

RESEARCH ARTICLE

Analysis of the application value of serum antibody detection for staging of COVID-19 infection

Yutong Zheng^{1,2}  | Meitian Yan^{1,2}  | Lan Wang² | Liang Luan² | Jing Liu² | Xiao Tian² | Nan Wan²

¹Dalian Medical University, Dalian, Liaoning, China

²General Hospital of Northern Theater Command, Shenyang, Liaoning, China

Correspondence

Nan Wan, General Hospital of Northern Theater Command, Shenyang, 110016 Liaoning, China.
Email: wannan@outlook.com

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Abstract

Coronavirus disease 2019 (COVID-19) has now spread all over the world. The National Health Commission of the People's Republic of China reported 78 439 cured and discharged cases, 4634 deaths, 83 462 confirmed cases and 760 818 close contacts as of 25 June 2020. Joint detection of nucleic acids and antibodies has become an important laboratory diagnostic for COVID-19 patients. Disease progression and infection stage can be established based on the biological characteristics of these tests. However, there have been few studies of the different infection stages of COVID-19. We conducted a retrospective analysis to explore the clinical characteristics of COVID-19 patients at different infection stages and to characterize the characteristics of specific serum antibodies at each stage. These pieces of data will provide a theoretical basis for clinical diagnosis and treatment.

KEYWORDS

ADE effect, COVID-19, infection stage, nucleic acid detection, SARS-CoV-2, serum antibody quantitative detection

1 | INTRODUCTION

At the end of 2019, an outbreak of an infectious disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) occurred in Wuhan city, Hubei Province, China. On 11 February, the World Health Organization (WHO) officially named the syndrome coronavirus disease 2019 (COVID-19). Many regions in China and abroad have been affected by the epidemic. As of 25 June 2020, China had reported a total of 78 439 cured and discharged cases, 4634 deaths, and 83 462 confirmed cases.¹ Outside China, the number of confirmed cases reached 9 211 083 and the number of deaths reached 479 133.²

SARS-CoV-2 is a β coronavirus with a positive sense RNA genome, and is the third coronavirus documented to cause severe pneumonia in humans following outbreaks of SARS-CoV and Middle East respiratory syndrome (MERS)-CoV. In the early stages of the outbreak, positive nucleic acid tests were taken as direct evidence for a diagnosis of COVID-19.³ However, false negative results of nucleic acid tests often appear in later clinical practice, making diagnosis and treatment of the

disease particularly challenging. In the later stages, combined nucleic acid and serum antibody detection greatly improved the accuracy of clinical diagnosis. In addition, the biological characteristics of nucleic acids and specific IgM and IgG antibodies can be used to identify the specific stages of infection. Therefore, detection of nucleic acid and serum antibody can help understanding of disease progression and infection stage in COVID-19 patients. In this study, we explored the clinical value of specific serum antibody detection in COVID-19 patients.

2 | METHODS

2.1 | Study participants

This study was approved by the Medical Ethics Committee of Wuhan Taikang Tongji Hospital. A total of 723 adult patients diagnosed with COVID-19 at Taikang Tongji (Wuhan) Hospital from February 13, 2020 to March 30, 2020 were enrolled. Diagnosis was made strictly according to the diagnostic criteria of the "COVID-19 Diagnosis and Treatment

Plan (trial version 7)," later known as "Plan 7".⁴ These criteria included: (a) positive nucleic acid detection of SARS-CoV-2 by real-time polymerase chain reaction (PCR); (b) viral gene sequencing results with high homology to SARS-CoV-2; and (c) positive serum SARS-CoV-2-specific IgM and IgG antibodies. Specific serum IgG against SARS-CoV-2 must have changed from negative to positive or increased by fourfold or more in the convalescent stage compared with the acute stage. Clinical classification was carried out strictly according to "Plan 7." Mild disease was diagnosed if clinical symptoms were mild and there were no manifestations of pneumonia observed in imaging. Moderate disease was diagnosed in patients with fever, respiratory tract and other symptoms, with manifestations of pneumonia observed on imaging. Severe disease was diagnosed in adults who had any of the following: shortness of breath with a respiratory rate over 33 breaths per min; oxygen saturation less than or equal to 93% in a resting state; or PaO₂/FiO₂ less than or equal to 300 mm Hg (1 mm Hg = 0.133 kPa). If lung imaging showed lesion expansion of more than 50% within 24 to 48 hours, patients were managed as if they had severe disease. Critical disease was diagnosed in patients who met one of the following conditions: respiratory failure requiring mechanical ventilation; shock; and other organ failure requiring intensive care unit monitoring.

2.2 | Nucleic acid and specific antibody detection

SARS-CoV-2 nucleic acids in nasopharyngeal swab samples were detected using a model 7500 PCR gene amplification instrument (ABI, Foster City, CA). A cycle threshold value of greater than 40 was considered negative and a value of less than 40 was considered positive. Fasting venous blood (2–5 mL) was collected and centrifuged. The serum was separated and stored at a –20°C model 7500 PCR gelM and IgG antibodies were quantitatively detected using an Axceed 260 magnetic particle-based chemiluminescence immunoanalyzer (Bioscience, Tianjin, China). A chemiluminescence signal cut-off value (S/co) of less than 1 was considered negative and greater than 1 was considered positive.

2.3 | Statistical methods

SPSS Statistics software version 25.0 (IBM, Armonk, NY) was used for all statistical analyses. Count data were expressed as frequency (%) and the χ^2 test was used to assess differences between groups. Continuous data with normal distributions were expressed as $\bar{x} \pm s$ and differences

between two groups or among multiple groups were assessed using Student's *t* test and analysis of variance, respectively. Nonnormally distributed variables were expressed as medians and interquartile ranges and differences between groups were assessed using the Mann-Whitney *U* test. Graphpad Prism 7.0 (Graphpad Software, San Diego, CA) was used to produce all figures.

3 | RESULTS

3.1 | Basic patient information

A total of 723 COVID-19 patients were enrolled, comprising 290 male patients and 433 female patients with an average age of 61.30 ± 14.55 years. Moderate cases made up the largest number of patients, accounting for 72.20% of the total. Mild cases were the rarest, accounting for only 1.11% of the total, while severe and critical cases accounted for 23.24% and 3.46% of the total, respectively.

3.2 | Combined detection of nucleic acids and serum antibodies

According to the biological characteristics of nucleic acids and specific serum IgM and IgG antibodies, the 723 COVID-19 cases were classified into infection stages (Table 1). Analyses of the characteristics of different periods were performed (Table 2). Patients who were nucleic acid negative at admission could be divided into two categories: (a) the nucleic acid test had a positive record, but was negative more than twice before admission, and remained negative many times after admission; or (b) nucleic acid test results were negative since the onset of the disease, with diagnosis made based on lung imaging, symptoms, epidemiological history and serum antibody results. As most patients had a long disease course when they were admitted to hospital, there were more cases in the active, middle/late and convalescent stages of infection ($P < .001$).

3.3 | Analysis of clinical data during different infection periods

According to the above analysis, the cases were classified according to infection stage. Due to the possibility of false negative nucleic acid test results, the patients whose nucleic acid remained negative

Nucleic acid results	Serum antibody results				P
	IgM ⁻ IgG ⁻	IgM ⁺ IgG ⁻	IgM ⁻ IgG ⁺	IgM ⁺ IgG ⁺	
Nucleic acid+ (505)	48 (6.64%)	7 (0.97%)	329 (45.50%)	121 (16.74%)	.000
Nucleic acid (188) ^a	26 (3.60%)	0	98 (13.55%)	64 (8.85%)	
Nucleic acid (30) ^b	15 (2.08%)	4 (0.55%)	3 (0.41%)	8 (1.11%)	

TABLE 1 Combined analysis of nucleic acid and serum antibody testing

^aThe nucleic acid test had a positive record, but was negative more than twice before admission, and remained negative many times after admission.

^bThe nucleic acid test result was negative since the onset of the disease.

TABLE 2 Analysis of COVID-19 infection stages

Nucleic acid	Serum antibody	Combined detection of two detection methods to determine the stage of infection
Nucleic acid ⁺	IgM ⁻ IgG ⁻	(a) Window period, (b) IgM begins to appear but is still below the detection limit in the early stage of infection
	IgM ⁺ IgG ⁻	The early stage of infection
	IgM ⁻ IgG ⁺	The middle and late stage of infection (the result of early antibody test of the patient is unknown, the possibility of recurrent infection cannot be ruled out)
	IgM ⁺ IgG ⁺	The active stage of infection, but at this time the body has developed a certain immune capacity
Nucleic acid ^a	IgM ⁻ IgG ⁻	It may be in the infection recovery stage where the nucleic acid turns negative, the IgM antibody disappears and the IgG antibody begins to appear but is still below the detection limit
	IgM ⁻ IgG ⁺	Previous infection
	IgM ⁺ IgG ⁺	The convalescent stage of infection, IgM decreased but still above the detection limit
Nucleic acid ^b	IgM ⁻ IgG ⁻	This type of patient was diagnosed by pulmonary CT, symptoms and epidemiological history on admission. (a) The possible "window period" of false negative nucleic acid. (b) The convalescent stage in which the nucleic acid turned negative, the IgM antibody disappeared and the IgG antibody began to appear but was still below the detection limit
	IgM ⁺ IgG ⁻	May be in the acute stage of infection, consider the possibility of false negative nucleic acid
	IgM ⁻ IgG ⁺	Previous infection
	IgM ⁺ IgG ⁺	Consider the possible active stage of infection with false negative nucleic acid

^aThe nucleic acid test had a positive record, but was negative more than twice before admission and remained negative many times after admission.

^bThe nucleic acid test result was negative since the onset of the disease.

throughout were removed from consideration. The remaining patients were divided into early, active, middle/late and convalescent stages. The clinical data of the four groups of patients were statistically compared and analyzed. The proportions of female patients in

the early, active, middle/late and convalescent stages were 58.18%, 49.59%, 64.74%, and 61.17%, respectively. Except for the active stage of infection, the proportion of female patients at each stage was higher than that of male patients ($P = .034$). There was no

TABLE 3 Analysis of clinical data during different infection periods

	Early stage (55)	Active stage (121)	Middle/Late stage (329)	Convalescent stage (188)	P
Age, y	58.62 ± 17.69	60.74 ± 12.53	61.00 ± 15.62	62.44 ± 13.13	.391
Sex					
Male	23 (41.82%)	61 (50.41%)	116 (35.26%)	73 (38.83%)	.034
Female	32 (58.18%)	60 (49.59%)	213 (64.74%)	115 (61.17%)	
Number of symptoms					
Asymptomatic	10 (18.18%)	23 (19.01%)	303 (92.10%)	178 (94.68%)	.000
One symptom	25 (45.46%)	27 (22.31%)	24 (7.29%)	8 (4.26%)	
Two symptoms	9 (16.36%)	17 (14.05%)	1 (0.30%)	2 (1.06%)	
Three or more	11 (20.00%)	54 (44.63%)	1 (0.30%)	0	
Serum specific antibody (log ₂ [S/co + 1])					
IgM antibody	0.31 (0.12-0.54)	1.76 (1.28-2.68)	0.40 (0.26-0.61)	0.62 (0.23-1.14)	.000
IgG antibody	0.64 (0.30-0.83)	3.83 (2.54-4.76)	3.32 (2.17-4.60)	3.24 (1.84-4.63)	.000
Laboratory index					
Lymphocyte count (×10 ⁹ L)	1.57 ± 0.63	1.55 ± 0.70	1.72 ± 0.88	1.68 ± 0.66	.196
Leukocyte count (×10 ⁹ L)	6.30 ± 2.36	6.20 ± 2.99	5.98 ± 2.07	6.42 ± 2.23	.253
C-reactive protein (mg/L)	0.5 (0.5-9.69)	1.21 (0.5-6.17)	0.5 (0.5-2.29)	0.5 (0.5-4.83)	.030
Hypersensitive troponin T (ng/mL)	9.31 (3.00-44.95)	8.32 (4.48-13.28)	7.95 (4.19-18.08)	8.81 (4.01-19.73)	.020
Albumin (g/L)	37.90 ± 5.73	38.17 ± 4.69	37.76 ± 4.80	43.89 ± 4.84	.000
Total protein (g/L)	67.67 ± 6.67	69.57 ± 6.72	68.02 ± 6.77	69.24 ± 6.57	.149
Interleukin-6 (pg/mL)	2.73 (1.50-8.06)	7.82 (6.50-11.39)	2.85 (1.56-8.67)	3.58 (1.56-9.07)	.044
Procalcitonin (ng/mL)	0.045 (0.030-0.093)	0.044 (0.031-0.064)	0.053 (0.033-0.085)	0.052 (0.032-0.104)	.790

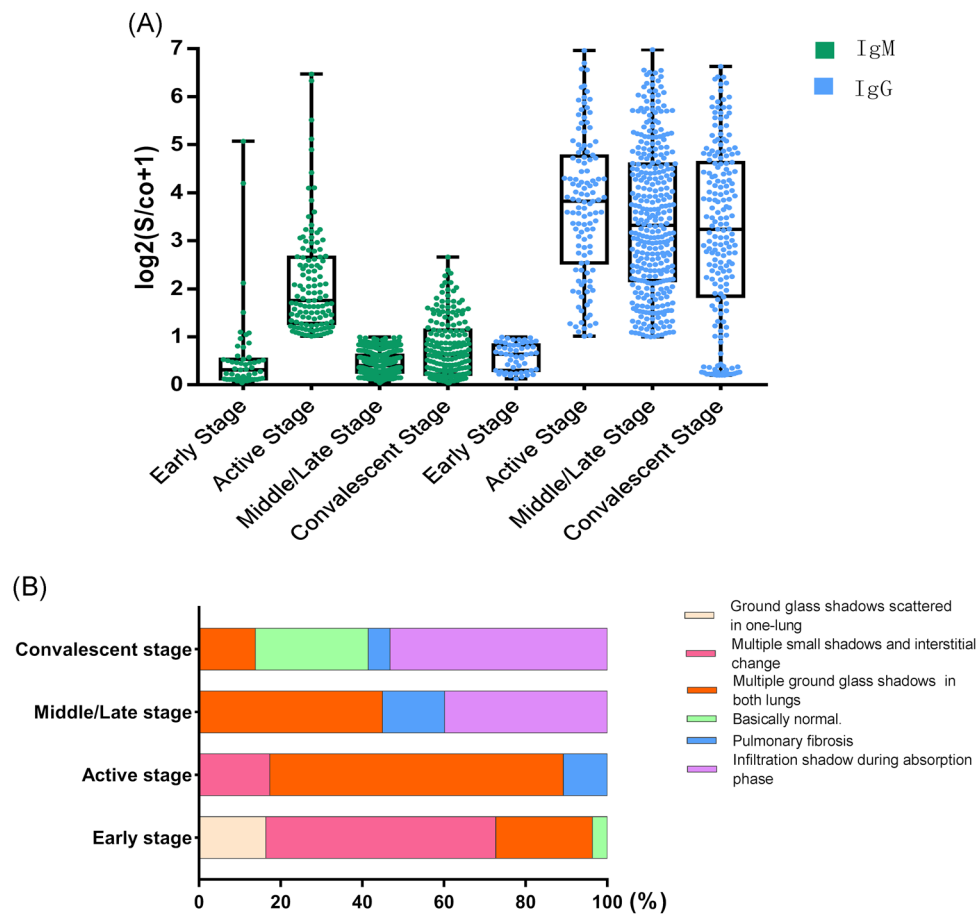


FIGURE 1 A, Comparison of specific serum antibody levels in COVID-19 patients at different infection stages. B, Comparison of lung computed tomography results in COVID-19 patients at different infection stages

significant difference in patient age at each stage of infection ($P = .391$). With disease progression, the number of symptoms showed a decreasing trend. The proportions of asymptomatic patients at the early, active, middle/late and convalescent stages were 18.18%, 19.01%, 92.10%, and 94.68%, respectively ($P < .001$). Levels of specific IgM were higher during the active stage of infection, while levels of specific IgG remained high in the active, middle/late and convalescent stage of infection ($P < .001$). Among laboratory parameters, C-reactive protein, hypersensitive troponin T, albumin, and interleukin (IL)-6 were significantly perturbed in the active stage of infection ($P < .05$). Although the lymphocyte count, leukocyte count, total protein, and procalcitonin were abnormal in varying degrees, these differences did not reach statistical significance ($P > .05$) (Table 3 and Figure 1A).

3.4 | Lung CT results in COVID-19 patients at different infection stages

Referring to the lung computed tomography (CT) results of the patients on admission and according to the above infection stage classification for statistical analysis, it was found that: (a) early stage:

56.36% of the patients showed multiple small shadows and interstitial changes; 23.64% of the patients showed multiple ground glass shadows in both lungs; 3.64% of the patients had no obvious abnormal manifestations. (b) Active stage: 71.90% of the patients showed multiple ground glass shadows in both lungs and the boundary was unclear; 10.74% of the patients showed different degrees of pulmonary fibrosis without normal CT results. (c) Middle/late stage: the number of patients with multiple ground glass shadow in both lungs decreased to 44.98%; 39.82% of the patients showed infiltration in both lungs or single lungs, which was a change in the absorption period. (d) Convalescent stage: severe results decreased further, with 53.19% of patients showing CT manifestations of the pneumonia absorption phase, and 27.66% of patients showed normal CT results or only a small amount of scattered shadow (Figure 1B).

3.5 | Quantitative analysis of specific serum antibodies in COVID-19 patients and relationship with disease severity and stages of infection

Patients with mild and moderate disease were classified as the nonsevere group, and those with severe and critical disease were

TABLE 4 Quantitative analysis of specific serum antibodies in COVID-19 patients with different disease severity at different stages of infection

Infection stage	Clinical type	Specific IgM antibody (log ₂ [S/co + 1])	Specific IgG antibody (log ₂ [S/co + 1])
Early stage	Nonsevere	0.32 (0.11-0.53)	0.64 (0.32-0.82)
	Severe/critical	0.16 (0.11-0.71)	0.62 (0.24-0.90)
	<i>P</i>	.597	0.919
Active stage	Nonsevere	1.91 (1.32-2.67)	3.58 (2.36-4.45)
	Severe/critical	1.56 (1.25-2.28)	4.51 (3.74-5.67)
	<i>P</i>	.208	.002
	The most Youden index		0.374
	Cut-off		3.9093
Middle/late stage	Nonsevere	0.39 (0.26-0.59)	3.13 (2.12-4.50)
	Severe/critical	0.47 (0.28-0.63)	3.69 (2.45-4.81)
	<i>P</i>	.109	.048
	The most Youden index		0.161
	Cut-off		3.0789
Convalescent stage	Nonsevere	0.58 (0.22-1.22)	3.22 (1.81-4.62)
	Severe/critical	0.69 (0.24-1.05)	3.59 (2.24-4.82)
	<i>P</i>	.899	.369

Note: There were significant differences in IgG levels among different infection stages ($P < 0.05$) (Table 4, Figure 2A-C). In addition, patients at different stages of infection were divided into groups according to the results of the above cut-off value, and the differences of laboratory indexes were compared. The abnormal degree of laboratory indexes was more obvious in the patients whose IgG antibody quantitative results were higher than the cut-off value in the active and the middle/late stage of infection. Except for IL-6 in the active stage, other laboratory indexes were significantly different in different infection stages ($P < .05$) (Figure 2D-G).

classified as the severe/critical group. To facilitate statistical analysis, quantitative results of antibody titers were log-transformed. Levels of specific serum IgM antibodies in patients were higher in the active stage of infection and increased in the convalescent stage of infection. Levels of specific serum IgG antibodies in patients were lower in the early stage of infection, but persistently high after the active stage of infection. Levels of IgG antibodies in the severe/critical group were significantly higher than those in the nonsevere group at the active and middle/late stage of infection ($P < .05$). By drawing the receiver operating characteristic (ROC) curve of IgG antibody levels in the active and middle/late stages of infection and calculating the Youden's index, we determined the optimal cut-off values for IgG antibody levels in patients with different disease severities. The highest Youden index values in the active and middle/late stages of infection were 0.374 and 0.161, respectively, and the optimal cut-off values of serum-specific IgG antibodies in nonsevere, severe/critical patients at these two stages of infection were 3.9093 and 3.0789, respectively. There were significant differences in IgG levels among different infection stages ($P < .05$). In addition, patients at different stages of infection were divided into groups, according to the results of the above cut-off value, and the differences of laboratory indexes were compared. The abnormal degree of laboratory indexes was more obvious in the patients whose IgG antibody quantitative results were higher than the cut-off value in the active and the middle/late stage of infection. Except for IL-6 in the active stage, the other laboratory

indexes were significantly different at different infection stages ($P < .05$) (Table 4 and Figure 2A-G).

4 | DISCUSSION

On 20 January 2020, the National Health Commission decided to include COVID-19 pneumonia in statutory infectious disease category B and to take preventive and control measures for category A infectious diseases.⁵ On 30 January the WHO called the epidemic "an emergency of international concern." SARS-CoV-2 is a novel enveloped β coronavirus with an RNA genome. In the early stages of the epidemic, nucleic acid detection was taken as direct evidence of infection. However, the accuracy of nucleic acid detection was affected by the quality of detection kits, sample collection methods, operator ability, RNA stability, patient condition, and concurrent drug use,⁶ resulting in a large number of false negative results in clinical practice. For this reason, the National Health Commission of the People's Republic of China emphasized in the "Technical Guide for COVID-19 Laboratory Testing" that COVID-19 infection could not be ruled out if the nucleic acid test results were negative. The serum antibody test was added to the COVID-19 laboratory diagnostic criteria of "Plan 7." The serum-specific antibody is a component of humoral immunity following viral infection. The IgM antibody emerges the earliest, but generally at low concentrations and for short

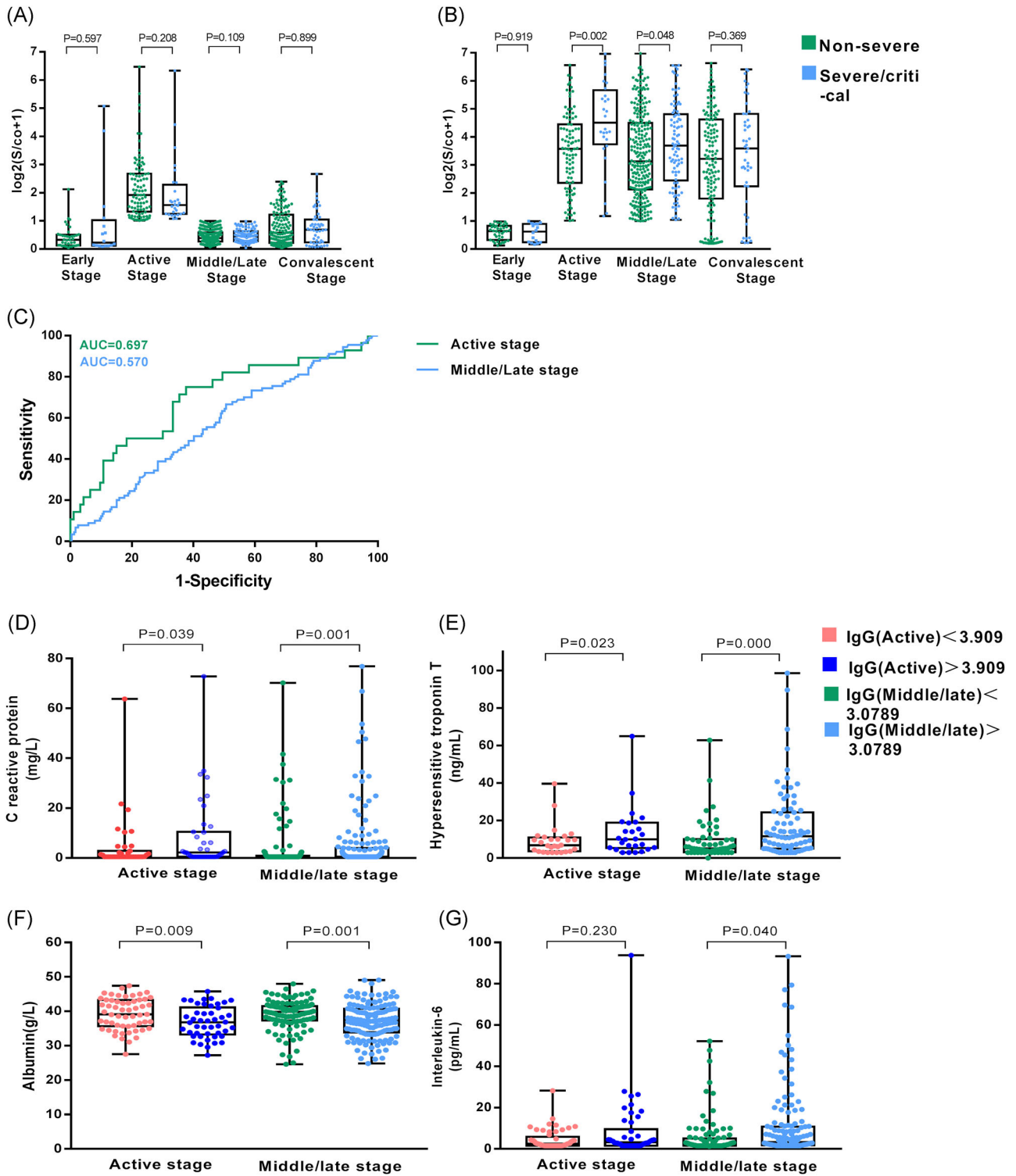


FIGURE 2 A, Quantitative analysis of specific serum IgM antibodies in patients with different disease severity at different infection stages. B, Quantitative analysis of specific IgG serum antibodies in patients with different disease severity at different infection stages. C, Receiver operating characteristic curve of the diagnostic utility of specific serum IgG level in discriminating between patients at the active and middle/late stage of infection. D-G, Comparison of laboratory indexes in patients with different infection stages after grouping according to the IgG antibody cut-off value

periods. Thus, IgM can be used as a marker of early viral infection. The IgG antibody usually appears after IgM at high concentrations and is maintained for long periods. Thus, IgG is often used as a sign of improvement and immunity during the later stages of infection. Therefore, detection of the serum-specific antibody is of great significance for clinical diagnosis and prognosis in COVID-19 patients. However, problems can occur in serum antibody detection. When the human body is infected with the virus, there is a period during which specific antibodies cannot be detected. In addition, some disease conditions can produce abnormal levels of antibodies or other proteins such as rheumatoid factor, alpha-fetoprotein, and complement, causing false positive results in antibody detection.⁷ Therefore, combined nucleic acid and serum antibody detection may greatly improve diagnostic accuracy while reducing the disadvantages of the two methods. Xu et al⁸ confirmed that serological antibody detection can effectively compensate for missed nucleic acid tests and increase the overall case detection rate.

According to the results of nucleic acid and serum antibody tests on admission, the infection stages of 723 COVID-19 patients were classified into the early, active, middle/late and convalescent stage. In comparative analyses of clinical data at different infection stages, we found that all the indexes in the active stage were significantly abnormal compared with other infection periods. With the development of the course of the disease, all the indexes tend to be normal gradually, especially the lung CT. The number of patients with a large ground glass shadow in both lungs decreased gradually, and the number of CT results which tended to be normal increased significantly. Therefore, the method of roughly classifying the infection stage by the results of nucleic acid and serum-specific antibody is feasible, and can quickly ascertain the disease degree of the patient and allow taking effective measures in time. Moreover, the levels of serum-specific IgM were higher in the active stage of infection and increased in the convalescent stage with a longer course of infection. This phenomenon may be related to antibody-dependent enhancement (ADE) of infection: nonneutralizing antibodies can be produced during the early stage of infection, and instead of neutralizing pathogens, promote viral infection of human cells.^{9,10} Recent studies have shown that this effect may be related to the activation of immune memory cells generated during previous infections with non-pathogenic coronaviruses.¹¹⁻¹⁴ Seven coronaviruses have been found to infect humans, of which SARS-CoV, SARS-CoV-2, and MERS-CoV can cause severe acute respiratory syndrome and death. The other four coronaviruses (HCoV-229E, -OC43, -NL63 and -HKU1) have low pathogenicity and can cause common cold symptoms. SARS-CoV-2 has more than 60% homology with these four low-pathogenicity coronaviruses, while the homology with SARS-CoV is more than 80%. SARS-CoV shares multiple cross-reactive epitopes with low-pathogenicity coronaviruses.¹⁶ When SARS-CoV-2 invades the human body, it activates memory B cells generated against other coronaviruses to produce antibodies. The antibodies produced are cross-reactive rather than SARS-CoV-2 neutralizing antibodies. These cross-reactive antibodies can promote viral entry into monocytes/macrophages by binding to Fc receptors on the cell surface.

Virions are then replicated and released. An objective survey of four low-pathogenic coronaviruses found that at least 70% of people had been infected with one of these coronaviruses.¹⁷ In addition, when the virus-antibody complex enters the cell, it can activate monocytes/macrophages to release a large number of pro-inflammatory cytokines, causing a cytokine storm. Furthermore, IL-6 can destroy T cells and inhibit the initiation of immune responses, thus aggravating and prolonging the course of the disease. Another study on the effectiveness of convalescent plasma therapy showed that this treatment was significantly more effective within 14 days of disease onset than after 14 days of onset.¹⁸ Therefore, the roles of antibodies at different stages of the disease likely differ.

In addition, we found that levels of IgG were persistently high after the active stage of infection, indicating that disease progression coincided with emergence of these antibodies. We found that levels of IgG in patients with different clinical severity were higher than those of IgM. This finding may be related to the high affinity and easy detection of IgG antibodies and the longer course of disease of the patients included in the study following their admission to hospital. However, the levels of serum-specific IgM antibodies in patients showed no significant differences at different infection stages. The levels of specific serum IgG showed no significant differences in the early and convalescent stages of infection, indicating that the humoral immune responses of patients with different disease severity were similar. Levels of IgG antibody in patients in the active, middle and late stages with critical and severe infection were significantly higher than those in patients with nonsevere infection, indicating that patients with severe illness in this period produced more IgG antibodies. Using a ROC curve of IgG levels in these two periods and calculating the optimal Youden's index, the cut-off value of IgG levels in patients with different disease severities was determined. The cut-off values for specific serum IgG in nonsevere and severe/critical patients in the active and middle/late stage of infection were 3.9093 and 3.0789, respectively. Meanwhile, patients with different infection stages were divided into groups according to the cut-off value to verify whether it was related to the severity of the disease. The results showed that an abnormal degree of laboratory indexes was more obvious in the patients whose IgG antibody quantitative results were higher than the cut-off value in the active stage and the middle and late stage of infection. Therefore, when the levels of specific serum IgG in the active and middle/late stage of infection exceed 3.9093 and 3.0789, respectively, severe or critical disease is likely to occur. However, because classification of the infection stage is not limited to nucleic acid and antibody testing, other indicators will need to be added to refine the classification of infection stages in future studies.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

YZ and NW contributed to data analysis, graphics, and writing the paper. YZ, NW, MY, LW, and LL contributed to data collection and graphics development. JL and XT contributed to editing the paper.

ORCID

Yutong Zheng  <http://orcid.org/0000-0001-5531-6270>

Meitian Yan  <http://orcid.org/0000-0002-1838-2831>

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