Time Kinetics of Viral Clearance and Resolution of Symptoms in Novel Coronavirus Infection

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Introduction

SARS-CoV-2 (previously 2019-nCoV) has infected >167,000 patients and killed >6600 people(1). It has been reported that a patient in Germany had high viral titers after the resolution of fever and infected two of the close contacts after the resolution of symptoms(2). In the wake of these cases, it is still unclear how long the patient was virus positive after the resolution of the symptoms. In this study, we aimed to determine the time kinetics of viral clearance in reference to the resolution of symptoms in 16 patients treated in Beijing, China, and show that half of the patients with COVID-19 were viral positive even after resolution of their symptoms.

Cases

We studied all 16 confirmed COVID-19 patients released from the Treatment Center of PLA General Hospital in Beijing, China, between Jan 28th - Feb 9th, 2020. All patients had throat swabs collected on alternative days and analyzed. Patients were discharged after their recovery and confirmation of “viral negative” status by at least two consecutive real-time PCR(3). There was only one case of a false negative result in our study where patient No.6 was detected negative followed by a positive detection and then two consecutive negative tests were obtained. Travel and possible exposure history were obtained from the patient and noted on their records. Epidemiologically, ten patients visited Wuhan after the outbreak, and three had exposure to a known infected patient, two came in contact with people from Wuhan while 1 had no known exposure. The basic clinical characteristics are given in Table1. The median age was 35.5 years (range 3-68 years), with 11/16 males. The major symptoms in these patients were fever (14/16), cough

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(11/16), pharyngalgia (5/16) and dyspnea (2/16). The day of onset and resolution of these symptoms were noted.

Ground glass opacities (GGO) were observed by CT chest in both sides of the lungs in six patients, only in the right lung in one patient. Levels of CRP and procalcitonin between the first sample obtained at the time of hospitalization and the last sample obtained before discharge were comparable (Table 1).

All the patients received various medical care to treat the COVID-19. Fifteen patients were treated with alpha-interferon, along with other antiviral drugs including oseltamivir (1/16), lopinavir/ritonavir (11/16), acyclovir (1/16), moxifloxacin (5/16), methylprednisolone (2/16), gamma globulin (2/16), vancomycin (1/16) and meropenem (1/16) either alone or in combination. Only one patient required respiratory support involving mechanical ventilation.

Time kinetics of symptom onset, duration of symptoms and viral clearance is described in Table 1. The viral detection test was performed upon clinical presentation and repeated every other day until the patient tested negative. The negative test was confirmed again the next day. Upon confirmation of the negative test, the patient was asked to quarantine at home for the next two weeks with a follow-up visit to the hospital after one week to confirm the viral negative status. The incubation periods were estimated based on the history of the patient's travel or potential exposure. Our data show an incubation period of 5 days (IQR 1-6 days) among the patients (except for patient 12 who had no specific exposure). The mean duration of symptoms was estimated to be 8 days (IQR 6.25-11.5). Most importantly, half (8/16) of the patient remained viral positive (a surrogate marker of

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shedding) even after the resolution of symptoms (Median 2.5 days, range 1 to 8 days). Some of our patients had other comorbidities, which included diabetes (2/16) and tuberculosis (1/16), both of which did not affect the time course of the disease. Similarly, the clinical course for the 3-year-old male did not significantly differ from the rest of the patients.

Discussion

The current COVID-19 pandemic is the third and the most lethal outbreak of coronavirus in the 21st century(4), where the number of infections and mortality has surpassed both MERS and SARS infections within a short period(1, 5). Although the infection appears to be milder with the most lethality in the older male population with pre-existing morbidities(3, 6), it is contagious. The ability to spread may arise from the ability of the virus to transmit from subclinical patients. Cases have been reported where a patient could infect their close contacts even after “apparent recovery” from the infection(2). This warrants us to investigate the “shedding window” after the clinical recovery of the patient. In this study, we report that half of the patients continued to be viral positive even after the resolution of symptoms up to eight days (Figure 1). The viral clearance kinetics were similar in another study by Young et al (12 days), where all the patients survived the infection(7). In contrast virus persisted for 20 days in other study, which had a significant high mortality of >40%(8). This information can provide useful tool for clinicians and policymakers to ensure that recovered patients do not spread the virus. It is important to note that all our patients were milder infections that recovered from the disease. However, it is currently unclear if there is a delayed viral clearance in the more vulnerable population such as those older or have immune deficiencies or are on immunosuppressive therapies.

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The current data are derived from mostly young and male subjects, which is consistent with our previous report in Beijing(9). Similar to previous study, here, we also demonstrate another child (3-year-old male) with COVID-19 indicating the ability of this virus to infect young children as described recently(10).

Our study is limited by the number of patients as there have been limited cases outside the epicenter of the coronavirus outbreak that has been successfully treated so far to be released from the hospital. Our study provides initial insights into the viral clearance kinetics and the ability of the virus to persist even after the resolution of the for as long as 8 days, which may pose a significant challenge in controlling the spread of the disease. However, further studies are needed to investigate if the real-time PCR-detected virus is capable of transmission at the later stage of the disease.

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Figure Legends:

Fig. 1. Time kinetics of viral presence in relationship with resolution of symptoms. Day 0 is the first day of symptoms while the blue dots indicate the resolution of symptoms. First orange box represents the day of first positive viral detection and the last orange box indicates the day of first negative viral qPCR. F and L indicates the first and the last time-point laboratory blood tests were conducted during the hospitalization.

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Table 1: Clinical Presentation and Two-time Pertinent Laboratory Findings of Patient Population With SARS-CoV-2

	Overall (n=16) Median (IQR)
Age (years)	35.5(24-43)
Days from onset of symptoms to hospital admission	3.5(3-4)
Days from onset of symptoms to positive viral test	3(2-4)
Days from onset of symptoms to virus negative	10.5(6-12)
Days from onset of symptoms to resolution of symptoms	8(6.25-11.5)
Days of hospitalization	6.5(5.25-11)
Days from virus positive to virus negative	5.5(4-8)
Days between virus negative to resolution of symptoms (In 8 patients who continue to be viral positive after resolution of symptoms)	2.5(1.25,4.5) (n=8))
incubation period	5(1,6)
Fever N, (%)	14 (87.5%)
Febrile Days	6.5(5-8)
Cough N, (%)	11 (68.75%)
Productive Cough N, (%)	3 (18.75%)
Pharyngalgia N, (%)	5 (31.25%)
Dyspnea N, (%)	2 (12.5%)
Diarrhea N, (%)	1 (6.25%)
Weakness N, (%)	5 (31.25%)
Dizzy N, (%)	2 (12.5%)
	Overall (n=16) Mean (SD)
	During admission / **Before discharge**
WBCs, ×109/L	5.484 (2.44) / 6.331 (1.564)
Neutrophils, %	58.22 (16.30) / 60.17 (14.45)
Absolute neutrophils, ×109/L	3.35 (2.60) / 3.879 (1.62)
Lymphocytes, %	32.47 (15.19) / 29.61 (13.68)
Absolute lymphocytes, ×109/L	1.633 (0.88) / 1.807 (0.91)
Monocytes, %	7.689 (2.01) / 7.359 (1.93)
Absolute monocytes, ×109/L	0.4053 (0.14) / 0.4513 (0.10)
Eosinophils, %	1.347 (1.15) / 2.499 (2.35)
Absolute eosinophils, ×109/L	0.08067 (0.09) / 0.1693 (0.22)
Basophils, %	0.28 (0.22) / 0.3853 (0.17)
Absolute basophils, ×109/L	0.01533 (0.01) / 0.024 (0.01)
RBC 10^12/L	4.498 (0.94) / 4.718 (0.64)
Hemoglobin, g/L	130.4 (28.9) / 136.5 (18.75)
Platelets, ×109/L	162.6 (59.44) / 233.5 (97.75)

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CRP, mg/L	24.81 (41.18)	11.52 (22.67)
PCT, ng/mL	0.6821 (2.45)	0.1325 (0.36)
Fe, µmol/L	16.24 (6.96)	15.71 (7.29)
IL-6, pg/mL	18.14 (18.83)	11.66 (17.69)
Serum Ferritin, ng/mL	341.4 (227.2)	402.4 (405.20)

Table 1: Clinical presentation and two-time pertinent laboratory findings of patient population with COVID-19.

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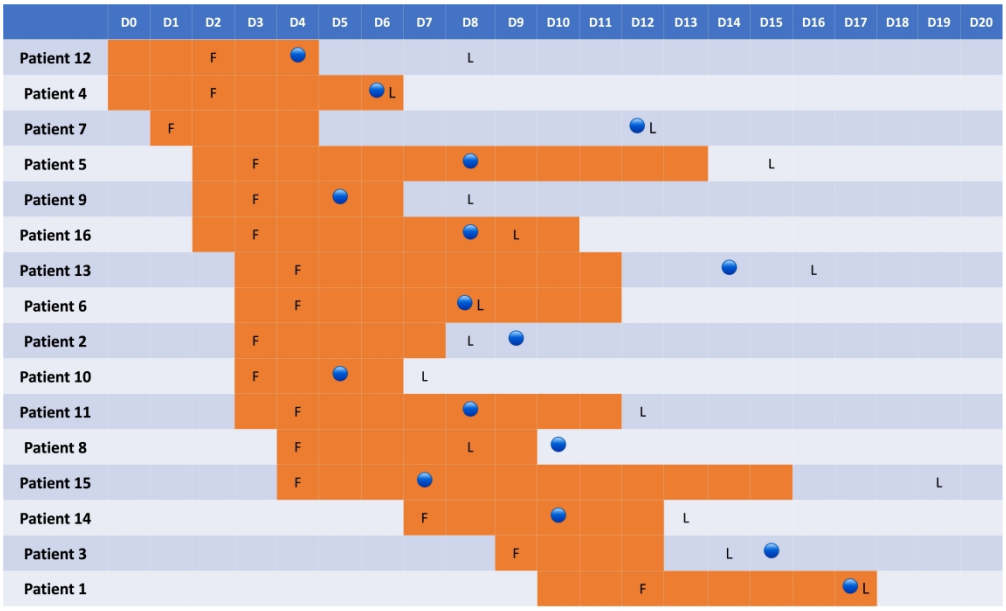

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