

RT-PCR Status and Antibody Response in Patients with Coronavirus Disease 2019

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Research

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Abstract

Background: Novel coronavirus (COVID-19) is a new viral species that causes pneumonia. Currently, RT-PCR and IgM/IgG antibody assays have been recommended for the diagnosis of COVID-19 infection. However, the correlation between RT-PCR status and antibody (IgG, IgM) response remains unknown.

Methods: Consecutive COVID-19 patients admitted to our department between February 10, 2020 and March 10, 2020, were diagnosed by guidelines issued by the World Health Organization (WHO) and included in this study. RT-PCR and antibody (IgM/IgG) assays for COVID-19 infection were performed for all patients according to the manufactures' protocols. Other data, such as demographic, clinical, laboratory, as well as treatment and outcome, were collected using data collection tables from electronic medical records.

Results: During the study period, a total of 103 patients were diagnosed as having a moderate type of COVID-19 at our department, including 55 males and 48 females, with an average age of 57.53 ± 1.65 years old (range 23 to 90 years old). The peak level of SARS-CoV-2 IgM antibody (243.10 ± 89.84 AU/ml) was reported 4 days after the negative RT-PCR (-) (all $P < 0.05$). Subsequently, the IgM decreased to 42.69 ± 22.39 AU/ml 21 days after RT-PCR (-). However, the IgG was maintained at a high level 4 days before RT-PCR (-) and later. The lymphocyte count was at the lowest level on day7 before the RT-PCR(-) result ($P < 0.05$), and then elevated after RT-PCR conversion (viral clearance).

Conclusions: SARS-CoV-2 IgM/IgG levels did not correlate with RT-PCR status in our study sample. We found that SARS-CoV-2 IgM/IgG could be a potential biomarker to monitor clinical course, determine discharge, and assess recovery of those infected patients with the novel coronavirus.

Trial registration: A prospective, open label, randomized, control trial for chloroquine or hydroxychloroquine in patients with mild and common novel coronavirus pulmonary (COVID-19). ChiCTR2000030054. Registered 18 Feb,2020. <http://www.chictr.org.cn/edit.aspx?pid=49869&htm=4>

Introduction

In December 2019, an outbreak of emerging coronavirus pneumonia (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, also known as COVID-19) occurred in Wuhan, China [1]. As of March 15, 2020, the virus has spread to more than 100 countries and regions, the number of confirmed cases has reached 111,000 worldwide, and 81,048 confirmed cases and 3,204 deaths were reported in China [2]. The health care system and preventive services face significant challenges, both in China and globally. Due to the high transmission, pathogenicity, and lethality of COVID-19, the World Health Organization (WHO) defined the epidemic as "Public Health Emergency of International Concern (PHEIC)" on January 31, 2020, and re-defined it as a global pandemic (Pandemic) on March 11, 2020 [3,4].

Because COVID-19 is a new viral species, no effective antiviral drugs or vaccines are in existence. Therefore, to control the severe epidemic situation, adequate control measures should be implemented to prevent transmission by tracing and isolating a larger proportion of contacts. Effective treatment is also required to control the infection. Currently, the diagnosis of COVID-19 mainly relies on reverse transcription-polymerase chain reaction (RT-PCR) assays. However, about 50% of COVID-19 cases have false negative (-) RT-PCR results, and this leads to inconsistency with diagnosing clinical symptoms and imaging examination. Due to the inappropriate collection of nasopharyngeal samples, repeated sampling and testing are required for most patients who are RT-PCR positive (+), which would significantly affect the diagnosis, prevention, and control of COVID-19 infection.

The most recent Chinese guidelines recommend antibody assays to diagnose COVID-19. A recent study found that the Immunoglobulin M / Immunoglobulin G (IgM/IgG) antibody assay is a useful diagnostic method to detect COVID-19, and that a positive IgM antibody assay and an IgG level of four times the initial value can be used to diagnose COVID-19 [5]. This method is considered as an adjunct assay when RT-PCR is not feasible. The absence or decrease of SARS-CoV-2 IgM antibodies and the increase of SARS-CoV-2 IgG antibodies indicate that these patients may successfully recover gradually, and immunity to the COVID-19 has been developed [5]. Since February 28, 2020, IgG and IgM antibodies against COVID-19 have been used as diagnostic biomarkers at Optics Valley Branch of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. To review the current status of diagnosis and treatment of COVID-19, we conducted a retrospective analysis of 103 COVID-19 cases (mild and moderate type) at Optics Valley Branch of Tongji Hospital (Wuhan, China) from February 10, 2020 to March 10, 2020. The levels of COVID-19 IgM and IgG antibodies and RT-PCR status were analyzed, aiming to improve the understanding of diagnostic assays.

Methods

Participants

All COVID-19 patients were diagnosed according to the medium-term guidelines issued by WHO [17]. Based on published guidelines [6], the diagnostic criteria of COVID-19 are as follows: 1) a positive real-time RT-PCR (+) for COVID-19; 2) viral gene sequencing that has high homology with known COVID-19; and (3) a positive IgM antibody assay for COVID-19, and an IgG level four times the initial value. A moderate type of COVID-19 case was defined as fever, respiratory tract symptoms, and imaging analysis indicative of pneumonia.

Demographic, clinical, laboratory and radiologic analyses, as well as treatment and outcome, data were collected using data collection tables by our team. The data were reviewed by trained doctors.

RT-PCR for COVID-19

Nasopharyngeal swab samples were collected from COVID-19 patients and sent for RNA extraction. Briefly, the nasopharyngeal swab was put in the collection tube containing 150 uL virus preservation

solution. The respiratory sample RNA separation kit was used to extract total RNA within 2 hours [18], and RT-PCR for COVID-19 was performed according to the manufacturer's protocol.

A negative COVID-19 result was characterized by 3 consecutive RT-PCR(-) results for each patient. Patient discharge was based on RT-PCR(-) results, clinical symptoms, and radiography. The time of the first RT-PCR(-) result was recorded for further analysis. For this study, we reviewed the time of the first RT-PCR(-) test. Samples were tested for COVID-19 RT-PCR on a predetermined date (usually Monday, Wednesday, and Friday).

SARS-CoV-2 IgM/IgG antibody assays

Briefly, serum levels of COVID-19 IgM and IgG antibodies were tested on a YHLO iFlash 3000 chemiluminescence immunoassay analyzer (all available from Shenzhen Yahuilong Biotechnology Co. Ltd.). The IgM and IgG were quantified using a method based on two-step indirect immunoassay. The levels of IgM, or IgG were positively correlated with the relative luminous intensity measured by the chemiluminescence analyzer, and the results were calculated using the calibration data. A positive result for IgM, or IgG assay was defined according to the reference scale (>10.0 Au/mL) [9,19]. The presence of SARS-CoV-2 IgM antibody indicated an acute infection of COVID-19, and an increasing IgG antibody level (4-fold increase) indicated a recovery state from COVID-19 infection [10].

Statistical analysis

Categorical variables are described by frequency and percentages, continuous variables are described by mean and standard error of mean. If the data was normally distributed, the mean value of continuous variables between groups was compared using an independent group t test. If the data were not normally distributed, the Mann-Whitney test was used. Data were analyzed using SPSS 17.0 software, and a P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 103 patients were diagnosed with having a moderate type of COVID-19 at Optics Valley Branch of Tongji Hospital (Wuhan, China) between February 10, 2020 and March 10, 2020. The baseline characteristics of these patients are shown in Table 1. Our study included 55 males and 48 females, with an average age of 57.53 ± 1.65 years old (range from 23 to 90 years old). The average time between admission and the RT-PCR(-) status was 7.69 ± 0.77 days (range from 2 to 26 days), and the average time between symptom initiation and the RT-PCR(-) status was 16.18 days (range from 1 to 45 days).

Antibody (IgM and/or IgG) positive ratio is 96.83% (61/63). Other data including baseline clinical and laboratory findings were presented in Table 2.

RT-PCR status and SARS-CoV-2 IgM and IgG antibody assays

As shown in Figure 1, the peak level of SARS-CoV-2 IgM antibody (243.10 ± 89.84 AU/ml) was reported on day 4 after the RT-PCR(-) result. This level was statistically different compared to other days of testing (all $P < 0.05$). The IgM level decreased to 42.69 ± 22.39 AU/ml 21 days after the RT-PCR(-) result.

The IgG level increased by approximately 20-fold that of the upper reference 4 days before the RT-PCR(-) result, reached peak value by day4, and then remained elevated at the peak level (Figure 1).

Lymphocyte counts and Interleukin-6

As shown in Figure 2, the lowest level of lymphocyte count ($1.09 \pm 0.09 \times 10^9/L$) was reported on day7 before the RT-PCR(-) result. This level was statistically different compared to other days of testing (all $P < 0.05$), and then elevated after the RT-PCR(-) result (viral clearance). In terms of IL-6 in serum, there was no significant association between IL-6 levels and RT-PCR status (viral clearance, Figure 3).

Discussion

In this retrospective study, we reviewed SARS-CoV-2 IgM/IgG antibody and RT-PCR assays of 103 cases with a moderate type of COVID-19 for the purpose of understanding the progression of COVID-19, the diagnostic utility of these assays, and ultimately finding better treatment strategies. According to the national guidelines, RT-PCR is considered one of the main diagnostic tools for COVID-19, but the RT-PCR assay for COVID-19 has a false negative rate of approximately 50%. Hence, the sensitivity of the RT-PCR assay is poor in clinical practice, and necessary measures need to be taken, such as repeated RT-PCR testing or collecting multiple samples from the same subject, to better understand a patient's status. Furthermore, a RT-PCR (-) result should not serve as the only criteria for determining patient discharge; evaluation of clinical symptoms and imaging, as well as antibody testing are also required [6]. We conducted this retrospective study to further improve our understanding of RT-PCR status in conjunction with variations in IgM/IgG antibody levels for determining clinical course and patient discharge. To the best of our knowledge, this is the first report investigating the correlation between RT-PCR status and IgM/IgG antibody levels in COVID-19 patients.

In this study, we observed that the SARS-CoV-2 IgM levels peaked on day4 and remained positive 21 days after the RT-PCR (-) result. The peak IgG level was approximately 20-fold greater than that of the upper reference at day4. The IgM levels decreased over time. Yu Chun *et al*, reported that the neutralizing antibody (NAb) against SARS-CoV was found in 85.9% of COVID-19 cases, and that most prevalent immunoglobulin class was IgG. NABs typically become detectable 5-10 days after the onset of symptoms. The NAb levels usually peak at 20-30 days and remain at these levels for > 150 days [7]. IgM levels are usually first detected at 20.5 days after infection, peak 80 days later, and then fall to baseline levels at 180 days [8]. In another SARS study [9], the conversion of IgG antibody (approximately 10 days after infection) occurred simultaneously and earlier than that of both IgM and IgA (approximately 11 days). IgG was detected as early as 4 days after the onset of illness, with the earliest detection of all three antibodies reaching peak levels at 15 days. Elevated IgG levels can persist for more than 3 months [9].

Yang *et al*, showed that in COVID-19 patients, the sensitivity of virus RT-PCR using sputum and nose swabs was higher than that of pharynx swabs at 0-7 days, 8-14 days, and ≥ 15 days, respectively [10]. With the progression of the disease, the rate of pharynx swab RT-PCR(+) results decreased significantly (from 61.3% at 0-7 days to 11.1% at ≥ 15 days) [10]. Hence, nucleic acid extraction and disease course can impact RT-PCR results. The COVID-19 IgM/IgG antibody assay has been shown to have good diagnostic performance for detecting infection. As such, the COVID-19 IgM/IgG antibody assay has been developed and recommended for clinical practice as a complement to standard RT-PCR testing. The use of this antibody assay may reduce the impact of COVID-19 false negative RT-PCR tests due to inappropriate extraction and collection methods (nasopharyngeal swab sample). In our study, the sensitivity of COVID-19 antibodies (IgM and/or IgG) for detecting infection was 96.83% (61/63), with only 2 COVID-19 patients testing negative after the IgM/IgG antibody assay among the 63 tested patients. This result is consistent with a previous finding [11], which reported a sensitivity of RT-PCR at only 30 - 50% [12]. Considering its diagnostic potential, the SARS-CoV-2 IgM/IgG antibody assay can be used to screen COVID-19 infection, monitor clinical course, determine discharge, and assess recovery. In addition, the RT-PCR for COVID-19 faces several challenges. For example, it is thought that the global supply is difficult to meet a huge demand for the PCR primers and positive controls. Hence, the antibody assay may be helpful as an alternative method in screening patients with COVID-19 [13]. Fortunately, in a recent study by Wang To KK, et al., posterior oropharyngeal saliva samples, as a non-invasive specimen for RT-PCR test, is proved to be a good choice for serodiagnosis of COVID-19, due to a high sensitivity [14].

The IgM/IgG antibody assay has several advantages over the RT-PCR assay for diagnosing COVID-19. First, RT-PCR requires respiratory samples acquired from a swab, sputum, and/or bronchoalveolar lavage fluid (BALF), and the assay must be conducted in a strictly regulated biological safety facility. The IgM/IgG antibody assay requires only a serum or plasma sample. Second, the false-negative rate of the antibody assay is much lower than that of RT-PCR assay, which will facilitate more rapid and more sensitive in identification of COVID-19 patients. It is supposed to be urgent values for large number of infected people screening, detecting, immune status evaluating, which would be useful in tracing suspected infection, guiding people back to work(including infected health-care workers getting back to work with immune), reopening the lockdown, finding asymptomatic infection and so on [13]. Third, the antibody assay used in our study is a qualitative biomarker, which will be useful for monitoring patient progression and outcome after infection. Fourth, the antibody test can be used to verify the effectiveness of new vaccine [13].

In our study, the findings supported that the level of lymphocyte count was positively correlated with viral load. When infected with the novel virus, the level of lymphocyte count was low, such as a lowest level occurs on day7 before the RT-PCR(-) status. But, under the circumstance of viral clearance and improvement of disease status, the lymphocyte count increased gradually. The variation of lymphocyte count may also be taken as a monitor biomarker for the management of COVID-19 patients and the normal level of lymphocyte could be thought as a recovery sign of COVID-19.

Our study found that in patients with moderate type of COVID-19, there was no statistically different relationship between IL-6 level and the course of disease. This finding is inconsistent with previous data reported by other literatures [15,16]. This may result from a moderate inflammatory reaction in moderate type of COVID-19, and further analysis should be performed in severe cases.

Our study does have some limitations that should be noted. First, only patients with a moderate type of COVID-19 were enrolled, and the data for severe infections remains uncertain. Second, due to the retrospective design, information about viral load in the nasopharyngeal swabs is not known. Thus, correlation analysis between viral load and IgM/IgG levels was not attempted. In the future, the time for IgM and IgG reversion should be evaluated carefully. In addition, the association between IgM/IgG levels and the recovery efficiency should also be investigated in a prospective manner.

Conclusions

IgM/IgG levels against COVID-19 can serve as qualitative markers of infection status. IgG levels remained elevated and IgM levels appeared to decrease after 4 days of the initial RT-PCR(-) result in our study population. Continuous high level of serum IgG is the recovery and self-protective immune marker after SARS-CoV-2 infection. Thus, IgM and IgG against COVID-19 may serve as useful biomarkers to screen the infection, monitor the clinical course of infection, determine patient discharge, assess recovery.

Abbreviations

COVID-19: Coronavirus disease 2019

RT-PCR: Reverse transcription-polymerase chain reaction

IgM: Immunoglobulin M

IgG: Immunoglobulin G

WHO: World Health Organization

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

PHEIC: Public Health Emergency of International Concern

NAb: Neutralizing antibody

BALF: Bronchoalveolar lavage fluid

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Optics Valley Branch of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, and oral consent was obtained from all enrolled patients. Tongji Hospital is one of the largest teaching hospitals, located at the epidemic center of COVID-19 in Wuhan City, Hubei Province. At the government's charge, Tongji Hospital is responsible for the management of COVID-19 patients. Our study team is from Xiamen, Fujian Province, and is providing healthcare services during the COVID-19 epidemic at Tongji Hospital.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data or used during the study are available by email to the corresponding author.

Competing interests

All authors declare no conflicts of interest regarding the contents of this article.

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Authors' contributions

Dr Chen and Prof Yin have the assessment of all the research data, and are responsible for the integrity of the data and the accuracy of data analysis.

Concept and design: Lan Chen, Zhen-Yu Yin

Data collection and analysis: Xiao-Bin Zhang, Zhen-Yu Zhang, Su-Zhen Zhang, Qiu-Ying Han.

Imaging analysis of lung: Zhi-Peng Feng

Statistical analysis: Xiong-Xiao, Hui-Min Chen, Xian-Li Chen

Manuscript drafting: Yu-Pei Lan

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Tables

Table 1. Baseline characteristics of COVID-19 patients

	Number (%)
Age (years old)	57.53 ± 1.65
Gender	
Female	48 (46.61%)
Male	55 (53.39%)
Underlying diseases	
Hypertension	27 (26.67%)
Diabetes	17 (16.67%)
Cardiovascular disease	5 (5.00%)
Malignant tumor	2 (1.67%)
COPD	2 (1.67%)
Chronic kidney disease	5 (5.00%)
Chronic liver disease	2 (1.67%)
Gout	2 (1.67%)
Time between symptom initiation and RT-PCR(-), days)	16.18
Symptoms	
Fever	62 (60.47%)
Dry cough	43 (41.86%)
Chest tightness	17 (16.28%)
Tired	14 (13.95%)
Expectoration	6 (5.81%)
Sore throat	4 (3.49%)
Myalgia	2 (2.33%)
Dizzy	2 (2.33%)
Diarrhea	1 (1.62%)
Asthma	1 (1.62%)
Testicular pain	1 (1.62%)
No symptoms, physical examination found	5 (4.65%)

Table 2. Baseline laboratory findings of COVID-19 patients

Laboratory findings	Average ± SEM
SpO ₂ (%)	96.89 ± 0.24
White-cell count (*10 ⁹ /L)	6.08 ± 0.23
Lymphocyte count (*10 ⁹ /L)	1.33 ± 0.06
Neutrophils (%)	64.93 ± 1.32
Platelet count (*10 ⁹ /L)	234.43 ± 9.30
Hemoglobin (g/L)	128.32 ± 1.78
C-reactive protein (mg/L)	29.64 ± 4.01
Procalcitonin (ng/mL)	0.08 ± 0.01
Albumin (g/L)	37.81 ± 0.60
Aspartate transaminase (U/L)	33.31 ± 1.90
Alanine transaminase (U/L)	29.29 ± 2.57
GFR (mL/min/1.73 m ²)	101.40 ± 15.07
Troponin (pg/mL)	16.53 ± 5.84
Myoglobin (ng/mL)	75.19 ± 8.91
CK-MB (ng/mL)	1.30 ± 0.18
D-dimer (µg/mL)	1.15 ± 0.27
Interleukin-1β (pg/mL)	2.36 ± 0.46
Interleukin-2R (U/mL)	379.82 ± 33.29
Interleukin-6 (pg/mL)	5.49 ± 1.11
Interleukin-8 (pg/mL)	10.51 ± 2.06
Interleukin-10 (pg/mL)	2.21 ± 0.39
TNF-α (pg/mL)	7.23 ± 0.48
CD4 cell count (/µl)	745.36 ± 45.90
CD8 cell count (/µl)	436.43 ± 26.37

Figures

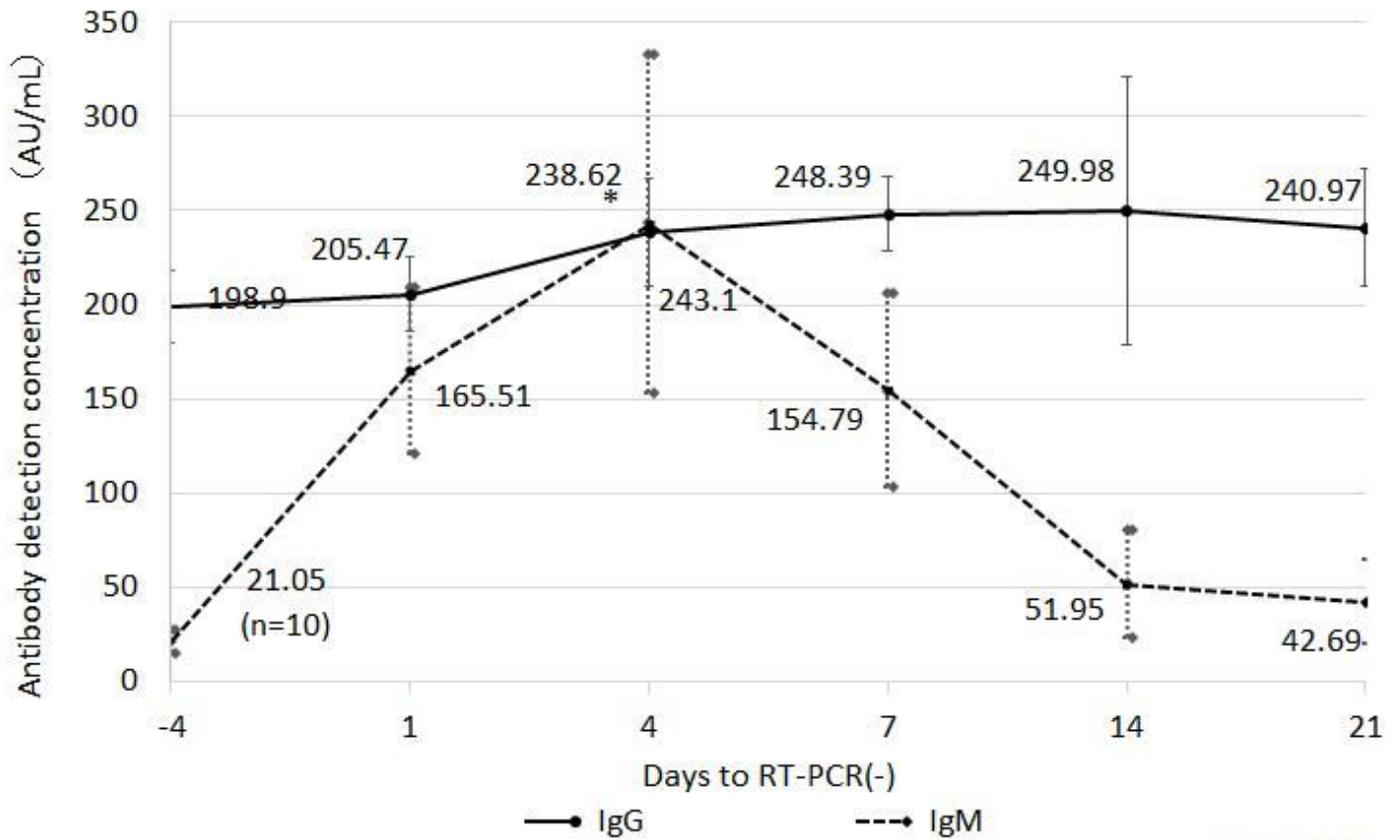


Figure 1

Figure 1

Levels of SARS-CoV-2 IgM/IgG antibodies according to the onset of RT-PCR(-) result *: $P < 0.05$. (Compare with the day 4 before the first RT-PCR(-) test, day 14 and day 21 after the first RT-PCR(-) test) Analysis of Variance (ANOVA) The X axis negative means the days before the first RT-PCR(-) test. The X axis positive means the days after the first RT-PCR(-) test.

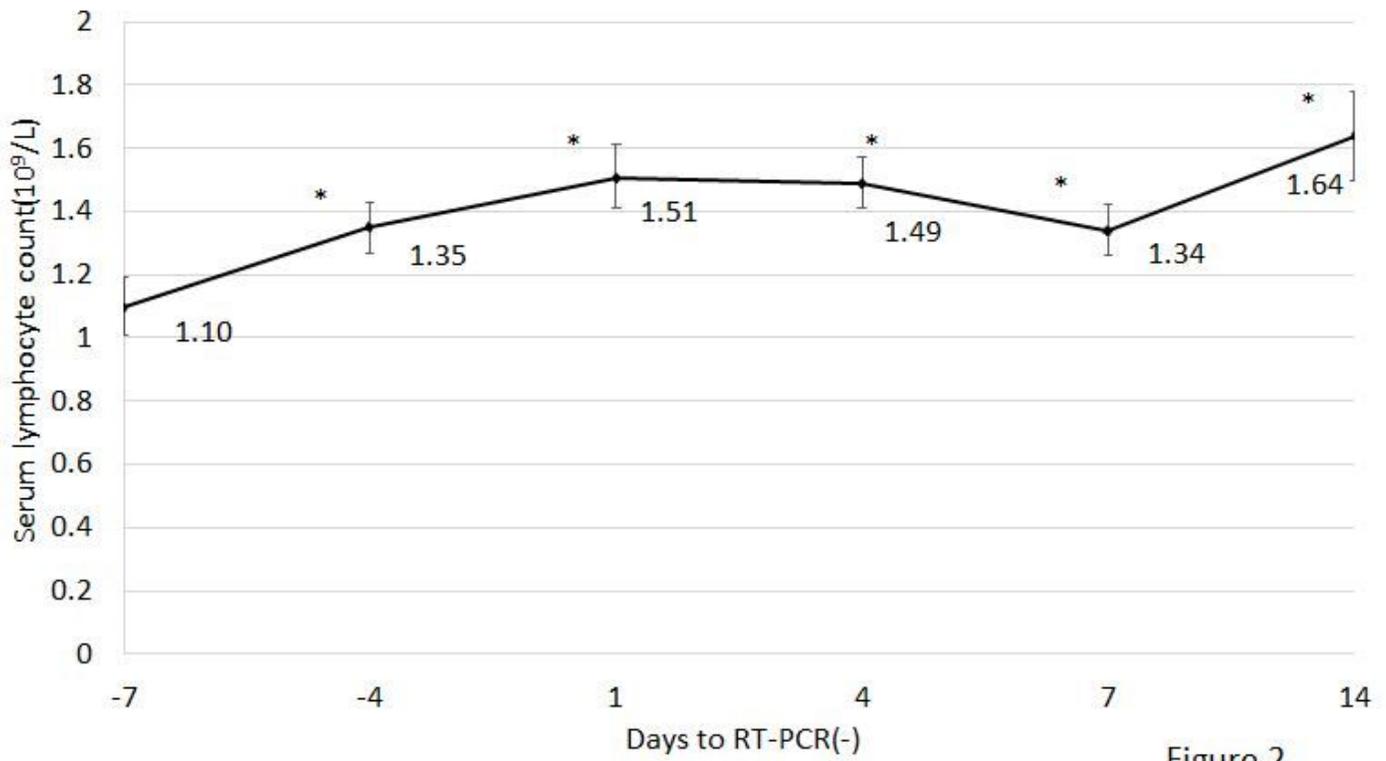


Figure 2

Figure 2

Levels of serum lymphocyte count according to the onset of RT-PCR(-) result *: P<0.05 (Compare with the day7 before the first RT-PCR(-) test) Analysis of Variance (ANOVA) The X axis negative means the days before the first RT-PCR(-) test. The X axis positive means the days after the first RT-PCR(-) test.

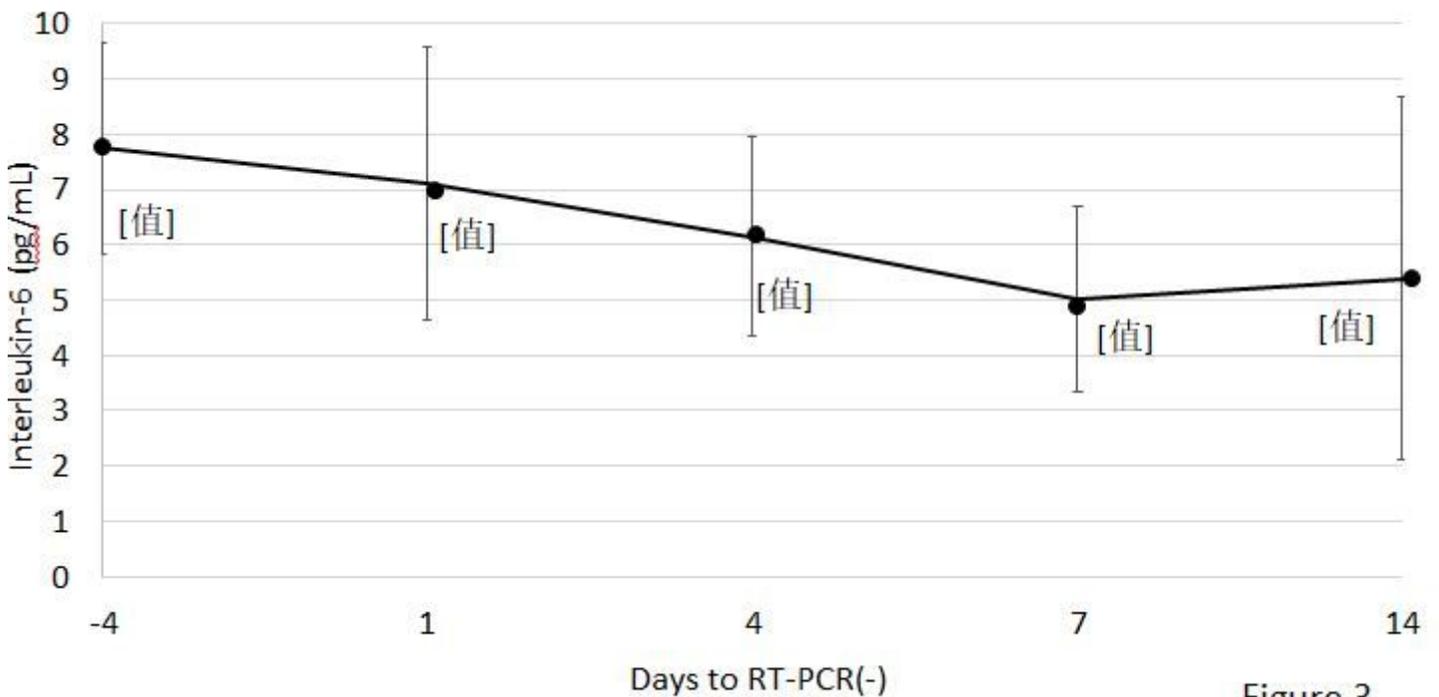


Figure 3

Figure 3

Levels of serum Interleukin-6 according to the onset of RT-PCR(-) result Analysis of Variance (ANOVA) The X axis negative means the days before the first RT-PCR(-) test. The X axis positive means the days after the first RT-PCR(-) test.