

Clinical Characteristics of COVID-19 Patients with Recurrent PCR Positivity After Hospital Discharge

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Research article

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Abstract

Objective: This study aimed to investigate the clinical characteristics of COVID-19 patients with recurrent SARS-CoV-2 positivity after hospital discharge.

Methods: This retrospective study included COVID-19 patients who were readmitted for recurrence of positive SARS-CoV-2 RNA. Univariate and multivariate analyses were performed to assess the risk factors associated to the duration of recurrent RNA positivity.

Results: Among the 287 discharged COVID-19 patients, 33 (11.5%) patients with recurrent PCR positivity were included. Among these patients, 21 (63.7%) patients were female, their mean age was 48.7 (± 19.7) years old. 22 (66.7%) patients were asymptomatic. The following clinical features were presented in other patients: cough, fatigue, sore throat, fever and expectoration. The chest CT findings revealed that 8 (24.2%) patients were characterized by deterioration compared to the previous results. The median duration of recurrent RNA positivity was 9.0 days (IQR, 6.0, 15.0). We found that increased serum SARS-CoV-2-specific IgG antibody titer, elevated serum creatinine level, and female gender were the risk factors for the prolonged duration of recurrent RNA positivity.

Conclusion: SARS-CoV-2 turned positive in a minority of discharged patients with COVID-19. Most patients experienced mild clinical course. Increased IgG antibody titer, creatinine and female gender were correlated to the prolonged RNA clearance time.

Introduction

Since December 8, 2019, the outbreak of the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) has become a serious epidemic worldwide[1–3]. According to the World Health Organization report, as of May 14, cases were reported in more than 200 countries, and the total number of confirmed cases and deaths has reached 424,8389 and 29,2046, respectively[4].

A number of studies have described the clinical characteristics of hospitalized patients with COVID-19 infection[5, 6]. Some studies have reported that few of these patients were still virus carriers after recovering from COVID-19 infection[7, 8]. Approximately 14.5% of discharged COVID-19 patients were sent to the hospital again due to positive RT-PCR results on virus again, and the median time interval from negative to recurrent positive for these patients was 7.32 ± 3.86 days[8]. There was a negative correlation between the serum D-Dimer level before discharge and the duration of treatment. Lymphocyte concentrations before discharge were positively correlated with the time interval for virus reappearance[8]. However, to date, the clinical and imaging features are not entirely clear. In addition, no study has revealed the viral shedding duration after recurrence and its influencing factors. The present study reports 33 patients with polymerase chain reaction (PCR) assays of SARS-CoV-2 recurrent positive after discharge, and analyzes the clinical characteristics of this population.

Methods

Study Design

East District of Renmin Hospital, Wuhan University, is a designated hospital for the treatment of COVID-19 patients in Wuhan, where all patients are diagnosed with COVID-19 according to the WHO Interim Guidance. When patients were discharged for the first time, these patients meet the following criteria proposed by the National Health Commission of China: (1) normal temperature that lasts longer than three days, (2) significant improvement in respiratory symptoms, (3) substantially improved acute exudative lesions on chest computed tomography (CT) images, and (4) the respiratory nucleic acid was negative for two consecutive times (with at least a 24-hour sampling time interval)[9]. After discharge, all patients were quarantined for two weeks, and nasopharyngeal swab samples were collected every three or four days for the RT-PCR detection of COVID-19, in the same manner as that performed in a hospital.

From February 1, 2020 to April 1, 2020, a total 287 COVID-19 infected patients were discharged from 23rd and 24th ward. Among these patients, 33 patients with recurrent PCR positivity after hospital discharge were readmitted to the hospital. The positive recurrence of PCR assays was defined as at least two RNA tests of SARS-CoV-2 was positive after discharge. The ethics approval was granted by the Ethics Board of the Institute of People's Hospital of Wuhan University (WDRY2020-K068). The informed consent was waived due to the retrospective nature of the study.

Data collection

The data of demographic information, clinical characteristics, laboratory results and treatment process were extracted from the electronic medical records of these patients. All data were reviewed by two doctors (K.W. and H.Z.), and a third researcher (P.T.) determined whether there was a difference in interpretation between the two reviewers.

Statistical method

The data were analyzed by the means of SPSS version 19.0. Continuous variables were presented as mean (SD) or median (IQR), and compared by Mann-Whitney U-test. Categorical variables were expressed in frequency (percentage), and compared by Chi-square or Fisher's exact test, when appropriate. A *P*-value of <0.05 was considered statistically significant. Simple linear regression analysis and multiple linear regression analysis were used to evaluate the correlation between these two variables.

Results

Clinical features and laboratory tests

A total 33 COVID-19 (11.5%) patients were readmitted for recurrent PCR positivity after hospital discharge. The mean age was 48.7 ± 19.7 years old, which ranged within 16–94 years old. These patients consisted of 12 males (36.3%) and 21 (63.7%) females. The healthcare workers accounted for 24%. The virus shedding duration for the initial SARS-CoV-2 infection was 33.8 ± 14.2 days. The demographic characteristics are presented in Table 1. The median time interval from RNA clearance on the first infection to positive again was 13.0 days (IQR: 9.0, 30.5). The symptoms of the readmitted patients included cough (4, 12.1%), fatigue (4, 12.1%), sore throat (3, 9.1%), fever (2, 6.1%) and expectoration (1, 3%). However, 22 patients (66.7%) were asymptomatic. Furthermore, 11 patients (33.3%) had comorbidities, including hypertension (24.2%), chronic bronchitis (9.1%), coronary heart disease (6.1%), hepatitis B (6.1%) and diabetes (3%). The laboratory tests, including hemograms, T cell subsets, D-Dimer, biochemical and inflammatory markers, within 24 hours of readmission are summarized in Table 2. The serum SARS-CoV-2-specific IgG antibody increased, with a mean value of 193.8 AU/ml (± 139.7). The median IgM antibody titer was 4.7 AU/ml (IQR, 2.9, 9.9).

Table 1
Clinical characteristics of COVID-19 patients with recurrent PCR positivity

	Total (n = 33)	Viral shedding duration after recurrence		P- value
		≤ 10 days (n = 19)	>10 days (n = 14)	
Age (y), median (Q1, Q3)	46.0 (31.5, 62.0)	36.0 (30.0, 56.0)	57.5 (42.3, 69.3)	0.106
Female, n (%)	21 (63.6%)	12 (63.2%)	9 (64.3%)	0.290
Signs and symptoms, n (%)				
Cough	4 (12.1%)	0 (0)	4 (28.6%)	0.052
Fatigue	4 (12.1%)	2(10.5%)	2 (14.3%)	1.000
Sore throat	3 (9.1%)	1(5.3%)	2 (14.3%)	0.781
Fever	2 (6.1%)	0 (0)	2 (14.3%)	0.172
Expectoration	1 (3.0%)	0 (0)	1 (7.1%)	0.424
Asymptomatic	22 (66.7%)	15 (78.9%)	7 (50.0%)	0.171
Comorbidity, n (%)				
Hypertension	8 (24.2%)	4 (21.1%)	4 (28.6%)	0.931
Diabetes	1 (3.0%)	1 (5.3%)	0 (0)	1.000
Hepatitis B	2 (6.1%)	0 (0)	2 (14.3%)	0.172
Coronary heart disease	2 (6.1%)	1(5.3%)	1 (7.1%)	1.000
Chronic bronchitis	3 (9.1%)	2 (10.5%)	1 (7.1%)	1.000
Interval from RNA clearance on the first time to turning positive again, median (Q1, Q3)	13.0 (9.0, 30.5)	13.0 (9.0, 30.0)	12.0 (8.8, 35.8)	0.843

Table 2

Laboratory results, treatment, and clinical outcomes of patients with recurrent PCR positivity after readmission

	Total (n = 33)	Viral shedding duration after recurrence		P-value
		≤ 10 days (n = 19)	>10 days (n = 14)	
Laboratory characteristics				
White blood cell count ($\times 10^9/L$), mean \pm SD	6.0 \pm 1.6	5.9 \pm 1.4	6.3 \pm 1.9	0.525
Neutrophil count ($\times 10^9/L$), median (Q1, Q3)	3.2 (2.4, 4.4)	3.2 (2.5, 4.4)	3.9 (2.3, 4.5)	0.706
Lymphocyte count ($\times 10^9/L$), mean \pm SD	1.7 \pm 0.5	1.8 \pm 0.6	1.6 \pm 0.5	0.474
Platelet count, ($\times 10^9/L$), median (Q1, Q3)	208.0 (171.0, 264.0)	225.0 (172.0, 275.0)	177.0 (168.0, 237.8)	0.174
Hemoglobin, (g/L), mean \pm SD	134.5 \pm 14.3	132.1 \pm 16.6	137.7 \pm 10.1	0.268
CD3 (/uL), mean \pm SD	1130.8 \pm 383.8	1158.9 \pm 452.4	1094.6 \pm 284.7	0.985
CD4 (/uL), mean \pm SD	655.9 \pm 227.0	670.7 \pm 266.6	636.9 \pm 170.9	0.684
CD8 (/uL), mean \pm SD	418.8 \pm 198.3	431.0 \pm 229.6	403.1 \pm 156.1	0.700
ALT (U/L), median (Q1, Q3)	21.0 (11.5, 31.5)	21.0 (13.0, 30.0)	18.0 (10.5, 36.0)	0.677
AST (U/L), median (Q1, Q3)	19.0 (16.0, 25.5)	21.0 (16.0, 26.0)	18.0 (16.0, 25.5)	0.545
Urea (mmol/L), median (Q1, Q3)	5.6 (4.3, 6.5)	4.8 (4.0, 6.1)	5.0 (3.7, 6.5)	0.677
Creatinine (umol/L), median (Q1, Q3)	52.5 (45.0, 65.3)	46.5 (43.0, 56.0)	63.0 (49.5, 72.0)	0.022
D-Dimer (mg/L), median (Q1, Q3)	0.3(0.2, 0.4)	0.2 (0.2, 0.6)	0.3 (0.2, 0.4)	0.773
IgG (AU / ml), mean \pm SD	193.8 \pm 139.7	143.6 \pm 69.8	276.0 \pm 185.4	0.043
IgM (AU / ml), median (Q1, Q3)	4.7 (2.9, 9.9)	3.6 (2.2, 6.8)	8.0 (4.7, 13.3)	0.044
CT findings on original lesions				
deterioration	8 (24.2%)	4 (21.1%)	4 (28.6%)	0.931
stable	4 (12.1%)	2 (10.5%)	2 (14.3%)	1.000

	Total (n = 33)	Viral shedding duration after recurrence		P-value
		≤ 10 days (n = 19)	>10 days (n = 14)	
improvement	9 (27.3%)	6 (31.6%)	3 (21.4%)	0.801
completely absorbed	12 (36.4%)	7 (36.8%)	5 (35.7%)	0.947
Antiviral therapy				
Total	12 (36.4%)	5 (26.3%)	7 (50.0%)	0.162
Abidol	10 (30.3%)	5 (26.3%)	5 (35.7%)	0.844
Hydroxychloroquine	8 (24.2%)	2 (10.5%)	6 (42.9%)	0.083
Ribavirin	2 (6.1%)	2 (10.5%)	0 (0)	0.496
Time of clinical course				
Duration of recurrent RNA positivity, days, median (Q1, Q3)	9.0 (6.0, 15.0)	6.0 (6.0, 8.0)	15.5 (13.0, 19.0)	0.000

Imaging features and treatment

Compared with the chest CT images before leaving the hospital, the CT findings at readmission to the hospital revealed that eight (24.2%) patients were characterized by deterioration of original lesions, four patients presented with stable lesions, nine patients presented with improved lesions, and 12 patients presented with disappearance of original lesions. When these patients were readmitted, 12 of these patients received antiviral therapy, including abidol, hydroxychloroquine and ribavirin. All patients recovered, and were discharged. The median duration of recurrent RNA positivity was 9.0 days (IQR, 6.0, 15.0; Fig. 1). No new COVID-19 was found among the close contacts of these patients during the study period.

Risk factors of the duration of recurrent RNA positivity

According to the duration of recurrent RNA positivity, these patients were divided into two groups: viral shedding after recurrence in the short-term group, in which the duration of viral shedding after recurrence was within 10 days (n = 19, 57.58%); viral shedding after recurrence in the long-term group, in which the duration of viral shedding after recurrence was beyond 10 days (n = 14, 42.42%). There was no distinguished difference in terms of age, gender, healthcare worker, signs and symptoms, or comorbidities between these two groups (Table 1). Compared with patients in the viral shedding after recurrence in the short-term group, the serum creatinine level, serum SARS-CoV-2-specific IgG antibody titer and serum

SARS-CoV-2-specific IgM antibody titer of patients significantly increased in the viral shedding after recurrence in the long-term group (Table 2). The correlation analysis indicated that the duration of recurrent RNA positivity was positively correlated with both serum creatinine level ($r = 0.429$, $P = 0.016$) and serum SARS-CoV-2-specific IgG antibody titer ($r = 0.507$, $P = 0.005$). A multiple linear regression analysis was carried out, with age, gender, serum IgG titer, serum IgM titer and serum creatinine level as independent variables. The results revealed that serum IgG antibody titer ($r = 0.016$, $P = 0.016$) and serum creatinine level ($r = 0.318$, $P = 0.002$) were risk factors for the prolonged duration of recurrent RNA positivity (Table 3).

Table 3

Multiple linear regression analysis of the correlation between different variables and duration of recurrent RNA positivity

Variables	Regression coefficient	Standard regression coefficient	t value	P value	95%CI
Creatinine (umol/L)	0.318	0.727	3.573	0.002	0.133 ~ 0.504
IgM (AU/mL)	0.028	0.030	0.174	0.864	-0.306 ~ 0.362
IgG (AU/mL)	0.016	0.381	2.610	0.016	0.003 ~ 0.029
Age	0.046	0.155	0.867	0.396	-0.065 ~ 0.157
Female (reference: male)	4.789	0.434	2.167	0.042	0.192 ~ 9.385

Discussion

The present study describes the clinical characteristics of 33 COVID-19 patients with recurrent PCR positivity after discharge. Most of these patients were asymptomatic during the duration of the recurrent RNA positivity. These asymptomatic carriers brought more challenges to the identification and control of the COVID-19 epidemic worldwide.

In the present study, some patients presented with mild nonspecific symptoms, including cough, fatigue, sore throat, fever and expectoration. In other reports, merely 32% of patients had mild cough during the duration of the recurrent RNA positivity[8]. Furthermore, many cases reported that the clinical symptoms of COVID-19 patients with recurrent PCR positivity did not aggravate[7, 10]. However, there has been no reports on the infectious capacity of COVID-19 patients with recurrent PCR positivity. Therefore, it remains difficult to identify and control such patients through clinical symptoms. In order to avoid such patients from becoming a potential source of infection again, all discharged patients should be quarantined and regularly tested for infectivity assessment by rechecking the PCR.

The median duration of recurrent RNA positivity was 9.0 days. Furthermore, it was found that serum SARS-CoV-2-specific IgG antibody titer, serum creatinine level and female gender were risk factors for the prolonged duration of recurrent RNA positivity. The duration of positive RT-PCR persistence was associated with antibody response and clinical manifestations. Patients with symptoms and the development of anti-SARS-CoV-2 IgM antibodies had a shorter duration of positive RT-PCR results, and had no worsening clinical conditions, when compared to patients without the presence of anti-SARS-CoV-2 IgM antibodies[11]. Specific IgG antibodies are important for protecting the host from infection by blocking viral entry into host cells after viral infection[12]. The median duration of IgG was detected at 14 days (IQR, 10–18) after symptom onset, with a positive rate of 77.9%[13]. There was no association between plateau IgG levels and the clinical characteristics of patients[14]. According to the report of Kaijin Xu, male gender was an independent risk factor for prolonged viral RNA shedding in COVID-19 patients[15]. In the present study, female patients presented with a longer duration of recurrent RNA positivity. Histopathological studies have provided direct evidence of the invasion of SARS-CoV-2 into kidney tissues[16]. Cheng Y *et al.* reported that elevated baseline serum creatinine was an independent risk factors for in-hospital death[17]. However, there has been no report on the relationship between serum creatinine level and the duration of recurrent RNA positivity. Hence, the influence factor on the duration of recurrent RNA positivity needs further studies.

The cause for the recurrent positive viral RNA test after discharge in COVID-19 patients remains unclear. The deficiency of cellular immune function may lead to the incomplete shedding of the virus, resulting to the occurrence of "recurrence". Yao X *et al.* reported a case with negative detection of SARS-CoV-2 virus nucleic acid from nasopharyngeal swabs. However, the autopsy revealed residual SARS-CoV-2 in the lungs. These results highlight the remaining of SARS-CoV-2 in the lungs of discharged COVID-19 patients[18]. Comorbidity and therapeutic drugs, such as antiviral drugs and glucocorticoids, may also affect virus shedding[19]. After becoming infected with the virus, the human body responds with specific antibodies production to avoid reinfection of the virus[14]. If SARS-CoV-2 mutates within a short period of time, similar to hepatitis C virus, the patient may be infected again[20]. The possibility of reinfection is unknown.

Two consecutive negative RNA tests is recognized as one of the discharge criteria[9]. According to the report of Wu *et al.*, the positive rate of the SARS-CoV-2 RT-PCR test of nasopharyngeal swab, sputum, blood, feces and anal swabs is 38.13%, 48.68%, 3.03%, 9.83% and 10.00%, respectively[21]. Xiao *et al.* reported that 21.4% of patients presented with a positive virus RNA test again after two consecutive negative tests. It has been speculated that these patients may have experienced a false negative RT-PCR result or prolonged viral clearance, rather than a "turn positive" or "recurrence". However, the clinical characteristics and subgroup analysis was not performed for these patients[22]. Hence, the false negative RT-PCR result or prolonged viral clearance may be the cause for these patients to turn from negative to positive after discharge. It has been suggested that performing more viral RNA tests, combined with clinical improvements, could avoid false negative and reduce the recurrence.

In order to prevent the missed diagnosis of discharged patients, whose PCR assays turned positive, the following suggestions are given: (1) Both nasopharyngeal and oropharyngeal swabs test for SARS-CoV-2 RNA should be performed to reduce the false-negative rate. Furthermore, more tests, more specimens, and more methods should be considered. (2) Patients in convalescence should also be regularly tested for infectivity assessment, and all discharged patients should be home quarantined for at least 14 days. (3) Some laboratory examinations, such as serum creatinine level, SARS-CoV-2-specific antibody titer, D-dimer, lymphocyte count and platelet count, should be combined with the RT-PCR negative test as an additional measure, in order to ensure that the infected patient has completely recovered, and can be released from quarantine[10, 23].

The present study had several limitations. First, merely 33 discharged patients were included. Collecting data from a larger cohort would provide a more comprehensive understanding of these discharged patients. Second, the present study lacks a control group of COVID-19 patients discharged at the same time. Furthermore, even if anti-virus medicine was used for these readmitted patients, it was difficult to assess its effect on virus clearance. The etiological mechanism of COVID-19 patients with recurrent PCR positivity after hospital discharge should also be investigated.

Conclusion

SARS-CoV-2 turned positive in a minority of discharged patients with COVID-19. Most patients experienced mild clinical course and recovered in a short time. Increased IgG antibody titer, creatinine and female gender were correlated to the prolonged RNA clearance time.

Abbreviations

COVID-19: Coronavirus disease 2019

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

RT-PCR: Reverse Transcription-Polymerase Chain Reaction

CT: computed tomography

Declarations

Ethics approval and Consent to participate

The ethical approval was granted by the Ethics Board of the Institute of People's Hospital of Wuhan University (WDRY2020-K068). Informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

Datasets used in this analysis are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

TPW and HZX contributed to the conception and design of the study. WKG, Liu D, ZQF, and Dong L collected the data. LYL, LWX, ZSM and Dong L contributed to data management. TPW, HZX, and Liu D conducted statistical analysis. WKG and ZQF drafted the manuscript and all authors contributed to subsequent revisions. All authors read and approved the final manuscript.

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Figures

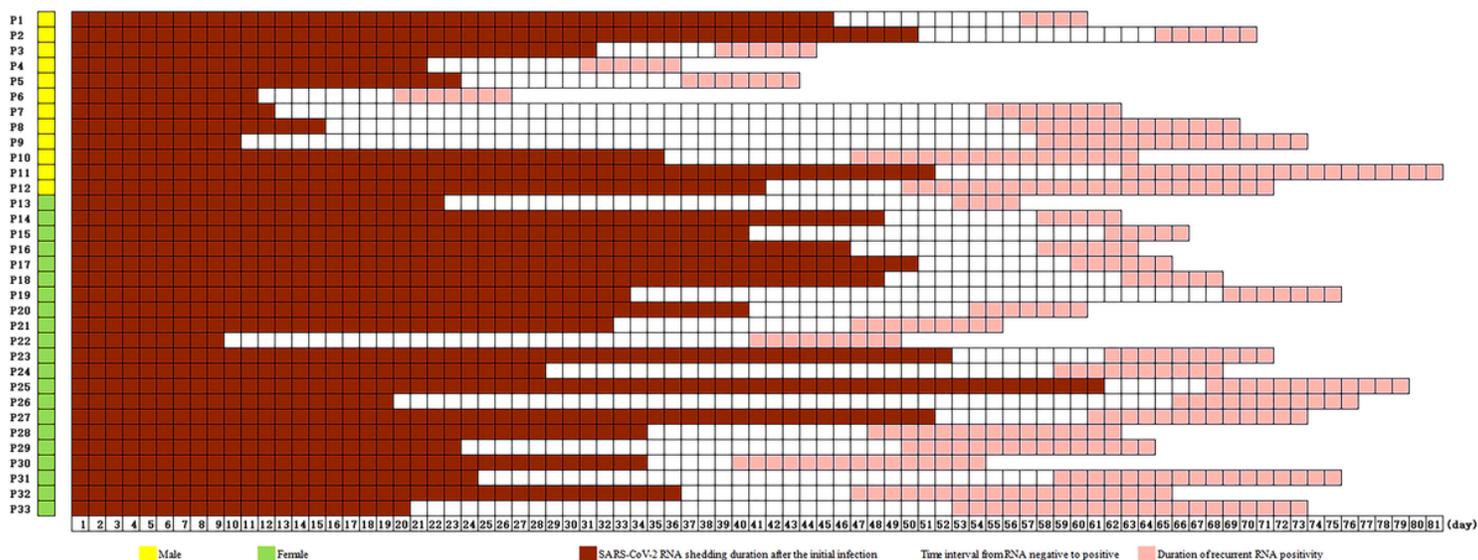


Figure 1

The dynamics of SARS-CoV-2 RNA results in 33 patients.

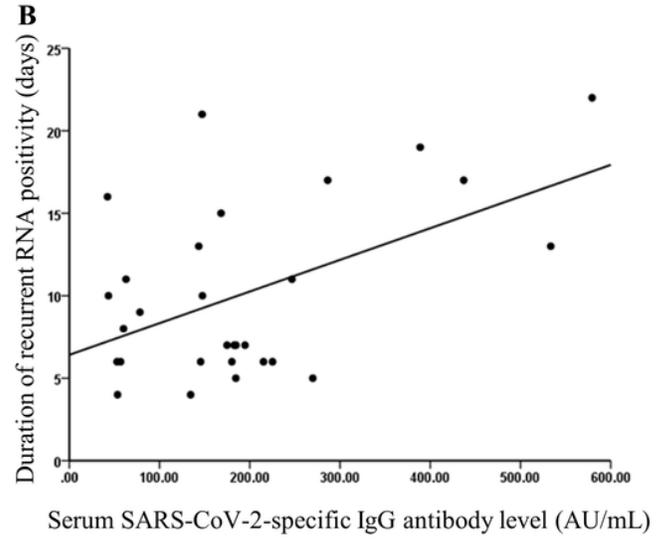
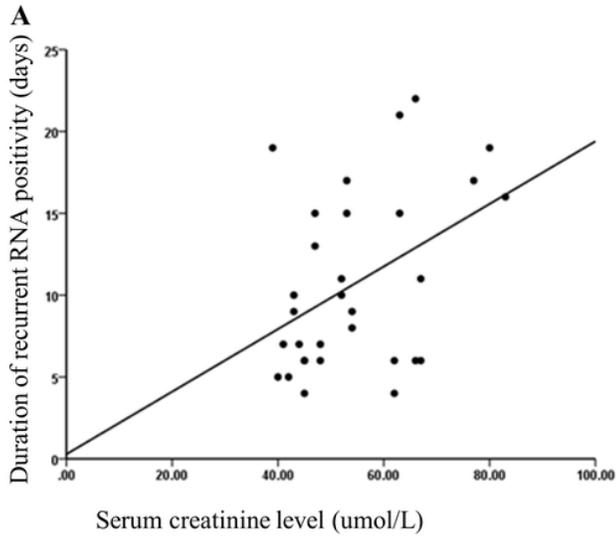


Figure 2

A: Correlation analysis on serum creatinine level and duration of recurrent RNA positivity. B: Correlation analysis on serum SARS-CoV-2-specific IgG antibody titer and duration of recurrent RNA positivity.