was <10.00 AU/mL. To ensure appropriate test performance, the quality control products were tested every 24 h or after each calibration.

Nucleic acid test of SARS-CoV-2

Upper airway specimens (pharyngeal swabs and nasopharyngeal secretions) and lower airway specimens (sputum and airway secretions) were obtained at admission according to the standard procedures. All laboratory procedures were carried out in a Biosafety Level 3 laboratory, according to the SARS-CoV-2 nucleic acid test kit instructions (BGI Biotechnology, Co., Ltd.,

Shenzhen, China). Total RNA was extracted using a nucleic acid extraction kit (DP315R; TIANGEN, Beijing, China). Thereafter, 10 μL RNA was used for real-time quantitative PCR, which was performed under the following conditions: 50°C for 20 min, 95°C for 10 min, and 40 cycles of amplification at 95°C for 15 s and 60°C for 30 s. The cutoff value of the kit was determined using a receiver operating characteristic curve (Ct ≤ 38).

Definitions

The diagnosis and severity of COVID-19 were defined according to the "Diagnosis and Treatment Plan of Coronavirus Disease 2019 (Tentative 7th Revised Edition)." Lymphocytopenia (peripheral blood lymphocyte count $<1\times10^9$/L) was determined based on the peak value detected in week 1.

Statistical analysis

Data were analyzed using SPSS 22.0 software (IBM Corporation, Chicago, IL, USA). Normally distributed continuous data are expressed as mean ± standard deviation. The mean was compared between pairs of groups using the *t*-test, χ^2-test, or exact probability method. Categorical data are expressed by median and interquartile range (IQR). The median was compared between pairs of groups using the Mann–Whitney *U* test. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

From February 20, 2020 to March 5, 2020, 179 patients (108 males and 71 females) underwent 202 quantitative tests for SARS-CoV-2-specific antibody IgM/IgG. The median age was 57 (44–69) years (58 [38–69] for males and 57 [49–68] for females). The mean duration of positive nucleic acid test was 2.32 (17.34–27.43) days. The mortality rate was relatively low (3/179, 1.68%). The clinical characteristics are summarized in Table 1.

Table 1
Clinical characteristics of 179 COVID-19 patients.

Clinical characteristics	Value
Age (years)	57 (44–69)
Male	108 (60.34)
Duration of positive nucleic test (days)	2.32 (17.34–27.43)
Non-survival cases	3 (1.68)
Mild	25 (13.97)
Moderate	100 (55.87)
Severe	26 (14.53)
Critical	28 (15.08)
Oxygen therapy	147 (82.12)
Nasal cannula	121 (67.60)
Mask oxygen therapy	12 (6.70)
NIV/HFNC	7 (3.91)
MV	7 (3.91)
ECMO	2 (1.12)
Underlying diseases	67 (37.43)
COPD	14 (7.82)
Diabetes	23 (12.85)
Hypertension	35 (19.55)
Coronary heart disease	15 (8.38)
Cerebral infarction	3 (1.68)

Data are presented as *n*(%) or median(IQR).
COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; HFNC: High-frequency nasal cannula; IQR: Interquartile range; MV: Mechanical ventilation; NIV: Non-invasive ventilation.

Profile of serum SARS-CoV-2-specific IgM/IgG levels

The percentages of cases with serum IgG detection from week 1 to 7 after illness onset were 50.00% (3/6), 100.00% (24/24), 100.00% (69/69), 100.00% (60/60), 100.00% (25/25), 100.00% (12/12), and 100.00% (6/6), respectively, while the percentages with serum IgM were 50.00% (3/6), 75.00% (18/24), 75.36% (52/69), 88.33% (53/60), 88.00% (22/25), 75.00% (9/12), and 0.00% (0/6), respectively.

Serum IgG was detected around week 1 (22.65 [2.21–80.61] AU/mL) after illness onset, then gradually increased from week 1 to 4 and peaked in weeks 4 (155.59 [116.79–171.23] AU/mL) and 5 (153.69 [102.55–170.66] AU/mL), followed by a decline in week 6 (80.54 [59.30–98.16] AU/mL) and week 7 (81.20 [76.13–126.34] AU/mL). Serum IgM was detected around week 1 (10.89 [1.47–25.40] AU/mL) after illness onset, peaked in weeks 2 (25.94 [10.77–91.94] AU/mL) and 3 (37.78 [9.54–105.45] AU/mL), and then gradually decreased from week 4 (34.91 [15.90–79.11] AU/mL) to 6 (18.68 [11.11–28.06] AU/mL). By week 7 (6.22 [2.61–7.43] AU/mL), the IgM level in all patients dropped to the normal range. These results are shown in Figure 1A and B.

SARS-CoV-2-specific IgM/IgG and age

All children (<18 years old; $n = 9$) had mild or moderate clinical symptoms. The median age of children was 6 (2–14) years, and that of adults ($n = 170$) was 58 (48–69) years. The median IgG level from week 2 to 5 in children was 73.08 (2.29–151.73) AU/mL, which was significantly lower than that in adults (146.28 [111.32–167.71] AU/mL; $P = 0.011$). The median IgM level was 11.23 (2.16–19.76) AU/mL in children, which was also significantly lower than that in adults (35.43 [15.81–87.16] AU/mL; $P = 0.001$; Table 2).

SARS-CoV-2-specific IgM/IgG and underlying diseases

The percentage of patients with underlying diseases (chronic obstructive pulmonary disease [COPD], diabetes, hypertension, coronary heart disease, and/or cerebral infarction) in the critical group was 60.71% (17/28), which was significantly higher than that in the mild group (12.00%; 3/25; $P = 0.007$) and moderate group (37.00%; 37/100; $P = 0.025$).

The duration of positive nucleic acid test in the COPD group ($n = 14$) was 30.36 (18.99–34.76) days, which was significantly longer than in the non-COPD group (21.52 [16.75–26.51] days; $n = 165$; $P = 0.025$; Table 2). There was no significant difference in the serum SARS-CoV-2-specific IgM/IgG ratio between the COPD and non-COPD groups ($P > 0.05$). There were also no significant differences in the duration of positive nucleic acid test and SARS-CoV-2-specific IgM/IgG ratios between groups with or without underlying diseases ($P > 0.05$).

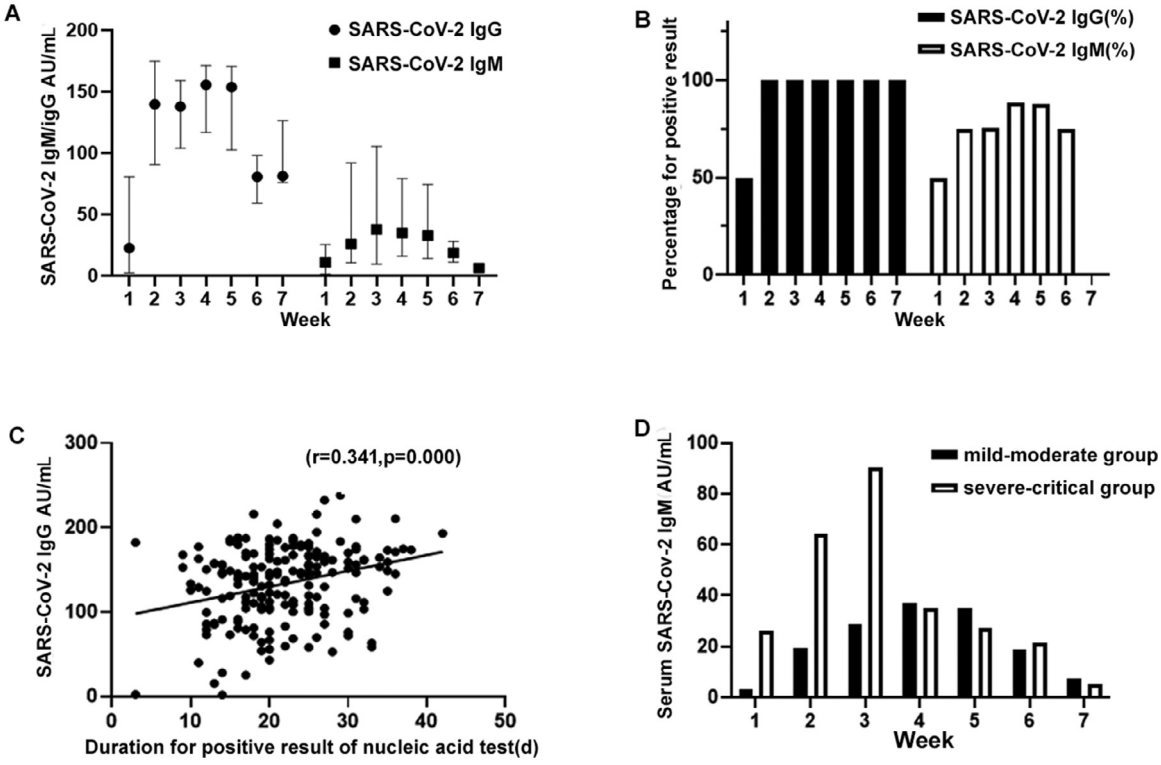

Figure 1. (A) Serum SARS-CoV-2-specific IgM and IgG levels in COVID-19 patients from week 1 to 7; (B) Percentage of COVID-19 patients with positive serum SARS-CoV-2-specific IgM and IgG from week 1 to 7; (C) Correlation between the peak SARS-CoV-2-specific IgG level (from week 1 to 5) and the duration of positive nucleic acid test in COVID-19 patients, showing the relationship between the antibody level and virus clearing ability. A higher antibody level, regardless of the time point, indicated a longer time to clear the virus (e.g., increased virulence); (D) Comparison of serum SARS-CoV-2-specific IgM between mild/moderate and severe/critical groups from week 1 to 7. COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

Table 2
Comparison of age, SARS-CoV-2-specific IgG/IgM, and duration of positive nucleic acid test in different COVID-19 groups.

Groups	Age (years)	SARS-CoV-2-specific IgG (AU/mL)	SARS-CoV-2-specific IgM (AU/mL)	Duration of positive nucleic acid test (days)
Children ($n=9$)	6 (2–14)	73.08 (2.29–151.73)	11.23 (2.16–19.76)	13.56 (2.00–22.44)
Adults ($n=170$)	58 (48–69)	146.28 (111.32–167.71)*	35.43 (15.81–87.16)†	22.47 (17.40–27.47)†
COPD ($n=14$)	70 (67–82)	147.04 (113.43–155.29)	44.95 (22.69–189.32)	30.36 (18.99–34.76)
No COPD ($n=165$)	57 (43–68)†	136.92 (98.60–165.51)	27.23 (10.89–74.25)	21.52 (16.75–26.51)*
No oxygen therapy ($n=32$)	50 (30–58)	120.97 (78.64–162.46)	24.21 (11.71–79.32)	20.47 (15.78–27.02)
Oxygen therapy ($n=147$)	59 (48–69)†	144.74 (100.56–165.94)*	28.38 (11.90–78.09)	22.39 (17.36–27.44)
Lymphocytopenia ($n=60$)	69 (56–80)	137.44 (99.88–157.61)	35.24 (17.61–103.44)	21.47 (17.40–27.40)
No lymphocytopenia ($n=119$)	55 (38–61)†	140.57 (98.16–166.53)	22.83 (9.89–63.59)*	22.44 (16.50–27.46)
Positive chest imaging ($n=154$)	58 (48–70)	136.92 (100.65–162.14)	31.91 (13.09–84.33)	22.44 (17.47–27.55)
Negative chest imaging ($n=25$)	52 (28–67)†	144.29 (86–169.54)	21.45 (8.79–49.29)*	19.58 (13.36–26.52)

Data are presented as median (IQR).
COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.
*$P < 0.05$.
†$P < 0.01$.

SARS-CoV-2-specific IgG and duration of positive nucleic acid test

The mean duration of positive nucleic acid test was 21.84 ± 7.69 days (range: 3.00–42.00 days), with 3 (1.68%), 25 (13.97%), 62 (34.64%), 59 (32.96%), and 30 (16.76%) cases having a mean duration of <7 days, 8–14 days, 15–21 days, 22–28 days, and >28 days, respectively.

The peak serum SARS-CoV-2-specific IgG level (from week 1 to 5) was significantly positively correlated with duration of positive nucleic acid ($r=0.341$; $P=0.000$; Figure 1C).

SARS-CoV-2-specific IgM and lymphocytopenia

The incidence rate of lymphocytopenia in hospitalized COVID-19 patients was 33.52% (60/179). The median serum SARS-CoV-2-specific IgM level was 35.24 (17.61–103.44) AU/mL in the lymphocytopenia group ($n=60$), which was significantly higher than that (22.83 [9.89–63.59] AU/mL) in the non-lymphocytopenia group ($n=119$; $P=0.038$; Table 2).

SARS-CoV-2-specific IgM and chest imaging

The incidence rate of positive chest imaging findings in hospitalized COVID-19 patients was 86.03% (154/179). The serum

Table 3
Comparison of age, duration of positive nucleic acid test, underlying disease, and SARS-CoV-2-specific IgG/IgM among mild, moderate, severe, and critical groups.

Severity of illness	Age (years)	Duration of positive nucleic acid test (days)	Underlying disease	SARS-CoV-2-specific IgG (AU/mL)	SARS-CoV-2-specific IgM (AU/mL)
Mild ($n=25$)	53 (23–58)	17.89 (13.42–24.60)§	6 (11.54)	118.27 (75.83–154.67)	23.83 (4.57–39.67)§
Moderate ($n=100$)	56 (42–66)*	21.47 (17.34–26.55)	37 (37.00)	144.56 (104.56–167.07)	26.21 (8.91–73.28)
Severe ($n=26$)	65 (52–76)†,‡	25.37 (18.03–27.38)*	11 (42.60)	145.94 (125.96–161.73)	61.37 (25.69–114.15)†
Critical ($n=28$)	69 (57–83)†,‡	25.36 (19.28–30.36)	17 (60.71)†,‡	115.65 (80.99–162.85)	29.70 (14.88–100.65)*

Values are presented as median (IQR) or n(%).
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.
*$P < 0.05$ *vs*. mild group.
†$P < 0.01$ *vs*. mild group.
‡$P < 0.01$ *vs*. moderate group.
§$P < 0.05$ *vs*. non-mild group.

SARS-CoV-2-specific IgM level in the negative chest imaging group ($n=25$) was 21.45 (8.79–49.29) AU/mL, which was significantly lower than that (31.91 [13.09–84.33] AU/mL) in the positive chest imaging group ($n=154$; $P=0.043$; Table 2).

SARS-CoV-2-specific IgM/IgG and severity of disease

To assess the relationship between the severity of disease and SARS-CoV-2-specific IgM level in the early stage of COVID-19, we analyzed a subset of patients with complete antibody data at 1 to 3 weeks from this cohort study. From week 1 to 3, the median serum SARS-CoV-2-specific IgM in the severe/critical group ($n=28$) was 69.25 AU/mL (IQR: 24.84–116.94), which was significantly higher than that in the mild/moderate group ($n=71$; 23.69 [7.28–73.93] AU/mL; $P=0.009$). The incidence rate of severe and critical cases in the IgM^{hi} group (using the median IgM level of 29.95 AU/mL from week 1 to 3 as the cutoff for grouping) was 38.00% (19/50), which was twice as much as that in the IgM^{lo} group (18.4%; 9/49) ($P=0.030$; Figure 1D).

The serum SARS-CoV-2-specific IgG level in the oxygen therapy group was 144.74 (100.56–165.94) AU/mL, which was significantly higher than that in the non-oxygen therapy group (120.97 [78.64–162.46] AU/mL; $P=0.045$; Table 2).

The duration of positive nucleic acid test in mild cases was 17.89 (13.42–24.60) days, which was significantly shorter than that in non-mild cases (22.52 [17.49–27.47] days; $P=0.022$). The median serum SARS-CoV-2-specific IgM in the mild group (n=25) was 23.83 AU/mL (IQR: 4.57-39.67), which was significantly lower than that in the non-mild group (n=154; 31.04 AU/mL [IQR: 13.12-81.88]; P=0.034). Age was correlated with disease severity, and the more severe the disease, the older the age. The incidence of underlying diseases was also significantly higher in the critical group compared to non-critical ones [Table 3].

Discussion

It is well-known that the production of antibodies against a particular virus is individual similar across patients (except for immunocompromised patients) during the acute phase of infection. Although SARS-CoV NP has high sensitivity for SARS, its specificity is not sufficient, as it cross-reacts with antibodies against several class I animal coronaviruses such as human coronavirus 229E, feline infectious virus, and pig infectious virus.[8,9] Therefore, using intact NP as an antigen for serological detection regarding SARS-CoV-2 may reduce the assay specificity. The S protein of SARS-CoV-2 is composed of the S1 and S2 subunits.[10,11] The S1 subunit contains the receptor binding domain (RBD), which is responsible for binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2). The S2 subunit mediates the subsequent membrane fusion process.[10,12] We assessed antibodies targeting the NP and S1 proteins of SARS-CoV-2 instead of NP alone to enhance the specificity of the assay.

Our results showed that serum SARS-CoV-2-specific IgG was detected around week 1 after illness onset, gradually increased until peaking in weeks 4 and 5, and then declined but was still maintained at a higher level than that in week 1. Serum IgM appeared around week 1 and peaked in weeks 2 and 3, earlier than serum IgG did. It then gradually declined and returned to the normal range by week 7 in all patients. Although the trend was similar, the details such as the peak timing and the duration of the antibodies differed from those in SARS and MERS. Lee et al.[4] found that serum SARS-CoV IgG was first detected on day 4 after illness onset, seroconversion occurred at a median of 16 days (range: 4–35 days), and IgG peaked in week 4. Another study revealed that serum SARS-CoV IgG increased after week 1 and peaked on day 60, and remained at a high level until month 6, at which point it declined gradually until month 24. IgM was detected around day 15 and rapidly peaked, and then declined until it was undetectable after 6 months.[13] MERS-CoV IgG was still detectable in patients with MERS infection in month 12.[5] In contrast, in our study, the IgM level in all patients dropped back to the normal range by week 7. We did not have data on the persistence of detectable SARS-CoV-2-specific IgG; however, 100% of patients had increased IgG level at week 7.

Regarding age, we found that children have milder respiratory symptoms, a shorter duration of positive nucleic acid test, and lower SARS-CoV-2-specific IgM/IgG levels. During the SARS-CoV pandemic, most children had a benign course of illness with milder symptoms and there were no deaths reported for children.[14] However, comparing the data from children and adults with SARS, Previous study found no significant differences in plasma viral load within week 1 after admission.[15] One explanation is a relatively blunted immune response against SARS-CoV in children.[16–18] Another explanation is the increased presence of high-affinity IgG against the common circulating human coronavirus strains in adults. Children aged <6 years lack anti-Coronavirus(CoV) IgG, and then they start to develop antibodies against the common circulating coronavirus strains in humans (NL63, 229E, OC43, and HKU1). The anti-CoV repertoire in children consists of IgG with low affin-

ity, which will gradually mature into high-affinity anti-CoV IgG after repeated infections.[15,19]

We found that patients with COPD had a longer duration of positive nucleic acid test. Kwak et al.[20] reported that patients with COPD had worse outcomes during viral infections such as rhinovirus, respiratory syncytial virus, coronavirus, and influenza A.[21] Smokers and chronic COPD patients were reported to be more susceptible to MERS-CoV infection.[22] Seys et al.[22] revealed that dipeptidyl peptidase 4 (DPP4) expression was upregulated in the lungs of smokers and COPD patients, which may, at least in part, explain why these individuals were more susceptible to MERS-CoV infection and had prolonged viral carriage.

The peak serum SARS-CoV-2-specific IgG (from week 1 to 5) was significantly positively correlated with the duration of positive nucleic acid test. It has been reported that the duration of MERS-CoV RNA detection (not the viral load) in sputum significantly correlated with the antibody level, with even neutralizing antibodies seeming insufficient to clear the infection.[5] IgG–virus complexes can facilitate viral entry and infection of host cells by antibody-dependent enhancement (ADE), aggravating the inflammation and infection severity. This phenomenon has been observed in SARS, MERS, Zika, HIV, and Dengue virus infections and vaccinations, making it a serious barrier to developing safe vaccines against these viruses. There is less with high-affinity anti-COVID-19 IgG in children, which may partly explain the decreased disease severity, due to decreased ADE.[4,15,23]

The patients with positive chest imaging and lymphocytopenia had a higher level of SARS-CoV-2-specific IgM. Lymphocytopenia is common in COVID-19 patients and might be a critical factor associated with lung injury, disease severity, and mortality.[24,25] In COVID-19 patients, the counts of peripheral CD4 and CD8 T lymphocytes are substantially reduced, and their immuno-status is hyperactivated, indicating severe immune injury in these patients.[26].

The severe/critical cases had a higher SARS-CoV-2-specific IgM levels, and more attention should be paid to patients with IgM level >29.95 AU/mL, as they had a two-fold increased risk of deteriorating into severe/critical cases. Although natural neutralizing IgG may contribute to viral clearance to some extent,[4,27] it is less likely that disease progression and clinical deterioration result from a depressed humoral response to SARS-CoV-2 because higher IgG levels were detected in patients with more severe disease compared to milder patients. Similar to SARS, it seems more likely that a robust humoral response to SARS-CoV-2 was one component of an overall exaggerated immune response in COVID-19, which is associated with cytokine storms (e.g., interferon [IFN]-γ and interleukin [IL]-6).[28,29] ADE modulates the immune response and elicits sustained systemic inflammation, lymphocytopenia, and organ dysfunction, one or all of which have been documented in many critical cases and deaths.[30] While the immunological host response to SARS-CoV-2 infection has not yet been fully elucidated to confirm whether ADE occurs, the current clinical evidence and our data suggest this is a possibility. Based on *in vitro* studies[31] and mouse models[32] of SARS-CoV infection, ADE decreases the ability to control inflammation in the lungs, kidneys, and elsewhere. This mechanism may account for the acute respiratory distress syndrome and other observed inflammation-based organ injuries seen in many severe and critical COVID-19 patients.[30] Further studies need to investigate how the virus interacts with the host immune system, leading to the great variation in clinical manifestations.

There are several limitations in this study. First, this was a study on aggregate data and we lacked dynamic patient-level data, so this may have affected the results. Second, although it was a multicenter study, the sample size was small, which weakened the strength of our findings. Third, the study duration was only 7 weeks, so the results cannot fully explain the whole immune process in humans. More large-scale, long-term clinical studies focusing on patient-level data are needed to further confirm the conclusions.

Conclusions

Quantitative measurements of SARS-CoV-2-specific IgM and IgG levels are helpful for the diagnosis, severity classification, and management of COVID-19 patients, and these levels should be monitored in each stage of this disease.

Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was provided by the patients or their family members. This study was approved by the Ethics Committee of Zhongda Hospital, Affiliated with Southeast University (2020ZDSYLL018-P01). This article does not contain any animal studies performed by any of the authors.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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