Relationship between the dynamic changes of serum 2019-nCoV IgM/IgG and patient immunity after discharged six months

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Abstract

Objectives To investigate the relationship between the dynamic changes of serum 2019-nCoV IgM/IgG and immunity alteration for patients after discharged six months.

Methods 1 with IgM(+) and IgG(-), 32 with IgM(+) and IgG(+), 38 with IgM(-) and IgG(+), and 40 with IgM(-) and IgG(-) were included. Demographic data were collected. IgM and IgG antibodies, hypersensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6) and lymphocyte subsets in serum were determined on weeks 0, 2 and 4.

Results Hs-CRP and IL-6 for all patients were within the normal ranges. All testing items of the lymphocyte subsets were 12/110 (10.9%) of weeks 0, 15/110 (13.6%) of weeks 2 and 18/110 (16.4%) of weeks 4 within the normal ranges. The percentages of CD8+, NK cells and B lymphocytes in the IgM(+) and IgG(+) group were quite different from the IgM(-) and IgG(+) group and the IgM(-)and IgG(-) group, with much more the percentages of CD8+ and much less the percentages of NK cells and B lymphocytes on weeks 0, 2 and 4. 12 patients with IgM(+) had converted to IgM(-) in the IgM(+) and IgG(+) group, and the percentages of NK cells and B lymphocytes were significantly increased on weeks 4.

Conclusions The changes of serum IgM and IgG are closely related to immunity for patients in recovery stage. However, immunity isn't recovery with the turning negative of antibodies.

Introduction

Since December 2019, the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caucused 2019 novel coronavirus (2019-nCoV) pneumonia has been threatened worldwide for millions people [1]. Till March 2020, the Coronavirus disease 2019 (COVID-19) epidemic had been effectively controlled in Wuhan city, China. Infected patients were hospitalized and were discharged from hospital with recovery. Currently, almost all of COVID-19 patients in China have been in recovery stage after infection and therapy [2].

Presently, lack of effective antiviral drugs [3], effective vaccines [4], convalescent plasma therapy [5] and specific human monoclonal antibody [6], the treatment of COVID-19 are still the greatest challenge for medical staff and scientific research workers [7]. As a novel coronavirus, the dynamic immunity and pathogenesis of human body are unclear [8-10].

In this study, we focused on COVID-19 patients in recovery stage after discharged six months and aimed to evaluate dynamic changes of IgM and IgG antibodies, the change levels of hypersensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6) and lymphocyte subsets alteration in plasma, and the potential correlation with the dynamic changes of serum IgM and IgG and patient immunity.

Materials And Methods

Patients

From July 1, 2020 to August 31, 2020, the consecutive COVID-19 patients in recovery stage after discharged six months who were admitted to the department of Novel Coronavirus Pneumonia Rehabilitation Clinic at Hubei University of Chinese Medicine Affiliated Hubei Hospital of Chinese Medicine were recruited.

All included patients who admitted to our department met the criteria of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) proposed at the National Health Commission of China (https://ncstatic.clewm.net/rsrc/2020/0311/22/781e459d414bf3f1579bcafef0d80f12.pdf). The severity in the acute stage was classified as mild, moderate, severe and critical as the criteria of the National Health Commission of China.

Inclusion and Exclusion Criteria

We did the four weeks clinical study for patients with COVID-19 at our department, which was registered in the Chinese Clinical Trial Registry (ChiCTR2000034794). Inclusion criteria were age between 18 and 70 years old, and signed informed consent by patients (or their families).

Exclusion criteria were: (1) patient was discharged less than 6 months. (2) patient with SARS-CoV-2 nucleic acid conversion positive again. (3) patient with infection after discharged; (4) surgery during the discharged time; (5) pregnant or lactating females; (6) patient with cancer; (7) patient with organ dysfunction during the discharged time; (8) patient with immune system diseases; and (9) patients in the other researches.

Treatment

The enrolled patients were treated with a standardized management, such as breathing training and oral Chinese medicine daily.

Ethics

The ethics was approved ethical approval by the Research Ethical Committee of Hubei Hospital of Chinese Medicine (granted No. HBZY2020-C26-01).

Data collection

The following data were collected from a consecutive series of 111 patients in four-week observation stage: i) demographic data including gender, age, severity of hospitalization, and chronic disorder histories (chronic cardiovascular disease, chronic respiratory disease, chronic cerebrovascular illness, and diabetes); ii) Serum biochemical data in included antibodies against SARS-CoV-2 (IgM and IgG), hs-CRP, IL-6 and lymphocyte subsets (including the percentage of CD3+/ CD8 +/ CD4+/natural killer (NK) cells/B lymphocytes).

Peripheral venous blood samples, using strict aseptic techniques, were obtained from patients on weeks 0, 2 and 4. The IgM and IgG was detected by colloidal gold method using novel coronavirus (2019-nCoV) IgM/IgG antibody detection kit (Livzon Reagent Co., Ltd., Zhuhai, China). The hs-CRP was determined by Modular PPI automatic biochemical analyzer (Roche Diagnostics (Shanghai) Co., Ltd., Shanghai, China). IL-6 was determined by fully automatic electrochemiluminescence immunoassay system (cobas e411 analyzer series, Roche Diagnostics (Shanghai) Co., Ltd., Shanghai, China). Lymphocyte subsets were detected and counted by BD FACSCalibur flow cytometer (BD, Bioscience, CA, USA). The following antibodies (BD, Bioscience, CA, USA) were used: FITC anti-human CD14, FITC-conjugated anti-CD4, ECD-conjugated anti-CD3, PC5-conjugated anti-CD8, PE-conjugated anti-CD19, and PC7-conjugated anti-CD16CD45.

Statistical Analysis

The software package SPSS 11 (Chicago, IL, USA) was used to all data management and analyses. Descriptive data of continuous variables and number (%) for categorical variables was presented as the mean ± the standard deviation (mean ± SD). Comparisons of multiple groups were analyzed with one-way analysis of variance. The $\chi 2$ test with Yates correction was used to compare the categorical variables between the two groups respectively. Correlations were evaluated with the Spearman rank test and $P < 0.05$ was statistically significant.

Results

Patients

This study included 111 patients (51 males and 60 females) with COVID-19 in recovery stage after discharged six months. The median age of the patients was 50.3 years (ranges, 24–70 years). Chronic disorder histories were chronic cardiovascular disease (21 person times), chronic respiratory disease (12 person times), chronic cerebrovascular illness (5 person times), and diabetes (10 person times).

The values of hs-CRP and IL-6 for all patients were within the normal ranges on weeks 0, 2 and 4, and the comparisons of groups were meaningless. The normal ranges of hs-CRP are 0-3 mg/L; the normal ranges of IL-6 are < 7 pg/mL.

A 54-years-old male patent with IgM(+) and IgG(-) was symptomless, negative of nucleic acid, 2019-nCoV open reading frame gene and 2019-nCoV nucleoprotein gene, no infection on chest CT manifestations, and was no chronic respiratory disease. Three antibodies tests for IgM and IgG were IgM(+) and IgG(-). The lymphocyte subsets were given in Table 1.

Table 1. Lymphocyte subsets of patient with IgM(+) and IgG(-)

	CD3+ (percentages)	CD8+ (percentages)	CD4+ (percentages)	NK cells (percentages)	B lymphocytes (percentages)
Normal ranges	62.64-76.76	19.17-33.63	30.0-46.0	9.5-23.5	8.48-14.52
0 weeks	79	56	43.0	10.0	7.0
2 weeks	80	45	44	11	9
4 weeks	80	35	45	9	8

Comparison of Patients with Different IgM and IgG Antibodies

There were 110 patents for analysis. Thirty-two (29.1%) of 110 patients were IgM(+) and IgG(+),Thirty-eight patients (34.5%) had IgM(-) and IgG(+), and 40 (36.4%) were IgM(-) and IgG(-).

There were no significant differences in age, gender, clinical classification of hospitalization, and chronic disorders among the IgM(+) and IgG(+) , IgM(-) and IgG(+), IgM(-)and IgG(-) groups (Table 2).

Table 2. Characteristics of patients with different IgM and IgG antibodies

	IgM(+) and IgG(+) (n=32)	IgM(-) and IgG(+) (n=38)	IgM(-) and IgG(-) (n=40)	*P*
Age (years)	50.7±12.7	51.1±13.1	49.9±11.4	0.6773
Gender				
Male	14(43.8%)	17(44.7%)	19(47.5%)	_
Female	18(56.2%)	21(55.3%)	21(52.5%)	0.9451
Clinical classification of hospitalization				
Mild	7(21.9%)	5(13.2%)	2(5.0%)	_
Moderate	21(65.6%)	28(73.7%)	31(77.5%)	_
Severe	4(12.5%)	5(13.1%)	7(17.5%)	0.3172
Chronic disorder				
Chronic cardiovascular disease	7(21.9%)	8(21.1%)	6(15.0%)	_
Chronic respiratory disease	5(15.6%)	4(10.5%)	3(7.5%)	_
Chronic cerebrovascular illness	1(3.1%)	2(5.3%)	2(5.0%)	_
Diabetes	3(9.4%)	4(10.5%)	3(7.5%)	0.8542

All testing items of the lymphocyte subsets were 12/110 (10.9%) of weeks 0, 15/110 (13.6%) of weeks 2 and 18/110 (16.4%) of weeks 4 within the normal ranges, which were 0 (0/32, 0.0%) in the IgM(+) and IgG(+) group, 4 (4/38, 10.5%) in the IgM(-) and IgG(+) group, 8 (8/40, 20.0%) in the IgM(-) and IgG(-) group on weeks 0, 1 (1/32, 3.1%) in the IgM(+) and IgG(+) group, 5 (5/38, 13.2%) in the IgM(-) and IgG(+) group, 9 (9/40, 22.5%) in the IgM(-) and IgG(-) group on weeks 2, and 3 (3/32, 9.4%) in the IgM(+) and IgG(+) group, 6 (6/38, 15.8%) in the IgM(-) and IgG(+) group, 9 (9/40, 22.5%) in the IgM(-) and IgG(-) group on weeks 4 (Table 3).

Table 3. Characteristics of total lymphocyte subsets in patients with different IgM and IgG antibodies

Groups		0 weeks	2 weeks	4 weeks	*P*
IgM(+) and IgG(+)	Normality	0(0.0%)	1(3.1%)	3(9.4%)	0.1610
(n=32)	Abnormality	32(100.0%)	31(96.9%)	29(90.6%)	
IgM(-) and IgG(+)	Normality	4(10.5%)	5(13.2%)	6(15.8%)	0.7493
(n=38)	Abnormality	34(89.5%)	33(86.8%)	32(84.2%)	
IgM(-)and IgG(-)	Normality	8(20.0%)	9(22.5%)	9(22.5%)	0.9521
(n=40)	Abnormality	32(80.0%)	31(77.5%)	31(77.5%)	
P		0.0257	0.0585	0.3244	

The percentages of CD8+, NK cells and B lymphocytes in the IgM(+) and IgG(+) group were quite different from the IgM(-) and IgG(+) group and the IgM(-)and IgG(-) group, with much more the percentages of CD8+ and much less the percentages of NK cells and B lymphocytes on weeks 0, 2 and 4 ($P<0.05$, Table 4). The comparisons of the three groups for the percentages of CD8+ at three time points, the IgM (+) and IgG (+) group was highest, IgM (-) and IgG (-) group was the lowest ($P < 0.05$, Table 4). The comparisons of the three groups for the percentages of NK cells and B lymphocytes at three time points, the IgM (-) and IgG (-) group was highest, IgM (+) and IgG (+) group was the lowest ($P < 0.05$, Table 4).

Table 4. Comparison of the dynamic percentages changes of lymphocyte subsets in patients with different IgM and IgG antibodies

	Groups	0 weeks	2 weeks	4 weeks	*P*
	IgM(+) and IgG(+)	67.0±10.8	69.5±8.7	69.7±9.7	0.4712
CD3+	IgM(-) and IgG(+)	69.4±8.9	69.1±9.3	70.1±9.9	0.8925
	IgM(-)and IgG(-)	70.3±10.7	70.6±10.2	69.1±10.1	0.7903
	P	0.3789	0.7704	0.9044	
	IgM(+) and IgG(+)	48.6±7.3	45.9±10.5	43.7±9.7	0.1117
CD8+	IgM(-) and IgG(+)	36.5±10.3	30.5±9.3●	28.5±10.4	0.0020
	IgM(-)and IgG(-)	25.5±9.3	26.1±11.3	25.9±10.1	0.9652
	P	0.0000	0.0000	0.0000	
	IgM(+) and IgG(+)	35.3±4.8	36.5±5.8	35.7±5.2	0.6530
CD4+	IgM(-) and IgG(+)	34.5±5.3	36.1±6.1	35.6±5.1	0.4359
	IgM(-)and IgG(-)	35.5±4.9	35.9±5.9	35.6±5.4	0.9426
	P	0.6550	0.9120	0.9959	
	IgM(+) and IgG(+)	13.7±7.4	14.9±8.7	15.0±9.6	0.7984
NK cells	IgM(-) and IgG(+)	15.9±6.9	17.4±8.5	19.5±8.9	0.1585
	IgM(-)and IgG(-)	25.7±6.3	26.7±8.1	27.1±8.3	0.6997
	P	0.0000	0.0000	0.0000	
	IgM(+) and IgG(+)	7.2±3.1	7.4±3.9	7.5±3.8	0.9446
B lymphocytes	IgM(-) and IgG(+)	10.1±3.9*	10.7±4.5*	15.4±5.2	0.0000
	IgM(-)and IgG(-)	16.1±6.4*	16.4±5.7*	16.7±5.5	0.9012
	P	0.0000	0.0000	0.0000	

- In the IgM(-) and IgG(+) group, the comparison of weeks 0 versus weeks 2 was difference significantly（*P*<0.05;

（For the CD8+ levels, the comparisons of the IgM(+) and IgG(+) group versus the IgM(-) and IgG(+)group on weeks 2 and 4 were significant difference（respectively (*P*<0.05).

（For the NK cells, the comparisons of the IgM(+) and IgG(+) group versus the IgM(-) and IgG(+) group on weeks 4 and the IgM(-) and IgG(+) group versus the IgM(-) and IgG(-) group on weeks 0, 2 and 4 were significant difference（respectively (*P*<0.05).

* For the B lymphocytes, the comparisons of the IgM(-) and IgG(+) group versus the IgM(-) and IgG(-) group on weeks 0 and 2 were significant difference respectively (P<0.05).

For the B lymphocytes, the comparison of the IgM(+) and IgG(+) group versus the IgM(-) and IgG(+) group on weeks 4 was significant difference (P<0.05).

Comparison of Patients within IgM(+) and IgG(+) Antibodies

During the 4-week observation period, 12 of 32 patients had IgM(+) converted to IgM(-).The 32 patients were divided into the IgM(+) group and the IgM(-) groups. There were no significant differences in age, gender, clinical classification of hospitalization and chronic disorders for the two groups (Table 5).

Table 5. Characteristics of patients within IgM(+) and IgG(+) antibodies

	IgM(+) (n=20)	IgM(-) (n=12)	*P*
Age (years)	52.1±13.7	49.3±13.0	0.5728
Gender			
Male	7(35.0%)	7(58.3%)	
Female	13(65.0%)	5(41.7%)	0.1977
Clinical classification of hospitalization			
Mild	4(21.9%)	3(13.2%)	
Moderate	14(65.6%)	7(73.7%)	0.7757
Severe	2(12.5%)	2(13.1%)	
Chronic disorder			
Chronic cardiovascular disease	3	2	-
Chronic respiratory disease	3	3	-
Chronic cerebrovascular illness	2	1	-
Diabetes	1	1	0.9623

The dynamic percentages changes of CD3+, CD8+ and CD4+ for patients in the IgM(+) group were unanimous with those outcomes in the IgM(-) group (P 0.05, Table 6). Compared with the IgM(+) group, the percentages of NK cells and B lymphocytes were significantly increased in the IgM(-) group on weeks 4 (P<0.05, Table 6). The comparisons of weeks 0 versus weeks 4, the percentages of B lymphocytes were significantly increased in the IgM(-) group (P<0.05, Table 6).

Table 6. Comparison of the dynamic percentages changes of lymphocyte subsets in patients within IgM(+) and IgG(+) antibodies

	Groups	0 weeks	4 weeks	*P*
	IgM(+)	67.5±10.9	69.1±9.7	0.6267
CD3+	IgM(-)	66.7±10.6	69.5±9.9	0.5106
	P	0.8405	0.9115	
	IgM(+)	48.8±7.6	43.8±9.8	0.0793
CD8+	IgM(-)	48.4±7.2	43.5±9.5	0.1685
	P	0.8842	0.9330	
	IgM(+)	35.2±4.9	35.6±5.3	0.8056
CD4+	IgM(-)	35.1±4.7	35.9±5.5	0.7054
	P	0.9551	0.8795	
	IgM(+)	13.9±7.5	13.1±7.3	0.7344
NK cells	IgM(-)	13.5±7.3	18.5±7.1	0.1031
	P	0.8837	0.0496	
	IgM(+)	7.3±3.3	6.5±3.0	0.4274
B lymphocytes	IgM(-)	7.0±3.0	10.5±3.4	0.0139
	P	0.7987	0.0016	

Discussion

Mortality of COVID-19 mainly occurs in the hospitalization in the acute stage, which carries a high mortality risk in Wuhan city of China, and the patient is at risk for lung and/or systemic complications [11]. SARS-CoV-2 is a very weird virus, which showed cellular immune deficiency and excessive immune response in the acute stage [12,13].

The production of antibodies is the host's immune response to viral infection, which serum 2019-nCoV IgM/IgG were detectable as early as 4 days and reached a peak in the second week after symptom onset [14,15]. Serological antibody testing may be helpful for the identification of suspected patients with negative of nucleic acid and for the diagnosis of asymptomatic infections [16].

The detection significance of antibodies in convalescent patients seems to be completely different from that in infection patients [17,18]. In this report, we enrolled 111 patients with COVID-19 in recovery stage after discharged six months, which were 1 with IgM(+) and IgG(-), 32 with IgM(+) and IgG(+), 38 with IgM(-) and IgG(+), and 40 with IgM(-) and IgG(-).

The important pro-inflammatory cytokines of hs-CRP and IL-6 cause cascade and amplify cytokine storm [19]. Hs-CRP is a nonspecific inflammatory marker widely used in the prediction of COVID-19 pneumonia [20], which is not affected by radiotherapy, chemotherapy, corticosteroids. IL-6 is the key proinflammatory cytokines in excessive immune response for SAP, which is a potential, reliable and easy-to-use predictor for COVID-19 prognosis [21]. However, our results suggested that the values of hs-CRP and IL-6 for all patients were within the normal ranges after discharged six months.

Lymphocyte subsets in peripheral blood play an important role in preserving immune function, which cellular immune regulate with each cell restricting and regulating one another. Previous researches revealed that T cell subset counts were significantly decreased for COVID-19 patients during hospitalization [22-24]. Our findings suggest that serum lymphocyte subsets counts is correlated with the dynamic changes of serum IgM and IgG and not related to inflammatory cytokines and severity of hospitalization. All testing items of the lymphocyte subsets were 12/110 (10.9%) of weeks 0, 15/110 (13.6%) of weeks 2 and 18/110 (16.4%) of weeks 4 within the normal ranges. The percentages of CD8+, NK cells and B lymphocytes in the IgM(+) and IgG(+) group were quite different from the IgM(-) and IgG(+) group and the IgM(-)and IgG(-) group, with much more the percentages of CD8+ and much less the percentages of NK cells and B lymphocytes on weeks 0, 2 and 4.

Recent studies had reported that lymphocyte subsets and inflammatory cytokines in plasma were associated with the severity of COVID-19 [25, 26]. Liu et al [25] found that the degrees of lymphopenia and proinflammatory cytokines in severe COVID-19 patients were higher than in mild cases, and were associated with the severity of disease. Jiang et al [26] reported that the counts of CD8+ and CD4+ cells of COVID-19 patients were used as predictors of disease severity. Our results tell that the immune status of patients (lymphocyte subsets and inflammatory cytokines) in the recovery stage is completely different from that in the acute stage.

We found that with the conversion of IgM(+) to IgM(-), the patient's immunity gradually improved, mainly manifested by the compensation of NK cells and B lymphocytes. In our study, we analyzed 12 patients with IgM(+) had converted to IgM(-) in the IgM(+) and IgG(+) group. Compared with the IgM(+) group, the percentages of NK cells and B lymphocytes were significantly increased in the IgM(-) group on weeks 4 (P<0.05, Table 6).

In conclusion, the dynamic changes of serum IgM and IgG are closely related to patient immunity for patients in recovery stage, which is dominate with CD8+ for IgM(+) and gradually improve by the compensation of NK cells and B lymphocytes with the conversion of IgM(+) to IgM(-). However, the immunity is not recovery with the turning negative of antibodies of SARS-CoV-2. Future large-scale

studies are required to clarify the dynamic changes of antibodies and immunity for the throughout course of COVID-19.

Declarations

Acknowledgment

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Conflict of interests

No

References

[1] Studdert DM, Hall MA, Mello MM. Partitioning the curve - interstate travel restrictions during the Covid-19 pandemic. N Engl J Med 2020; published online Aug 5. DOI: 10.1056/NEJMp2024274.

[2] Peng M. Outbreak of COVID-19: An emerging global pandemic threat. Biomed Pharmacother 2020;129:110499.

[3] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-78.

[4] Srivastava S, Verma S, Kamthania M, et al. Structural basis for designing multiepitope vaccines against COVID-19 infection: in silico vaccine design and validation. JMIR Bioinform Biotech 2020;1:e19371.

[5] Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324:1-11.

[6] Shanmugaraj B, Siriwattananon K, Wangkanont K, et al. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). Asian Pac J Allergy Immunol 2020;38:10-18.

[7] Kabir MT, Uddin MS, Hossain MF, et al. nCOVID-19 pandemic: from molecular pathogenesis to potential investigational therapeutics. Front Cell Dev Biol 2020;8:616.

[8] Schönrich G, Raftery MJ, Samstag Y. Devilishly radical NETwork in COVID-19: oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression. Adv Biol Regul 2020;77:100741.

[9] Bal A, Agrawal R, Vaideeswar P, et al. COVID-19: an up-to-date review - from morphology to pathogenesis. Indian J Pathol Microbiol 2020;63:358-66.

[10] Shenoy S. Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality. Inflamm Res 2020; published online Aug 7. DOI: 10.1007/s00011-020-01389-z.

[11] Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146:110-8.

[12] Sun X, Wang T, Cai D, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev 2020;53:38-42.

[13] Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. J Gen Virol 2020; published online May 20. DOI: 10.1099/jgv.0.001439.

[14] Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med 2020;26:845-8.

[15] Peterhoff D, Glück V, Vogel M, et al. A highly specific and sensitive serological assay detects SARS-CoV-2 antibody levels in COVID-19 patients that correlate with neutralization. Infection 2020;1-8.

[16] Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol 2020; published online Feb 27. DOI:10.1002/jmv.25727

[17] Bryan A, Pepper G, Wener MH, et al. Performance characteristics of the abbott architect SARS-CoV-2 IgG assay and seroprevalence in boise, idaho. J Clin Microbiol 2020;58:e00941-20.

[18] Theel ES, Slev P, Wheeler S, et al. The role of antibody testing for SARS-CoV-2: is there one? J Clin Microbiol 2020;58:e00797-20.

[19] Sordillo PP, Helson L. Curcumin suppression of cytokine release and cytokine storm. A potential therapy for patients with Ebola and other severe viral infections. In Vivo 2015;29:1-4.

[20] Liu YP, Li GM, He J, et al. Combined use of the neutrophil-to-lymphocyte ratio and CRP to predict 7-day disease severity in 84 hospitalized patients with COVID-19 pneumonia: a retrospective cohort study. Ann Transl Med 2020;8:635.

[21] Han H, Ma Q, Li C, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 2020;9:1123-30.

[22] Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020;221:1762-9.

[23] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71:762-8.

[24] Ni M, Tian FB, Xiang DD, et al. Characteristics of inflammatory factors and lymphocyte subsets in patients with severe COVID-19. J Med Virol 2020; published online May 29. DOI: 10.1002/jmv.26070.

[25] Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020;55:102763.

[26] Jiang M, Guo Y, Luo Q, et al. T-cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of Coronavirus disease 2019. J Infect Dis 2020;222:198-202.