The Journal of Infectious Diseases

MAJOR ARTICLE

Longitudinal Change of Severe Acute Respiratory Syndrome Coronavirus 2 Antibodies in Patients with Coronavirus Disease 2019

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Background. A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has recently emerged and caused the rapid spread of coronavirus disease 2019 (COVID-19) worldwide.

Methods. We did a retrospective study and included COVID-19 patients admitted to Renmin Hospital of Wuhan University between 1 February and 29 February 2020. Antibody assay was conducted to detect COVID-19 envelope protein E and nucleocapsid protein N antigen.

Results. One hundred twelve patients were recruited with symptoms of fever, cough, fatigue, myalgia, and diarrhea. All patients underwent antibody tests. Fifty-eight (51.79%) were positive for both immunoglobulin M (IgM) and immunoglobulin G (IgG), 7 (6.25%) were negative for both antibodies, 1 (0.89%) was positive for only IgM, and 46 (41.07%) were positive for only IgG. IgM antibody appeared within a week post–disease onset, lasted for 1 month, and gradually decreased, whereas IgG antibody was produced 10 days after infection and lasted for a longer time. However, no significant difference in levels of IgM and IgG antibodies between positive and negative patients of nucleic acid test after treatment was found.

Conclusions. Our results indicate that serological tests could be a powerful approach for the early diagnosis of COVID-19.

Keywords. SARS-CoV-2; COVID-19; antibody; serological test; humoral immunity.

In December 2019, a rapidly spreading coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in Wuhan, China [1]. Currently, the disease has emerged as an explosive epidemic in many countries, showing the characteristics of a global pandemic. Whole-genome sequencing results show that COVID-19 is classified under the *Betacoronavirus* 2B subgroup because of its typical coronavirus family characteristics [2], of which the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are well known to people because of their previous outbreaks. The genome sequencing data of SARS-CoV-2 showed >80% identity with SARS-CoV and 50% identity with MERS-CoV [3, 4]. While the origin of SARS-CoV-2 remains unclear, current evidence suggests its transmission from bat to humans through a potential intermediate host [5]. Autopsy results show that inflammatory storms play an important role in the pathological changes of the disease. The latest reports show that $CD4^+$ and $CD8^+$ T-cell counts in the peripheral blood of SARS-CoV-2–infected patients are significantly reduced [6]. The most common clinical manifestations of COVID-19 include fever, dry cough, and fatigue. Other symptoms include sputum production, myalgia, headache, and diarrhea [7, 8].

Currently, there is still no effective drug for COVID-19 treatment, and the vaccine is in the stage of clinical trials. Early diagnosis, isolation, and treatment are essential to cure the disease and control the epidemic. Serum antibody detection is of great significance in the diagnosis of infected patients, especially for patients with negative nucleic acid test results. Simultaneous detection of both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies helps to identify the stage of the infectious. Generally, the antibody profile against SARS-CoV has a typical pattern of IgM and IgG production: The SARS-specific IgM antibodies appear about 2 weeks after infection and disappear at the end of week 12, whereas the IgG antibodies last for months or even many years [9]. For COVID-19, however, the longitudinal pattern of the antibodies remains unclear. We performed this study to investigate the potential relationships between immune antibodies and disease progression.

METHODS

Patients and Samples

We conducted a retrospective study of medical records from 112 patients diagnosed with COVID-19 admitted to Renmin

Received 30 March 2020; editorial decision 27 April 2020; accepted 28 April 2020; published online May 2, 2020.

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The Journal of Infectious Diseases® 2020;222:183–8

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DOI: 10.1093/infdis/jiaa229

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Hospital of Wuhan University between 1 February and 29 February 2020. All patients were diagnosed based on the New Coronavirus Pneumonia Prevention and Control Program (fourth edition) published by the National Health Commission of China, with positive results for SARS-CoV-2 using quantitative reverse-transcription polymerase chain reaction (RT-PCR) with samples from the respiratory tract. This study was approved by the Hospital Ethics Committee of the Renmin Hospital of Wuhan University (WDRY2020-K136).

Data Collection

Epidemiological, clinical, and laboratory information was obtained with data collection forms from electronic medical records and were reviewed by trained physicians. The date of disease onset was defined as the day when the symptom was noticed. Nasopharynx swab and oropharynx swab samples were collected and tested for SARS-CoV-2 open reading frame 1ab (*ORF1ab*) and nucleocapsid protein (*N*) genes with the double nucleic acid detection kit (BioGerm, Shanghai, China), following World Health Organization guidelines [10, 11]. An IgM and IgG antibody detection kit (Yahuilong Biotechnology, Shenzhen, China) was developed to detect COVID-19 envelope protein E and nucleocapsid protein N antigen. The background antibody titer in uninfected healthy individuals is < 10 AU/mL. Any test that is > 10 AU/mL was considered positive.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 software. Continuous variables were expressed directly as a range. Categorical variables were expressed as number (%). Two-sided $P < .05$ was considered statistically significant.

RESULTS

This retrospective study included 112 patients, with 33 (29.5%) males and 79 (70.5%) females. All patients had a positive result in the nucleic acid test. The median age of the subjects was 38.625 ± 14.9 years (range, 25–78 years). With the exception of 10 patients who reported no symptoms (8.93%), the most common symptoms were fever (61 [54.46%]), cough (52 [46.43%]), fatigue (29 [25.89%]), dizziness (2 [1.79%]), pharyngeal pain (15 [13.39%]), diarrhea (11 [9.82%]), vomiting (2 [1.79%]), myalgia (2 [1.79%]), headache (4 [3.57%]), and eye discomfort (1 [0.89%]) (Table 1). Most of the participants in this study were young people without previous medical history. All patients had mild symptoms, and no one was sent to the intensive care unit. Of the 11 patients with diarrhea, 3 (27.27%) were anal swab positive.

Serological antibody tests were performed at different times post–disease onset. The overall antibody positivity was 93.75% (105/112). Fifty-eight of 112 patients (51.79%) were positive for IgM (20.93 ± 45.94 AU/mL, mean ± SD) and IgG (122.26 ± 60.94 AU/mL), 7 (6.25%) were negative for both antibodies, 1 (0.89%) was positive for IgM with no response to IgG, and 46 (41.07%) were positive for IgG but not for IgM. Further group subtypes were analyzed based on the course of the disease (Table 2). Compared to the IgG titers tested within 10 days after the onset of COVID-19, the IgG titers tested at 20–29 days ($P = .0025$), 30–39 days ($P = .0147$), and 40–49 days ($P = .0049$) after disease onset were significantly higher (Table 2). Figure 1 shows the distribution of antibody according to the time point after disease onset.

Among the 7 patients who were tested for serological antibody within 10 days after the onset of the disease, 4 were positive for both antibodies (6–8 days after disease onset), 1 was positive for only IgM (4 days after the onset of the disease), and 2 patients were negative for both antibodies.

Among the 10 patients who underwent serological antibody testing 10–20 days after disease onset, 5 were positive for both IgM (37.42 ± 18.69) and IgG (161.19 ± 16.80) antibodies, 3 were positive for IgG (43.46 ± 20.42), and 2 subjects were negative for both IgM and IgG. Furthermore, only the initial PCR test was positive for these 2 subjects. All of the subsequent PCR tests were negative.

Among the 38 patients who were tested for serological antibody 20–30 days after infection, 17 were positive for both IgM (21.07 ± 9) and IgG (144.56 ± 20.78) antibodies, and 21 were positive for IgG (115.74 ± 51.38) but not IgM (5.51 ± 2.57); 20 of 38 (52.63%) patients still showed a positive nucleic acid test when the antibody test was implemented.

Among the 49 patients who underwent serological antibody testing 30–40 days after the onset of the disease, 27 were positive for both IgM (49.67 ± 81.44) and IgG (155.00 ± 31.59) antibodies, 19 were positive for IgG (123.07 ± 68.55), and 3 were negative for both antibodies. Twenty-six of 38 patients showed a positive nucleic acid test when an antibody test was performed.

Table 1. Demographics, Baseline Characteristics, and Clinical Symptoms of the 112 Patients Infected With Coronavirus Disease 2019

Variables	Total Patients (N = 112)	Male (n = 33 [29.5%])	Female (n = 79 [70.5%])
Age, y, mean ± SD	38.625 ± 14.9	39.79 ± 15.94	38.14 ± 14.44
Symptoms			
Fever	61 (54.46)	26 (78.79)	35 (44.30)
Dry cough	52 (46.43)	15 (45.45)	37 (46.84)
Fatigue	29 (25.89)	6 (18.18)	23 (29.11)
Dizziness	2 (1.79)	1 (3.03)	1 (1.27)
Pharyngeal pain	15 (13.39)	3 (9.09)	12 (15.19)
Diarrhea	11 (9.82)	3 (9.09)	8 (10.13)
Nausea	2 (1.79)	1 (3.03)	1 (1.27)
Myalgia	2 (1.79)	1 (3.03)	1 (1.27)
Headache	4 (3.57)	1 (3.03)	3 (3.80)
Ocular symptoms	1 (0.89)	0 (0)	1 (1.27)
No symptoms	10 (8.93)	1 (3.03)	9 (11.39)

Data are presented as No. (%) unless otherwise indicated.
Abbreviation: SD, standard deviation.

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Table 2. Comparison of the Results of Antibody Detection in Patients With Coronavirus Disease 2019 According to Days Post–Disease Onset

	IgG																	
	< 10 d			10–19 d			20–29 d			30–39 d			40–49 d			Sum		
IgM	(+)	(–)	Total	(+)	(–)	Total	(+)	(–)	Total	(+)	(–)	Total	(+)	(–)	Total	(+)	(–)	Total
(+), No.	4	1	5	5	0	5	17	0	17	27	0	27	4	0	4	58	1	59
(–), No.	0	2	2	3	2	5	21	0	21	19	3	22	4	0	4	46	7	53
Total No.	4	3	7	8	2	10	38	0	38	46	3	49	8	0	8	104	8	112
IgM titer, AU/mL	17.65 ± 18.40			14.98 ± 21.85[a]			10.89 ± 9.34[a]			28.99 ± 64.12[a]			27.03 ± 17.35[a]			20.93 ± 45.94		
IgG titer, AU/mL	31.53 ± 51.33			76.81 ± 63.59[a]			126.54 ± 44.80[b]			130.19 ± 63.57[c]			165.46 ± 18.92[d]			122.26 ± 60.94		

Data represent mean ± standard deviation unless otherwise indicated.

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M.

[a]Compared to the IgM and IgG titer in patients < 10 days after coronavirus disease 2019 onset, no statistical difference was shown.

[b–d]Compared to the IgM and IgG titer in patients < 10 days after coronavirus disease 2019 onset, there is a significant difference of IgG titer in patients' disease onset at 20–29 days (P = .0025[b]), 30–39 days (P = .0147[c]), and > 40 days (P = .0049[d]), respectively. The rest showed no statistical difference in other subgroups.

Among the 8 patients who underwent serological antibody testing 40–50 days after disease onset, 4 patients were positive for both IgM (35.48 ± 10.74) and IgG (174.53 ± 12.17) antibodies, and the rest were positive for IgG (86.01 ± 71.63); 5 of 8 patients showed a positive nucleic acid test when the antibody test was implemented.

Of the 112 patients included in this study, 26 underwent 2 successive antibody and nucleic acid tests. Eleven were positive for the second nucleic acid test, and 15 were negative. Of these 26 patients, the initial IgM and IgG titers were 21.65 ± 26.35 AU/mL and 112.96 ± 47.67 AU/mL, respectively. The positivity rates of IgM and IgG were 50% (13 patients) and 100% (26 patients), respectively. Of the 11 patients who were positive for the second nucleic acid test, the initial IgM and IgG titers were 22.83 ± 35.39 AU/mL and 106.78 ± 44.31 AU/mL, respectively. The positivity rates of IgM and IgG were 45% (5 patients) and 100% (11 patients), respectively. Of the 15 patients who were negative for the second nucleic acid test, the initial IgM and IgG titers were 20.79 ± 18.55 AU/mL and 112.59 ± 51.03 AU/mL, respectively. The positivity rates of IgM and IgG were 87% (13 patients) and 100% (15 patients), respectively. (Table 3). In addition, Figure 2 shows the trend lines for the IgM and IgG antibody levels at visits 1 and 2.

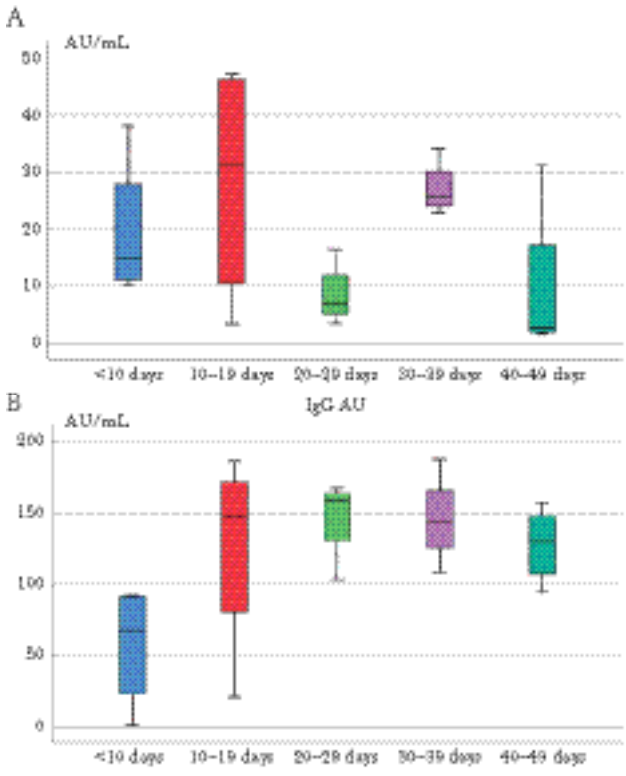

Figure 1. Titers of immunoglobulin M (*A*) and immunoglobulin G (*B*) antibodies at different times post–disease onset. Data represent mean ± standard deviation.

In addition, we did a subgroup analysis according to patients' age (Table 4). In the groups of patients aged 20–30 years, 30–40 years, 40–50 years, 50–60 years, 60–70 years, and 70–80 years, IgM titers were 13.10 ± 12.71 AU/mL, 17.70 ± 20.04 AU/mL, 10.74 ± 10.89 AU/mL, 40.74 ± 40.86 AU/mL, 22.66 ± 16.50 AU/mL, and 103.95 ± 137.65 AU/mL, respectively; IgG titers were 125.70 ± 56.31 AU/mL, 117.80 ± 57.16 AU/mL, 123.64 ± 82.84 AU/mL, 155.97 ± 24.92 AU/mL, 149.74 ± 28.12 AU/mL, and 164.58 ± 19.64 AU/mL, respectively. Compared with the patients 20–30 years old, only patients in the subgroups of 50–60 years (P = .0065) and 70–80 years (P = .0028) had a difference in IgM titers.

DISCUSSION

The COVID-19 diagnosis and treatment plan recommended RT-PCR for the detection of SARS-CoV-2 nucleic acid. A positive nucleic acid test is needed for the diagnosis of suspected cases. However, the diagnostic value of nucleic acid detection is greatly affected by the sample quality, experimental conditions, and operation protocols. Serological surveys can aid the investigation of an ongoing outbreak and retrospective assessment of the attack rate or extent of an outbreak. In cases where there is a strong epidemiological link to COVID-19 infection, paired serum samples (in the acute and convalescent phase) are

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Table 3. Comparison of the Results of the Nucleic Acid Test With the Second Antibody Detection of Coronavirus Disease 2019

		Second Antibody Test		First Antibody Test	
Variables	Patients, No.	IgM Titer, AU/mL	IgG Titer	IgM Titer	IgG Titer
Total	26	16.60 ± 18.79[a]	136.03 ± 54.22[a]	21.65 ± 26.35	112.96 ± 47.67
NAT (+)	11	18.29 ± 24.72[a]	134.71 ± 52.82[a]	22.83 ± 35.39	106.78 ± 44.31
NAT (–)	15	15.37 ± 12.65[a]	136.99 ± 55.20[a]	20.79 ± 18.55	112.59 ± 51.03

Data are presented as mean ± standard deviation. *P* values < .05 were considered statistically significant.

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; NAT, nucleic acid test.

[a]Compared to the results of the first antibody test, the second antibody test showed no statistical difference in titer levels of either IgM or IgG antibody.

another key evidence for the diagnosis of infection. The antibody detection is simple and repeatable, with a low risk of infection for medical staff during the process of sample collection and detection, and thus is an important way of rapid screening.

Among the 112 patients included in this retrospective study, 1 patient presented with dry cough was positive for IgM and negative for IgG. This patient's IgM antibodies appeared in about 4 days post–disease onset, the time of which was earlier than SARS-specific IgM antibodies that appeared in about 2 weeks after infection, and disappeared at the end of week 12 [9]. This finding highlights the importance of collecting the serum sample of COVID-19 patients as early as possible. However, the titer of IgM antibody is usually low, and lasts for a short time. Contrarily, IgG production indicates the middle and later stages of infection or previous infection, along with high concentration, longer duration, and higher affinity. When IgG in a patient during convalescence is 4 times or higher than that in the acute period, it indicates recurrent infection.

Among the 7 patients who were tested for serological antibody within 10 days after onset of the illness, 2 were negative for IgM antibody. These subjects might be in the "window period" of SARS-CoV-2 infection. During this period, it is difficult to detect the antibody. The advantage of nucleic acid detection over serum antibody detection is that it shortens the detection window of infection. Two subjects were negative for both IgM and IgG 10–20 days after disease onset. They were negative for all subsequent PCR tests performed after the initial positive test. Considering the quickly relieved symptoms of headache and sore throat, the result of a first nucleic acid test might be false positive.

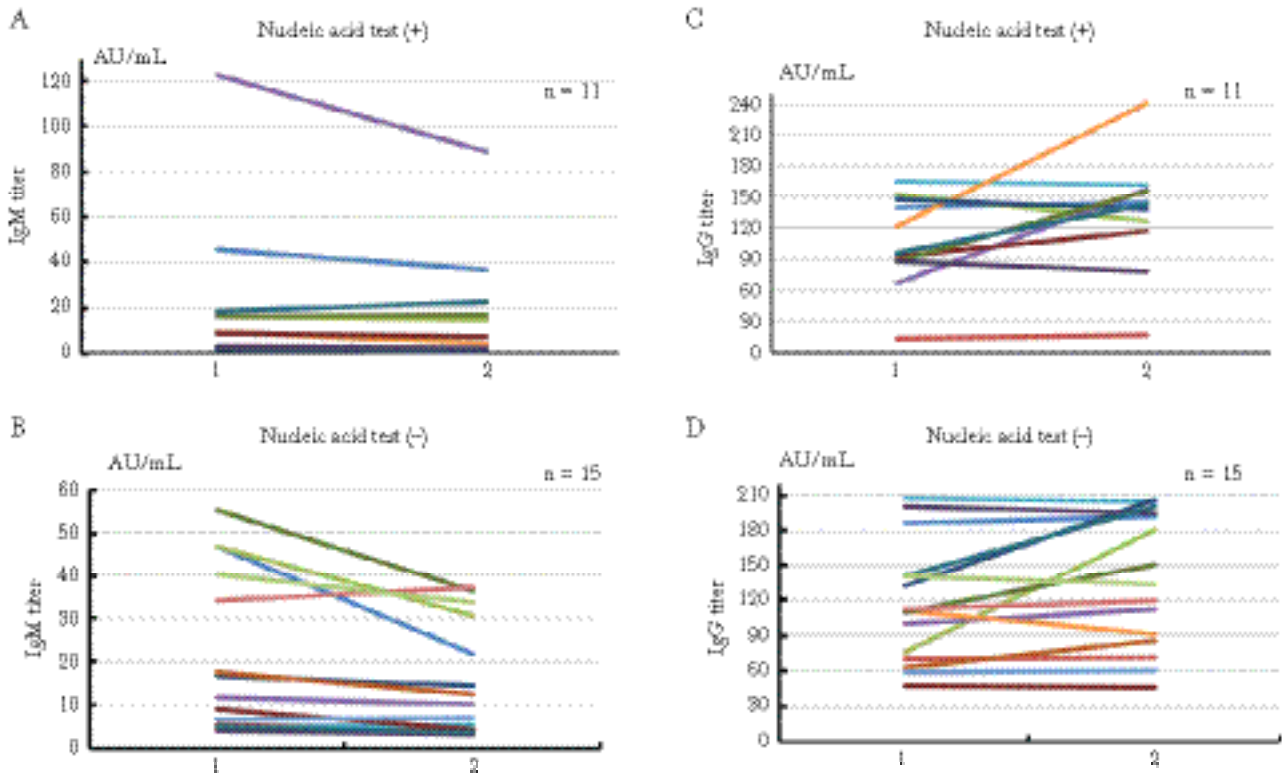

Figure 2. Trend lines of antibody titers for the first and second tests. *A* and *C*, Change of antibody titers for the 11 patients who were positive for the second nucleic acid test. *B* and *D*, Change of antibody titers of the 15 patients who were negative for the second nucleic acid test.

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Table 4. Comparison of the Results of Antibody Detection in Patients With Coronavirus Disease 2019 According to Age

	Age, y					
Titer	20–29	30–39	40–49	50–59	60–69	70–79
No.	38	41	11	9	8	5
IgM titer, AU/mL	13.10 ± 12.71	17.70 ± 20.04	10.74 ± 10.89	40.74 ± 40.86[a]	22.66 ± 16.50	103.95 ± 137.65[b]
IgG titer, AU/mL	125.70 ± 56.31	117.80 ± 57.16	123.64 ± 82.84	155.97 ± 24.92	149.74 ± 28.12	164.58 ± 19.64

Data are presented as mean ± standard deviation unless otherwise indicated.

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M.

[a]Compared to the IgM titers in patients < 30 years old, there is a significant difference in patients aged <60 years ($P = .0065$).

[b]Compared to the IgM titers in patients < 30 years old, there is a significant difference in patients aged <80 years ($P = .0028$).

Antibody responses begin to appear over a period of days to weeks after SARS-CoV-2 infection, which, to some extent, are dependent on the sensitivity of the detection and the viral protein used as an antigen. In our study, patients were detected positive for IgM by enzyme immunoassay to nucleoprotein as early as 4 days, the time of which was consistent with the observation shown that IgM can be detected 3–6 (median, 5) days after onset of COVID-19 symptoms [12, 13]. However, IgG in our design was seen 6–8 days after disease onset, earlier than that is detected 10–18 (median, 14) days after onset of symptoms [12]. Tan et al reported that the antinucleocapsid protein IgM started on day 7 and the positive rate peaked on day 28, whereas that the corresponding values of IgG were on day 10 and day 49 after disease onset [14]. However, antibody to the receptor-binding domain of the spike protein was detected a median of 11 days after onset of symptoms, but the timing of seroconversion did not correlate with clinical course [13, 15]. Moreover, studies in patients with SARS and MERS suggest that antibody responses for SARS-CoV and MERS-CoV are not durable [16–18]. Tang et al reported waning of antibodies that were undetectable in 91% (21/23) samples tested 6 years after SARS-CoV infection [19]. It is still unclear whether the antibodies to SARS-CoV-2 also disappear within years.

In addition, studies in subjects infected with MERS-CoV found that antibody levels were higher in those experiencing severe infection compared to those with mild infection [17]. With regard to SARS-CoV-2, titers of IgM and IgG are significantly higher in patients with severe disease than in nonsevere disease ($P < .05$). The weak responders for IgG had a significantly higher viral clearance rate than that of strong responders [14]. Similar result was found in another study reporting that a higher titer of antibody was independently associated with a worse clinical classification [13]. However, only patients with mild symptoms were included in our study, and there was no difference between nucleic acid–positive and –negative patients when retesting the antibody titers. Owing to the small sample size, whether elderly patients are more likely to experience increase of antibody titer needs to be further tested.

There are many limitations to this study. First, the antibody detection kit was designed for COVID-19 envelope protein (E) and nucleocapsid protein (N) antigen but not for the spike protein (S). S protein is believed to be the key site that mediates the human-to-human transmission by binding to the cellular receptor angiotensin-converting enzyme 2 (ACE2) [5]. Second, limited to this single-center study, it is necessary to investigate the relationship between the dynamic change of antibody and the course of COVID-19 in a multicenter study with a larger sample size. Third, the longitudinal changes of antibodies should be traced to understand the disease progression.

CONCLUSIONS

In summary, in addition to being used for the supplementary detection of SARS-CoV-2 nucleic acid test–negative cases, antibody detection can, to some extent, track disease progression. Through retrospective analysis, we found that antibody test is useful for the early diagnosis of COVID-19. IgM antibody appeared within 1 week after SARS-CoV-2 infection, and this antibody was present in the body for 1 month or even longer and then gradually decreased until it was lower than the detection limit. IgG antibody is usually produced in about 10 days, but the time it will persist in body remains unclear. However, after treatment, no significant difference in the level of IgM and IgG antibodies was found between nucleic acid–positive and –negative patients. Further investigation of duration of protective immunity for SARS-CoV-2 and acquired immunity to reinfection will be critical to understand the efficiency of vaccination, the possible therapy of COVID-19 with immune plasma, and potential monoclonal antibody treatment. Assessment of humoral and cellular immune response may also be informative to predict recovery and to help determine when patients are no longer infectious. Longitudinal data from the large numbers of recovered COVID-19 patients in multiple geographies, with different severity degrees of disease and different ethnic background, will give us insight into the temporal dynamics of antibody titers to this virus.

Notes

Financial support. This work was supported by the National Natural Science Foundation of China (grant numbers 81822016 and 81771382 to Zhentao Zhang).

Potential conflicts of interest. All authors: No reported conflicts of interest.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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