

The dynamic antibody responses on COVID-19 patients with different severity: A retrospective research

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Abstract

Objectives

We aimed to explore the association between dynamic antibody responses and the clinical severity of COVID-19.

Methods

We collected complete follow-up data of 777 pathogen-confirmed COVID-19 patients with corresponding IgG/IgM testing results.

Results

We found the overall 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 with non-severe patients ($P=0.026$). Through further analysis, our results showed that the statistical difference in the IgG only significant in serum samples taken ≤ 14 days from disease onset ($P<0.001$). In 74 patients who taken detection more than three times, by analyzing the antibody expression levels at different time points, we found that the difference between IgG was more obvious than that of IgM among severe/non-severe patients. In multivariate logistic regression models, after adjusting for cofactors, the higher anti-SARS-CoV-2 IgG level before 14 days from disease onset was independently associated with severe disease in COVID-19 (OR=1.310, 95%CI= 1.137-1.509).

Conclusion

We observed differences in antibody responses among COVID-19 patients with different disease severity. A high IgG level in the first 14 days from disease onset might positively associate with severe disease.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide in the past months. As of August 6th, 2020, there are more than 18 million people affected by SARS-CoV-2 globally. At present, the virus-specific IgM/IgG antibodies detection could be necessary measurement to predict population immunity against the coronavirus disease 2019 (COVID-19) and screening of SARS-CoV-2 infected population, besides, it is also critical for patients with undetectable viral load, below the lower limit of RT-PCR assays [1-3].

Among the COVID-19, about 80% were non-severe patients, while for patients who progressed to severe/critical disease, the mortality rates would increase significantly [4, 5]. Therefore, the potential indicators which could help to predict disease progression will have great significance in clinical practice. Previous studies indicated that the immune response would be different between the severe and non-severe patients [6, 7], we speculated that the difference in immune response might also affect the

expression of specific antibodies. However, whether the levels of antibodies against SARS-CoV-2 related to the progress and prognosis of the COVID-19 might not be clear, the clinical studies related to this issue are controversial. Phipps et al. reported that the antibody responses were useless for predicting disease progression [8]. In contrast, Liu et al. found that serum IgM titer changed as the COVID-19 progresses, and high level of IgM was associated with Acute Respiratory Distress Syndrome (ARDS) in severe/critical patients [9].

For this study, we included 777 patients with pathogen-confirmed COVID-19, and analyzed the results of SARS-CoV-2 antibodies test. We found that the IgG level of severe patients would be significantly higher than that of non-severe patients on the first 14 days after symptoms onset, however, this association would not be obvious after 14 days. Our study suggests that early antibody response might be related to the prognosis of the COVID-19.

Methods

Study design and participants

The 777 COVID-19 patients were hospitalized at Tongji Hospital in Wuhan, China, from January 18th and April 26th. All patients were pathogen-confirmed COVID-19 individuals and accepted serological specific antibodies detection. The SARS-CoV-2 infection was confirmed by reverse transcriptase-polymerase chain reaction assay (RT-PCR) consistent with the previous study [10].

All the patients (100%, 777/777) with complete follow-up data have reached to the endpoints of observation (discharged or died from the hospital). Clinical and demographic data of the confirmed cases were collected from their medical records. The severe COVID19 cases were defined as oxygen saturation of 94% or less while breathing ambient air or needing oxygen support, consistent with the study of Ohmagari et al. [11].

The detection of antibodies against SARS-CoV-2

The SARS-CoV-2 IgM/IgG antibody tests were conducted by YHLO-CLIA-IgM, YHLO-CLIA-IgG kits, which were supplied by YHLO (YHLO Biotech Co. Ltd Shenzhen, China), All operations were carried out according to the provided instructions. The expression of antibody was measured in arbitrary unit (AU) per mL. The positive results were indicated by >10 AU/mL both in IgM/IgG, and negative results were indicated by ≤ 10 AU/mL. The method for the detection of antibodies against SARS-CoV-2 was consistent with reported in the previous article [12]. All serum samples were dated from the day of symptom onset.

Statistical analysis

All analyses were conducted with SAS version 9.4 (SAS Inc). The measurement data were expressed as the mean and standard deviation [13] or median and interquartile range (IQR) values. The comparison between two or three different groups was performed by t tests or F test when the measurement data

were normally distributed. Otherwise, the Mann-Whitney U test or Kruskal-Wallis test was applied. Enumeration data were summarized as frequency rates and percentages. Intergroup comparison of enumeration data was performed using chi-squared tests. The logistic analysis was adopted to exploring the influence of the log-transformed level of IgG in different sampling times from disease onset on the risk of non-severe or severe. $P < 0.05$ was considered statistically significant.

Results

In this study, we performed a retrospective analysis of 777 patients with SARS-Cov-2 infection. According to the severity of the disease, we divided the patients into two types: severe patients (417/777, 53.7%), and non-severe patients (360/777, 46.3%). Table 1 illustrates the baseline characteristics of 777 patients with COVID-19. The mean age of the cohort was 58.1 years. The proportions of males and females did not differ significantly between the two groups. Patients in the severe group (62.2 ± 13.8 years) were significantly older than the non-severe group (53.5 ± 16.7 years). The most common comorbidity was hypertension (31.2%). Besides, it was also the only comorbidity that existed a significant difference in prevalence between the two groups. Also, diabetes and coronary heart disease were common comorbidities of patients. In terms of symptoms, the most common symptoms in more than half of patients were fever (67.8%) and cough (54.8%). Furthermore, expectoration (40.5%) was also one of the common symptoms of patients. The results indicated that among the symptoms with statistically different distributions ($P < 0.05$), such as fever, cough, dyspnea, which were happened in severe patients more frequently than in non-severe patients. All the patients have reached the endpoints of the observation by April 26, and the clinical outcomes are summarized in Table 1. 5.3% (41/777) patients were deceased. 94.7% (41/777) of patients were discharged, and all the dead patients were severe cases.

In Figure 1, we observed the dynamic changes of the positive rates of IgG and IgM in severe/non-severe patients. In the first 14 days from the onset of the symptoms, the positive rate of IgG was significantly higher in severe patients (91.8%) compared with non-severe patients (74.2%, Figure 1a), and the same trend was also observed in IgM (77.6% to 61.7%, Figure 1b). In addition, the phenomenon of higher a positive rate of IgM remained in severe patients within 15-21 days. After 21 days, the positive rates of IgG and IgM were similar in two groups. In addition, in severe patients, the positive rate of IgG maintained at a relatively high level (>90%) during the whole duration. However, the positive rate of IgG of the non-severe patients had an obvious ascent process, and it reached a peak of 93.2% after 21 days.

To further explore the characteristics of the patients' immune response to the SARS-Cov-2 infection, we analyzed correlations between levels of specific antibodies and clinical progression. The average levels of IgG and IgM of COVID-19 patients are shown in Figure 2a-2b. The level of IgG was significantly higher in severe patients compared to non-severe patients. However, there was no difference in the average level of IgM among the two groups. Due to the antibody positive rates changed over time, we suspected the antibody levels would also be time-dependent. The average levels of IgG and IgM from the beginning of the symptom until the first detection of corresponding antibodies are shown in Figure 2c-2d. During the first two weeks after disease onset, there were increases in the level of IgG of severe patients, and then it

began a slow decline. We observed that in the first 14 days, the IgG level of severe patients was significantly higher than that of non-severe patients. Whereas the change law of IgM with time is not obvious, there was no such time point among severe-non-severe patients. We statistically tested the antibodies levels of the two groups ≤ 14 days and ≥ 15 days. A significant difference was only observed in the level of IgG ≤ 14 days post-disease onset (Figure 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 or not. Then, we compared the levels of specific antibodies among distinct groups. Among the 19 laboratory parameters, in the normal range groups and the abnormal range groups of most laboratory indicators, most of parameters had no significant difference in IgG, except IL-10 ($P = 0.035$), procalcitonin ($P < 0.0001$), albumin ($P = 0.049$), total bilirubin ($P = 0.0092$) which have shown significant difference among the groups. However, these statistical differences of normal/abnormal range groups of laboratory parameters became more pronounced in specific IgM. There were 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 ($P = 0.0091$), tumor necrosis factor α ($P = 0.0069$) have reached statistical difference among the different groups.

To investigate the profile of dynamic changes of IgG and IgM among the same person during the course of COVID-19, we screened 74 cases in patients who took serological specific antibodies detection at least 3 times. T1 represents the first detection after hospital admission, T2 represents the detection closest to the midpoint of the whole hospital stay, and T3 detection the last test before discharge. We observed that both the levels of IgG and IgM were in a downward trend. The severe patients had a higher average level of IgG and IgM compared with non-severe patients among the whole three time points. In addition, we further found that the difference in IgG was more evident than IgM, especially in T1 and T2 time points. The levels of IgM in severe/non-severe groups were relatively close at different time points.

Logistic regression was conducted to identify the correlation between the log-transformed level of IgG and the progression of COVID-19. In the multivariate logistic regression, we included comorbidities, age, sex as the potential co-factors, which have reported may influence the progress of COVID-19 or differential distribution among the patients of different severity. After adjustment for co-factors, we observed a higher level of IgG before 14 days from disease onset independently associated with severe illness (odds ratio [OR]=1.310, 95% confidence interval [CI]: 1.137-1.509). However, this significant correlation did not hold after 15 days from disease onset (OR=0.930, 95%CI: 0.799-1.083).

Discussion

Our study aimed to explore the characteristics of serological immunity of SARS-Cov-2 infection, to gain further knowledge of the correlation between patients' immune response with disease severity of COVID-19 and disease pathogenesis.

In the most viral infection diseases, virus-specific IgM is usually the first antibody identified positively in the acute stage, followed by an increase in specific IgG in the later stage. However, this situation may be a little bit different in COVID-19. In Zhang et al. study, they detected virus-specific IgM and IgG by enzyme-linked immunoassay, and found that more patients were identified positive for IgG than IgM on the first sampling day and after five days [14]. In addition, Long et al. also reported the virus-specific antibody IgM response could be observed within the one week from symptom onset, and the specific level of IgG could also be detected at high levels in serum at the same time or even earlier than IgM against SARS-CoV-2 [15]. Notably, Jin et al. found the positive rate of specific IgG was significantly higher than that of IgM during COVID-19 course [16]. A similar phenomenon was also observed in our study, the positive rate of virus-specific IgG was significantly higher than virus-specific IgM in the first and second weeks. It seems that existed mechanisms could not explain this result, and one possible reason for this phenomenon is that unlike Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe acute respiratory syndrome coronavirus (SARS-CoV) infections, which the peak viral load of patients infections generally occurs at about 7–10 days after disease onset [17, 18], patients with COVID-19 have the highest viral load around the time of disease onset, which is similar to that of influenza [2, 19]. The level of specific IgG against SARS-Cov-2 has been proved to correlate with virus neutralization titer [2]. In *Helicobacter pylori* infection, the IgG antibodies against *Hpyloni* is positively correlated to the density of *Hpyloni* colonization [20]. Through the underlying mechanisms of strong IgG response in the early stage of COVID-19 is unclear, we suspected these might relate to the high viral load.

Whether the illness severity of COVID-19 could influence the specific antibody detection results, prior articles have reported this issue differently. In a 23 cases study, the researchers found that serum antibody levels were not correlated with clinical severity [2]. However, Hou et al. observed that both the levels of specific IgG and IgM against SARS-Cov-2 were significantly different among the 338 COVID-19 patients of different illness severity. In our research, we found that sampling time from symptom onset is an important factor when testing specific antibodies levels. In the early stage of the disease, severe and non-severe patients might have distinct efficiency of the immune response. Before the 14 days from symptom onset, we found that patients with severe illness had a significantly higher level of specific IgG against SARS-Cov-2 than non-severe patients. Age, sex, and comorbidities were reported to be associated with severe COVID-19 [21-23]. Therefore, we further combined these co-factors that related to the illness severity in a multivariate analysis, which confirmed that a higher level of IgG was significantly associated with severe illness. However, this phenomenon becomes less obvious after 15 days from disease onset. The previous study indicated the detection of specific IgG antibody against SARS-CoV-2 might have a more significant role during the COVID-19 pandemic [24]. In SARS-Cov infection, the researchers have observed a more robust IgG response might be associated with severe illness, which was a similar conclusion as in our present study in SARS-Cov-2 [25]. In the prior study, over 90% of individuals with SARS-CoV-2 infection became specific IgG seropositive after 14 days of disease onset, which has also been confirmed in our study [15]. In addition, we found that the level of specific IgM of severe/non-severe patients might also be different in the early stages of the disease, but this difference was not as obvious as IgG. In a study focused on the serological results of asymptomatic patients, Long et al. found that, in

the acute phase, the specific IgG levels in the asymptomatic group were significantly lower compared to that of the symptomatic group [26], which also suggested that the immune response may be related to the disease severity.

The pro-inflammatory cytokines released by various immune cells could contribute to the pathogenic inflammation and related to the severity of COVID-19 [27, 28]. In our study, we also observed the differences in the levels of cytokines and other laboratory indicators might associate with the level of specific antibodies against SARS-CoV-2.

Several limitations should be noted in our study. Serological antibodies tests vary in their sensitivity and specificity. Previously infection of other kinds of coronaviruses might confound the results. In addition, if there were potential immunodeficiency patients, their specific antibody production could also be affected.

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

Declarations

Ethics approval and consent to participate

The Ethical Committee of Tongji Hospital approved the study. Due to the retrospective nature of the study, informed consent was waived. All data were analyzed anonymously

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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No.

Authors' contributions

J.L. conceived and designed the study. W.L. and P.W. prepared this paper, L.H., Y.M., P.W., and W.D participated in the data collection and data management, W.L. and P.W. contributed to clinical analysis and the data analysis. The authors read and approved the final manuscript.

Availability of data and materials

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

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Tables

Table 1. The baseline characteristics of 777 COVID-19 patients

	Non-severe (n=360)	Severe (n=417)	Total (n=777)	<i>p</i> ^a
Sex (n[%])				0.15
Male	168(46.7)	216(51.8)	384(49.4)	
Female	192(53.3)	201(48.2)	393(50.6)	
Age (y- mean[SD])	53.5(16.7)	62.2(13.8)	58.1(15.9)	<0.0001
Days post disease onset (median[IQR])	25.0(23.7- 27.0)	13.0(15.1- 17.5)	15.0(19.5- 21.6)	<0.0001
Comorbidities (n[%])				
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
The signs and symptoms (n[%])				
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)	249(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
Prognosis				
Recovered	360(100.0)	376(90.2)	736(94.7)	<0.0001
Death	0(0.0)	41(9.8)	41(5.3)	<0.0001

^a *P* values comparing different groups are from χ^2 test, *t* test or the Mann-Whitney U test.

Table 2. Comparison of anti-SARS-CoV-2 IgG and IgM among different laboratory parameters groups

Laboratory parameters (normal range)	IgG	<i>p</i> ^a	IgM	<i>p</i> ^a
White blood cell count (×10 ⁹ /L- median [IQR]) (3.5-9.5)		0.50		0.23
<3.5	154.9 (93.1-194.3)		42.0 (13.2-138.9)	
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 (×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 (×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 (×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 (ug/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 (ug/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)	
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)		<0.0001	0.21
<0.05	182.0 (135.4-222.0)	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 α(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)	

^aCalculated using the Mann-Whitney U test or Kruskal-Wallis test.

Table 3. Logistic regression analysis of IgG level^a and disease severity.

Sampling time from disease onset	OR(95%CI)	
	Crude ^b	Model1 ^c
≤14 days	1.359(1.188-1.555)*	1.310(1.137-1.509)*
≥15 days	0.955(0.829-1.101)	0.930(0.799-1.083)
All	1.113(1.012-1.224)*	1.077(0.973-1.191)

^aLog scale (10 log).

^bCrude: unadjusted.

^cModel 1: adjusted for sex, age and comorbidities.

*Significant at $P < 0.05$.

Figures

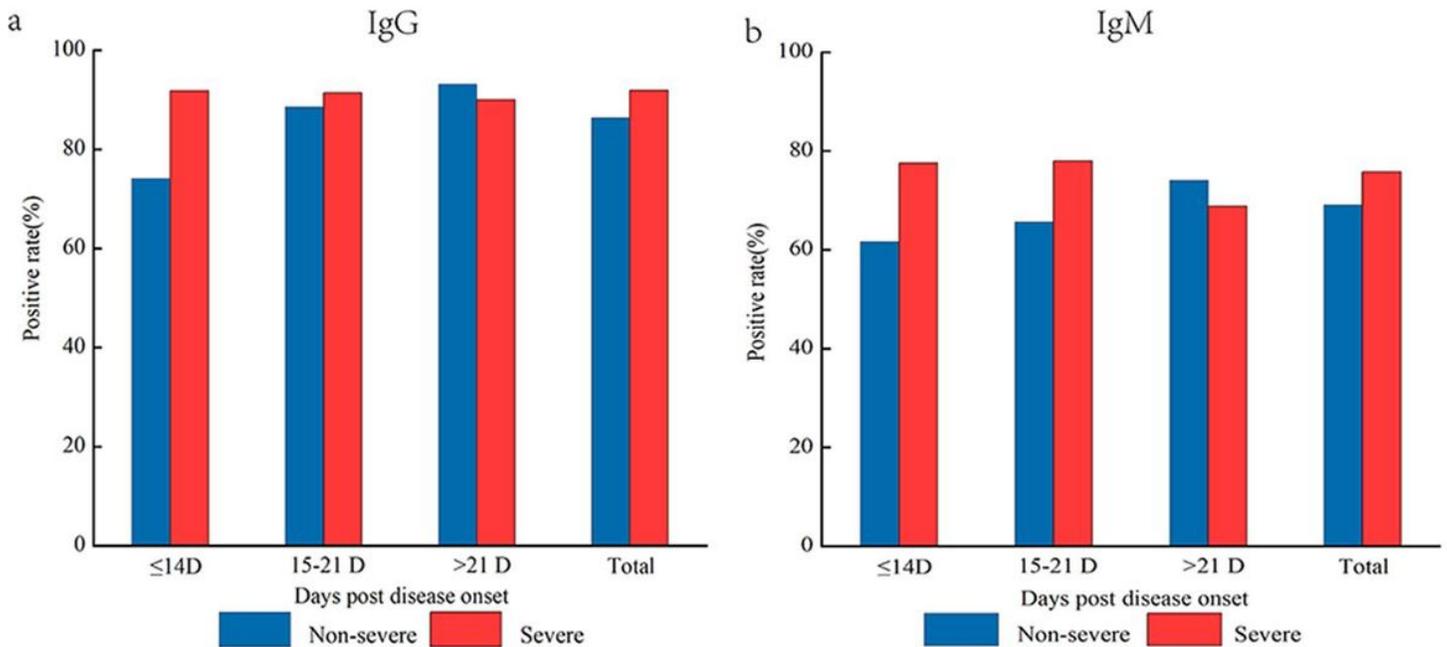


Figure 1

The positive rates of SARS-CoV-2 specific antibodies during different disease progression periods. (a) IgG, and (b) IgM.

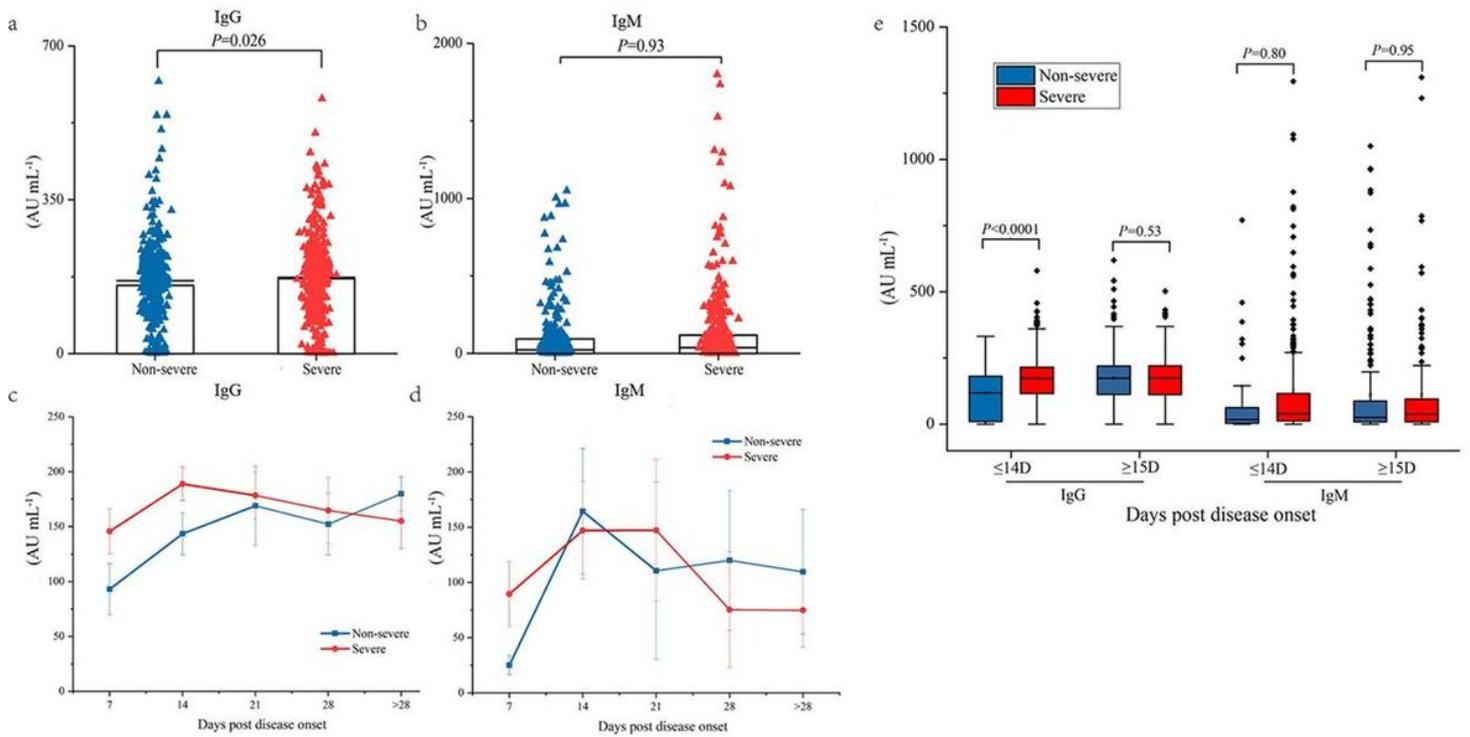


Figure 2

Levels of specific antibodies against SARS-CoV-2. IgG (a) and IgM (b) levels in severe and non-severe patients. SARS-CoV-2-specific IgG (c) and IgM (d) dynamics of COVID-19 patient during different disease progression periods. Comparison of the specific IgG and IgM levels of COVID-19 patients with different severity (e).

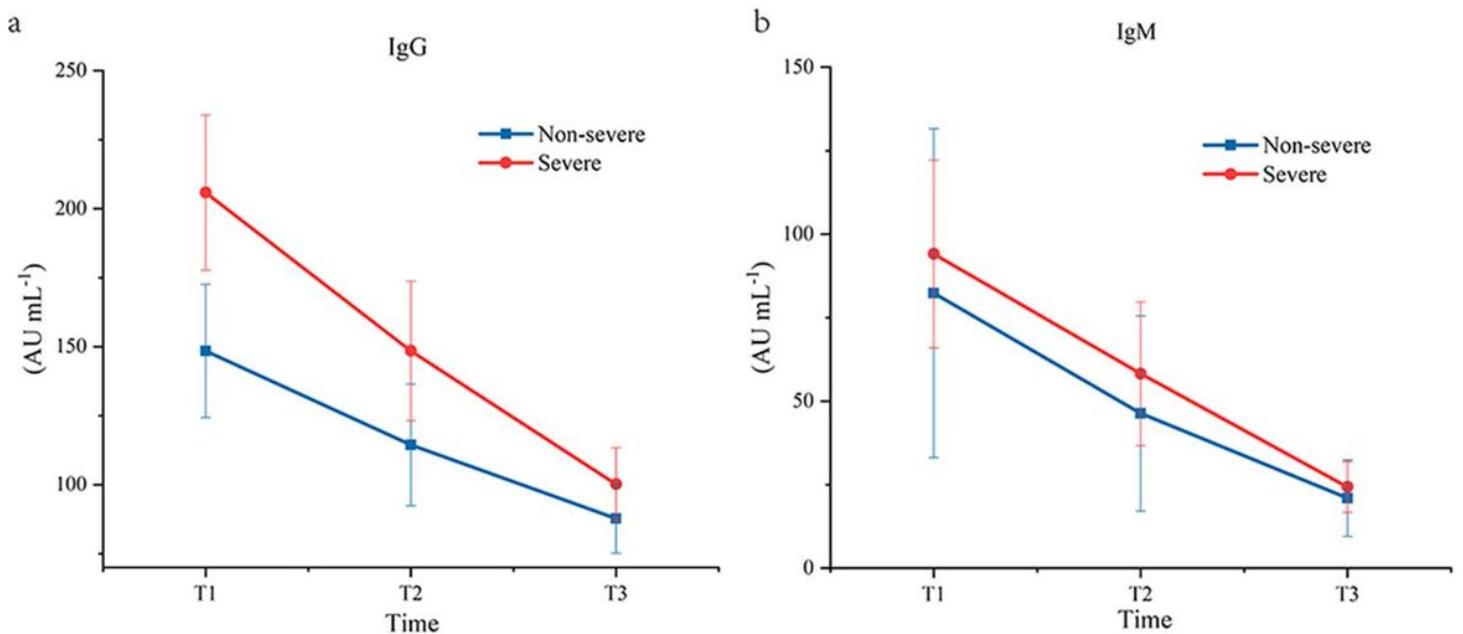


Figure 3

The dynamic changes of antibody responses in selected patients during the course of COVID19. (a) IgG, and (b) IgM.